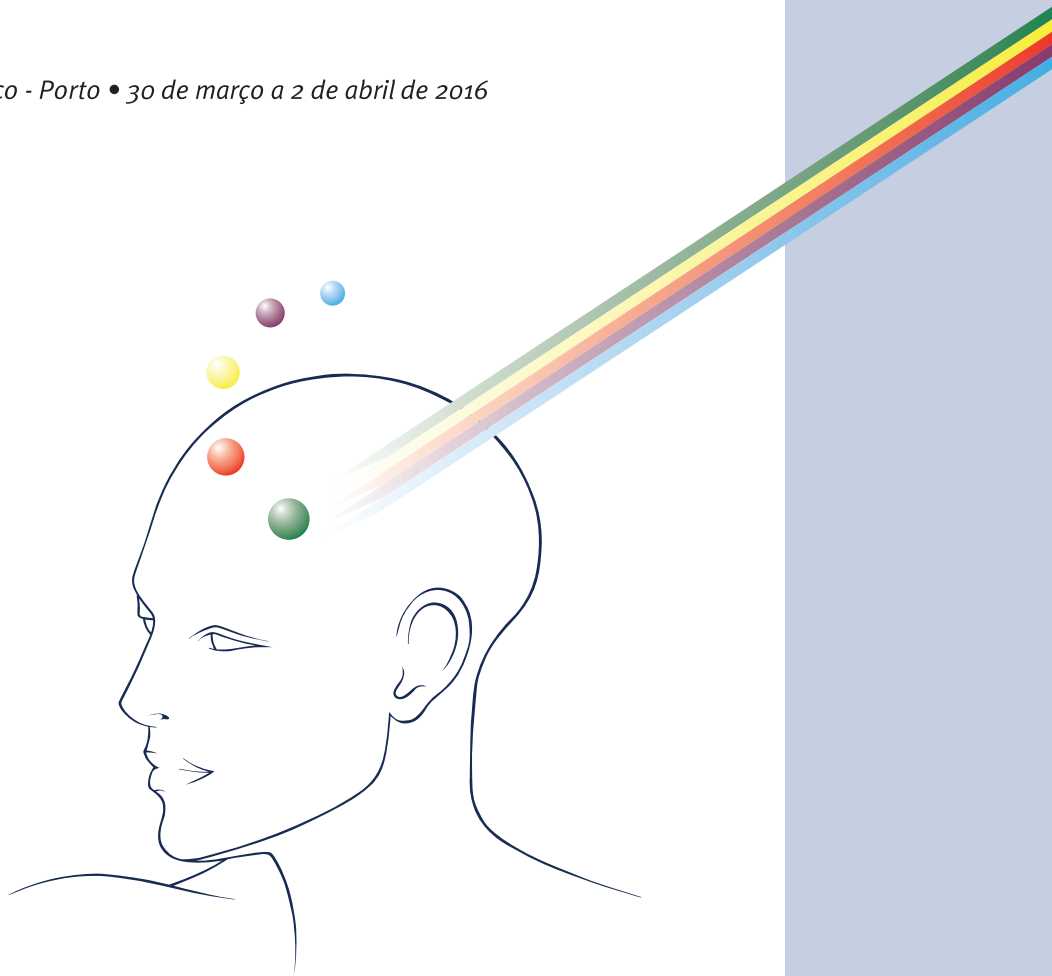
11º Simpósio da Fundação Bial

11

Aquém e Além do Cérebro

Behind and Beyond the Brain

Casa do Médico - Porto • 30 de março a 2 de abril de 2016



FUNDAÇÃO Bial

Instituição de utilidade pública
Institution of public utility

Efeitos de placebo, curas e meditação

Placebo effects, healing and meditation

O livro "Aquém e Além do Cérebro" contém as atas do 11º Simpósio da Fundação Bial, realizado na Casa do Médico, de 30 de março a 2 de abril de 2016, tendo como membros da Comissão Organizadora os Senhores Professores Fernando Lopes da Silva, Dick Bierman, Miguel Castelo-Branco, Axel Cleeremans, Rainer Goebel, Mário Simões e Caroline Watt.
Os textos estão disponíveis em www.fundacaobial.com.

The book "Behind and Beyond the Brain" includes the texts of the Bial Foundation's 11th Symposium, held at Casa do Médico, from March 30th to April 2nd 2016, having as members of its Organizing Committee the following Professors: Fernando Lopes da Silva, Dick Bierman, Miguel Castelo-Branco, Axel Cleeremans, Rainer Goebel, Mário Simões and Caroline Watt.
The texts are available at www. fundacaobial.com.

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SESSÃO DE ABERURA
OPENING SESSION

DISCURSO DO PRESIDENTE DA FUNDAÇÃO BIAL

Luís Portela

Boa noite. Bem-vindos ao 11º Simpósio Aquém e Além do Cérebro, sob o tema "Efeitos de placebo, curas e meditação". Muito obrigado a todos pela vossa presença. Um agradecimento especial à Senhora Secretária de Estado da Ciência, Tecnologia e Ensino Superior, Prof. Maria Fernanda Rollo, que aqui está em representação do Senhor Ministro da Ciência, Tecnologia e Ensino Superior. Muito obrigado pela sua presença e pelo facto de se ter disponibilizado para vir de Lisboa ao Porto no meio deste temporal, apenas para estar connosco, quando eu sei que está com uma agenda muito sobrecarregada. Muito obrigado pela sua presença.

Os nossos agradecimentos, por todo o apoio que têm dispensado à Fundação Bial, ao Conselho de Reitores das Universidades Portuguesas, na pessoa do seu Presidente, Prof. António Cunha; e à Ordem dos Médicos, na pessoa do seu Bastonário, Prof. José Manuel Silva.

O nosso muito obrigado pela presença do Senhor Presidente da ARS Norte, Dr. António José Pimenta Marinho, que representa o Senhor Secretário de Estado Adjunto e da Saúde, da Senhora Bastonária da Ordem dos Farmacêuticos, Prof.ª Ana Paula Martins - tenho muito gosto que esta seja uma das suas primeiras sessões públicas no desempenho das suas novas funções -, e do Senhor Presidente da Comissão de Coordenação e Desenvolvimento Regional do Norte, Prof. Emídio Gomes.

Cumprimento as demais autoridades presentes e também os membros da Comissão Organizadora deste simpósio, a quem manifesto o nosso reconhecido agradecimento pelo excelente trabalho desenvolvido. Um abraço ao seu Presidente, Prof. Fernando Lopes da Silva.

Penso que quase todos sabem que a Fundação Bial é uma instituição sem fins lucrativos, criada pela empresa farmacêutica Bial e pelo Conselho de Reitores das Universidades Portuguesas em 1994, tendo em vista incentivar a investigação científica sobre o ser humano saudável, quer sob o ponto de vista físico, quer sob o ponto de vista espiritual. A Fundação é gerida por representantes das duas instituições.

O que muitos provavelmente não saberão é que esta instituição tem vivido de uma enorme dedicação de um conjunto de pessoas que, ao longo dos anos, tem tornado muito bonito o trabalho que aqui se faz. Pessoas competentes, mas também pessoas de grande dedicação e de grande qualidade interior.

Deixem-me lembrar-lhes os nossos dois primeiros administradores, Professores Nuno Grande e Manuel Baganha. Dois seres humanos excecionais que, comigo, idealizaram a constituição da Fundação, com a configuração que ela tem. Depois, foram nossos administradores, durante 16 anos, no caso de Nuno Grande, e 8 anos, no caso de Manuel Baganha.

E a estes dois grandes obreiros desta casa, sucederam os Professores Maria de Sousa e Daniel Bessa. E que grande admiração tenho também por estes dois amigos! O Daniel continua em funções, mas a Maria terminou-as, por limite de idade, em 2014.

Maria de Sousa é uma grande investigadora na área da Imunologia, que trabalhou perto de vinte anos em Glasgow e em Nova Iorque, mas que, depois, se radicou no Instituto de Ciências Biomédicas Abel Salazar e no IBMC. Com uma elevada produção científica, publicou em muitos sítios, nomeadamente na *Nature* e na *Science.*

Ao longo da carreira, tem sido diversas vezes distinguida, salientando-se as condecorações como Grande Oficial da Ordem do Infante D. Henrique (1995) e Grande Oficial da Ordem de Sant'lago da Espada (2012).

Mulher de grande inteligência e de grande capacidade de trabalho, bem como de elevado nível de exigência - isso acho que todos nós sabemos muito bem -, assume com grande dedicação, eu diria mesmo com paixão, os projetos em que se envolve. E assim aconteceu na JNICT, quando, sob a batuta do Prof. José Mariano Gago, promoveu uma revolução no sistema de avaliação da ciência em Portugal. Todos lhes ficámos a dever esse notável trabalho.

O seu primeiro contacto com a Fundação Bial foi, penso eu, em 1994, quando lhe foi atribuído o nosso Grande Prémio. Depois, foi membro de três júris do Prémio Bial, sendo presidente em 2000. Finalmente, foi nossa administradora entre 2010 e 2014, replicando ao nosso nível o que tinha feito na JNICT: reorganizou as nossas atividades, incutindo-lhes um mais elevado nível de exigência de qualidade.

A Prof. Maria de Sousa será sempre uma das nossas, embora agora sem funções explícitas. Maria, em meu nome e no da administração da Fundação Bial, muito obrigado por tudo o que realizou em prol da Fundação.

Mas, falando de pessoas que têm marcado a vida da Fundação Bial, deixem-me lembrar-lhes as mais de uma centena de personalidades que têm passado pelos nossos Conselhos Científico e Fiscal, pelo Júri do Prémio Bial e pela Comissão Organizadora deste Simpósio. De entre todos, permitam-me que destaque, o Prof. Fernando Lopes da Silva.

Ele é um grande investigador na área das Neurociências, que saiu para Londres em 1962, de onde se transferiu, ainda na década de 60, para a Holanda, onde trabalhou nas Universidades de Utrecht, Twente e Amesterdão. Foi e é um dos mais notáveis investigadores da atividade elétrica do cérebro e da epilepsia.

Ao longo da sua carreira publicou mais de 220 artigos em revistas científicas *peer-reviewed,* nomeadamente no *Journal of Neuroscience* e na *Brain.* Recebeu muitas distinções, entre as quais a de Grande Oficial da Ordem de Sant'lago da Espada, que lhe foi atribuída em 2000, durante o nosso 3º simpósio.

O Fernando participou em quase todos os nossos simpósios, tornou-se membro da Comissão Organizadora em 2003 e seu presidente em 2009. É também, desde 1997, membro do nosso Conselho Científico.

Discreto, mas muito eficiente, senhor de um enorme sentido de equilíbrio, sempre atento e atuante, tem sido o principal responsável pelo nível de qualidade que estes simpósios têm tido, o que muito lhe agradecemos.

Por sua vontade, o Prof. Fernando Lopes da Silva deixará no final deste simpósio a presidência da sua Comissão Organizadora, passando a presidir ao nosso Conselho Científico, onde continuaremos a contar com a sua dedicada e superior contribuição. Fernando, muito obrigado por tudo aquilo que tem dado à Fundação Bial. Um grande abraço.

Também de saída da Comissão Organizadora está o Prof. Dick Bierman, que foi palestrante no nosso quinto simpósio e que é membro da Comissão desde 2007, sendo ainda membro do Conselho Científico desde 2010. Foi, além disso, nosso bolseiro em três projetos, entre 2002 e 2012.

Com uma reconhecida carreira de investigador científico e professor universitário, o Dick sempre procurou, com muito entusiasmo, o

equilíbrio entre a investigação mais tradicional das Neurociências e a investigação científica que nas últimas décadas tem sido feita na área da Parapsicologia. Estamos muito gratos por toda a colaboração que até agora prestou à Fundação e continuaremos a beneficiar do seu saber, enquanto membro do Conselho Científico. Um abraço também. Thank you very much Dick.

A Prof. Maria de Sousa foi substituída em 2014 pelo Prof. Nuno Sousa, tendo o Conselho de Administração sido reforçado com dois membros não executivos: o Prof. Pedro Teixeira e o meu filho Miguel.

Quanto à Comissão Organizadora do nosso próximo simpósio, será presidida pelo Prof. Axel Cleeremans, que já era seu membro desde 2011. Entrarão como seus novos membros o Prof. Etzel Cardeña e o Doutor Rui Costa. Agradeço aos três terem aceite os nossos convites. Manter-se-ão Caroline Watt, Mário Simões, Miguel Castelo-Branco e Rainer Goebel.

Claro que também se mantém a nossa Secretária-Geral, Paula Guedes, com as suas reconhecidas dedicação e competência e a nossa mais recente aquisição Sylvie Marinho.

Entretanto, permitam-me que, com satisfação, lhes anuncie que a Fundação Bial vai de novo apoiar projetos de investigação científica, nas áreas da Psicofisiologia e da Parapsicologia, de forma semelhante ao que temos feito desde 1994. O regulamento e a documentação do concurso estarão disponíveis a partir de amanhã no nosso espaço *www.fundacaobial.com* e o prazo de entrega das candidaturas termina em 31 de agosto próximo. Sublinho que não apoiaremos projetos de patologia ou de terapêutica, por desejarmos separar claramente a atividade mecenática da Fundação, da investigação realizada pelos Laboratórios Bial.

Finalmente, umas muito breves palavras sobre o simpósio que agora se inicia. O tema foi, naturalmente, escolhido pela Comissão Organizadora, no usufruto da autonomia que lhe é devida, mas que teve a gentileza de consultar o Conselho de Administração, como sempre tem, de resto, sucedido. E a Administração aceitou o tema. Nós entendemos que os assuntos – polémicos ou não – devem ser tratados com honestidade e com transparência, procurando-se as soluções que mais e melhor possam beneficiar as pessoas.

A indústria farmacêutica tem desempenhado um fantástico papel no aumento da esperança de vida do ser humano, bem como no aumento

da sua qualidade de vida. Mas, reconheçamo-lo, há áreas onde se pode melhorar o excelente trabalho que tem sido feito. Por outro lado, parece indubitável haver pela frente também um grande percurso de melhoria nas chamadas áreas alternativas ou medicinas alternativas.

Ora, o que desejamos é que este simpósio possa dar um bom contributo nesse sentido. Que, de uma forma serena e civilizada, mas rigorosa e competente, possamos em conjunto contribuir para que a investigação científica conduzida em torno do ser humano possa sair enriquecida, melhor beneficiando a humanidade. E que o possamos fazer com satisfação, com alegria, com prazer, ao longo destes quatro dias.

Acreditando que só a Verdade fará o homem livre, mas também completo, desejo que, nestes próximos dias, saibamos criar condições para um melhor conhecimento da Vida, quer sob o ponto de vista físico, quer na dimensão espiritual. Desejo que saibamos todos aproximar-nos da Verdade Total.

Bem hajam pela vossa presença.

Muito obrigado pela vossa atenção.

DISCURSO DO PRESIDENTE DA COMISSÃO ORGANIZADORA

SPEECH OF THE PRESIDENT OF THE ORGANIZING COMMITTEE

Fernando Lopes da Silva

Ladies and gentlemen. I would like to start in English and then I will switch to Portuguese, if you don't mind.

On behalf of the Organizing Committee of the Bial Foundation Symposium, I have the honor and pleasure to introduce you to the 11th symposium of the Bial Foundation that is dedicated, as you have already heard to "Placebo effects, Healing and Meditation".

It should be emphasized that this 11th Symposium has a theme that may be controversial and may be considered daring or even audacious, since the Bial Foundation is of course the supporter and the sponsor of the Symposium, but for most people, I think the name BIAL would be more readily associated with the word remedy or medicine, rather than with the word placebo. The fact that BIAL Foundation is supporting this Symposium dedicated to placebo effects is a testimony of the healthy impartiality of the Foundation regarding scientific freedom, what is very important for us. There is no interference whatsoever of BIAL as a pharmaceutical enterprise on our scientific program. The latter is the entire responsibility of the Symposium Committee, that is completely independent of the business activity of Bial as a pharmaceutical enterprise. We respect and cherish this independence very much. We should also emphasize that this possibility is a very important asset of the Bial Foundation that wants always to promote the scrutiny of scientific questions in an objective way. This applies most clearly to the particular theme of this Symposium.

Now, I will switch to Portuguese for a short time.

Não quero terminar esta breve intervenção sem dirigir em Português umas palavras de apreço e amizade em relação ao Presidente da Fundação Bial e a todos os membros da direção da Fundação, pelo apoio que sempre nos deram no desempenho da nossa tarefa de membros da Comissão Organizadora destes Simpósios, pela liberdade que nos deram sempre de

exercer esta função de acordo com a nossa consciência, com as nossas convicções e com a integridade científica. Depois de cerca de 10 anos como presidente desta Comissão é agora a ocasião de passar o testemunho ao meu sucessor.

Now I switch to English. Actually, I could switch to French or to Flemish if you like.

I wish success to my successor, Axel Cleeremans, from Brussels, hoping that he will have success in carrying out this very gratifying task of chairing the Symposium Committee in the years ahead. Thank you.

DISCURSO DO BASTONÁRIO DA ORDEM DOS MÉDICOS

José Manuel Silva

Boa noite a todos. Quero cumprimentar o Senhor Presidente da Fundação Bial, a Senhora Secretária de Estado da Ciência, o Senhor Presidente do Conselho de Reitores, o Prof. Fernando Lopes da Silva, todos os presentes e permitam-me que cumprimente a Senhora Bastonária da Ordem dos Farmacêuticos aqui presente; é um prazer vê-la aqui também.

Sejam todos bem-vindos - colegas portugueses e colegas estrangeiros -, às instalações da Ordem dos Médicos, nesta magnífica Secção Regional do Porto da Ordem dos Médicos. É um prazer recebê-los aqui, é uma honra estar nesta circunstância a dar-vos as boas-vindas e, sobretudo, a congratular a Fundação Bial por mais esta organização, o 11º Simpósio Aquém e Além do Cérebro.

Lembro-me que aquando do primeiro, a Bial foi olhada um pouco de soslaio por se atrever a este tipo de organização e a abordar estes temas. Mas sem dúvida que a Bial, e a Fundação Bial são duas instituições de grandes desafios e de grandes êxitos e aqui estamos no 11º Simpósio, a discutir um tema absolutamente fascinante como é o placebo, o efeito da meditação e a cura por mecanismos que têm a ver com o efeito placebo, e que obviamente cada vez mais se conhecem e se identificam pela investigação científica como mecanismos neuroquímicos de mediação, e de um efeito que poderá cada vez mais - e deverá cada vez mais -, ser utilizado pela medicina clássica. A medicina clássica desprezou, erradamente, o efeito placebo. O campo do efeito placebo tem sido ocupado, e bem, pelas terapêuticas não convencionais e deve ser, cada vez mais, objeto de investigação e de integração no exercício diário da medicina alopática, na medida em que é ciência, na medida em que consegue afinal efeitos semelhantes ao efeito de tantos medicamentos.

Eu hoje, quando vinha para aqui, pensava "bem vou à sessão de abertura e regresso à minha província, Coimbra". Mas o tema desta conferência de abertura é um enorme desafio, é um tema que nos deve fazer pensar e encarar também, com humildade, a forma como exercemos

medicina e como afinal a ciência nos pode induzir em caminhos, que nem sempre serão os mais corretos, e que devemos manter sempre o espírito crítico relativamente às nossas práticas e exigir cada vez mais transparência e divulgação de dados da investigação científica para que possam ser devidamente escrutinados pela comunidade científica na avaliação da sua veracidade e verdadeiros efeitos. É algo que é extraordinariamente importante para o exercício da medicina, porque todos nós conhecemos circunstâncias em que a verdade científica foi voluntariamente deturpada para induzir a comunidade médica num sentido que não é o mais correto e que não é o mais adequado para os doentes.

Por isso eu saúdo e cumprimento a Fundação Bial por mais este Simpósio, espero que continue, e só tenho pena de não ser, enfim sendo, mas de não ser neste momento um médico despido destas funções que me permitisse estar aqui todos estes dias a assistir a este magnífico Simpósio. Cumprimento a Comissão Científica por ter construído um conjunto de temas tão interessantes, que merecem uma grande divulgação no meio da comunidade médica portuguesa, para nos obrigar a pensar sobre o exercício da medicina e sobre aquilo que não temos valorizado para melhor servir, e melhor conseguir resultados junto dos nossos doentes. Parabéns à Fundação Bial e muito obrigado pelo convite.

DISCURSO DO PRESIDENTE DO CONSELHO DE REITORES DAS UNIVERSIDADES PORTUGUESAS

António Cunha

Muito boa noite, minhas senhoras e meus senhores. Saúdo e cumprimento a Senhora Secretária de Estado, a Professora Fernanda Rollo, o Senhor Presidente da Fundação Bial, caríssimo, querido, Luís Portela, o Senhor Bastonário da Ordem dos Médicos e o Senhor Professor Fernando Lopes da Silva.

Para muitas, diria para mesmo muitas pessoas, estejam elas ligadas ao mundo do tecido económico produtivo, ao mundo académico, à investigação, às ciências da vida e da saúde, ou a outras áreas, o nome Bial é uma referência; é um nome que associamos quase a um imaginário de excelência, a um imaginário que aprendemos a respeitar. Certamente um paradigma de uma empresa, de uma entidade que soube, desde há muito tempo, utilizar - e é um exemplo em Portugal -, conhecimento como base da sua atividade económica. É também um paradigma de uma empresa que faz quase tudo bem feito, eu estou apenas a dizer o quase, porque não conheço tudo o que a Bial faz, apenas por isso. E uma das coisas que a Bial fez bem-feita, foi a criação da Fundação Bial. E também foi muito bem feito, quando desafiou o CRUP, o Conselho de Reitores, para participar nesta organização, nesta estrutura; num processo que muito apraz ao Conselho de Reitores, no qual as Universidades Portuguesas têm beneficiado muito e a Ciência Portuguesa também. E, certamente, quer o Prémio Bial, quer este Simpósio, são exemplos que mostram aquilo que esta Fundação tem sido capaz de fazer, são exemplos importantes nesta área científica, exemplos marcantes, mas são também forma diferentes, mas muito, muito relevantes, de uma entidade económica, uma empresa, cooperar com as universidades e com as estruturas de investigação.

Por tudo isto, muito obrigado à Fundação Bial por todo o trabalho que tem feito. Tenham a certeza que, do lado do Conselho de Reitores, continuaremos, dentro do que é possível, a tratar com todo o carinho e com todo o interesse esta iniciativa, e a certeza que vamos continuar a ter muitas boas notícias daquilo que a Fundação Bial faz pela comunidade científica. Muito obrigado.

DISCURSO DA SECRETÁRIA DE ESTADO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR, EM REPRESENTAÇÃO DO SENHOR MINISTRO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

Maria Fernanda Rollo

Muito boa noite Senhor Presidente da Fundação Bial, Doutor Luís Portela, muito obrigada pelo desafio, mas sobretudo por estas atividades. Senhor Presidente do Conselho de Reitores, querido amigo, Professor António Cunha, Senhor Bastonário da Ordem dos Médicos, Senhor Presidente da Comissão Executiva deste encontro e permitam-me, não posso deixar de cumprimentar a Professora Maria de Sousa, pelo carinho, pelo respeito e pela admiração.

Tenho muito gosto por estar aqui presente, por várias razões, entre as quais, não posso deixar de confessar uma, é que eu sou historiadora e há muitos anos que olho para a Bial como uma referência num contexto nacional que tem as suas singularidades.

Sobretudo, uma dessas singularidades foi um atraso persistente e um atavismo enorme no que diz respeito ao seu tecido económico, social, produtivo e onde no tempo em que a Bial é criada, e se não me falhar a memória, em 1924, surge como algo absolutamente, diríamos hoje, disruptivo naquilo que era a realidade nacional. Um país sem indústria, um país sem grande ambição, mas sobretudo um país sem indústrias e sem a capacidade de uma visão que exigisse ciência, que exigisse conhecimento e que apostasse de forma persistente; e a Bial foi isso. Portanto, quando nós fazemos a história económica do século XX, e quando fazemos a história económica do nosso país, contamos quase pelos dedos as entidades que podemos nomear de sucesso, sobretudo na primeira década do século XX, e não melhorou muito na segunda, mas bastante, e entre essas a Bial pontua num período particularmente complicado, como foi este de pós-guerra, mas que também deu muitas oportunidades. A Bial, além do mais, reunia outras características - esta ligação que hoje reconhecemos todos como um círculo virtuoso, entre a empresa, o tecido empresarial,

o tecido social, a investigação ou a universidade; e isso a Bial fê-lo com algum protagonismo e pioneirismo em Portugal. Aquilo que era evidente em países como a Alemanha e outros, em Portugal não existia, e a Bial fá-lo de forma persistente e num contexto de empresa familiar que vem sobrevivendo em quatro gerações, se também não estiver errada, o que é também quase um record no plano nacional, pois muitas destas empresas acabam por soçobrar normalmente à segunda geração.

E, portanto, eu acho que é desde logo um grande orgulho para todos ter uma empresa como os Laboratórios Bial, que foi de facto fundamental também para criar a convicção de que podemos fazer coisas bem-feitas, mas sobretudo para nos continuar a convencer que não é possível construir empresas desta natureza, e empreendimentos desta natureza, sem persistência, sem continuidade e, nestes contextos, sem uma relação muito íntima com a investigação.

A esse nível a Fundação Bial é mais uma prova também daquilo que representa a sua responsabilidade social, e a sua responsabilidade científica, num contexto que também não é muito comum, e sobretudo não era muito comum em 1984. Enfim, já aqui foi nomeado a JNICT, e até a Maria de Sousa, e todos nós temos presentes também o que era o nosso país por esses idos anos 80 e o certo arrojo que se associa à criação da Fundação Bial. De facto, poderá ter suscitado várias descrenças, mas provou, uma vez mais, a importância também desta relação com a comunidade científica. A Fundação Bial é hoje uma instituição de referência pelos Prémios, pelas atividades e por estes Simpósios que evidentemente organiza e que, claro, são fundamentais para todos nós.

Na ótica do Ministério da Ciência, Tecnologia e Ensino Superior, e sobretudo em contextos como o nosso, este círculo ou encontro virtuoso é absolutamente determinante. É determinante por aquilo que significa também em termos de responsabilidade e em termos de afirmação e de presença do investimento privado na área de investigação científica, associando, evidentemente, esta ligação determinante com as universidades, e o Senhor Presidente do CRUP já o referiu. Mas, por outro lado, continuando a apostar na renovação da investigação, investindo diretamente nas pessoas, na sua formação, de uma forma persistente, assumida e fundamental. Além do mais, apoiando projetos de investigação científica, constitui aqui uma parceira fundamental para o esforço público que tem que acontecer nestas áreas.

A Fundação Bial é hoje também essa confirmação daquilo que têm sido os Laboratórios Bial, e que todos gostaríamos que continuasse a acontecer em muitos mais contextos. Oxalá tivéssemos muitas réplicas para, no fundo, nos continuar a marcar e a pontuar na fronteira do conhecimento. Eu penso que devemos olhar para a Bial e para a Fundação Bial com essa indicação, na fronteira do conhecimento, rasgando com coragem - porque é precisa alguma coragem -, mas sobretudo com muita curiosidade - porque é isso que a ciência também nos ensina a ter como horizonte -, e com a capacidade de sermos criativos numa renovação persistente para o conhecimento e para a investigação.

Por isso penso que todos temos de estar gratos a estas iniciativas, estimular para que elas continuem e se aprofundem, e que mantenham esta relação e esta consciência, porque é fundamental também para a informação das políticas públicas, para as acompanhar, para as estimular, e no fundo, é necessário para termos mais conhecimento. Sobretudo num país como o nosso, que também tem estas áreas onde a saúde pontua com a excecionalidade, que devemos, e eu não queria deixar de o reconhecer, uma expressão de grande visibilidade no plano nacional, e sobretudo no plano internacional, e por isso também esse agradecimento e esse reconhecimento à comunidade dos médicos que aqui estão e que continuam também a criar novos passos em frente, avançando para estas áreas do conhecimento e estas áreas de reflexão, como este congresso de alguma maneira sintetiza - Aquém e Além do Cérebro.

Desejo a todos um excelente encontro. Será, com certeza, muito estimulante. Penso que ficamos todos um bocadinho, mesmo os não médicos, como é o meu caso, muito entusiasmados e de certa forma seduzidos e quase com inveja de não poder acompanhar também o que será a aprendizagem e a partilha de conhecimentos neste encontro. Muito obrigada.

CONFERÊNCIA INAUGURAL
OPENING CONFERENCE

THE EMPEROR'S NEW DRUGS: MEDICATION AND PLACEBO IN THE TREATMENT OF DEPRESSION

Irving Kirsch*

Summary

Antidepressants are supposed to work by fixing a chemical imbalance, specifically, a lack of serotonin in the brain. But analyses of the published and the unpublished data that were hidden by the drug companies reveal that most (if not all) of the benefits are due to the placebo effect. Some antidepressants increase serotonin levels, some decrease serotonin, and some have no effect at all on serotonin. Nevertheless, they all show the same therapeutic benefit. Instead of curing depression, popular antidepressants may induce a biological vulnerability making people more likely to become depressed in the future. Other treatments (e.g., psychotherapy and physical exercise) produce the same short term benefits as antidepressants, show better long term effectiveness, and do so without the side effects and health risks of the drugs.

On February 26, 2008, an article about antidepressants that my colleagues and I wrote was published in the journal PLoS Medicine (Kirsch et al., 2008). That morning, I awoke to find that our paper was the front-page story in all of the leading national newspapers in the United Kingdom. A few months later, Random House invited me to expand the article into a book, entitled *The Emperor's New Drugs: Exploding the Antidepressant Myth*, which has since been translated into French, Italian, Japanese, Polish, and Turkish (Kirsch, 2009). Two years later, the book, and the research reported in it, was the topic of a five-page cover story in the influential American news magazine, *Newsweek*. Two years after that, it was the focus of a 15 minute segment on *60 Minutes*, America's top-rated television news program. Somehow, I had been transformed from a mild-mannered university professor into a media superhero – or

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super villain, depending on whom you asked. What had my colleagues and I done do warrant this transformation?

To answer that question, we have to go back to 1998, when a former graduate student, Guy Sapirstein, and I published a meta-analysis on antidepressants in an online journal of the American Psychological Association (Kirsch & Sapirstein, 1998). Meta-analysis is a statistical tool for pooling the results of large numbers of studies on the same topic and analyzing them together. When they were new, meta-analyses were somewhat controversial, but now they are published in all of the major medical journals, where they are widely considered to be the best and most reliable way of making sense of the data from studies with different and sometimes conflicting results.

When Sapirstein and I began our analysis of the antidepressant clinical trial data, we were not particularly interested in antidepressants. Instead, we were interested in understanding the placebo effect. I have been fascinated by the placebo effect for my entire academic career. How is it, I wondered, that the belief that one has taken a medication can produce some of the effects of that medication?

It seemed to Sapirstein and me that depression was a good place to look for placebo effects. After all, one of the prime characteristics of depression is the sense of hopelessness that depressed people feel. If you ask depressed people to tell you what the worst thing in their life is, many will tell you that it is their depression. The British psychologist John Teasdale called this being depressed about depression. If that is the case, then the mere promise of an effective treatment should help to alleviate depression, by replacing hopelessness with hopefulness –the hope that one will recover after all. It was with this in mind that we set out to measure the placebo effect in depression.

Sapirstein and I searched the literature for studies in which depressed patients had been randomized to receive an inert placebo or no treatment at all. The studies we found also included data on the response to antidepressants, because that was the only place one finds data on the response to placebo among depressed patients. I was not particularly interested in the drug effect. I assumed that antidepressants were effective. As a psychotherapist, I sometimes referred my severely depressed clients for prescriptions of antidepressant drugs. Sometimes the condition of

my clients improved when they began taking antidepressants; sometimes it did not. When it did, I assumed it was the effect of the drug that was making them better. Given my long standing interest in the placebo effect, I should have known better, but back then I did not.

Analyzing the data we had found, Sapirstein and I were not surprised to find a substantial placebo effect on depression. What surprised us was how small the drug effect was. Seventy-five percent of the improvement in the drug group also occurred when people were given dummy pills with no active ingredient in them. Needless to say, our meta-analysis proved to be very controversial. Its publication led to heated exchanges. The response from critics was that these data could not be accurate. Perhaps our search had led us to analyze an unrepresentative subset of clinical trials. Antidepressants had been evaluated in many trials, the critics said, and their effectiveness had been well established.

In an effort to response to these critics, we decided to replicate our study with a different set of clinical trials (Kirsch et al., 2002). To do this, we used the Freedom of Information Act to request that the Food and Drug Administration (FDA*) send us the data that pharmaceutical companies had sent to it in the process of obtaining approval for six new generation antidepressants that accounted for the bulk of antidepressant prescriptions being written at the time. There are a number of advantages to the FDA data set. Most important, the FDA requires that the pharmaceutical companies provide information on all of the clinical trials that they have sponsored. Thus, we had data on unpublished trials as well as published trials. This turned out to be very important. Almost half of the clinical trials sponsored by the drug companies have not been published. Only the drug companies and the FDA knew the results of the unpublished trials, and most of them failed to find a significant benefit of drug over placebo. A second advantage of the FDA trials in the FDA dataset is that they all used the same primary measure of depression—the Hamilton depression scale (HAM-D). That made it easy to understand the clinical significance of the drug-placebo differences. Finally, the data in the FDA files were the basis upon which the medications were approved. In that sense, they have a privileged status. If there is anything

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wrong with those trials, the medications should not have been approved in the first place.

In the data sent to us by the FDA, only 43% of the trials showed a statistically significant benefit of drug over placebo. The remaining 57% were failed or negative trials. The results of our analysis indicated that the placebo response was 82% of the response to these antidepressants. Subsequently, my colleagues and I replicated our meta-analysis on a larger number of trials that had been submitted to the FDA (Kirsch et al., 2008). With this expanded data set, we found once again that 82% of the drug response was duplicated by placebo. More important, in both analyses, the mean difference between drug and placebo was less than two points on the HAM-D. The HAM-D is a 17-item scale on which people can score from 0 to 53 points, depending on how depressed they are. A 6 point difference can be obtained just by changes in sleep patterns, with no change in any other symptom of depression. So the 1.8 difference that we found between drug and placebo was very small indeed – small enough to be clinically insignificant. But you don't have to take my word for how small this difference is. The National Institute for Health and Clinical Excellence (NICE), which drafts treatment guidelines for the National Health Service in the United Kingdom, has established a 3 point difference between drug and placebo on the HAM-D as a criterion of clinical significance (NICE, 2004). Thus, when published and unpublished data are combined, they fail to show a clinically significant advantage for antidepressant medication over inert placebo.

Some have argued that the NICE criterion is arbitrary (e.g., Turner and Rosenthal, 2008), and they are correct. It is as arbitrary as using $p < .05$ as a cutoff for statistical significance. However, Joanna Moncrieff and I have discovered a non-arbitrary criterion for clinical significance (Moncrieff and Kirsch, 2015). In 2013, Stefan Leucht and his colleagues (Leucht et al., 2013) compared ratings on the HAM-D with those made on the Clinical Global Impressions.

Improvement (CGI-I) scale (Guy, 1976). The CGI-I is a 7-point scale, on which clinicians rate patients from 1 (very much improved) through 4 (no change) to 7 (very much worse). Using patient level data from 43 clinical trials, involving 7,131 patients, Leucht established that the mean change on the HAM-D for patients rated on the CGI-I as

not having changed at all was 3 points, exactly what NICE had set as a criterion of clinically meaningful improvement. So as it turns out, the problem with the NICE criterion is that it is too lenient. A 3-point difference on the HAM-D is not even detectable by clinicians as any change at all in their patients. A more reasonable criterion would be the HAM-D change that corresponds to a CGI-I rating of "minimal improvement." Leucht et al.'s data indicates that a rating of "minimal improvement" is equivalent to a 7-point decrease in HAM-D scores.

I should mention here the difference between statistical significance and clinical significance. Statistical significance concerns how reliable an effect is. Is it a real effect, or is it just due to chance? Statistical significance does not tell you anything about the size of the effect. Clinical significance, on the other hand, deals with the size of an effect and whether it would make any difference in a person's life. Imagine, for example, that a study of 500,000 people has shown that smiling increases life expectancy – by five minutes. With 500,000 subjects, I can virtually guarantee you that this difference will be statistically significant, but it is clinically meaningless.

Our analyses have since been replicated repeatedly (Fountoulakis & Möller, 2011; Fournier et al., 2010; NICE, 2004; Turner et al., 2008). Some of the replications used our data; others analyzed different sets of clinical trials. The FDA even did its own meta-analysis on all of the antidepressants that they have approved. (Khin et al., 2011) Despite differences in the way the data have been spun, the numbers are remarkably consistent. Differences on the HAM-D are consistently small - always below the level corresponding to a CGI-I rating of "no change." Thomas P. Laughren, the director of the FDA's psychiatry products division, acknowledged this on the American television news program *60 Minutes.* He said, "I think we all agree that the changes that you see in the short-term trials, the difference in improvement between drug and placebo, is rather small."

It is not only the short-term trials that show a small, clinically insignificant difference between drug and placebo. In their meta-analysis of published clinical trials, NICE (2004) found that the difference between drug and placebo in the long term trials were no larger than those in short-term trials. The difference between drug and placebo is small – it is so small that clinicians cannot detect it at all.

Severity of Depression and Antidepressant Effectiveness

Critics of our 2002 meta-analysis have argued that our results were based on clinical trials conducted on subjects who were not very depressed. In more depressed patients, they argued, a more substantial difference would certainly be found. In fact, it was this criticism that led my colleagues and I to reanalyze the FDA data in 2008 (Kirsch et al., 2008). We categorized the clinical trials in the FDA database according to the severity of the patients' depression at the beginning of the trial, using conventionally used categories of depression. As it turns out, only one of the trials were conducted on moderately depressed patients, and that trial failed to show any significant difference between drug and placebo. Indeed, the difference was virtually nil (0.07 points on the HAM-D). All of the rest of the trials were conducted on patients whose mean baseline scores put them in the "very severe" category of depression, and even among these patients, the drug-placebo difference was below the level of clinical significance.

Still, severity did make a difference. Patients at the very extreme end of depression severity, those scoring at least 28 on the HAM-D, showed an average drug-placebo difference of 4.36 points. This is above the criterion for clinical significance proposed by NICE (2004), but it is well below the 7-point difference that corresponds to a CGI-I rating of "minimal improvement."

Attempts by other researchers to evaluate the association between initial severity and drug-placebo differences have yielded mixed results. Some find the same association that we found (e.g., Fournier et al., 2010; Khin et al., 2011), whereas others find no association between severity and drug-placebo differences (e.g., Fountoulakis et al., 2013; Locher et al., 2015). But all meta-analyses find overall drug-placebo differences that are below the NICE criteria for clinical significance. So the question is, is there a subset of very severely depressed patients for whom antidepressants are clinically effective, or do they lack effectiveness at all levels of severity?

Predicting Response to Treatment

Severity of depression is one of the few predictors of response to treatment. Type of antidepressant has little if any impact on treatment response. As summarized in a 2011 meta-analysis of studies comparing one antidepressant to another:

On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions... Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. (Gartlehner et al., 2011)

Although type of medication does not make a clinically significant difference in outcome, response to placebo does. Almost all antidepressant trials include a placebo run-in phase. Before the trial begins, all of the patients are given a placebo for a week or two. After this run-in period, the patients are reassessed, and anyone who has improved substantially is excluded from the trial. That leaves patients who have not benefitted at all from placebo and those who have benefited only a little bit. These are the patients who are randomized to be given drug or kept on placebo. As it turns out, the patients who show at least a little improvement during the run-in period are the ones most likely to respond to the real drug, as shown not only by physician ratings, but also by changes in brain function (Hunter, Leuchter, Morgan, & Cook, 2006; Quitkin et al., 1998).

How Did These Drugs Get Approved?

How is it that medications with such weak efficacy data were approved by the FDA? The answer lies in an understanding of the approval criteria used by the FDA. The FDA requires two adequately conducted clinical trials showing a significant difference between drug and placebo. But there is a loophole: There is no limit to the number of trials that can be conducted in search of these two significant trials. Trials showing negative results simply do not count. Furthermore, the clinical significance of the findings is not considered. All that matters is that the results are statistically significant.

The most egregious example of the implementation of this criterion is provided by the FDA's approval of Viibryd in 2011. Seven controlled efficacy trials were conducted. The first five failed to show any significant differences on any measure of depression, and the mean drug-placebo difference in these studies was less than ½ point on the HAM-D, and in two of the five trials, the direction of the difference actually favored the placebo. The company ran two more studies and managed to obtain small but significant drug-placebo differences (1.70 points). The mean drug-placebo difference across the seven studies was 1.01 HAM-D points. This was sufficient for the FDA to grant approval, and the information approved by the FDA for informing doctors and patients reads, "The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials." No mention is made of the five failed trials that preceded the two successful ones.

The failure to mention the unsuccessful trials was not merely an oversight; it reflects a carefully decided FDA policy dating back for decades. To my knowledge, there is only one antidepressant in which the FDA included information on the existence of negative trials. The exception is citalopram, and the inclusion of the information followed an objection raised by Paul Leber, who was at the time the director of the FDA Division of Neuropharmacological Drug Products. In an internal memo dated May 4, 1998, Leber wrote:

"One aspect of the labelling deserves special mention. The [report] not only describes the clinical trials providing evidence of citalopram's antidepressant effects, but make mention of adequate and well controlled clinical studies that failed to do so...The Office Director is inclined toward the view that the provision of such information is of no practical value to either the patient or prescriber. I disagree. I believe it is useful for the prescriber, patient, and 3rd-party payer to know, without having to gain access to official FDA review documents, that citalopram's antidepressants effects were not detected in every controlled clinical trial intended to demonstrate those effects. I am aware that clinical studies often fail to document the efficacy of effective drugs, but I doubt that the public, or even the majority of the medical community, is aware of this fact. I am persuaded that they not only have a right to know but that they should know. Moreover, I believe that labeling that selectively describes

positive studies and excludes mention of negative ones can be viewed as potentially 'false and misleading'."

Hooray for Paul Leber. "I have never met or corresponded with this gentleman, but because of this courageous memo, he is one of my heroes."

The Serotonin Myth

Over the years, I have noticed something very strange in the antidepressant literature. When different antidepressants are compared with each other, their effects are remarkable similar. In the STAR*D trial, for example, which, at a cost of $35,000,000, is the most costly clinical trial of antidepressants ever conducted, patients who did not respond to the prescribed SSRI were switched to a different antidepressant. Some were switched to a SNRI, a drug that is supposed to increase norepinephrine as well as of serotonin in the brain. Others were switched to an NDRI, which is supposed to increase norepinephrine and dopamine, without affecting serotonin at all. And still others were simply given a different SSRI. About one out of four patients responded clinically to the new drug, but it did not matter which new drug they were given. The effects ranged from 26% to 28%; in other words, they were exactly the same regardless of type of drug.

The most commonly prescribed antidepressants are SSRIs, drugs that are supposed to selectively target the neurotransmitter serotonin. But there is another antidepressant that has a very different mode of action. It is called tianeptine, and it has been approved for prescription as an antidepressant by the French drug regulatory agency. Tianeptine is an SSRE, a selective serotonin reuptake enhancer. Instead of increasing the amount of serotonin in the brain, it is supposed to decrease it. If the theory that depression is caused by a deficiency of serotonin were correct, we would expect to make depression worse. But it doesn't. In clinical trials comparing the effects of tianeptine to those of SSRIs and tricyclic antidepressants, 63% of patients show significant improvement (arbitrarily defined as a 50% reduction in symptoms), the same response rate that is found for SSRIs, NDRIs and tricyclics, in this type of trial. It simply does not matter what is in the medication – it might increase serotonin, decrease it, or have no effect on serotonin at all. The effect on depression is the same.

What do you call pills, the effects of which are independent of their chemical composition? I call them 'placebos'.

Antidepressants as Active Placebos

All antidepressants seem to be equally effective, and although the difference between drug and placebo is not clinically significant, it is significant statistically. This leads to the obvious question: What do all of these active drugs have in common that make their effect on depression slightly, but statistically significantly, better than placebo?

One thing that antidepressants have in common is that they all produce side effects. Why is that important? Imagine that you are a subject in a clinical trial. You are told that the trial is double blind and that you might be given a placebo. You are told what the side effects of the medication are. The therapeutic effects of the drug may take weeks to notice, but the side effects might occur more quickly. Would you not wonder to which group you had been assigned, drug or placebo, and noticing one of the listed side effects, would you not conclude that you had been given the real drug? In one study, 89% of depressed patients in the drug group correctly 'guessed' that they had been given the real antidepressant, (Rabkin et al., 1986), and in a study examining antidepressants and benzodiazepines in the treatment of panic disorder, 95% of patients in the active drug groups broke blind (Margraf et al., 1991).

It is not only patients who break blind, but also the clinicians who rate them on the HAM-D (Margraf et al., 1991; Rabkin et al., 1986). In fact, clinicians do better than patients at figuring out the group to which the patient has been assigned. Patients given the real drug do well at 'guessing' that they are in the drug group, but those in placebo arms are much accurate. In contrast, clinicians doing the ratings are very accurate in identifying the group to which the patient has been assigned for both those in the drug arms and those in the placebo arms. Clinician rated scales have been designated as the primary outcome in all antidepressant trials submittted to the FDA. It is possible that the use of scales on which patients rate their depressive symptoms would produce more accurate estimates of drug-placebo differences.

In other words, clinical trials are not really double blind. Many patients in clinical trials realize when they have been given the real drug and so do the clinicians who are rating their levels of depression, most likely because of the drug's side effects. What effect is this likely to have in a clinical trial? We do not have to guess at the answer to this question. Bret Rutherford and his colleagues at Columbia University have provided the answer. They examined the response to antidepressants in studies that did not have a placebo group with those in studies where they did have a placebo group (Rutherford, Sneed, & Roose, 2009). The main difference between these studies is that in the first case, patients and raters were certain that the patients were getting an active antidepressant, whereas in the placebo-controlled trials, they knew that they might be given a placebo. Knowing that all patients were getting an active drug boosted the effectiveness of the drug significantly. This supports the hypothesis that the relatively small difference between drug and placebo in antidepressant trials are at least in part due to 'breaking blind' and discerning that the patient is in the drug group, because of the side effects produced by the drug.

What to Do?

To summarize, there is a strong therapeutic response to antidepressant medication. But the response to placebo is almost as strong. This presents a therapeutic dilemma. The drug effect of antidepressants is not clinically significant, but the placebo effect is. What should be done clinically in light of these findings?

One possibility would be to prescribe placebos, but this entails deception. Besides being ethically questionable, it runs the risk of undermining trust, which may be one of the most important clinical tools that clinicians have at their disposal. Another possibility that has been proposed is to use antidepressants as active placebos. But the risks involved in antidepressant use render this alternative problematic. Among the side effects of antidepressants are sexual dysfunction (which can affect more between 70% and 96% of patients on SSRIs; Clayton et al., 2006; Serretti et al., 2009), long term weight gain, insomnia, nausea, and diarrhea. Many people who attempt to quit taking antidepressants

show withdrawal symptoms (Rosenbaum et al., 1998). Antidepressants have been linked to increases in suicidal ideation and violent criminal activity among children, adolescents, and young adults (Molero et al., 2015; Stone, 2014; Stone et al., 2009). Older adults have increased risks of stroke and death from all causes (Andrews et al., 2012). Pregnant women using antidepressants are at increased risk of miscarriage, and if they don't miscarry, their offspring are more likely to be born with autism, birth malformations, and persistent pulmonary hypertension (Dolmar et al., 2013). Furthermore, some of these risks have been linked to antidepressant use during the first trimester of pregnancy, when women may not be aware that they are pregnant.

Perhaps the most surprising health consequence of antidepressant use is one that affects people of all ages. Antidepressants increase the risk of relapse after one has recovered. People are more likely to become depressed again after treatment by antidepressants than after treatment by other means – including placebo treatment.(Andrews et al., 2012; Babyak et al., 2000; Dobson et al., 2008) Furthermore, the degree to which the risk of relapse increases depends on the degree to which the particular antidepressant used changes neurotransmission in the brain.

Given these health risks, antidepressants should not be used as a first-line treatment for depression. A better alternative is the use of non-drug treatments. My colleagues and I have conducted a meta-analysis of various treatments for depression, including antidepressants, psychotherapy, the combination of psychotherapy and antidepressants, and "alternative" treatments, which included acupuncture and physical exercise (Khan et al., 2012). We found no significant differences between these treatments or within different types of psychotherapy. When different treatments are equally effective, choice should be based on risk and harm, and of all of these treatments, antidepressant drugs are the riskiest and most harmful. If they are to be used at all, it should be as a last resort, when depression is extremely severe and all other treatment alternatives have been tried and failed.

The best-researched alternative to antidepressant is cognitive behavioral psychotherapy. In the short-term, it is as effective, though more expensive, than drug treatment. In the long-term, however, it is more effective and less expensive than pharmacotherapy (Dobson et al.,

2008). It is also preferred over antidepressant treatment by depressed patients by a 3 to 1 margin (McHugh et al., 2013). Finally, there is evidence that adding hypnosis to cognitive behavioral treatments can enhance their effectiveness (Alladin, 2013; Kirsch et al., 1995) and that hypnotic treatment is vastly preferred over antidepressant medication (Dobbin et al., 2009).

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PALESTRAS
LECTURES

TEACH THE T CELLS: HOW LEARNING CAN SHAPE IMMUNITY

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The learned immune response

Learning and memory are fixed expressions in the immunological terminology describing recognition processes of antigens by T and B lymphocytes. In a less classical sense, immune responses can also be learned and memorized by associative learning or Pavlovian conditioning (Ader, 2003). Conditioning of immune functions commonly involves the pairing of an immunomodulatory compound such as an antigen or immunosuppressive drug (unconditioned stimulus, US) with a neutral (conditioned) stimulus (CS). Following several CS/US pairings, an association between the two stimuli is established, and the mere presentation of the CS induces immune responses closely mimicking the effect of the US (Ader, 2003, Schedlowski and Pacheco-Lopez, 2010).

A prerequisite for behavioral conditioning of immune functions is the interaction between central nervous system (CNS) and the peripheral immune system. For a long time, the CNS and the immune system were thought to be independent systems each working on its own. However, within the last decades there is growing evidence that both systems share a common chemical language and are continuously exchanging information (Dantzer et al., 2008, Tracey, 2010b). Indeed, it has been suggested that the immune system acts as a sensory organ with immune cells being mobile sentinels that inform the brain about the peripheral immune status (Blalock and Smith, 2007).

Within this framework, the learned immune response is not only a fascinating example of the bidirectional communication between the CNS and the immune system but can be conceived of as a learned placebo response that might offer possibilities for applications in the clinical

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setting as a supportive therapy to immunopharmacological regimens. In this review, the different approaches and paradigms in the field of conditioned immunomodulation will be summarized. In particular a well-established paradigm of learned immunosuppression in rodents and humans using Cyclosporine A (CsA) as an US will be highlighted. Subsequently, the therapeutic potential and possible applications of conditioned immunosuppression will be discussed.

Conditioned immunomodulation - different approaches and paradigms

A conditioned immune response was firstly demonstrated in guinea pigs by coworkers of Ivan Petrovic Pavlov, who reported a conditioned increase in peripheral leucocyte numbers after repeated injection of the plant extract Tapioka (US) together with a slight slit or heating of the skin (CS) (Metalnikov and Chorine, 1926). These early observations were later followed up and experimentally elaborated by Ader & Cohen (Ader and Cohen, 1975), who showed that the increase of antibody titers after injection of sheep erythrocytes was diminished not only in rats which received the immunosuppressant cyclophosphamide, but also in conditioned rats that were re-exposed to the CS (saccharine).

Since those pioneer studies, a large number of animal studies have shown that various immunological parameters can be affected by conditioning protocols. In these studies, typically a flavor or odor is employed as CS along with a pharmacological agent as US. The parameters affected comprise on humoral immune functions such as antibody responses (Cohen et al., 1979, Alvarez-Borda et al., 1995) as well as cellular immune functions such as mitogen-induced lymphocyte proliferation (Lysle et al., 1988), leucocyte numbers (Klosterhalfen and Klosterhalfen, 1987), the circulation of lymphocyte subpopulations (Husband et al., 1987), the activity of natural killer cells (Ghanta et al., 1985) or acute phase reactions (Exton et al., 1995, Janz et al., 1996).

Several studies demonstrated that it is not only possible to suppress immune functions via conditioning protocols, but also to induce conditioned immune enhancement. A conditioned increase in natural killer cell activity has been shown in rodents (Solvason et al., 1988) as

well as in healthy humans who received a sherbet sweet as a CS together with epinephrine injections (Buske-Kirschbaum et al., 1994, Buske-Kirschbaum et al., 1992). Furthermore, it was shown in rodents that the enhanced activity of cytotoxic T-lymphocytes through immunization can be conditioned by pairing the immunization procedure with camphor odor (Hiramoto et al., 1993). Another study showed that the immune activation in response to human recombinant interferon gamma can be conditioned in healthy subjects, using oral propylene glycol as conditioned stimulus (Longo et al., 1999).

Another line of research demonstrated that conditioning protocols can affect allergic reactions such as bronchial asthma and histamine release in guinea pigs (Justesen et al., 1970, Russell et al., 1984). In human studies, type 1 hypersensitivity reactions have been shown to be modulated by behavioral conditioning, measured by mast cell tryptase (Gauci et al., 1994), nasal airflow, histamine release and subjective symptoms (Barrett et al., 2000) and wheal size (Booth et al., 1995) (reviewed in (Vits et al., 2011). One study that is particularly interesting with regard to its clinical relevance showed an anti-allergic response in patients with house dust mite allergy who underwent a conditioning protocol with the antihistamine desloratadine as US (Goebel et al., 2008). While wheal sizes and subjective measures where influenced even in the absence of a distinct conditioned stimulus when desloratadine was replaced by a placebo pill (which points to an expectation-induced placebo response), a reduced basophil activation was only observed in the group who was re-exposed to a distinct conditioned stimulus (a novel tasting drink). This supports the assumption that unconscious immunological functions can be modulated by conditioning, whereas conscious processes can be modulated also by expectation (Benedetti et al., 2003).

Conditioned taste aversion and immunosuppression - the CsA paradigm

Cyclosporine A (CsA) is a calcineurin inhibitor which reduces the synthesis of TH_1-cytokines and is often employed in in clinical routine wherever a suppression of immune functions is required. A robust paradigm in rats was established with CsA as US and saccharine taste as

a CS. When the two stimuli are repeatedly paired, two things occur: at the behavioral level, the rats avoid the saccharine solution drinking less of the saccharine solution. More importantly however, the re-exposure to the taste is inducing a learned immunosuppression. This paradigm has been repeatedly applied in rodents showing a conditioned reduction in spleen and thymus weight (Exton et al., 1998c), reduced proliferation rates of spleen lymphocytes (Exton et al., 1998c, Exton et al., 1998b) and decreased interleukin-2 (IL-2) and g-interferon (g-IFN) concentrations (Exton et al., 1998b, von Horsten et al., 1998).

The CsA paradigm has also been successfully applied in humans (Goebel et al., 2002, Wirth et al., 2011, Ober et al., 2012, Albring et al., 2012). In these studies, healthy men receive CsA as US together with an unusual flavored and colored drink (CS). After several CS-US pairings, CsA was replaced by placebo capsules, which were now consumed together with the distinct CS. A learned immunosuppression after repeated re-exposure to the CS was demonstrated by reduced IL 2 and IFN-gamma levels as well as mRNA expression. The underlying pathways and biological mechanisms steering the learned placebo response on immune functions for this specific model have been elucidated in rodents.

Afferent pathways

How does an immunopharmacological agent become an unconditioned stimulus? Either the drug itself directly acts on the brain or the CNS may "sense" the drug-induced immunological changes via two pathways: On the humoral way, the involved messengers such as cytokines or prostaglandins may either cross the blood brain barrier (Banks, 2005) or reach the brain via circumventricular organs (Goehler et al., 2006). The neural pathway on the other hand would require activation of neurons in the periphery that signal to the brain. The vagus nerve is well positioned to detect and inform the brain about changes in the immune status (Tracey, 2002). It has been experimentally demonstrated that many effects in the CNS that are induced by changes in the immune system can be alleviated by prior vagotomy (Konsman et al., 2000, Luheshi et al., 2000). Thus, it has been proposed that in CsA-induced conditioned immunosuppression, the vagus nerve may act as well as a major afferent route.

A recent study analyzed whether CsA is sensed via the chemosensitive vagus nerve or whether CsA directly acts on the brain. Data revealed that a single peripheral administration of CsA increases neuronal activity in the insular cortex and the amygdala as evident from increased electric activity, c-Fos expression and amygdaloid noradrenaline release. However, this increased neuronal activity was not affected by prior vagal deafferentation but rather seems to partially be induced by direct action of CsA on cortico-amygdaloid structures (Pacheco-Lopez et al. 2013). Together, these data indicate that CsA as an unconditioned stimulus may directly act on the brain by a still unknown transduction mechanism.

Central structures

The insular cortex and the amygdala as well as the ventromedial nucleus of the hypothalamus (VMH) are essential brain structures involved in conditioned immunosuppression (Pacheco-Lopez et al., 2005). Confirming earlier observations, exitotoxic lesions showed that the insular cortex is necessary for both, acquisition and retrieval of the conditioned response (Pacheco-Lopez et al., 2005, Bermudez-Rattoni and McGaugh, 1991, Cubero et al., 1999). In contrast, the amygdala only seems to mediate the input of visceral information necessary for acquisition, whereas the VMH appears to be involved only in the output pathway to the immune system.

Efferent pathways

The sympathetic nervous system is one of the major pathways via which the CNS is communicating with the peripheral immune system in general. Specifically, this seems to be the major efferent pathway in the taste-immune learning paradigm, since the surgical denervation of the sympathetic nerve innervating the spleen blocked the conditioned reduction of cytokine production and lymphocyte proliferation (Exton et al., 1998b). However, another study suggests that this is not the only efferent pathway for conditioned immunosuppressive effects as denervation of the splenic nerve still allows a conditioned reduction of ear swelling in contact hypersensitivity (Exton et al., 2000a). Regarding involved transmitters and receptors, it was shown that noradrenaline is the predominant neurotransmitter mediating the learned immunosuppressive

effects via beta-adrenoceptors (Exton et al., 2002). Recently it has been shown that this beta-adrenoceptor activation inhibits calcineurin activity in $CD4^+$ T-lymphocytes (Riether et al., 2011), demonstrating that both, the conditioned response and the pharmacological agent CsA are inducing immunosuppression via inhibition of calcineurin activity, however using different intracellular pathways.

Clinical relevance of learned immunosuppressive placebo effect and outlook

Behavioral conditioning of immune functions is not only an excellent model to study the bidirectional communication between the CNS and the peripheral immune system but also offers a new therapeutic approach that might allow to reduce the amount of medication required by supporting the therapeutic benefit through learned placebo effects.

Studies in rodents clearly document the therapeutic potential of conditioned immunosuppression, showing that the outcome of various diseases can be positively affected through learning protocols. The mortality rate and development of proteinuria in mice with lupus erythematosus were retarded in conditioned animals receiving a saccharine solution (CS) together with the immunosuppressive drug cyclophosphamide (US) (Ader and Cohen, 1982). Likewise, other studies showed that inflammatory processes can be reduced in rats with adjuvant arthritis (Klosterhalfen and Klosterhalfen, 1983), skin and heart allograft survival prolonged (Gorczynski, 1990, Grochowicz et al., 1991, Exton et al., 1998a) and tumor growth can be delayed (Ghanta et al., 1987, Ghanta et al., 1988, Ghanta et al., 1990) by using conditioning procedures. A therapeutic approach using a conditioning protocol has been tested in patients with multiple sclerosis. In this study, patients who received their treatment with cyclophosphamide together with a conditioned stimulus showed a decrease in peripheral leukocyte counts when re-exposed to the CS together with a subtherapeutic dose of cyclophosphamide (Giang et al., 1996).

A prerequisite for applying learning protocols in a clinical setting is the reproducibility of learned immunosuppressive effects over time. This has been recently documented in rodents as well as humans (Wirth

et al., 2011, Exton et al., 2000b). Regarding the recall of the learned immunosuppression, one study in healthy participants showed that the effect is not present after one re-exposure to the conditioned stimulus, but after four re-exposures (Albring et al., 2012). This is in line with an earlier study in rats that proposed that the engram is strengthened with repeated re-exposures to the CS (Niemi et al., 2007).

Within the framework of conditioned immunosuppression as a learned placebo response, an interesting question is whether immunosuppression can be induced by mere expectation of the participants as well. Recently, this was investigated within the CsA paradigm showing that expectation alone does not induce an immunosuppression (Albring et al., 2012), confirming earlier observations which proposed that neuroendocrine and immunological functions can be affected by learning processes but not via cognitive factors such as expectation (Benedetti et al., 2003).

When thinking about employing conditioning protocols in clinical routine, the goal will be to employ conditioning procedures to support pharmacological therapies rather than to replace it. Placebo-controlled dose reduction (PCDR), in which a certain amount of the usual dose of a drug is replaced by a placebo is a concept that might maintain the efficacy of a treatment while reducing the dose of medication and unwanted side effects (Doering and Rief, 2012). In one study, the partial replacement (25% or 50%) of corticosteroids with a placebo in patients with psoriasis, induced a similar symptom reduction compared to a full dose treatment (Ader et al., 2010). A placebo controlled dose reduction was also tested in children with attention-deficit hyperactivity disorder (ADHD) (Sandler et al., 2010) and cough (Leech et al., 2012).

Instead of employing partial reinforcement protocols, another possibility is to continuously reinforce the conditioned response by presenting the CS together with subtherapeutic doses of the US. The effectiveness of this concept was demonstrated in heart allograft model in rats. Those rats that were given subtherapeutic doses of CsA together with the CS during evocation, showed a significant longer survival time compared to the control groups (Exton et al., 1999). Putting these findings into learning theory, this synergistic effect may be attributable to a reconsolidation process, with a reconsolidation of the memory trace

(immunosuppression) when it is activated via re-exposure to the CS. The consistent "reminder" by the otherwise ineffective subtherapeutic dose of CsA might have strengthened the engram and counteracted the extinction processes of learned immunosuppression. This hypothesis remains to be tested in future sophisticated experimental studies.

Another important aspect within the framework of placebo responses in general is the question, who will respond to a "placebo therapy" and are there predictors of placebo responses (Kaptchuk et al., 2008). These predictors might be stable features such as personality traits, genetic or other physiological factors or situational factors included in an experimental of clinical setting. With identifying stable predictors within persons, that is, distinguishing between "placebo responders" and "placebo non-responders", quick decisions which person would benefit from a commensurate therapy could be made. Evidence for such predictors to distinguish between "placebo responders" and "placebo non-responders" is scarce, but some variables have been identified. In the case of conditioned immunosuppression, recent evidence shows that state anxiety as well as plasma noradrenaline together with IL-2 concentrations at baseline predicted almost 60% of the variance in the conditioned response, measured by suppressed IL-2 levels (Ober et al., 2012).

The applicability and effectiveness of employing conditioning procedures together with immunopharmacological regimen across various immune-related diseases are not thoroughly investigated yet. However, there is a growing body of evidence that the learned immunosuppression offers great potential for therapeutic applications that could maximize the patient´s benefit by minimizing unwanted aspects of the treatment such as intensive medication costs or unwanted drug side effects.

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THE NEUROPHYSIOLOGY OF PLACEBO EFFECTS: A WINDOW ON THE WORKINGS OF MIND-BODY MEDICINE

Tor D. Wager [*]

Thank you very much for that warm introduction and for inviting me to be here today. I'm really honored to be part of this Symposium, and I think it is really a terrific opportunity to come together to talk about placebo treatments and placebo effects.

Humanity has believed in the power of the mind to heal for thousands of years. Hippocrates, the father of modern medicine, wrote *"…the patient, though conscious that is condition is perilous, may recover his health simply through his contentment with the goodness of the physician*".

This statement is as relevant today as it was in Hippocrates' time. One example comes from a recent gene therapy trial for Parkinson's disease. Parkinson's disease is a neurodegenerative disorder, so people don't just get better on their own. The study team followed patients for 24 months. The treatment was an invasive gene therapy injection of a dopamine-promoting gene into the striatum. Loss of striatal dopamine is the major neuropathology in Parkinson's disease. The trial found that clinical symptoms dropped and then stayed low for 24 months after treatment. The company invested basically all their remaining resources in this clinical trial, after a smaller preliminary trial failed. Unfortunately for the company, in spite of these promising data, the trial failed. Why? Patients in the placebo group, who received a sham injection into the brain, also got better to approximately the same degree. There were no significant drug vs. placebo differences.

This result had a major impact on the progression of this drug company: It was sold, and testing discontinued. It wasn't because people didn't improve on the drug, but because they improve on the placebo. So what's going on? Maybe there is something about taking the treatment

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itself and about the social support and context that surrounds treatment that is quite important.

People mainly believe in the power of placebo. A recent survey found that 45% of physicians reported using placebo treatments in their clinical practice. The same percentage of people in America use prayer for health reasons. They are apparently investing tremendous amounts on alternative medicine and alternative therapies.

But I can also say that we don't really believe in the power of placebo, and we need to do a lot more work to understand placebo effects. I can say this using a simple economical argument. U.S. pharmaceutical sales in 2004 were approximately 235 billion dollars. 90 billion dollars were spent on research development by the top 10 ten pharmaceutical companies, and about half of that was spent on R&D and half of it on marketing. Compare that to the entire U.S. NIH budget for behavioral science spending, which is less than 5 billion dollars. So, basically, we are not investing resources in the study of placebo and other kinds of behavioral and psychosocial interventions, even when we know that they are critical for preventing and even reversing adverse health effects, for example, as in a coronary heart disease.

That is why we began investigating placebo effects using brain imaging, autonomic physiology, and other methods, and I think that is why the Bial Foundation is very special in this regard for supporting this Symposium on placebo effects.

Placebo effects are causal effects of a treatment context on outcomes. The placebo could be a pill, an injection, a nasal spray, a cream. We have used all of these things. A main advantage of experimental research is that we get to give one group a placebo and another group no treatment and we get to see what the causal difference is. The classical double-blind clinical trial design cannot estimate the causal effects of placebo treatment. It compares an active drug group to a placebo group, which is suitable for estimating the drug effect (Figure 1). However, to estimate the placebo effect, you have to compare the placebo treatment to a natural history (no treatment) group (Figure 1), as Dr. Kirsch discussed yesterday.

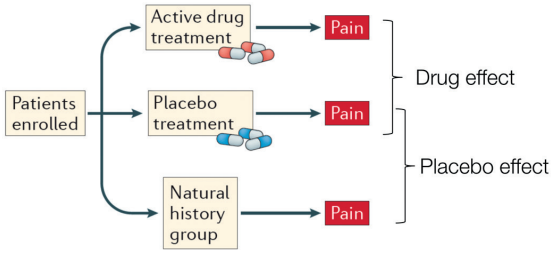

Figure 1.

We do it a little bit differently when we move to brain imaging: We usually use each person as their own control in a within-person crossover design. Every person gets treated twice, in counterbalanced order to prevent confounds. For example, if the treatment is a cream, we take one patch of skin and we say "*We are applying lidocaine cream to this skin site. It is going to be highly effective in relieving your pain. We want to understand how it works in the brain*". Then we apply the placebo cream. On a nearby patch of skin we say "*This is a control cream, it won't have any effect*". Then we apply the control cream. The creams we apply are identical. The only difference is in the instructions that we give to the patients. We also typically use a conditioning procedure to reinforce those instructions: In a conditioning phase, we lower the painful stimulus intensity when stimulating the placebo-treated site, and keep the intensity high when stimulating the control-treated site. The instructions combine with reinforcement to create robust placebo effects.

An example placebo effect from such an experiment is shown in Figure 2. The difference between the red bar and the blue bar is the causal effect of the placebo. Effects like this have been found in many, many studies now, and they can be produced quite reliably. In our new studies we can obtain such effects in nearly every single person tested [1, 2]. I will come back to that later.

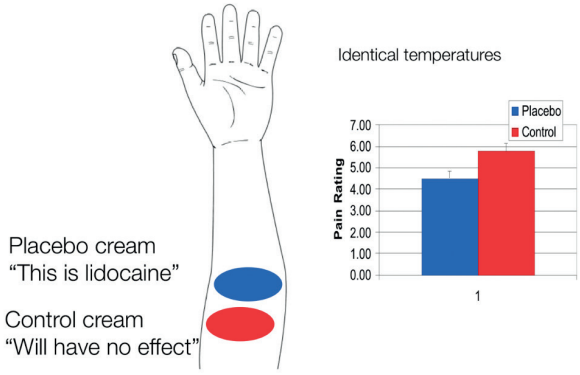

Figure 2.

Placebo effects across disorders

Such placebo effects have been shown to exist across domains. Pain is the most well studied. Parkinson's disease is also increasingly studied, and produces placebo effects [3, 4]. Dr. Zubieta is going to talk about depression later in this session. Dr. Schedlowski talked about conditioned immunosuppression. Outcome that show significant causal effects of placebo treatment include both physiological and behavioral outcomes, clinical outcomes and experimental ones [4].

When we think about what are the active ingredients of placebo treatments, they are many. If you think about a typical treatment context, there are numerous things happening. There are suggestions by a physician. The patient is being treated in a center where there is supportive care that is being provided. There is the competent authority of the physician, there are social cues related to how the physician looks at the patient, how they touch the patient, how they interact with the patient. And of course there are specific treatment cues: the feeling of the needle, the look of the pills, etc. There is also an internal context that mediates these effects, including effects of expectations about the outcome. The future is uncertain, and if we can develop in our own minds a more promising, optimistic view of future outcomes, then we are likely to feel better and start a path towards thoughts and behaviors that promote feeling better.

Another part of 'internal context' is one's emotional state, and what many researchers have called 'meaning schemas' (e.g., [5]). These relate to a person's understanding of where they are in the entire illness and treatment context. Right now, there is a schema playing out in my brain, in which I'm standing here and giving you a talk, you are listening, this is a relationship that we are having. Very subtle differences in this context can cause large effects on what I feel about the situation. Now I'm feeling OK.

So there are many placebo effects, many mechanisms. I won't cover them comprehensively, but I will just focus on a couple of things. There are two ingredients that I want to focus on here. One is 'appraisal', which comes from emotion theory. Appraisal is about the meaning of things, the meaning of events, and that is the right side of the branch in Figure 3. The left branch has to do with brain plasticity, and the tendency for all useful responses in the brain to become automated through the strengthening of neural connections. It encompasses multiple kinds of learning.

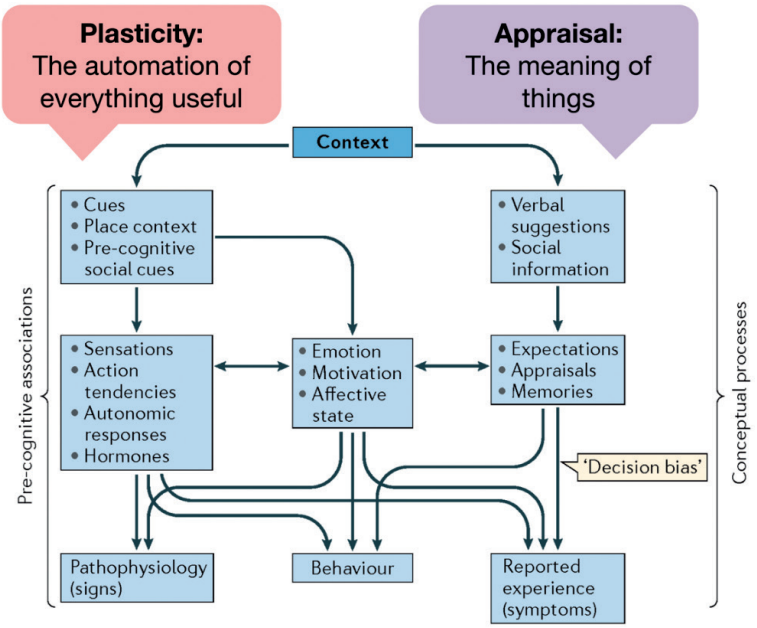

Figure 3.

Brain principles: The dance of the placebos

Why would placebo effects exist? The brain is organized to predict and anticipate needed responses at multiple levels of analysis. The "lower brain," the medulla and pons, contain nuclei whose neurons serve as visceral pattern generators. Activating them produces very complex coordinated responses in the body. For example, if one stimulates thermoregulatory nuclei in the pons, coordinated responses are produced in about 6 different bodily systems that are all centered around maintaining body temperature. So these thermoregulatory nuclei are really coordinating centers. If you move up into the upper brainstem - and I focus here on the periaqueductal gray (PAG) and other surrounding areas - one finds what I call "affective pattern generators" that have to do with organism-environment interactions. This includes regulation of physiological and behavioral outcomes, particularly related to survival-relevant threats and opportunities. The brainstem alone can coordinate behavior in very complex ways.

So what's the cortex for? Surely it's not just to keep the brain warm. Broadly speaking, the cortex contains a set of *conceptual* pattern generators, so we can extend ourselves into the past and into the future, and we can start to understand what the longer-term implications are of what we are doing now. So when you are watching the stock market and you see the stock prices fall, there is nothing in our evolutionary environment that prepares us for this. But we can experience strong emotions, and correspondingly strong changes in brain activity, driven by our conceptual understanding of what's happening. Such conceptual processes begin with thought, but they can have a profound impact on the body.

There are multiple different types of conceptual influences that are mediated by different cortical systems. These include effects of social context; the interoceptive context or the state of the body, including the sense of the position of its body and its integrity, sensation of inflammation, infection, illness and more; specific outcome expectancies; explicit or episodic memories of the past; and other processes. All these processes contribute to *appraisal* of the self-in-context, which is what creates a sense of situation meaning. Representing the "self in context" is what you need the pre-frontal cortex, particularly the ventromedial prefrontal

cortex (vmPFC), for. We appraise the meanings of situations, we express them in term of emotions, in term of autonomic and neuroendocrine responses, and long-term behavioral decisions.

As such appraisals are made repeatedly, they - like other processes - become easier to re-activate or re-engage. The neural pathways that are used, including connections within the cortex and connections between the cortex and the brainstem, become stronger. So if you appraise a situation in a particular way at one time, that makes it easier for you to generate a appraisal next time. We experience appraisals as products of free will, decisions that "we" make – but they are learned and, although they are complex decision processes, they can become automatic.

Thus, there are two principles at play in the generation of placebo effects and any other type of "meaning response" to one's situational context: First, the appraisal of the meaning of a situation, and second, and strengthening of that meaning set or schema over time, which can lead to stronger and more robust responses. These two principles, interacting in various patterns, underlie placebo effects. I refer to this as "the dance of the placebos."

Key brain findings on placebo

We just talked about two principles - beliefs and learning - that interact to create many types of placebo effects. Now I'm going to some key brain findings, expand a little bit more on what I call the 'meaning axis,' the medial prefrontal-forebrain-brainstem axis, and then finally end with some empirical work on two "ingredients" of placebo.

The basic placebo fMRI study procedures are as follows. They follow the within-person crossover design pattern that I mentioned earlier. First, we apply the placebo and control creams to the person's arm or leg, along with instructions that this will be a "highly effective painkiller" or an "ineffective control," respectively. Then we attach a thermode to their arm, which can delivery heat at precisely controlled temperatures (intensities). We put them into the fMRI scanner, and we can study the effects of every single thermal stimulus - on placebo - and control-treated skin sites - on people's ratings of pain and on the brain activity elicited by the painful stimulus.

I'm going to talk at a very high level here, so I'm going to zoom out to what we know about the neurophysiology of placebo analgesia from what is now about 50 or so brain imaging studies [4]. Let's start with what happens in activity in regions of the brain that process painful events. These areas receive projections from pain-related or 'nociceptive' neurons in the spinal cord, and activity in these areas goes up when experiencing a more painful stimulus. These "pain processing regions" include those in the brainstem, thalamus and in the cortex. Overall, activity in these areas is reduced with placebo treatment, including parts of somatosensory cortex, thalamus, anterior and mid-insula, and dorsal anterior cingulate cortex, which is important for determining the avoidance value of pain. The anterior insula plays broad roles in motivation, decision-making, and affect, and is critical for conditioned immunosuppression. Activity in these areas is decreased when you are experiencing pain with a placebo.

Other areas show increases in the brain when you are experiencing pain with a placebo versus without. These are placebo-caused increases, and they include areas like the lateral prefrontal cortex, which is important for expectations and for maintaining a sense of where you are what your current goals are. They also include orbitofrontal cortex, which is associated with outcome expectancies. The vmPFC is also increased; this area is strongly associated with meaning schemas. Increases in the nucleus accumbens are common. This area is important for shaping motivation and hedonic value. Finally, the periaqueductal gray (PAG) is reliably increased, which is associated with strong emotional responses and pain control in invasive animal and human studies. I will return to some of these regions soon, particulary the PAG.

Figure 4 shows a summary [4]. Now, you can see all the individual placebo studies. Each of the spheres is an activated location from one individual study. Blue points are areas that decrease with placebo, and the reds and oranges increase with placebo. The lighter colors, the orange and light blue, indicate areas in which the larger the brain difference with placebo, the larger the difference in reported pain with the placebo, i.e., the larger the placebo effect.

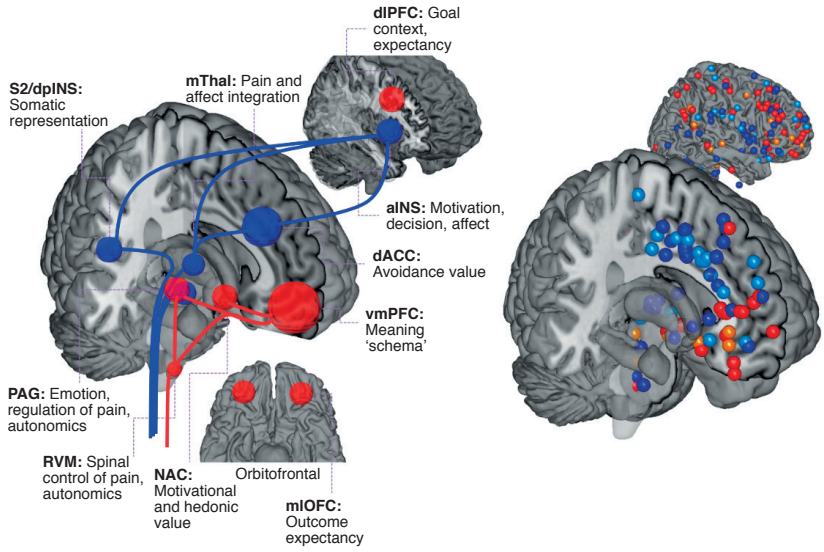

Figure 4.

I will just focus on one of those studies as an illustration. This is the first study that we did on placebo effects [6]. In this study, we found reduced response to painful stimulation in some of these key pain related areas. For instance, reductions in the anterior cingulate cortex were correlated with the magnitude of behavioral analgesia. The largest effects, however, were found in anticipation of pain. When participants are anticipating pain with the placebo, they anticipate the pain differently. It doesn't mean the same thing, and correspondingly, during anticipation we see placebo-induced increases in the lateral prefrontal cortex. These increases are correlated with increases in the PAG, in the midbrain. The PAG is an important area because it receives direct projections from the pre-frontal cortex, and it plays a critical role in modulating pain and emotion in a variety of ways. It projects down the spinal cord, and it is one of the major producers of opioids in the brain. Blocking opioids with naloxone can block placebo effects in some cases without otherwise changing pain. I think Amanzio and Benedetti showed this most convincingly in 1999 [7] (cf. [8]). That study really put placebo effects back on the map as a neurobiological phenomenon.

Placebo treatments also affect the brain's opioid system, which is a key system for modulating pain. A study Jon-Kar Zubieta and I did in 2007 showed that getting a placebo treatment causes opioid release as measured with carfentanil binding [9]. Placebo treatment caused increases in opioid system activity in multiple regions, including the PAG in the midbrain and many of its targets in the prefrontal cortex, including the vmPFC.

Finally, there is evidence that placebo treatments can, in some cases, affect the transmission of pain in the spinal cord. Falk Eippert, Christian Büchel, and colleagues did something very innovative [10]. They used fMRI of the spine to image functional spinal cord responses to pain on and off placebo. As expected, they observed a response to heat pain ipsilateral to the site of painful stimulation. With placebo treatment, the response was significantly reduced. This finding suggested that there can be very deep effects of placebo treatment, at least under some conditions.

A 'meaning system' in the brain

Now I'm going to zoom again and talk a little bit more about the ventromedial prefrontal cortex (vmPFC) and what I call the 'meaning axis'. Let's first just consider pain systems. There are five major ascending pathways. They target brain regions at multiple levels of the neuraxis. Every one of those regions is also targeted by descending projections from the prefrontal cortex and other areas of the forebrain, including the vmPFC, which is particularly critical. So there might not be any area of the brain that registers pain in the absence of any input about the context in which it occurs. These interactions are mediated by a rich pharmacology that includes opioids and dopamine, serotonin, CCK, cannabinoids, and others – this is just really the tip of the iceberg. And what are these systems for? These systems are for controlling pain and pain related signals based on an animal's environmental context.

So, can you get placebo effects in a rat? Sure, of course you can, because these systems are intact and functioning. You can do this with conditioning, by pairing an effective drug with otherwise neutral cues, like an injection. After pairing, the injection alone (i.e., of saline) can induce drug-like effects. But these 'control systems' in the brain did not

evolve to respond to fake drugs. Rather, they evolved to shape pain and other processes based on the environmental context. Drug treatment cues are just one kind of context. Thus, it is possible to modulate pain by doing other things that change its significance. One system that mediates multiple forms of pain modulation projects from the PAG down to the rostroventral medulla (RVM) and to the spinal cord [11]. This system is rich in cannabinoids, opioids, CCK, oxytocine and dopamine, and neurochemical actions in this system are thought to mediate many effects of behavioral interventions [4, 11]. For example, if an animal is hungry or if it is chasing food, that is important, and it creates a competing motivational demand that can reduce pain signaling [12, 13]. 'Nocebo' cues intended to increase pain and safety cues both have effects mediated at least in part via this system. Some effects of social context are also likely mediated by the PAG-RVM system. If you are fighting with another person or otherwise experiencing extreme stress, you are likely to experience analgesia.

Importantly, the PAG itself is regulated by inputs from the vmPFC, among other areas, providing a substrate for conceptual control of pain by thoughts, beliefs, and expectations. New work on brain stimulation is showing how this system can really have profound impact on pain, even in animal models. In one of my favorite recent studies, Lee et al. [14] from Jing Wang's lab used optogenetics to activate the prelimbic cortex, which is part of the vmPFC, to relieve pain. They know that it is specifically the pathway from the vmPFC to the nucleus accumbens (which is going to be important in a moment) that mediates pain relieving effects. So what did they do? I will walk you through this very quickly. First, they created a partial nerve injury in the animal, which is a well validated model of chronic pain. These animals show pain behaviors, like mechanical allodynia. They also show depression-like behavior: They don't like sucrose as much, they don't pursue natural rewards. Optogenetic stimulation of the prelimbic cortex projections to nucleus accumbens completely reversed both the pain behaviors and depression-like behaviors caused by the spared nerve injury. That is very exciting.

We think that the vmPFC is doing something that extends far beyond pain itself. And we think it has a lot to do with appraisal and meaning, and a lot to do with how negative expectations can turn into symptoms

over time. In another study, we combined evidence from fMRI imaging during an avoidance learning paradigm with models of circuit dynamics to better understand the circuits that underlie expectation and learning [15]. We found evidence consistent with the idea that vmPFC stores an expected value for how bad (how painful) the consequences of an action are going to be. This is related to questions patients ask themselves, like: "how much should I avoid doing this action". The PAG is involved in updating expectations based on aversive prediction errors – deviations from expectations in the "worse than expected" direction. When a painful outcome is experienced, signals come up the spinal cord and synapse in the PAG. The PAG, in addition to playing a role in modulating pain, acts as a comparator, and it says "*Oh! That's worst that I expected!*" If pain is worse than expected, two things happen: 1) You say "*I should expect more pain. That is pretty bad*" and update the expected value representation in vmPFC; 2) You update an action policy, effectively saying "*I better not do that thing again*".

What happens if you have a dysregulated vmPFC-PAG circuit is: You feel pain in your back, it is always worse that you expected, and so whatever you were doing, you avoid doing that thing again. So everything becomes bad for you. It is not about the pain-related signals that are coming from the spinal cord alone. It is really about how your brain is learning to avoid all of these pain associated things. That is closely aligned with what we think of as "distress". The vmPFC is important for understanding, "*What does this action or event mean for me? What should I learn from this?*"

If we think about all of the different things in brain imaging studies that activate the vmPFC, it is a pretty interesting set of things. We created a summary of over one thousand studies that activate the vmPFC, collected using automated meta-analyses and software created in the lab. The set includes conditions like remembering events from your past - like your last birthday. It also includes self-referential tasks, for example asking "*Does the word honest refer to me? How well does it describe me?*" So, thinking about yourself activates the vmPFC. So does thinking about other people, and generating emotions. Some people think it vmPFC is a "reward area," because it is responsible for helping to evaluate whether you'd like to have the ham or the chicken for lunch.

And it is also a visceromotor center that is involved in sending inputs directly to brainstem areas that cause changes in blood pressure, heart rate, and neuroendocrine responses. Thus, the vmPFC is really important for a whole set of things which all have to do with conceptualizing the self in context, beyond pain. And so when we look at studies of stress, the vmPFC interacts with the PAG to mediate stress-induced increases in heart rate [16, 17]. In addition, under some circumstances stress can also impair working memory. When you have a stressor like having to prepare a public speech, working memory can be impaired, and this effect is also mediated by increases in the vmPFC during stress that disrupt connectivity in dorsal networks that support memory [18].

The vmPFC is also a circuit that responds to self-regulation, the generation of cognitive 'frames' that influence how we feel. For example, if you were to see a picture of a large, hairy spider, and you are afraid of spiders, cognitively reappraising to generate a positive context might be helpful. This is what we ask people to do in reappraisal experiments. You might tell yourself: "*It turns out this is a mommy spider with her little baby spider on her back, so that is pretty cute."* When you generate that positive frame, your negative emotion goes down. What we found in an earlier study is that a pathway from the vmPFC through nucleus accumbens mediates the effects of reappraisal [19]. Participants who activated the vmPFC showed greater activity in the nucleus accumbens, and those who did that reported less negative emotion. We did a later study on pain regulation with the same procedures [20]. We trained people to self-regulate pain, imaging pain as a warm blanket on a cold day spreading over your body, vs. imaging nothing or imagining the painful stimulus burning, blistering the skin. When participants reappraised to make the pain better, accumbens activity went up, vmPFC activity went up, and pain went down. So we think this circuit is critical for self-regulation and placebo effects alike, and if it is important for placebo it might be important for placebo effects beyond pain.

Placebo effects in Parkinson's disease

Parkinson's disease is a useful comparison to pain because it shows evidence for susceptibility to placebo [21, 22], and because placebo effects

in Parkinson's appear to involve some of the same circuitry, particularly the vmPFC "meaning axis". Returning to the start of this talk, Parkinson's is a neurodegenerative disorder involving loss of dopamine in the ventral tegmental area (VTA) and striatum, including nucleus accumbens. Interactions between the vmPFC and nucleus accumbens are thought to be very important in determining and learning to associate stimuli and actions with reward, and this circuitry is impaired in Parkinson's disease.

In healthy individuals, the vmPFC is thought to maintain expectations about what the value of an item is. Is this something I want to purchase or acquire? These signals are compared with signals in the VTA dopamine system, which projects to nucleus accumbens. If something is better than expected, dopamine is released in this circuit, and that strengthens the memory that the stimulus or action should be pursued again in the future. Theories of drug addiction focus on this system above all others, thus far.

In a recent study of Parkinson's patients [23], we took their daily medication (which was similar for all participants: levodopa and carbidopa), crushed it up, and dissolved it in orange juice in front of them. We told participants we'd scan their brains with fMRI OFF medication and then ON medication. But the ON condition was really a placebo condition: We gave them a glass of orange juice without the drug in it, just some bitters to make it taste medicinal. After the OFF and ON Placebo conditions, everybody got the really medication, and we scanned them again.

The test we focused on is an operant learning test. Basically, what you have to do is learn to choose one of two symbols, which are differentially paired with reward. The faster you learn, the better you do. In another condition, the symbols are paired with punishment, and you have to learn to choose the symbol that best avoids punishment. Parkinson's disease is associated with impaired reward learning. This is what we found as well: Patients don't learn well in the reward condition when OFF drug. ON their real drugs, they learn. And when ON Placebo, they learn just as well as they did when they actually got the really drug, and significantly better than control.

vmPFC signals related to expected value show similar results. OFF drug, we don't see much evidence for learning across time. ON drug we see a robust expected value related signal. What about the placebo? We see the same signal ON Placebo as ON drug, and there is a significantly

greater expected value-related signal ON placebo versus no drug. The bottom line from this study is that, placebo enhances reward learning and value signals.

This study demonstrates an important role for the vmPFC "meaning axis" in shaping how we learn and make decisions, in addition to playing multiple roles in directly influencing visceromotor and neuroendocrine responses. I think the effects of placebo on decision-making are at least as important as the direct effects on autonomic and neuroendocrine responses.

Meaning and learning

In this talk, I discussed two key ingredients of placebo effects: Conceptual *meaning* and learning processes that 'stamp in' meaning-guided responses over time. When researchers perform standard conditioning procedures, including the conditioning-supported placebo effects in most neuroimaging studies, they elicit both expectations and brain plasticity. Both work together, and both are essential under most circumstances. But under the right conditions, either process alone can create placebo effects.

Two recent studies from our lab illustrate the importance of learning and expectation, respectively. In the first, we attempt to eliminate expectations, and ask whether conditioned pre-conceptual associations really play an important role [24]. In this study there are two groups: A short conditioning group and long conditioning group. The long conditioning group underwent 4 days of repeated conditioning that a placebo cream was an effective painkiller. The short conditioning group underwent only a single, short conditioning session. We found placebo effects on pain in both groups, though they were somewhat stronger in the long group. After an initial placebo test, we peeled the label off of the placebo cream and said, "*Look, this was never a real drug, this was always a placebo. We are going to mix the placebo cream and the drug cream together, and show you that this was never real."* After this "reveal", the long conditioning group still showed a significant reduction in pain, a significant placebo effect. The short conditioning group did not. Even though the long group showed an effect, their expectations for pain relief were basically at zero. So after several days of conditioning, placebo effects can persist without expectations.

The other study attempted to eliminate pre-conceptual associations, to reveal the role of conceptual processes [1]. We did this using a procedure we call "symbolic conditioning." Participants see shape cues, which are associated with high and low temperature levels. The catch, though, is that there is never any heat, and so no primary reinforcement. We paired the symbols with *pictures* of thermometers. So they form an association between the shape cues and heat, but it is a conceptual association only. Then, in a subsequent test phase, we delivered high- and low-temperature cues followed by real, painful heat. Heat at multiple temperatures is delivered, but the distribution is identical following each cue, so there is no real difference in heat intensity following the different cues. We found very strong effects of the stimulus temperature on pain and autonomic function. And, critically, we also found very strong effects of the cues. Pain and autonomic responses (skin conductance) were substantially higher following high-temperature than low-temperature cues. This effect was found in just about every person that we tested in this kind of paradigm; the effect size here is substantially larger than most "fake drug administration" placebo studies. And it is purely conceptual, based on expectations about what is going to happen following each cue.

Conclusions

Placebo treatments can have real effects on pain-related brain activity and neurochemistry. They require a combination of conceptual expectations and learning processes that has not yet been fully elucidated.

One final, surprising thing about placebo effects is that they don't go away with extinction. They are often stable across time, and can sometimes increase across time and be self-reinforcing. This has much to do with the "dance of the placebos." What I think is happening is this: You start with the right kind of conceptual appraisal, and that produces a reduction of symptoms. You perceive that reduction of symptoms and you learn that this was an appropriate appraisal to make, that "*yes, this is helping me*". So the positive initial expectation reduces negative experience, and is reinforced. This creates a feedback cycle, an "upward spiral," and a transition from (a) immediate, acute responses that are very flexible and

conceptually driven to (b) responses that are learned, robust, and resistant to changes in expectations. After learning, it doesn't matter of what you think, because your brain has learned that the response is real.

So in conclusion, I leave you this quote from Hippocrates: "*I'd rather know the person that has the disease than the disease the person has"*. I think by studying the brain mechanisms and understanding how placebo effects work, we can understand the person, and help to translate that into clinical understanding and eventually to advances in clinical practice.

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NEUROCHEMICAL SYSTEMS INVOLVED IN THE FORMATION OF PLACEBO EFFECTS IN PAIN AND IN MAJOR DEPRESSION

Jon-Kar Zubieta *

The "placebo effect", the experience of clinical benefit occurring after the administration of an inert substance, or of a sham physical treatment such as sham surgery[1] is increasingly recognized as a critical factor in the eventual success of randomized clinical trials, the traditional process by which treatment effectiveness is established. Similarly, the opposite effect, or nocebo, the development of adverse events or worsening of symptoms during placebo administration are also commonly observed and reported by individuals participating in clinical trials.

Historically, placebo effects have been consistently noted since the emergence of placebo-controlled trials in the 18th century. Factors such as the effects of natural history of the disease, which can spontaneously remit or change in severity without intervention; cognitive-emotional biases, such the "halo" effect, related to the individual response to the characteristics of the study or treatment team or individual (e.g., frequency of appointments, rapport with the clinician); the knowledge that the individual is being studied, termed the Hawthorne effect, have all been thought to participate in placebo effects, particularly so when subjective measures (e.g., self-report) are the primary outcomes and therefore subject to non-specific psychological influences.

However, what makes the formation of placebo responses an important area for research and discovery is the uncontroversial evidence that the engagement in treatment, even if ineffective in nature, can elicit changes in neurobiological mechanisms that modify the disease in question. The initial observations that lead to the development of a neurobiology of placebo effects date back now nearly three decades,

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with the findings that opioid antagonists were capable of reducing the formation of analgesic effects after the administration of a placebo in a trial of analgesics for dental extractions[2], therefore invoking endogenous opioid mechanisms in the formation of placebo analgesia. Subsequent work has shown that placebo effects appear in response to the individual expectations and subsequent conditioning, both positive and negative, depending on the individual experience with prior interventions[3,4]. It has also been noted that the neural systems activated by placebo administrations at least partly overlap with those affected by the pathology and treatments under study. For example, similar brain regions are modulated by placebo administration and antidepressants in Major Depression [5]. The neurotransmitter dopamine, involved in the development of Parkinson Disease and psychostimulant dependence, is also activated when placebo is administered in these disorders[6-8]. Opioid, dopamine and cholecystokinine neurotransmission, which also regulate each other, have been shown involved in placebo-induced analgesia [9-11], and can induce either analgesic or hyperalgesic effects, depending on whether they are activated or deactivated [12-14] adding complexity and biological variability in addition to that naturally associated with the pathologies and treatments under study.

The largest body of mechanistic studies on placebo neurobiology comes from the field of pain, but the knowledge acquired in this area is also being translated to areas beyond analgesia. Both endogenous opioid mediated (elicited by the expectations created during treatment procedures and conscious processes) and non-opioid (which may depend on previous conditioning and learning mechanisms that the individual may not be consciously aware of) have been described as participating in placebo analgesic effects[15]. This has lead to the use, for example, of traditional Pavlovian conditioning procedures to induce immunosuppressive responses in humans during placebo administration, which allowed for the reduction of chemotherapeutic agents and their toxicity after prolonged administration[16,17].

An initial report examining the overlap between placebo and active treatments showed that the brain regional effects of the short-acting μ-opioid receptor agonist remifentanil overlapped with those elicited by a placebo under conditions of expectation of analgesia in the rostral

anterior cingulate cortex (rACC), an area involved in pain regulation, but also in cognitive-emotional integration[18]. Subsequent work has described placebo-associated changes in the activity of brain regions involved in pain representation and regulation, including the rACC, prefrontal and insular cortex, thalamus, amygdala and periaqueductal gray[19-21]. When these processes were examined with molecular imaging tools (e.g., selective radiotracers and positron emission tomography, and using placebo administration as an experimental challenge to elicit the release of neurotransmitters), direct evidence of endogenous opioid release in response to placebo administration during experimental pain was observed in cognitive regions (dorsolateral prefrontal, orbitofrontal cortex), emotional-cognitive integrative areas (rACC, dorsal ACC), and subcortical areas involved in responses to and regulation of pain and emotionally valenced sensory stimuli (nucleus accumbens, thalamus, amygdala, periaqueductal gray). The activation of the endogenous opioid release induced by placebo administration was further associated with the suppression of both sensory and affective domains of the pain experience[12,13]. From a broader perspective, these opioid system responses to placebo are in line with the known role of this neurotransmitter system in the induction of endogenous and exogenous analgesia, reward and stress responsiveness regulation[22,23], as well as the regulation of emotion[24] and hedonic responses to natural stimuli, including food[25] and social interactions[26,27], serving as a mechanism that reinforces the organism response to potentially rewarding environmental cues (e.g., reduced pain and improved emotional response during a therapeutic encounter). Of importance to understand the observation that placebo responses parallels that of active treatments in clinical trials, opioid mechanisms are also being linked to the formation of positive reward learning, whereby initial expectations are compared to subjectively assessed outcomes in neutral, positive or negative directions. Positive (or for that manner, negative) comparisons between what is being expected and is being subjectively perceived as helpful have been associated with the magnitude of endogenous opioid system activity during placebo administration, potentially reinforcing (or diminishing) the organism response to an otherwise inactive agent[28,29].

If reward responses and reward-based learning were to be involved in the formation and interindividual variations in placebo effects, it would be expected that neurotransmitter systems and circuitry central to reward valuation, such as dopamine released in the nucleus accumbens, would also be implicated in placebo neurobiology. That indeed appears to be the case, with initial observations showing that in Parkinson Disease, placebo-induced enhancements of dopaminergic neurotransmission in the nucleus accumbens were associated with the patient's initial expectations of recovery during placebo administration, while dorsal basal ganglia dopamine release were linked with motor function improvement[6,7]. Changes in single neuron recording in an output area of the basal ganglia, the subthalamic nucleus, during Parkinson Disease surgery and placebo administration were subsequently ascertained[30]. During experimental pain, dopamine neurotransmission in the nucleus accumbens is enhanced by placebo administration, likely serving as a salience, reward expectation signal that triggers the downstream engagement of antinociceptive mechanisms[13]. Of interest, the responsiveness of the nucleus accumbens during expectation of monetary rewards were additionally linked to both placebo-induced dopamine release in the same region and the formation of placebo analgesic responses, directly linking interindividual variations in nucleus accumbens responses to reward expectation and the individual capacity to develop a placebo response[31].

The definition of biological systems responsive to treatment cues, and which through learning and conditioning are involved in the development and maintenance of therapeutic responses clearly helps in the understanding of the systems inducing variance in clinical trial. Trait and biomarker measures, such as those described accounting for variance in the formation of placebo effects[17,32,33] would also aid in the study of non-specific responses in clinical trials, whereby control for those variables or patient stratification can take place. In addition, and perhaps more importantly, they provide simple measures that could be readily implemented in the field. These biomarker measures also point to specific biological systems that promote disease resiliency and improved outcomes, and therefore point to novel mechanisms of intervention and targets for the development of therapeutics. If particular mechanisms are involved in treatment response regardless of the effectiveness of the

intervention tested, those mechanisms can be enhanced to promote recovery from illness. As an example of potential novel targets identified through this research, functional variation in the gene encoding for brain derived neurotrophic factor (BDNF) and through dopamine and reward response modulation, influenced placebo-effects in experimental pain[34]. Common variations in the gene encoding for fatty acid amide hydrolase (FAAH), the principal enzyme metabolizing the endocannabinoids, a system recently implicated in the formation of conditioned placebo responses [35] have been also linked to greater opioid-mediated, but not dopamine driven, placebo analgesic effects [36]. Not surprisingly, a functional polymorphism of the μ-opioid receptor gene affected both responses to pain and placebo administration as well as personality traits linked to risk for neuropathology (e.g., centrally mediated pain and depressive symptomatology)[37].

Placebo-activated neural mechanisms so far identified (e.g., dopaminergic, opioid, cholecystokinine, endocannabinoid) have been minimally explored in areas outside of the field of pain. However, these neurotransmitter systems are also implicated in a substantial number of pathophysiological states and could be potentially modulated to enhance treatments and improve therapeutic outcomes across pathologies. That maybe the case of dopamine, which by its role in responses to salient stimuli, as noted above, may be one of the triggers inducing placebo responses throughout a variety of conditions, by the engagement of reward-responsive mesolimbic systems. The endogenous opioid system, through its role in stress, emotion and mood regulation[24,38] may also be posed to centrally participate in placebo responses in pathologies such as the mood and anxiety disorders, in addition to it proven role in placebo analgesia.

These possibilities were recently tested in a recently conducted trial where thirty-five medication-free patients diagnosed with moderate to severe Major Depression were studied during placebo administration and dopamine D2/3 and μ-opioid receptor radiotracers. In this initial exploration, we performed a single-blinded two-week cross-over randomized controlled trial of two identical oral placebos (described as having either "active" or "inactive" fast-acting antidepressant-like effects) followed by a 10-week open-label treatment with a selective serotonin reuptake inhibitor (SSRI), or in some cases, another antidepressant

agent as clinically indicated. The volunteers were studied with PET and the radiotracers [^{11}C]*carfentanil, selective for* μ-opioid receptors, and [11C] raclopride, labeling dopamine D2/3 receptors, *after 1-week each of "inactive" and "active" oral placebo treatment. In addition, 1 mL of isotonic saline was administered intravenously (i.v.) within sight of the volunteer during PET scanning every 4 min over 20 min after the 1-week active placebo treatment, with instructions that the compound may be associated with the activation of brain systems involved in mood improvement.* This *challenge stimulus was utilized to test the individual capacity to acutely activate endogenous opioid neurotransmission under expectations of* antidepressant *effect, a procedure otherwise identical to that employed in previous studies examining placebo analgesia (e.g.,*[12,13,36]. We then examined changes in depressive symptoms in response to "active" placebo and antidepressant and baseline and activation measures of endogenous opioid system function.

We observed that higher baseline μ-opioid receptor binding in the nucleus accumbens was associated with more robust responses to antidepressant treatment. In addition, reductions in depressive symptoms after 1-week of "active" placebo treatment, compared to those observed during the "inactive" placebo treatment, were associated with increased placebo-induced μ-opioid neurotransmission in a network of regions long implicated in emotion, stress regulation, and the pathophysiology of Major Depression, such as the subgenual anterior cingulate cortex, nucleus accumbens, midline thalamus and amygdala. Placebo-induced endogenous opioid release in these same regions was also associated with better antidepressant treatment response, predicting 41% of the variance in symptom improvement at the end of the 10-week antidepressant trial (see full description of the study in[39]).

On the contrary, while the administration of placebo i.v. during scanning significantly activated dopamine neurotransmission in the nucleus accumbens, this effect was not associated with clinical responses to placebo or antidepressant treatment. Baseline dopamine D2/3 receptor concentrations in the nucleus accumbens were, however, significantly higher in patients diagnosed with Major Depression than a control comparison group and were associated with the severity of anxiety symptoms. Furthermore, patients that did not remit after the 10-week open antidepressant trial, compared to healthy controls and remitters,

also showed significantly greater baseline $D_{2/3}$ receptor availability in the nucleus accumbens. The latter observation then suggests that alterations in dopamine receptor concentrations are associated with both higher levels of anxiety symptoms, and poorer treatment response to antidepressants. Nevertheless, dopamine responses to placebo administration, contrary to the effects observed on the endogenous opioid system and μ-opioid receptors, were not associated with treatment responses to either placebo or antidepressant. This observation would be consistent with its role in responding to saliency, "expectations", but requiring other systems, such as the endogenous opioid, to induce mood changes and improvements in depression symptoms[40].

The data obtained in these studies demonstrate that placebo-induced activation of the μ-opioid system is implicated not just in placebo analgesia, but also in the formation of placebo antidepressant effects in patients diagnosed with Major Depression. It also seems to participate in mood improvement during open antidepressant administration, with endogenous opioid system responses accounting for nearly half of the recovery observed during the antidepressant trial.

Rather than discounting placebo responses as irrelevant noise, the investigation of biological interfaces engaged during intent to treat represents an opportunity to examine predictors of treatment response and novel therapeutic targets not previously contemplated in medication, device or psychotherapeutic approaches to disease recovery. At the very least, these mechanisms point to neurotransmitter systems that are involved in conferring illness resiliency during expectations of improvement and patient-clinician interactions, accounting for a significant proportion of the variance in illness recovery, and obscuring the potential effects of therapeutic agents in randomized trials.

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THE CHALLENGE OF MAPPING PLACEBO MECHANISMS ACROSS DISEASES

Fabrizio Benedetti*

One of the main challenges in placebo research is to characterize placebo mechanisms across a number of medical conditions and therapeutic interventions. Here I describe some of the biological underpinnings that have been identified so far (see Benedetti, 2014b for details). Expectation of therapeutic benefit and learning/conditioning have been identified as the principal mechanisms. Expectation is a conscious event whereby the subject expects a therapeutic benefit, although this notion has recently been challenged in a study on nonconscious placebo responses (Jensen et al., 2012). The link between expectation and the clinical improvement is twofold. First, positive expectations may reduce anxiety, and anxiety is known to affect different symptoms, such as pain, in opposite directions, i.e. either decrease or increase, depending on the circumstances (Colloca and Benedetti, 2007). Second, expectation of a positive event, i.e. the therapeutic benefit, may activate reward mechanisms. Learning mechanisms, ranging from behavioral conditioning to social learning, are crucial, because the previous experience of effective treatments leads to substantial placebo responses. It is important to point out that expectation and learning are not mutually exclusive, since learning can lead to the reinforcement of expectations or can even create de novo expectations. Therefore, although today it is not always clear when and how expectations and learning are involved in different types of placebo responses, they may overlap in a number of conditions (see Buchel et al., 2014 for a recent review).

The opioid system activated by placebos is the most understood. The μ opioid antagonist, naloxone, prevents some types of placebo analgesia, thus indicating that the opioid system plays an important role (Amanzio and Benedetti, 1999; Eippert et al., 2009a; Levine et al.,

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1978). By contrast, the cholecystokinin (CCK)-antagonist, proglumide, enhances placebo analgesia on the basis of the anti-opioid action of CCK (Benedetti, 1996; Benedetti et al., 1995), whereas the activation of the CCK type-2 receptors by means of the agonist pentagastrin disrupts placebo analgesia (Benedetti et al., 2011a). Therefore, the activation of the CCK type-2 receptors has the same effect as the μ-opioid receptor blockade, which suggests that the balance between CCKergic and opioidergic systems is crucial in placebo responsiveness in pain. Some brain regions in the cerebral cortex and the brainstem are affected by both a placebo and the opioid agonist remifentanil, thus indicating a related mechanism in placebo-induced and opioid-induced analgesia (Petrovic et al., 2002). In vivo receptor-binding techniques show that a placebo activates μ-opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens (Wager et al., 2007; Zubieta et al., 2005). Although all these studies have been performed in humans, more recent studies in rodents confirm these pharmacological findings (Guo et al., 2010; Nolan et al., 2012; Zhang et al., 2013). For example, by using different antagonists of different subtypes of opioid receptors (m, d, k), Zhang et al. (2013) found that placebo analgesia is mediated specifically by the m opioid receptors only.

The CCK pro-nociceptive system has also been found to mediate the nocebo hyperalgesic response. The nocebo response is a phenomenon that is opposite to the placebo response, whereby negative expectations may lead to clinical worsening. For example, expectations of pain increase lead to nocebo hyperalgesia, and this increase can be blocked by the CCK antagonist proglumide (Benedetti et al., 1997, 2006a). Anticipatory anxiety plays a key role here, for nocebo verbal suggestions are anxiogenic and induce negative expectations. Support to this view comes from a social-defeat model of anxiety in rats, in which CI-988, a selective CCK type-2 receptor antagonist, prevents anxiety-induced hyperalgesia (Andre et al., 2005).

When nonopioid drugs, like ketorolac, are administered for two days in a row and then replaced with a placebo on the third day, the placebo analgesic response is not reversed by naloxone, whereas the CB1 cannabinoid receptor antagonist, rimonabant, blocks this placebo analgesia completely (Benedetti et al., 2011b). Therefore, in some

circumstances, for example following previous exposure to nonopioid drugs, placebo analgesia is mediated by the CB1 cannabinoid receptors. Interestingly, there is compelling experimental evidence that the whole lipidic pathway, involving arachidonic acid, endogenous cannabinoid ligands (e.g., anandamide), and the synthesis of prostaglandins and thromboxane, is important in the modulation of the placebo response in pain. For example, the functional missense variant Pro129Thr of the gene coding fatty acid amide hydrolase (FAAH), the major degrading enzyme of endocannabinoids, affects the analgesic responses to placebo as well as placebo-induced μ opioid neurotransmission (Pecina et al., 2014). In addition, cyclooxygenase activity, which is involved in prostaglandins and thromboxane synthesis, has been found to be modulated by both placebo and nocebo in hypobaric hypoxia headache with a mechanism similar to that of aspirin (Benedetti et al., 2014). Overall, the involvement of all these lipidic mediators represents a challenge for future research. In particular, what we need to understand is when they are activated.

Dopamine is involved in placebo responsiveness in at least two conditions: pain and Parkinson's disease. In placebo analgesia, an increase in dopamine binding to D2/D3 receptors and in opioid binding to μ receptors occurs in the nucleus accumbens, whereas a decreased binding to the same receptors is present in nocebo hyperalgesia (Scott et al., 2007, 2008). Likewise, dopamine receptors are activated in both ventral (nucleus accumbens) and dorsal striatum when a placebo is administered to patients suffering from Parkinson's disease (de la Fuente Fernandez et al., 2001, 2002; Lidstone et al., 2010). The release of dopamine corresponds to a change of 200% or more in extracellular dopamine concentration, and is comparable to the response to amphetamine in subjects with an intact dopamine system, although a more recent study by the same authors (Lidstone et al., 2010) found this effect only when expectation of drug was around 75%. Certainly, this requires further analysis, but the fact that dopamine has been found to be involved in both pain and Parkinson's disease makes these two conditions excellent models to understand whether common placebo mechanisms can be involved in different pathologies. For example, dopaminergic activation in the nucleus accumbens in both pain and Parkinson's disease suggests that reward mechanisms could play an important role in many conditions.

Intraoperative single-neuron recording in Parkinsonian patients during the implantation of electrodes for deep brain stimulation shows that the firing rate of the neurons in the subthalamic nucleus and substantia nigra pars reticulata decreases, whereas the firing rate of thalamic neurons in the ventral anterior and anterior ventral lateral thalamus increases, along with the disappearance of bursting activity in the subthalamic nucleus (Benedetti et al., 2004, 2009; Frisaldi et al., 2014). Although the dopamine findings and the electrophysiological data were obtained in different studies (de la Fuente-Fernandez et al., 2001, 2002 and Benedetti et al., 2004, 2009, respectively), it is tempting to speculate that the changes in firing pattern of the subthalamic and thalamic neurons were triggered by dopamine release.

Modern brain imaging techniques have been fundamental in the understanding of the placebo response, particularly placebo analgesia, and many brain imaging studies have been carried out to describe the functional neuroanatomy of the placebo analgesic effect (e.g., Bingel et al., 2005; Eippert et al., 2009a,b; Hashmi et al., 2012; Kong et al., 2006, 2007; Lui et al., 2010; Meissner et al., 2011; Petrovic et al., 2002; Price et al., 2007,2008; Scott et al., 2007, 2008; Tracey, 2010; Wager et al., 2004, 2007, 2011; Zubieta et al., 2005). A meta-analysis of brain imaging data using the activation likelihood estimation method identified two phases: the expectation phase of analgesia and the pain inhibition phase (Amanzio et al., 2013). During expectation, areas of activation are found in the anterior cingulate, precentral and lateral prefrontal cortex, and in the periaqueductal gray. During pain inhibition, deactivations are found in the mid- and posterior cingulate cortex, superior temporal and precentral gyri, in the anterior and posterior insula, in the claustrum and putamen, and in the thalamus and caudate body. Overall, many of the regions that are activated during expectation are likely to belong to a descending pain inhibitory system that inhibits different areas involved in pain processing.

In social anxiety disorder, positron emission tomography has been used to assess regional cerebral blood flow during an anxiogenic public speaking task, before and after 6-8 weeks of treatment with selective serotonin reuptake inhibitors (SSRI) under double-blind conditions (Faria et al., 2012, 2014). Conjunction analysis reveals a common attenuation of regional cerebral blood flow from pre- to post-treatment

in responders to SSRI and placebo in the left basomedial/basolateral and right ventrolateral amygdala, including amygdala-frontal projections to dorsolateral prefrontal cortex and rostral anterior cingulate cortices. This pattern correlates with behavioral measures of reduced anxiety and differentiates responders from nonresponders, with no differences between SSRI responders and placebo responders. Therefore, this pattern is capable of differentiating responders from nonresponders to both SSRI and placebos, which indicates that drugs and placebos act on common amygdala targets and amygdala-frontal connections (Faria et al., 2012, 2014).

Immune and endocrine responses can be behaviorally conditioned (Pacheco-Lopez et al., 2005). When an unconditioned stimulus (US), e.g. the effect of a drug, is paired with a conditioned stimulus (CS), e.g. a gustatory stimulus, after repeated pairings the CS alone can mimic the effect of the drug (conditioned response, CR). Since the CS is a neutral stimulus, it can be conceptualized as a placebo in all respects. Indeed, both immune mediators, like interleukin-2 (IL-2) and interferon-γ (IFN–γ), and hormones, like growth hormone (GH) and cortisol, can be conditioned in humans. After repeated associations of a CS with cyclosporine A or sumatriptan, which produce IL-2/IFN- γ decrease and GH increase/cortisol decrease, respectively, the CS alone can induce the same immune and hormonal responses (Benedetti et al., 2003b; Goebel et al., 2002).

An association of placebo responsiveness with some genotypes has been described in some conditions. Patients with social anxiety disorder have been genotyped with respect to the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter. Only patients homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism show robust placebo responses and reduced activity in the amygdala, whereas carriers of short or T alleles do not show these effects (Furmark et al., 2008). In addition, in patients with major depressive disorder, polymorphisms in genes encoding the catabolic enzyme monoamine oxidase A are associated to the magnitude of the placebo response. Patients with monoamine oxidase A G/T polymorphisms (rs6323) coding for the highest activity form of the

enzyme (G or G/G) show small placebo responses (Leuchter et al., 2009). Functional Val158Met polymorphism of the catabolic enzyme catechol-*O*-methyltransferase (COMT) has been found to be associated with the placebo response in irritable bowel syndrome. The lowest placebo responses occur in Val/Val homozygotes (Hall et al., 2012). As already described above, also the functional missense variant Pro129Thr of the gene coding FAAH has been found to affect the analgesic responses to placebo (Pecina et al., 2014). It should be emphasized, however, that these genetic data must be considered with some caution, because all these studies have investigated rather small samples, particularly when compared to modern genetic standards.

As for drug development, placebos (and nocebos) can also exert their influence on physical performance. In general, all available data indicate athletes' expectations as important elements of physical performance, in spite of the fact that very different experimental conditions have been investigated (Beedie and Foad, 2009; Pollo et al., 2011).

In a simulation of sport competition in which subjects had to compete with each other in a competition of pain endurance, placebo administration on the day of competition was found to induce longer pain tolerance compared to an untreated group. However, if pharmacological preconditioning is performed with morphine in the pre-competition phase, the replacement of morphine with a placebo on the day of the competition induces an increase in pain endurance and physical performance that is significantly larger than placebo without prior morphine preconditioning. The placebo effect after morphine preconditioning can be prevented by administration of the opioid antagonist, naloxone, which suggests that this placebo response is opioid-mediated (Benedetti et al., 2007). Similar findings can be obtained with a non-pharmacological conditioning procedure (Pollo et al., 2008).

The increase in performance following placebo administration may have practical applications, but it also raises important questions as to how these effects should be exploited in sport competitions. The ethical issue is particularly significant when one wants to induce opioid- mediated placebo responses by means of pharmacological preconditioning with illegal drugs, as done by Benedetti et al. (2007).

Nocebo effects are also important in physical performance. For example, in a 30-m repeat-sprint protocol, placebo capsules coupled with different positive or negative instructions lead to increased and decreased speed, respectively (Beedie et al., 2007). Likewise, it is possible to negatively modulate the performance of subjects carrying out a muscle exercise to volitional maximum effort by employing discouraging suggestions and negative conditioning (Pollo et al., 2012). These findings may have profound implications for training strategies, because negative expectations may counteract the positive effects of training programs.

What I have described in this article represents the principal mechanisms of the placebo response that have been characterized across a variety of medical conditions and interventions. Future research should be aimed at further characterizing the biological underpinnings of placebo and nocebo in other diseases as well as in physical and cognitive performance.

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UNSOLVED, FORGOTTEN, AND/OR IGNORED FEATURES OF THE PLACEBO RESPONSE IN MEDICINE

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Introduction

Placebo effects (PE) and placebo responses (PR) are immanent components of all and every medical intervention, be it during placebo-controlled randomized clinical trials (RCT) of novel diagnostics and therapeutics, or during clinical routine management of patients at his/her physician´s office or hospital. Evidently, PR and PE are to minimize and to control for during RCTs for the development of better therapies, but to maximize and harness in medical routine for the benefit of the individual patients [1].

Over the past 20 years, placebo research has fostered a much better understanding of the underlying neurobiological and psychological mechanisms of placebo responses (and to a lesser extent also the nocebo responses)[2,3]. More recently, the search for genetic predictors of the PR have replaced the long and fruitless search for individual "personality" markers of placebo responders[4], and novel designs of RCT and experimental approaches have taken increasing PR in a number of clinical conditions into account [5]. The number of genuine publications dealing with the placebo and nocebo effect has risen from a few hundreds to now more than 3,000 and highlights the relevance in medicine and beyond.

Despite this progress, however, a number of issues have remained unsolved in placebo research during the past decade, or even have been generated by the recent progress but require novel solutions. They will be discussed here with respect to 1) experimental placebo research, 2) clinical components of the placebo effect, and 3) societal and 4) technical dimensions of it.

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To manage these more than 3,000 references, a few tools are available and have been used for this review: All papers are included in a self-designed literature database (operating similar to Endnote®) for quick title, author, abstract and MESH term search, available through our website (www.psychosomatikforschung.uni-tuebingen.de/litdb/) and the link on the Journal of Interdisciplinary Placebo Research (JIPS) (www.jips.online). A detailed full-paper semantic analysis was made possible via the semantic analysis program Luxid® of TEMIS Expert System *(www.expertsystem.com)*, courtesy of the company. The summary reported here is a combination of both a heuristic and an empirical analysis, first presented during a meeting in Porto, Portugal, April 2016 [6].

1. Experimental placebo research

While we all acknowledge that the placebo effect is an immanent component of all medical (and many non-medical) interventions, we still lack systematic knowledge on a number of experimental issues related to the intra-individual stability of the response, on the cross-modality of the response, on the contribution of age and gender, on cross-cultural aspects and long-term efficacy.

Intra-individual stability

Only a few studies have attempted to assess whether a person (a healthy volunteer or a patient) who has responded to a placebo treatment will exhibit a similar response when tested a second time, either under the same condition or under different circumstances.

Kaptchuk et al. [7] - in summarizing the existing older literature before 2008 - concluded that "much of the existing evidence […] was performed before 1967. This early evidence is contradictory, methodologically weak and is sufficiently old to be considered medical history" (p 587). Since then, the results of respective research "are not unequivocal, and may not be equivalent to non-deceptive conditions" (ibd., p 587).

Whalley et al. [8] argue that stability of response requires the within-subject response to be equal with two identical placebo tests (e.g. of placebo analgesia) separated by time only, and reasonably equal between two tests with marginal difference, e.g. with changing the name of the

presumed medication. While they found high inter-correlations with the first set of tests (and explained variance of approximately 50%), within-subject placebo analgesia was not significantly associated in the second set (with a change in context, i.e. the name of the drug), and was not predictable by personality variables assessed. In another experimental setting, a previously experienced placebo response did not predict the response to another test of the same modality [9].

Within-subject stability or instability of placebo responsiveness may also be tested in RCTs, if individualized data of patients enrolled in RCTs would be available and could be used in subsequent trials. This requires however, that the patients´ identity would need to be protected, e.g. by introducing a patient registry for recruitment and repository of the collected data; registry trials may allow this in the future [10].

Cross-modality

Most experimental settings have only one test modality available, thus cannot test placebo susceptibility in more than one modality. However, for laboratories dealing with placebo analgesia it would be easy to adopt more than one pain stimulation paradigm and to compare placebo responsiveness of individuals across different analgesia paradigms. Apparently this was rarely done, or in case it was done resulted in negative outcome, but even in this case the results would be worthwhile reporting. Cross-modality reports for pain sensitivity have been reported for visceral versus somatic pain [11,12] in healthy volunteers, and for nausea with different stimuli [13]; this may allow to predict poor transmission of placebo responses from one to another setting, but unless this has been shown the opposite might as well be true. While Beissner et al. [14] investigated three different modalities to induce placebo analgesia and found equal properties among all three in terms of qualitative and spatial pattern, they used different volunteers in different experiments and therefore could not assess cross-modality consistency.

Sex contribution

Age and gender contributions to the placebo effect have long been suspected to contribute to the PE, and specifically female sex has been linked to it [15,16], often due to rather simple assumptions of its nature: the

PE was often seen as a neurotic or otherwise psychiatric trait (e.g. anxiety,[4]). Also, the sex of the treating physician or experimenter may contribute to the placebo effect [17,18], and complex interactions between the gender of the experimenters and the volunteers have been observed occasionally [19,20]. However, the data with respect to sex as moderator of the placebo response remained inconclusive and was not confirmed in other experiments [21]. Too few data-sets exist with experimental data in children and adolescents, and direct comparison of the placebo response of children, adolescents, and adults using the same paradigm are very rare [22].

Age contributions

With respect to age as contributing factor in randomized clinical trials (RCTs), re-analyses and meta-analyses of the placebo response have not revealed its significant contribution. We found a contribution of age in only 6 of 75 analyses across 40 medical conditions including 1,500 RCTs with 150,000 patients in all areas of medicine, but with contradictory results: in some analyses lower age was associated with a higher PR, in other analyses higher age was associated with a higher PR [23]. While the behavioral response in a placebo analgesia paradigm may be similar between sexes, the central processing may be quite different [24]; this allows to speculate whether conditioning and expectations (as the two distinct mechanisms of the placebo response) may operate with different relative intensity between men and women, e.g. due to the relative importance of the symptom under investigation, e.g. nausea [25].

It has to be noted that these associations in meta-analyses were based mostly on mean age data and percentage of males/females in these RCTs, and not on individualized data; the latter would be necessary to answer the question.

"Placebo by proxy"

The term "placebo by proxy" [26] was created to indicate that medical decisions and treatments of a patient could be influenced by a patient's social environment if it is pleased about a treatment, too. This may especially be true for treatments of children as the placebo response in children was frequently associated with parents' characteristics and their perception of the clinical situation and communication with the treating

doctor [27]. Furthermore, the "placebo by proxy" effect could explain why many of the predictors of placebo effects in adults are not effective in children, e.g. the amount of time children spent with medical staff [28].

However, this concept that our social environment (families, relatives, friends, peers) contributes to treatment outcomes is not novel but almost completely ignored when it comes to placebo responses. It is, for instance, assumed that the claimed "healing power" of religious prayers [29,30] when demonstrated in well-designed trials [31,32] may not as much be due to the prayer but to a stronger social network in religious families; however, a specific brain-effective analgesia of religious symbols and prayers cannot be ruled out [33]. While we agree that it may be complicated if at all possible to assess the influence of the "social environment" of a patient during evaluation of placebo responses, efforts can and should be made toward a standardized assessment of features of this network.

Moreover, while social learning of placebo and nocebo responses has been demonstrated [34,35], it is unknown to what extend such learning is enhanced within families, and with relatives, peers, or unbeknown "models". This is specifically related to the possibility to separate environmental and genetic contributions to a complex behavior via the examination of monozygotic and dizygotic twins, for which pain sensitivity data are available [36] but no data about placebo analgesia and other placebo responses so far.

Cross-cultural influence

Despite known influences of the socio-cultural background of patients and healthy volunteers in pain perception and tolerance[37], no study ever assessed whether the cultural background of a patient and/or volunteer contributed to placebo analgesia, not to speak of other placebo paradigms, although this has been proposed [38]; even the color of drugs may play a differential role across cultures [39]. This could easily be done within a single laboratory setting by using patients with a variable migration history, but less easy across different national, geographical, or cultural settings. However, since the experimental paradigms to induce placebo analgesia are highly standardized across many laboratories around the world, merging of experimental data from different settings might also be feasible.

With another experimental paradigm - rotation induced nausea - cultural variability between volunteers with an Asian and non-Asian background has long been known [40], as have complex interactions with sex and other variables [41,42]. The paradigm is one of many well established ones to explore the placebo and nocebo responses [43,44]. It would be easy to test whether this applies also to conditioned and expected responses in other established paradigms of placebo research.

Cultural differences might also directly apply to clinical settings and clinical applications [38], down to the fact that the color of drugs may signal different meanings and different efficacy in patients from different ethnic backgrounds [45]. It may be speculated that occasional differences in drug efficacy between the US, Europe, and Asia [46-49] may be due to such ignored cultural factors; certainly, differences in the placebo use across borders [50,51] are likely also due to cultural differences in perception and acceptance of the placebo concept.

Long-term efficacy

Most placebo and nocebo experiments in respective experimental settings test placebo effects for their duration in terms of hours and days, and some may go beyond and explore e.g. conditioning effects after weeks [52]. Clinical trials overlook the size of the placebo effect in terms of weeks to months, but rarely beyond. Long-term placebo controlled drug trials have demonstrated that the placebo effect can persist over a year or longer [53], but whether placebo effects seen outside of such trials in medical routine also exhibit such long effects is unknown. The experimental and clinical determinants of such long-term effects are unknown, but likely include trial characteristics.[23,54]

The size of the placebo response in daily medical practice is not even established, due to the nature of clinical routine that rarely allows assessment of efficacy to the same degree than clinical trials. When Kaptchuk et al. [55] tested placebo responses under real-life conditions they found that open-label placebo use was superior to no treatment, and that placebo effects accounted for nearly 50% of the drug effect, and a drug labeled as placebo had similar effects than a placebo labeled as drug. In contrast, when Petersen et al. [56] tested chronic pain patients in a laboratory setting with acute experimental pain stimuli, they found

lower placebo responses than those reported by healthy volunteers under the same condition, and poor associations between acute (experimental) and chronic (clinical) pain responses.

A frequently discussed example of long-term placebo effects in medicine is the knee arthritis surgery study by Moseley et al. [57]. They found that after two years improvement was similar in the sham (surgery) treated group than in both other groups which received knee surgery; however, when looking at the improvement reported in all three groups it turns out the effect size is rather small (6 points on a 100-point VAS, which can be regarded as clinically irrelevant), so that the study does not actually demonstrate the efficacy of placebo intervention but rather the inefficacy of the surgery.

2. Clinical aspects of the placebo effect

Similar to the experimental issues discussed above, of which many also and immediately apply to clinical placebo research and the effects of placebo application in randomized controlled trials (RCT), clinical placebo research has focused mainly on drug therapy and grossly ignored to investigate placebo effects in nutritional interventions, in physical therapy and related manual therapies, and with psychotherapy.

Nutritional interventions

While many nutrient and nutrient supplement studies have included some form of placebo control groups, no meta-analysis has quantified the size, or the determinants, of the placebo effect in studies of nutrient effects; such analyses have been performed for drug studies in all areas of medicine including gastroenterology. Neither have the placebo responses in drug trials been directly compared to those in dietary trials for the same clinical condition, e.g. a disease. The only known exception is a meta-analysis of studies in pediatric autism spectrum disorders [58], in which the response to the medicinal placebo was found to be significantly larger than the response to a dietary placebo.

To the best of our knowledge, trials with nutrients have not yet explored whether specific mechanisms underlie the placebo response [59] or whether they follow similar mechanisms (expectation, learning)

than with drugs; for example, expectation of a high- versus low-fat drink significantly affected symptom scores, irrespective of the actual fat content of the (yoghurt) meal [60,61], a neurocognitive phenomenon which has been called "mindset" recently in this context [62] according to a person's set of associations and attitudes which shape respective expectations and behaviors. In another study with healthy volunteers [63] information to have received a nutrient supplement facilitating weight loss increased the belief in the supplement over the course of the study, although it decreased the person´s self-efficacy towards weight control. Similarly, information about the potential health benefits of bodily work (room cleaning) resulted in beneficial health outcomes (decrease in blood pressure, BMI, etc.) as compared to controls with the same amount of exercise but without respective information [64].

Physical exercise and therapy

Because bodily exercise has been shown to be under placebo control (both conditioning and expectation) in experimental settings[65,66] placebo responses may also play a major role in sports performance of professional and lay athletes[67], and many athletes consume nutrients and nutrient supplements as presumed ergogenic aids[68]. Here, a conditioning (learning) model would favor higher responses following a pill, while a perceptual salience (novelty) model would favor the food intervention[69] as producing stronger placebo effects, but empirical evidence is still missing.

Placebo control of physical therapy, e.g. in low-back pain remains a methodological challenge[70], as the reported effects of treatment are rather small[71], and the vast proportion of treatment effects (84%) are due to unspecific rather than specific effects[72]; this seems also to be true for passive (e.g. massage) rather than active treatment options [73], and for all other treatment options available [74]

Psychotherapy

Because placebo effects are immanent components of all treatments, they also must occur in psychotherapy. While the discussion about placebo effects in psychotherapy is ongoing for quite a while now[75], it has not found a reasonable solution[76]: unspecific effects as seen in drug RCT may eventually be active components of a psychotherapeutic intervention, and

this needs adequate control and separation from unspecific psychotherapy effects through a "sham" intervention. Most often, psychotherapy has been controlled for unspecific effects with a "waiting list" group, but waiting to receive active treatment may develop its own dynamics[77], may be less effective than a psychotherapy placebo[78], and may produce disappointment and increased drop-out rates [5]. Waiting list effects account for 50% of the placebo response according to a meta-analysis of respective trials across a variety of diseases[79]. Novel designs (e.g. step-wedge) may overcome these limitations[5]. Blinding remains impossible[80], and the respective biases need to be overcome by other measures[54].

The situation is not that different from e.g. acupuncture trials[81] where the sham acupuncture procedure, e.g. the Streitberger needle[82] is also suspected of inducing minimal (acupressure) effects, so that the "verum" treatment requires to demonstrate higher efficacy to reach superiority: minimal psychotherapy or "treatment as usual" thus should be contrasted with enhanced (optimal) doctor-patient communication[83] (psychotherapy). This situation is, however, complicated by the fact that even electronic and internet-based psychotherapy without direct doctor-patient interaction may exert substantial clinical effects[84] (see below).

3. Societal dimensions of the placebo effect

While the two above discussed aspects (clinical and experimental) of the placebo effect still may be regarded as immanent to the topic and just reflecting a lack of knowledge that can and will be filled in time, the societal dimension include issues that have so far more or less been ignored by placebo research and are of interest only for a small number of respective experts. Among these topics are ethical dimensions of placebo research (and not necessarily of the placebo use in RCTs), its legal and juridical limits, especially with focus on ethical and legal diversity in different cultures and societies, and economic aspects of the placebo effect in medicine and beyond.

Ethical and legal diversity of placebo use

Following a strict interpretation of the Declaration of Helsinki (DoH) by the World Medical Association[85], some countries have legally

banned the use of placebos completely (e.g. Brazil), and rely on studies performed in other countries, as well as on Comparative Effectiveness Research (CER)[86]. CER studies however, as we have pointed out earlier[87], produce an ethical dilemma by itself, as they require more patient to be included into a trial (and to be withheld from receiving the best medical treatment, as required by the DoH) than placebo-controlled trials. While ethical rules are thought to be universal across nations, countries, and societies[88], legal rules are not. Since this reflects (among others) also the diversity of the cultural background in each setting, there is a need for cross-cultural comparison not only of the placebo response (see above) but also of the ethical and legal rules applied.

Ethical and legal diversity of placebo research

Ethics of placebo use in clinical trials and clinical routine must be distinguished from the ethical and legal handling of placebo research: This is almost inevitably associated with deception of patients and healthy volunteers[89], even in case of authorized deception[90]. Again, ethical rules are thought to be universal, but common practice shows that even within a country such as Germany or the US, local ethics committees and institutional review boards may decide quite heterogeneously whether or not to approve a deceptive protocol, and within Europe and for cross-European research trials, not even a common set of rules are available but still depend on national ethic decisions. Harmonization is required, but a prerequisite for this will be an updated survey of various national rules and laws[88].

Economical relevance of placebos

While "harnessing" the placebo response in day-to-day medicine is called for[91], and is seen as "for the benefit of patients and the society[92], however, societal benefit has never been demonstrated convincingly. Two such options would be to substantiate that implementation of a "placebo medicine" would save health care costs, or would improve patient adherence; both are feasible and need to be investigated.

They could be the result of a planned study on "dose extending placebos"[93] utilizing an associative learning paradigm called "partial reinforcement" [94]. Two experimental trials have demonstrated efficacy in clinical research in psoriasis [95] and ADHD [96], but final proof of its societal

relevance will be a test in a clinical area of high visibility and cost, e.g. in acute and chronic pain therapy.

One personality concept of the placebo effect is based on the assumption that high placebo response is associated with low self-efficacy[4], low optimism[97], and an external locus of control [98]. Improving the adherence of patients and their participation in shared decision making, as is the goal of many contemporary attempts in patient education [99], may therefore result in lower placebo response rates instead of its increase and harnessing.

4. Technical dimensions of placebo interventions

While most placebo research paradigms limit themselves to traditional concepts of a doctor-patient relationship (e.g. the open/hidden paradigm[100]), medical reality has already bypassed this with integrated eHealth and mHealth technology. Their relevance for placebo effects has just even been touched upon[101] but soon will become relevant for many areas of medicine.

Ambulatory (mHealth) devices

Currently, there appear more than 150,000 medical apps available for smartphones and related mobile technology[101], most of which without any quality control and without data on their day-to-day usage[102]. These devices not only collect a variety of physiological, behavioral and subjective data[103], but also initiate and guide interventions and monitor their adherence. Efficacy data show that this can have significant treatment effects[104], but a distinction between specific and unspecific (placebo) effects is lacking, due to the missing "sham" intervention in a RCT[76]. Even well-developed and scientifically solid internet-based psychotherapy RCTs, e.g. for the treatment of depression[105] often run without placebo control and rely exclusively on the traditional waiting list controls (see above).

Virtual doctors & experimenters

In many cases, these apps are a substitute for a remote doctor-patient relationship, either because of local distance or because of economic reasons for more effective data collection. From a different angle of view,

these electronic (eHealth, mHealth) doctor substitutes can also be used to standardize interventional procedures in the clinic, similar to what has been attempted earlier with video-guided patient information, and patient recruitment and assessment[106] to overcome biases in patient inclusion and exclusion in RCT[107]. Their ability to induce placebo and nocebo effects is without doubts, but this need to be explored in the future.

These electronic aids can also be used to standardize laboratory procedures beyond RCT, to further explore the contribution of doctor characteristics (age, sex, race, language, gesture, personality etc.) to the placebo effects, much like the modulation of physician behavior (except touch) in a face-to-face situation. In one such attempt, we have recently developed a "virtual experimenter" for pain and placebo analgesia research[108] that may become a tool also for other applications, e.g. to simulate doctor-patient communication in a brain scanner with limited direct accessibility and communication options.

Summary and conclusions

While placebo research has gained substantial progress over the last two decades, it has not resolved all its puzzles, it has ignored some obvious and some less obvious facets of the placebo topic, and it has overlooked that during these years, medicine has further developed and progressed, as has the doctor-patient relationship and the social environment in which this communication happens.

Its strength is the fact that it called the relevance of the doctor-patient communication back into our attention and into attention of the general public, and the importance of the clinical setting and all its features that affect medical treatment. Its weakness is the still obvious negative connotation the term placebo bears, and the fact that this has not been overcome through a new terminology, e.g. "meaning" [109].

The biggest threat for placebo research is that it may outdate itself by declaring all and everything as a placebo effect even if there may be better terms and concepts (e.g. patient expectations, doctor-patient communication, empathy), and by ignoring that medicine continuously changes its face, for patients as well as for clinical researchers. Its biggest opportunity is the fact that it - as no other topic in medicine - requires both medical and psychological experts for its exploration, and to stay updated.

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PLACEBO EFFECTS IN CLINICAL PRACTICE

Ted Kaptchuk [*]

Placebo effects are often described as the positive health benefits that come from treatment by an "inert" substance. This oxymoron - "the effect of something that has no effect" - is a sign of how poorly mainstream biomedicine has conceptualized the question of placebo. Placebo effects are not the effects of something that has no effect. A better definition may be something like: "placebo effects are the improvements in patients' symptoms that are due to the rituals, symbols and behaviors of the clinical counter. Placebo controls are a sort of surrogate marker for everything that surrounds the medication and procedures of health care interventions. These processes in clinical practice are called "non-specific" and in drug development "nuisances." Placebo studies foregrounds such effect as opposed to the common practice ignoring what is an uncomfortable background.

This talk is for those people in the audience who have not read over 100 papers on placebo effects. So I apologize to those people in the room who are experts and research colleagues. For this talk, I have selected three experiments performed by our Harvard team. I picked these three studies because they were not laboratory studies on volunteers; they were performed with clinical patients, who have real illness. I want to talk to be relevant for clinical practitioners in the room.

The three questions that these studies address are:

First: Can you break up placebo effects into component parts and incrementally add them in a way that is analogues to dose dependence? Can placebo operate in a way that is analogous to a drug in the patient population of irritable bowel syndrome (IBS)? Ultimately the study asks: are placebo effects real?

Second: What is the relationship of placebo effects to an effective pharmaceuticals in clinical practice? We picked acute episodic migraine

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as our study target. The study can also be described as what would happen to commonly used effective medication if we changed one word in the clinical encounter

Third: Do we have deceive patient patients in order to produce placebo effects using placebo pills? Again the target population is IBS.

So let's look at the first study which was published in *BMJ 2008*. The idea can be summarized as: "*I want you to take this placebo two times a day for ten days. If your condition doesn't improve, I'll give you a stronger one*". Is this possible? To answer this question we recruited 262 patients with IBS and randomized them to three arms. The first group was just a baseline medical intake, a battery of questionnaires, a physical exam, and an interview with our chief a gastroenterology, Dr. Anthony Lembo. No treatment was given. This arm served as a no-treatment group and controlled for spontaneous improvement and regression to the mean. You could also say that it controlled for Hawthorne Effects, the effects of just being in a study with all its attendant extra attention.

The second group had the same intake from Dr. Lembo and then saw an acupuncturist. In this arm the treatment was placebo acupuncture. The acupuncturists introduced themselves and told the patient that they had read the intake, but for this experiment they were not going to talk too much because we want to study to be about acupuncture and didn't want to get the patient-clinician relationship to get into the mix. A pure science experiment. The acupuncturist said that they might ask if patient were comfortable and if they could turn around but if there were otherwise going to be disconnected to the patient. If the patient had any other questions that should ask the study nurse, study physician or study coordinator. We separated out the patient-clinician relationship from the paraphilia of treatment, in this case placebo acupuncture. Patients received twelve fake acupuncture treatments over six weeks. The acupuncture needle looks like a real acupuncture pin; the patients felt a scratch and the patient saw the needle penetrate the skin. But actually, the needle went up the shaft of the needle like a magic sword.

The third treatment groups had the same intake as group one, and the same intake plus fake acupuncture as group two but also had a warm, attentive, supportive interaction with the acupuncturist. We added a strong patient-physician relationship. Personal questions were asked: *I've*

read the intake chart but I want to hear what you say is going on, in your own words; I want to know how IBS affects your life, how it affects your relationship to work, your family; I want to know why you think you got this disease; I want to know what you think it makes it better".

Importantly we also asked the acupuncturists to do five behaviors. (The entire trial was videotaped to insure fidelity to protocol.) One of them was Attentive Listening - "*I'm trying to fully understand what you are saying. Can you explain that better?* Another behavior was Expressing Confidence - "*I have treated people outside the hospital with irritable bowel syndrome and I've got very good results. I want to show to the medical community that it works"*. A third behavior was to Touch the patient, do some palpation in the abdomen or the radial artery. A fourth behavior thing was Empathy - "*I understand how you are feeling because…something*". And the fifth thing, to make sure that this would work, we asked all the practitioners to do 20 seconds of Thoughtful silence - meaning, they had to say: "*Give me a moment. I heard what you said. Let me think about this*" and then the practitioner had to say "*Can you explain that better to me?"* or "*What exactly did you mean by?*"

Our clinical outcomes were the four outcomes that the US FDA requires for labeling a new drug for IBS. I'm only going to look to the first one, because it is very simple - Adequate Relief. And we did correct for multiple comparisons, of course. We found that after three weeks people in the no-treatment arm intake had 28% Adequate Relief ("time heals"); the arm with fake acupuncture also added to intake and showed 44% Adequate Relief and the arm with intake, plus fake treatment plus a supportive relationship produced 62% Adequate Relief ($p<0.001$). By incrementally adding components of the placebo effect (Hawthorne Effect, then Fake Treatment, and then Supportive Relationship) we were able to incremental increase the "non-specific" components of treatment in way that are analogous to dose dependence. Just being examined at intake (and time) had an effect; adding the appearance of treatment (paraphernalia) had a bigger effect and then adding a genuine clinical encounter had an even bigger effect. No medicine was given, just incremental component of the "non-specific" components of the medical encounter. The trial demonstrated that placebo effects can be manipulated like a dosage of a drug and can vary from modest to dramatic. Our no-treatment control,

besides representing a measure of Hawthorne Effect also was a control for spontaneous improvement and regression to the mean.

The second experiment I want to present concerns the question of what is the relationship of placebo effects to actual clinical practice when active physiological drugs are used. Where is the placebo effect then? We published this trial in *Science Translational Medicine* (2014). We also wanted to see if changing "one word" in a clinical encounter could change medication effects. To this end, we recruited 66 migraine patients who we asked to allow us to treat and examine them for seven acute episodic migraine headaches. This created 456 baseline migraine headaches. We explained that the experiment was not for their benefit but for science *("we wanted to see how taking medication and placebo worked when taking it many times*") and they would receive a reasonable monetary compensation. In effect, we bought seven migraine headaches. For each headache, would monitor them for 2.5 hours and then they could take rescue medication if still necessary. For 3 of the seven headaches patients randomly received 10 mg rizatriptan (Maxalt); for 3 of the headaches patients received placebo; and for one headache patients received no treatment for 2.5 hours (our no treatment control). For each of the drug treated headaches patients the envelop patients received were randomly labeled: "Maxalt," "Maxalt or placebo" or "placebo". The same three labels were randomly applied to the placebo pill. (This is the 3x2). There was also a single no-treatment headache which was single headache (hence the +1).

	Placebo	Maxalt
Label		
Placebo	Correct	Incorrect
Maxalt or Placebo	Correct	Correct
Maxalt	Incorrect	Correct

(There are some serious ethical issues here concerning deception here. One time we gave patients placebos and deceptive informed them it was Maxalt; and one time we have Maxalt and told them it was placebo. I didn't expect the ethical committee to give us approval. I had our ethicist attend the ethics meeting and advocated using "authorize deception", but the head of the ethics committee said "*If you need deception for scientific validity, why don't you just do that and informed participants at the end that's what you did? You can invite them to withdraw their data.*" He felt that is was reasonable to allow for this as we were clear that the experiment was only for science and there are regulations for performing psychological experiments with this model. I suspect it will be difficult to replication our ethics committee decision.)

For our team the two boxes that involved "incorrect information" or deception were very important. We wanted to find out, what would happen when the drug was given and we removed expectation by telling them it is placebo. We thought this would represent the "pure pharmacology of the drug" without any surrounding of positive expectations. Our other deception arm was "pure expectation" a placebo described as a drug. This was an important pre-planned secondary comparison.

The results were interesting. When participants were given placebo labeled as (i) placebo, (ii) Maxalt or placebo, and (iii) Maxalt, the placebo effect increased progressively. Maxalt had a similar progressive boost when labeled with these three labels. Using a generalized linear mixed model that effect was highly significant. The effect of "drug labeled placebo" (pure pharmacology) was similar to "placebo labeled drug" (pure expectation). The pharmacology was the drug was not statistically different from the pure expectation ($p= 0.127$). Relative to no treatment, the placebo under each information condition, accounted for more than 50% of the drug effect. Increasing "positive" information incrementally boosted the efficacy of both placebo and medication during these migraine attacks. Changing the word "Maxalt" to "placebo" - albeit an important word - dramatically impacted the effect of the drug. In clinical practice, expectations and sometimes every word counts.

The third experiment is involves the question of whether honestly described placebo treatments (open-labeled placebo) could actually produce positive benefit clinical conditions. We published this trial in

PLoS One (2010). My motive for the experiment has to do with the fact that when people ask "*Ted, what you do for research?*" and I say "*I study placebo effects."* And the response would be: "*Oh you trick patients and lie to them.*" I began to wonder there was a possibility to directly harness placebo effects with deceptive administration of pills? In this experiment, we randomized 80 patients with irritable bowel syndrome (IBS) to two arms: an open-label placebo treatment or a not-treatment arm (that controlled for regression to the mean and spontaneous improvement.) We used the same outcomes we did in our earlier IBS experiment. Again, I'm going to focus on the simplest outcome. After three weeks, patients on placebo treatment reported 60% Adequate Relief while the no-treatment reported 35% improvement (p=0.03). It seems possible that placebo could work without concealment. The experiment needs to be replicated and expanded. Furthermore, the question raises questions about the mechanisms of placebo responses. To what extent are non-conscious mechanisms involved? Implicit expectations? Embodied cognition? The study asks for re-consideration of common theories of placebo mechanism.

Now I want to talk about something that is very exciting to me. A Portuguese team at Hospital Egas Moniz, in Lisboa under the leadership of Dr. Cláudia Carvalho, a research psychologist has just completed and submitted for publication an amazing similar experiment. One of her mentors for her doctorate was my colleague, Irving Kirsch. About two and a half years ago, she visited us in the US and said "*I want do your IBS experiment in Portugal.*" She showed us a protocol targeting chronic low back pain patients; it was really good and she asked Irving Kirsch and I to comment on in and we said her design was "*much better than the one we did!" And please tell us how we can help you?"* I don't think we helped her very much. Her study is under currently peer review. Because the study has not been published yet I can only present a summarize announcement that her results were very similar to ours. Claudia's clinical trial is the first approximate replication of our study (obviously in a different patient population) and was done in a different culture, with different patients, and in a different language. We all look forward to seeing it in print. Congratulations, Claudia.

In summary the three experiments (and the addition of Claudia's) makes three points: 1. Placebo effect can be dramatic in clinical practice and are especially augmented by the patient-provider interaction; 2. Expectation play a significant role and words matter in clinical practice; 3. Open-label placebo may have a role in clinical practice. More research is needed on this question.

Thank you for your attention. I also want to thank the organizers of meeting; thank you for all your help and consideration. It has been wonderful being in Portugal and meeting new colleagues and friends. And the food is delicious.

PLACEBO SCIENCE: MAGIC YOU CAN REALLY BELIEVE IN

Amir Raz [*]

Thank you very much Miguel. It is a pleasure to be here. I would like to thank also, first and foremost, Axel, my friend and colleague who actually told me about the Bial Foundation. I didn't know about the Bial Foundation before. So thank you Axel. I would like thank the Bial Foundation for flying me over here and also sponsoring my research. I would also like to thank you, Luís, friends and colleagues, to have Irving give the keynote address in this conference. It is very important to listen to him because he is saying things that, in my opinion, should be heard more researchers and by more people. And finally, I want to say that my interest in placebo science and many of the research projects that I pursue is due to some of the people who are here, Irving and others. Over the years they have spoken to me, fueled, and honed my interest in specific aspects of these phenomena.

As a disclaimer, I should say that when I started out, when I was a lot younger and thinner and smarter, and more handsome, I was a magician – a performing magician, a professional magician – and through magic I actually learned quite a bit about placebos, about how to fool audiences and how to create all kind of expectations in people, and how to use misdirection. And I did that as sort of a clinical and entertainer clinician, if you want to think about this in that way, and it was very interesting to me to ask my fellow magicians friends about how they do things and I often realized that they don't know how they do things, they sort of follow all kind of weird scripts.

As I got a little bit more sophisticated about things, I started doing things like neuroimaging and I got into doing this kind of placebo stuff. This is very powerful placebo stuff, because when people see neuroimaging they automatically assume that it is true or that what you see is particularly scientific or particularly powerful.

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Rainer can tell you more about that. He has made not just scientific contribution, but a career of helping people with this stuff, with all kind of computation and you know my colleague Tor and other people. We certain enjoy this kind of stuff, this is on the loop, the all lecture, especially if you know that it is my brain and you know people do all kind of research where they measure particularly structures, and in this particular case the hippocampus, we see how it changes in the function of this or that and you can ask questions such as "*Would highly hypnotizable people for example, people that respond to hypnosis, would they have bigger hippocampus or smaller?"* People that are good placebo responders and stuff like that and often we get bug down with the details and when we sudden think about these things through all kinds of very neuro lenses that we have a tool for, and we forget about one off the biggest questions.

And I would like to start with you today talking about some of the biggest questions and how we actually use some of the tools that we have to try to begin to orientate ourselves to some of the interesting questions that lurk about.

This is a Chinese elevator. How do I know that this picture is from a Chinese elevator? Because it is missing the number 4. The number 4 in China is, at least at some parts of China, where people is very traditional, usually not in the big cities, but out in the villages, the number 4 is sinister for all kind of reasons that we are not going to go into right now. You can see that the number 4 is missing from the elevator. The number 4 is so sinister in China that people don't want to have 4 in their phone number, or in their license plate. They won't wear a jersey that has number 4. Is not like number 13 in North America, is a lot worse. People will not travel on the 4th of the month. Sometimes people won't travel on the 14th of the month or the 24th because it also has the 4. That really limits your conference time and your ability to be productive, but people are very superstitious about this thing. I have 4 kids so I should be careful. But the interesting thing is that when people do studies with this kind of things, for example here a study of a guy called Phillips in San Diego and colleagues that was published in BMJ. I'm not going duel in this study too much. Just to show you that when he looked at people who died from heart attacks who were Chinese inherit or Japanese (this is also true in some parts of Japan), you can see that on the 4th of the

month there is a peak. Something happened to these people compared to people who don't believe in this kind of things. So there is something strange happening on the 4th of the month to people who believe that 4th is sinister and if you think, you start to think about whether, you think if this is good research or not this is not important. The question that it raised is "*What's going on here?* What is going on here is symbolism and we are human beings, we are very big on symbols, and on symbolism and sometimes we underappreciate how much of a symbol process machine we are.

This is the symbol [toilet paper] for you know what and this will be the symbol for a Swiss you know what, and if you take another symbol and you put it together you get something that is so weird. Some people would laugh, some people would say "*What's going on?*", but these are all symbols, there are symbols for certain things, and with symbols you can do many strong things.

One of the therapeutic techniques that has been around long enough – we even find variations thereof engraved in hieroglyphs – reminds us of hypnosis and all kinds of relaxation therapy and suggestibility interventions. And if you had 35 cents in 1954, of course you can learn everything you want to know about how to hypnotize pretty women and have sex with them, I guess. But the notion that I'm trying to put forward is that we are actually in the middle of a revolution without really noticing it. This revolution is not the neuroimaging revolution (that we know a little bit about, that has been a little bit disappointing by the way); it is not the genetics revolution (that we actually know quite a bit about – everyone can get their genome sequence at a fairly low cost today). It is the "top-down" versus "bottom-up" revolution that not enough people are stopping to think and think about properly.

Placebo is part of the top-down revolution in a big way. The bottom-up revolution is the revolution that is basically part of reductionism in science. Is the fact that when people go to medical school, when people study physiology, biology, it is all about molecular and cellular stuff and goes up to system and we understand how certain things happen, from the photons and so everything goes up until get to the cortex and we see all kind of interesting things and I have good theories how things start at very, very low level, and then they started to build up and we understand

how vision works, if we take vision as an example. We like this kind of theories because we can understand them pretty well.

Here we are talking about a set of phenomena that are largely top-down, in other words, they start with an idea, they start with a higher level of abstraction, they start with the notion that I'm experiencing something and then somehow, by some weird coincidence the physiology lines itself in such a way that these experiences seem real or real enough that they actually let people feel that this is what is happening. This is quite amazing! If you come to think about it and the resistance that we get is the resistance that is based on the reductionist model. This is not an empty reduction. The fact that we have talked top-down effects is not anti-reductionism but it is difficult to reconcile top-down effects with the bottom-up reductionist model. So I want you to think about that because many of the things that we talked about here are top-down effects. And top-down effects require a slight different approach and I think it is not just a slightly different approach experimentally, it is also a slightly different approach scientifically, about how to answer some of these questions, how to test them and what we should do in order to verify what we are measuring is real, is not an artifact and so on.

Hypnosis in that regards is very attractive. It is an advantageous tool, because it can combine a set of techniques or ideas that start with given suggestions to people and the kind of actions that comes as a result of these suggestions and often as a result of this kind of hypnotic interaction. Weird things happens when the person who is behaving is under the impression that these behaviors are happening to their own, they are not the authors of these behaviors. We are going to explore this in just a little bit.

The top-down, bottom-up, I once saw this in some kind of caricature competition and I liked that. The top-down, bottom-up debate that I often see when I speak to others scientists as to do with how down is top-down, in other words, we all understand what top is, something starts with you thinking about, you have a particular idea, you think something is happening, but how down is top-down? Does it go all the way down to the sensory organs? Are we for example, when we imagine that we see something, do we have actually activity happening in our retinas? Or it is just happening at the cortical level or it is happening at the thalamic level? How down is top-down? When we say how up is bottom-up that is

not a difficult question to answer. How up? All the way! Up to the cortex. We understand it. It start with the sensory organization, all the way up to the highest level of cortical processing, but how down is top-down? That is a slightly more difficult question to answer. It is a question that we can begin to answer when we do all kind of triangulation, all kind of brain tools that we have, physiological mechanism that we have in order to try to look at these questions more scientifically.

Just like we have problems defining placebos, we have problems defining many others phenomenon or phenomena that are related to top-down processes. Hypnosis is one of them. There are many good scholars around, they have given, including Irving and other people, who have set in committees and tried to come up with very good, concise definitions. For example, not just what placebo is or is not, but also what is hypnosis, for example. Hypnosis has been around just as placebo, probably longer and people come now with all kind of definitions. This is one: Hypnosis is a social interaction in which one person designated the subject, responds to suggestions offered by another person, designated the hypnotist, for *imaginative* experiences involving alterations in conscious perceptions and memory, and the voluntary control of action. In the classic instance, these experiences are accompanied by subjective conviction bordering on delusion, and feelings of involuntariness bordering on compulsion (Kihlstrom, 2012). This definition is not particularly good and the reason that it is not particularly good is not because John Kihlstrom is not very smart and creative scholar, is because it is not specific enough. And how can I demonstrate to you that this definition is not specific enough to hypnosis? Because I can take this, as my friend Erik Woody does, and change one word on it and you see that this definition works for courtship, not just for hypnosis, just by changing one word. So, if you can do this, if you can take a definition that you think defines a particular thing and then change one word and then it actually defines something that is completely different, but has a similar field, it means that your definition is to general, is not capturing the essence of what it is you are trying to capture in a real way.

So what I tried to do in my research? I tried to illuminate or elucidate particular processes that are relatively objective and when I say relatively objectively, in another words, there is this consensus, at least at

the scientific community, that what you see is what you get, what you measure is real, so I tried to go not so much to esoteric or subjective things, but things that have a certain scientific consensus that we think we understand, we have a good theory of the measure.

So for example, this is the think-drink effect. I don't know how many persons know about the think-drink effect but, it has been around since the lasted 1960 and documented in the psychological literature. These are situations where people drink non-alcoholic beverages that they think they are alcoholic, these are completely virgin drinks. You can create the context and create the expectation to people, that they think they are drinking alcohol. There are all kinds of ways to do that and as a result of thinking that these are alcohol beverages; these people show signs, or some people show sign, of intoxication after drinking some of these drinks. So they will have slow speech, they can't walk at a straight line, people will puke, some will have a hangover, some people are so drunk that when you actually tell them that this is a virgin drink they cannot understand you anymore. This makes the termination of the experiment very difficult. But these kind of phenomena, these kind of things have been around for a long time and they are well-documented. It was only around, I would say, 1990 that people have started to systematically attack some of these things with some kind of rigor that I considered to be interesting for the purpose of what I'm about to relate to you.

This is a study from 1998 in a pet scanner. A very quiet scanner, it makes no sound, but of course it has radioactivity associated with it, where people are lying on the scanner. These are highly hypnotizable people, people who respond very well to hypnosis, whatever that means, and these people got a baseline condition when nothing was happening, they were just lying on a quiet scanner, the scanner was quite old at the time, remember this is a pet scanner. In this condition they are just listening to a recording and when they listen to the recording they have some activation of these areas related to (this is a subtraction of some things that I'm not going to bother you about right now), and then they are asked to imagine that the voices they are listening to the recording. So it is a little if I asked you to imagine the taste of a banana or something and you are trying very hard to do that. This is the hallucination of when they are giving a hypnotic suggestion and on a hypnotic suggestion they

are told not to imagine, but they are told that the recording is actually playing, although the recording is not playing actually, but they think that it is playing because they were giving a suggestion that the recording is playing. And it turned out that these two conditions are very similar. So when you think under hypnotic suggestion that the recorder is playing, although is not playing, and when you are hearing the recording you get very similar activation as opposed to when you are trying to imagine that the recorder is there. So there is something different about imagining that something is happening when you are being told or you are under the impression that it is actually happening to you.

This is an important distinction that I want to point out to you, because a lot of people are confused a little bit about what the difference if I take placebo, if somebody gives me a placebo, if I treat myself, or somebody treats me. There is big difference between telling you that there is a helium balloon connected to your arm and your arm goes up versus if you do the same, the exact same movement yourself. When you do the exact same movement yourself you are the author of this movement and you know it. And where you are under the impression that a helium balloon is lifting something up your arm, you are not the author of this movement, and the helium balloon is doing it, of course you are the author of this movement. I can show you a video that there isn't no helium balloon connected and you are doing, but there is some kind of a game, there is some kind of a context in which you are under the impression that this is happening to you as opposed to you are doing this to yourself. This is an important thing to remember as we are beginning to get deeper and deeper into this.

Other studies, including studies that have to do with this, is an fMRI study, but it really doesn't matter because I'm going to show you all bunch of studies related to this.

You can take people and suggest them that they are experiencing a particular kind of pain; you can give them the pain that you are suggesting and you can see the activation are pretty similar and you can ask to imagine that they are experiencing this pain. And again, of course, I selected these examples very carefully so I can impress you. If you look at the literature it is not so beautiful. This is like a vanilla kind of demonstration of these things, but the point I'm trying to put forward is that, sometimes and

in some contexts, when you are very carefully you can actually create, with hypnosis activation, experiences that feel so real that is difficult for us to tell that they are not real, that they are not actually happening in the world. They have all the signs, all the smells, all the textures, all the real kind of measures or flags, or whenever you want, that they are really happening, even based on objective measurement or what we consider to be objective measurement.

Now in cognitive science, or when people are trying to understand these things, they usually divide the world in two kind of processes: automatic and controlled. The controlled processes is just like I told you before about the hand going up, and we have control over it, it is a little bit slower, it is more resource intense, we have to invest, think about it, all these things have to do with deliberate actions and so on; the other set of automatic behaviors is something that happens fast, ballistic, involuntarily, it happens in a way that is resource light, because we don't have to pay attention, it is effortless, it happens as his own. This is an important distinction because when we do certain tasks, such as on the stroop task, we ask people to name the ink color of these words and it is very easier to say blue because the word is blue and the ink is blue. It is a little bit more difficult to say green when you see a word like knife because it is relatively neutral the word, of course you can have a green knife, but you can also have a black knife, knife are usually in sliver color, so that is fine. And of course you can have green written in red and then the correct response will be red if I'm asking you to name the ink color, but most people would read green, and then would say red. So these are the kind of things that we have, some kind of a theory about how they work and we think about, that we understand it pretty well and part of the reason we think we understand a little bit about this is because we have more than nearly 5 thousand papers written on the stroop effect. When you have more than 5 thousand papers written in a particular topic, you think that you understand it a little bit and when you do this kind of tests in people and you ask "*What is the ink color?"* Most people can do it pretty quickly and pretty well and it is quite astonishing that you can take this particular study. You can take people and give them a suggestion, a hypnotic suggestion, that what they see, even though they are proficient, let's say English speakers or Portuguese (that doesn't really matter), you

tell them that what they are seeing is actually a foreign language, that they don't understand, let's say Chinese or Greek, a different alphabet, a completely different thing and they just have to respond to the ink color and then all the interference of the Stroop effect disappears and if that happens, and it does happen, if that happens there is a question know - if it disappears or if it reduces - but these are details, because the question is "*What is happening? How can you tell someone that they can read, without telling them that they can't read, just telling them that this is a foreign language that you don't understand? What is happening in their brain? Is this a top-down effect?* Well it seems to be a top-down effect, because it starts with the fact that you say to yourself this is a foreign language that you don't understand and then something happens in the way that you process the information, in a way that you would process it as if you don't understand it, but you are a proficient reader of that language.

These were stroop effects in English, that were done in English speakers individuals and this kind of research or this kind of research question raises all kind of very deep critical questions about placebo as I will show you in just a second.

First of all, we have a replication crisis in psychology, we need to replicate these things, and this replicated pretty well all over the years and with all kind of studies, including with a study that I did with Irving, because you know I was also skeptical of my own findings initially, when I started out. But then I asked myself more difficult questions and I said "*If I can do with the Stroop, can I do it with other things? Can I find something that is even more ballistic, more automatic, more, I would say, involuntary, than the stroop*?" Because for the stroop you have to read and some people cannot read and some people are very slow readers. *Can you do something that would take an automatic process and turned it on a controlled process?* Which is sort of what I'm trying to understand when I try to understand placebo effects. *Can I understand how you lose control over something or gain control over something, when something is happening to you*?

Well, in order to do that I had to come up with another paradigm and I'm going to show you just in the few minutes that we have together. I'm going to show you just some paradigms that I used in order to illuminate

some of these questions, and I'm going to show you what are the brain or the neural correlates that likely participated in some of these networks and what we can summarize of this kind of findings.

So here I want to show you something that is called the McGurk effect. The McGurk effect again is one of those effects that has been documented very sorely in psychology, any cognitive psychologist knows about it and I can demonstrate it to you very, very quickly. If you look at this particular demo, you listen to it, listen to the sound that this person his making, look at him. So what is he saying? Da, Da, Da…Ok. Whatever he is saying, he is not saying it. How can I show it to you? Listen to him again but now close your eyes! Ok close your eyes, don't look at the image and just listen to the sound. Here it goes. Could you hear it? It is a very clear Ba Ba, Ba Ba, Ba Ba. But what I did? I took a person and doctored the sound and the video to be incongruent so what happens now is that your visual system overrides your auditory system. Now if I do imaging of this kind of things, these people actually hear a different sound, they actually do hear a different sound, they don't hear Ba, they hear Da or whatever. They hear a different sound, because the visual system actually informs the auditory cortex about what they should be earing. So I asked a question here and the question was "*Can I tell people with suggestion, let's say, that their earing is stronger than their vision, that they are supper auditory processers and that their earing is more important and will they will be able to override the McGurk?"* In the literature this is unheard of because the definition of the McGurk is that it is as ballistic as possible, people who know about the McGurk, who do McGurk experiments cannot override the McGurk. That is the all point of automatic processes, it is so involuntary that even if you know about it, you can do anything about it. So you do a study and you prepare all this stimuli very carefully and you select your people very carefully to be highs and lows and when you do this you find (and here I can only show you some data that we have already published), you see, without statics, that in high hypnotizable people, there are special people who are very susceptible, very responsive to hypnotic suggestion, these people can actually do away with this kind of illusory McGurk weird sounds and they can actually ear what they are saying while they are looking at the sounds. By the way, all these people are McGurk naïve. So it seems like there is something special about this group of people, this group

of highly hypnotizable people or this people who are highly suggestible and they are somehow capable of overriding some processes that we think are complete ballistic, complete automatically, so they are able to exercise some kind of control. But when you speak to them, when you ask them "*How did you do it? What did you do?*" Sometimes they are even downfallen by the question. "*What do you mean? What did I do!?*" They aren't even sure that they did anything of value, because they don't understand exactly what it is the deal. This is very peculiar.

I started an all line of research trying to find tasks that are extremely difficult, that would require a regular person, let's say visual aid, you will need a visual aid in order to solve a problem and I wanted to see whether I could introduce this visual aid hypnotically in order to help highly hypnotizable people to solve a problem. Here is the task that I came up with in this particular case (this is one of many), where I showed them a moving image of this sort and I tell them "*On which direction are these lines going*? *Can you tell me?*". First of all I'm showing that these two lines are going together and these two lines are going together. "*Can you see here some kind of a movement of these lines?"* When I put occluders on the corners, you can see that it is actually going in this direction. And you can see that when a take of the occluders away it all falls apart. It is very difficult to see. But when I put the occluders it is very easy to see the direction of this geometric shape is going. So one of the, this is a very well-known task from the visual science literature and what I asked myself was "*Can I take people and show them the image, look what is happening in their brain and maybe as I asked them what direction is going, maybe I can suggest them hypnotically that these occludes are there*". So for example, if I show you this image, because I can do it with all kind of geometric shapes, I can tell them that these occluders are there or they are not going to be there and my question is, whether they are going to be able to see the motion, you know the transpirers very easily. If this happens, this is very dramatic, this is a very important kind of finding because people cannot regularly do this. So this is the paradigm. You show the moving image, you tell them with hypnotic suggestion that you are imposing these kind of things and you basically compare this kind of groups, you do all kinds of controls to make sure what you are measuring is true and again it's very easy to see, even without any statistics, that there is a big difference and

there is no difference in people who are low. *So how are they doing this? How is it possible that they impose mentally these occluders and actually do a task computationally?* It is very difficult to do it without occluders. But they can somehow impose these occluders as if they are there and then it becomes effortless to see the motion. Do you see the point of this task? So by doing this kind of things I started thinking how this trajectory, this trajectory of hypnosis research and tried to think about these questions, how do actually dovetails nicely with some placebo effects?

I hosted at McGill an International Placebo small Conference with a funding that I had from SSHRC which stands for, the Social Sciences and Humanities Research Council of Canada, and they also helped me to sponsor the publishing of this book, of Oxford University Press - Placebo talks, that has just came out and talks about all kind of placebo effects outside of medicine. So, for example, Placebos in diets. You know everybody know, Jessica was just next to me, gluten free diets, you know, people are going in all kind of diets. What is the really component of these things, what are the placebo components of these things? So we got a lot bunch of experts to comment on these things, very interesting ideas there and then through some of my students, I started getting more and more interested over the years in the field of meditation and hypnosis and how they certain come together from a self-regulation stand point.

I have a few students who are very advanced meditators in the sense they have been meditating for many, many years and they are connected with the mindful organization of the United States that is sort of promoting mindfulness research. And we came out with this book that it is coming out at the end of this month, Oxford University Press again, that talks about the neural correlates, or what we know about the science of hypnosis and the science of meditation, where they overlap and where they diverge, points of similarity, historical, current and some even future prospects about how can these be done for a scientific stand point. I think that you know, you would enjoy it.

And this is also a time to comment about the mindfulness revolution. I think most of you will realize if you read papers and look at journals, that today mindfulness is all the rage, but most people are "speciously sophisticated" about mindfulness, what it means and what it does. So what we are very clear on is that mindfulness is a very large business – a big industry. Forbes magazine puts it over the billion dollar mark annually.

One thing that people don't appreciate so much is when we do imaging for example, most the imaging we do is done supine, whereas most of the meditation is done upright and we actually demonstrated that when you imaging people, and this is an image scanner in this particular case, but most people who are imaged sitting up had a very different baseline responses that people who are lying done. This is very important, because if you are looking at baseline differences between people as I show you latter. For example, I have reasons to think that highly hypnotizable people have responded baseline very different from people who are not highly hypnotizable. This is probably also true for people who are good placebo responders, there is more pf leap that we have to make over there. It is very interesting to sort of explore some of the differences that have to do with body postures and things of that nature, which really introduce all kinds of interesting parameters. This is a kind of discussion that I'm having with my neuroimaging friends.

But when you look at people who are expert meditators, very similar to highly hypnotizable people, sometimes we call them hypnotically virtuosos, they are so good at hypnosis that they can get into this sort of weird conscious plains very quickly and with very little, if any, induction, they can do it on their own. And these guys, after many, many years of meditation, sometimes in a cave in Tibet, as part of being a monk, when you measure them, when you do all kinds of imaging studies on them, you find results that are actually very reminiscent of the kind of things we see when we look at people that are highly hypnotizable. Again this gives you a taste of what's happening in the book of Meditation and Hypnosis. And the idea is that you can actually take a medically approach of these things. For example, in neuroimaging we have certain tools like ALE, a particular statistical approach to look at multiple studies that I'm not going to bother you with the actual technicalities, but you can actually look and measure things like the default-mode network, something like a resting, what are people doing when they are not meditating, what are people doing when they are not under hypnosis and you can actually measure these things in time.

By the way, one of the earliest studies that influenced me to think about these things, even before the all resting states things started, was a paper that I read of George Bush, not George Bush the former president

of the United States, but the Bush scientist of Harvard Medical School at the time, I think he is still there, who actually shows that if you take kids with ADHD and you let them do a particular task, they can perform the same way, but their brain activation is completely different and when you look their brain activation you can see that the ADHD kids, for example, use a lot more of their insula and so on whereas the healthy kids don't. So in terms of their behavior it's the same, so I wanted to see whether I can actually, if I look at all kind of hypnosis studies, and I just look at the peaks of what are common themes that emerge as some kind, as part of some a meta-analysis, I was able to - oh well this was a work that I did with Matthew Henry from my lab - we were able to demonstrate that there is a particular kind of visual imagery that is always present in these things and there is some kind of pre-frontal activation that again we associated a lot with a particular area of the brain called antero-cingular-cortex and sometimes areas around it, that have to do with particular kind of monitoring or particular kind of thinking about the task.

We are going to skip some of these things just because we don't have time, I'm keeping the eye on the clock. We also have deactivations, we also have certain areas in the brain that are going below their baseline and this is probably related to things like suspended of disbelief or letting yourself go in a particular way and you know, in hypnosis, one of the things about hypnosis is, if I try to explain it to somebody that doesn't know too much about hypnosis or what they know about hypnosis comes mostly from Woody Allen movies, that in hypnosis you have to certain let you go under control, in a controlled fashion, you lose control, which is sort of a weird concept, if you think about it, because most of us are not necessarily a control freaks, but we like to be in control and then to lose control under control is some kind of a counter-intuitive concept. This kind of a cognitive analysis that I don't have time to go into, so I'm just going to skip it real fast for time.

One more study and I'm going to conclude just because I have the clock in front of me. It is very important to understand that you can actually teach people, without teaching them formally, how to lose control or how to empower them. This is an idea that I got from Irving Kirsch, who else. So Irving did a study, shortly after I was born, where he took people and he made them think that they are special by telling them all

kinds of things. He said, "*If you see a red light, when this and this happens, it means that you are super-special*". And I really like that paradigm, so I created this room, it is a real weird room, where you have a concealed red light, that you can't see, and you have concealed speakers in the ceiling and people come and we play. This is like the magic room. So people come here and we basically tell them "*If you are highly hypnotizable, if you are really prone to hypnosis you will notice that this room turns pink at some point. If you just seat here and relax, the room will turn pink and if you see it pink that means you are really hypnotizable. And if you can see, if you can hear some television statics in the back".* Sure enough this television statics plays through the speakers and the red light comes from this particular lamp that they can't seem. Can you hear the television statics? So this is the experiment they get when they sit on the room, but it happen very gradually over time and suddenly they say to themselves "*Holly smokes, this is a pink room and I can hear the statics!*" So they come out and then I say "*Did you see the pink room?*", "*Yes, I did it!*", "*Did you hear the statics?*", "*Yes, I did it*". I say "*Wow, we have to do some experiments because it means, you know, that you are…*" And I wanted to see how far I can push these people. Are they going to perform like really highly hypnotizable people? Because they think they are, they are under the impression that they are, for a short period of time, so can I get them to this kind of things? And the answer is "No!" There is something about them, even if they think, they can improve a little bit, they can do all kind of interesting things but there are very far away from their highly hypnotizable brothers and sisters.

And I want to tell now something in conclusion about how to put it together because I didn't wanted to say anything that would compromise Damien lecture or something that would double tell nesting.

This is stuff that you can get on the internet. Ok if you have twenty bucks, I can get you a product like this, which you can spray under the bed, and it would keep the monsters away. I cannot tell, you know, about the secret ingredients inside, but it works. A lot of people when they see this, they say "*What kind of garbage! This would work for my 5 years old kid. It is never going to work for me*". I have news for you. For a little bit more than twenty bucks, I would give you in my lab, something that cost a little bit more, it is called neurofeedback. Neurofeedback is very popular in North America and it is beginning to be very popular in Europe as

well, very expensive. Here we are showing with MEG. You are not going to find with MEG at most clinics, because it is way too expensive. You will find with EEG and you will find sometimes with other imaging modalities. All the research that we have done in my lab suggest that this is a huge placebo effects, and then the question is: *Now that I'm sort of getting to the point where I'm pretty confident that it is largely a placebo effect, what do I do? Do I say – ah this doesn't work*? Now is the time when I have to take an Irving Kirsch position on this. What will you do? It works. It really does work but it doesn't work through the brain mechanism that we think, or that we advertise. It works to a very strong placebo effect. Placebo effect is the function of the cost and how big the upside down toilet is, you know, you put on the top of your head and it is the function of many other things that are going on, so the question is "*What do you do?*" The same conundrum sort of applies to homeopathic. We know that from a bottom-up perspective it goes against the fabric of science, we know that it doesn't suit well with chemistry and physics, we know about Avogadro's numbers, we know all these things, but from a top-down perspective it may work very well. Because from a top-down perspective it has a complete different mechanism that it works by. Sometimes things work not necessarily because of the mechanisms that we are identifying as the correct mechanism of action. In neurofeedback, for example, we know that it is very effective for certain things, but it is not necessarily for the reasons that are being pushed forward, the reasons that are the mechanisms that are making it work. So these are things to think about.

I see myself as an ethical person, but I certainly don't see myself as an ethicist. As a matter of fact, I don't know who an ethicist is, because it is slightly a weird title to have in my opinion. But it is important to understand that our job as scientists, in my opinion, is too largely under promise and over deliver to the extent that we can. We have to put a lot of data out there, we have to investigate, we have to do all these things, but we have to under promise and over deliver. Sometimes, I sense particularly with these kind of things that there is a lot of overpromising and under delivering and that is very dangerous. When things like that happen this is when things you know get a little bit dangerous. I'm very excited about this revolution of top-down science and I think that to the extent that I can and to the extent possible I'm thrilled to be a part of it.

Thank you very much.

PLACEBO ANALGESIA - OPPORTUNITIES AND CHALLENGES IN CLINICAL PRACTICE

Damien Finniss *

The term placebo has been used in the medical literature for over two hundred years, although it has only been in the last fifty years that there has been growing interest in the effect seen after placebo administration (Beecher 1955). The study of placebo effects is directly relevant to the field of pain management, providing further understanding of the mind-brain interaction in the modulation of pain and is a core element of routine clinical management (Finniss, Kaptchuk et al. 2010).

Concepts and Definitions

Placebo effects are psychobiological effects that are attributable to the psychosocial context (or treatment ritual) surrounding the patient. Importantly, these genuine effects must be distinguished from other causes of improvement following administration of a placebo, such as spontaneous remission, regression to the mean and the natural history of acute pain (Price, Finniss et al. 2008). Defining placebo and placebo effects has been difficult, primarily due to the traditional definition which uses the word "inert", therefore theoretically rendering it as being unable to have any power to elicit an effect (Moerman and Jonas 2002). Modern re-conceptualisations of placebo effects have emphasised several key points which are very relevant to modern pain management practice (Miller and Kaptchuk 2008, Finniss, Kaptchuk et al. 2010)

The key aspect of placebo administration is the act of simulating a treatment context or ritual, regardless of the content of the placebo.

It is the simulation of a specific treatment context that generates placebo effects, and by replacing a "real" treatment (such as an analgesic medication) with a placebo, one studies the effect of the treatment context on the patients mind, brain and body.

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Routine clinical care occurs in a rich therapeutic context, and on this basis, placebo effects exist in everyday practice even though no placebo is given. The overall outcome of a treatment is related to both the treatment itself and the context in which it is given (the component attributable to placebo effects).

The notion that placebo effects (and therefore mechanisms) may be a component of routine pain management practice is an important one (Finniss and Benedetti 2009). If one can study how psychosocial factors around the patient alter nociception and the experience of pain (by running experiments in which placebos are given), this has direct implications for clinical care (even though no placebo is given, placebo effects are present).

A practical clinical framework

Placebo mechanisms (or determinants) have traditionally been studied under biological and psychological categories. Although some interest in placebo effects, particularly their magnitude, has come through assessment of responses to placebo administration in the placebo arms of clinical trials, the focused research on placebo mechanisms has largely come from experimental conditions or short-term clinical interventions (Finniss, Kaptchuk et al. 2010). To this extent, there is still much work needed in understanding the application of what is known about placebo mechanisms to routine clinical practice, with several relatively new studies attempting to answer some of these questions (Kaptchuk, Kelley et al. 2008, Kaptchuk, Friedlander et al. 2010). The focus of this presentation was to take a pragmatic look at the clinical environment and to provide a framework to better understand the application of placebo effects to health care, specifically placebo analgesia. The clinical framework can be divided into pre-treatment, treatment and post-treatment and this may represent one way to practically incorporate elements of placebo research into practice. Within this framework, key psychological determinants are discussed.

Expectancy has been one of the most studied psychological mechanisms, and relates to patients expectations of future response. Expectancy has been associated with placebo effects in studies where the verbal cue ranges from a simple instruction "this is a powerful painkiller" (Price, Milling et al. 1999)

to the use of conditioning protocols to maximise expectancy (Voudouris, Peck et al. 1989, Voudouris, Peck et al. 1990). Furthermore, a "graded" effect can be seen in studies with variable levels of expectancy (such as the classic "double blind" instruction which carries a 50% uncertainty), to more certain information about treatment expectations "the drug I will give you is a powerful painkiller" (Pollo, Amanzio et al. 2001, Vase, Robinson et al. 2003, Verne, Robinson et al. 2003). One of the key issues with this construct (in practice) is that is highly likely to be dynamic, with some data supporting this notion (Vase, Robinson et al. 2005). To this extent, one needs to better understand how patients expectancies are shaped from the initial onset of symptoms and process of seeking a health care provider (the pre-treatment phase) to how these expectancies are modulated over the time course of a clinical intervention and to what effect this has on the maintenance of placebo effects (treatment phase and post treatment phase). One elegant study conducted some years ago demonstrated that a targeted pre-treatment (surgery) visit by an Anaesthetist which involved normalising expectations about post-operative pain (with reinforcement of management strategies) resulted in significant reduction in opioid requirements in the post-operative phase (Egbert, Battit et al. 1964). The role of pre-treatment manipulations in expectancies (and meaning of symptoms) have been supported in the experimental setting more recently (Benedetti, Thoen et al. 2013). The dynamic nature of expectancies and ability to harness these before, during and after treatment remains an important area of applied research.

Classical conditioning is a learning phenomenon whereby repeated associations between a neutral stimulus and an active treatment (unconditioned stimulus) can result in the ability of the neutral stimulus itself being able to elicit an effect similar to that of the unconditioned stimulus (Finniss, Kaptchuk et al. 2010) Typically, an opioid analgesic is given on repeated occasions and then replaced with the treatment simulation (a placebo). This phenomena has been demonstrated in animals (Pacheco-Lopez, Engler et al. 2006) and in humans (Voudouris, Peck et al. 1989, Voudouris, Peck et al. 1990, Benedetti, Amanzio et al. 2011). In addition to classical conditioning, there is growing evidence that social or observation learning may also be a determinant of placebo effects (Colloca and Benedetti 2006). For example, placebo effects were larger in subjects

who had higher empathy after witnessing another volunteer in pain (Colloca and Benedetti 2009). This suggests that consideration can be given to social context in which treatments are given, for example individual or group treatments in the setting of pain management. There is some data supporting the use of conditioning principles in the graded reduction of opioid medicine for chronic pain management, although there is no data in the "post-treatment" phase relating to maintenance of the conditioning processes and clinical response (Ralphs, Williams et al. 1994).

The doctor-patient relationship has been studied from many different perspectives and this is not unique to the field of placebo. There have been very elegant studies which have investigated elements of this relationship in placebo administration (Kaptchuk, Kelley et al. 2008). Similarly, one older but relevant study investigated the pre-treatment interaction between Anaesthetist and patient, whereby a targeted pre-surgical interaction resulted in greater "preparedness" for surgery (Egbert, Battit et al. 1963). Prospective research in the field of pain has identified that trust, empathy and explanation of symptoms are important elements of the therapeutic encounter and were associated with better longer term outcomes (Farin, Gramm et al. 2013). This has been supported by a recent systematic review (Pincus, Holt et al. 2013). The large field of research that encompasses the doctor-patient relationship is not the focus of this presentation; nevertheless, the field of placebo effects permits further systematic examination of some of the factors involved in the treatment ritual (of which the doctor-patient relationship is a key aspect) and represents an important direction in both research and clinical practice.

Conclusions

Placebo effects are inherent in routine health care, as is demonstrated when a treatment is replaced with a treatment simulation (a placebo). One of the current challenges in the field is to extend the results of well-designed experiments in healthy volunteers and studies in clinical pain to progress our understanding of the application of this research to routine clinical practice. A framework was proposed which may provide some direction for future research and a practical way to apply this research at the bedside.

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CROSS-CULTURAL ASPECTS OF HEALTH AND DISEASE

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In recent decades, Ethnomedicine, which deals with health procedures in a temporal-spatial vision, offering preventive and therapeutic strategies of different cultures in the world, is again considered an important issue in health research. From an initial historical and ethnographic interest of this discipline, it has turned in recent years into research laboratory involving biomedicine in particular pharmacology, thanks to the the World Health Organization initiatives.

In fact, the WHO Traditional Medicine Programme is a response to the needs of renewed interest in popular therapies and the identification and eventual use within National Health Services. The Declaration of Alma Ata, in the international conference on primary health care in 1978, builds the historical foundations for the official policy of the Traditional Medicine Programme (WHO,1978) thus opening the door to a dialogue between several different health systems, traditional ones and modern ones, however, putting the condition that the support given to traditional medicines and to professionals who practice and use traditional remedies, should be developed through a process which will promote those practices that are safe and effective, on the basis of adequate medical and scientific experimentation.

The Traditional Medicine Programme has developed through a series of resolutions adopted by the World Health Organization and by WHO regional committees. In 1987, the 40th World Assembly urged Member States to promote integrated programs on the preparation, cultivation and plant conservation medicines. The 41st Meeting (declaration of Chiang Mai) concerned about "Saving lives by saving plants ", recognizing the traditional medicines as an essential element of care. During the 42nd Assembly it was encouraged inventory of traditional practices in different countries.

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In 1991 (44th meeting) a resolution aimed at encouraging cooperation between those who practice traditional medicine and modern health care providers was adopted, with special regarding use of scientifically proven remedies, safe and effective, in order to reduce the national pharmaceutical costs. Future stated goal is to achieve the synthesis between modern medicine and traditional one, opening a path where the two health strategies cohabit, enriching a contact of the other.

Scholars from different cultural backgrounds are increasingly turning to a new form of Ethnomedicine linked just to the laboratory: if on one hand allow more depth knowledge of the therapies, on the other hand is likely to lose observer contact with the involved therapeutic act.

In fact, much of the traditional medicine, even in its events apparently the most basic, is the result of intuitive processes and proceed in the knowledge of the phenomena due to numerous empiric evidences.

If in the era of economic globalization and the amazing successes of biomedicine, when Ethnomedicine may look interesting only from a historical point of view, it may be useful to recall some facts: 70% of the inhabitants the planet take care of his health thanks to traditional medicine (Farnsworth, 1989). In China more than 5100 plant and animal species are exploited by only traditional medicine.

In Russia, around 2500 species of plants have been used for medical purposes and the need for medicinal plants in the world has tripled over the last decade. With reference to modern medicines, a quarter of prescriptions issued in the United States of America contains active principles from plant extracts, compounds extracted from plants, microorganisms and animals have served the development of the twenty top-selling drugs in the US corresponding, in 1988, the value in the global market is of $ 6 billion.

In a pharmaceutical laboratory more than 60% of the drugs originate, directly or indirectly, from plants. Indeed we have not to forget that molecules serve as a model to elaborate chemical molecules: like artemisinin contained in artemisia annua as antimalarial.

About half of the inhabitants of our planet does not use Biomedicine and uses only traditional medicine. Even in “developed countries” the use of such practices is common: it seems astonishing the affirmation of Kleinmann (1980; 1995) according to which between 70% and 90% of

episodes of disease that afflict American citizens are treated, in the first instance, within the popular remedies.

If we think that in Italy at least 30% of the citizens recurs to self responsible for light and noise are increasing, as throughout Europe, the products "over the counter" (OTC), the system needs a necessary and urgent a reformulation (and theory) of the "cure".

These few data should be sufficient to understand how medical pluralism, the remedies of traditional medicines and, in general, the cultural attitude to the disease and treatment are not at all academic matters or folkloric relevance, but that they are directly wellness and health promotion of the world's population in the near future. Ethnopharmacology, ethnobotany, ethnozoology, and ethnopsychiatry, constitute research arguments whose contents are taught how to discipline autonomous in US university or college courses or seminars within parauniversitari Europeans. The ethnopharmacology would like to help developing countries to increase their wealth (Fleurentin, 1993). For these populations the cultivation of medicinal plants is not some a negligible economic potential. But there is the risk of a neocolonialism and an insane exploitation of biodiversity.

This is unfortunately a sad reality. Attempts of legislative solutions, however, are in place: in Western Samoa, thanks to Prof. P. Cox (1994), it was implemented an initiative aimed to support economically the country "owner" of the plant and not the packaged medication.

The *"homo medicinae"*

With regard to future prospects, V. Giacomini (1977) expressed "The plants are therefore no longer only objects of culture, but have penetrated and penetrate more and more deeply the culture of human populations. This interest, as repeatedly reaffirmed constitutes the most fundamental dignity the ethnobotanical research as any other science to pool nature and humanity. "As the sub-discipline of medicine, the ethnomedicine appears in the thirties as *Demoiatrica* and *Etnoiatria*. However, the exchange and the relationship between the ethno-medicine and Modern Medicine began already in the late nineteenth century with the early research in tropical disease. The early work that, in retrospect, can be

considered Ethnomedical interest are those of Scarpa and anthropologists who in describing the traditional cultures, the subject of their studies, they devoted some attention to systems of care: Rivers (1924), Clements (1932), Evans -Pritchard (1937), Ackerknecht (1943, 1946), Douglas (1966) and Turner (1967). The next roots of ethnomedicine are instead in the convergence, at the end of World War II, of different perspectives of intervention and research that create medical anthropology, new doctrine that emphasizes the study of Western medical systems.

Around the fifties, in fact, many anthropologists were involved in the political ambit in international health issues (Caudill, 1953). The initial work of these anthropologists was made possible, and was facilitated by the contemporary researches of cultural and ethnological school personality, from a solid foundation of physical anthropology, and by the convergence of a broad international movement for public health (Johnson & Sargent, 1990; Diasio, 1999).

In addition to these roots, it should be mentioned that at least three other theoretical areas have influenced the current development: ecological anthropology, emphasizing that the continuous interaction between environment and Culture has developed a new conceptual framework.

Medical anthropology provided the necessary temporal and evolutionary background -and that is historical; finally studies on mental health and behavioral disorders specific to particular cultures, that led to the formulation of the concept discussed of "culturebound syndrome" (McElroy and Townsend, 1989). Over the past three decades these disciplines have gained increasing importance, thanks to the wishes and resolutions the World Health Organization (Guerci, 1997; 1998; 1999), as was already previously stressed. The work of Worseley (1982), Young (1982) and Landy (1983) are excellent introductions to the history and medical anthropology studies for a wide overview of the state of the art, see also Guerci and Lupu (1997).

The theoretical approaches

To account for the complexity of the interaction between human society and the disease, the ethno-medicine and medical anthropology

have developed several conceptual frameworks; one may distinguish three major theoretical approaches: the medical-ecological theory, the cultural theory, and critical medical anthropology (Guerci and Board, 2003).

Medical and ecological theory

Fully formulated by Alland in 1970, the medical-ecological theory rests on the concept of biologic and cultural adaptation, individual and group environment. Health is evaluated as a measure of a effectively made environmental adaptation, and can be studied through ecological models. According to the layout proposed by McElroy and Townsend (1989), the ecosystem in which they move human populations is composed of elements biotic (such as predatory, available foods, carriers of disease, etc.), by abiotic factors (such as climate, the energy available, the materials, etc.) and from cultural elements (such as social organization, ideology, technology, etc.). The dynamic equilibrium or disequilibrium of the elements of the ecosystem is measured, precisely, in terms of health and disease, where the Health testifies the integration of the elements, while the disease is caused, although not in terms deterministic or reductionist, from components of imbalance (Armelagos, 1978).

Cultural Theory

The cultural theory was born in response to the flattening of culture over nature implicitly signed by the medico-ecological theory, the disease that leads only to the state of imbalance of the population with the environment. Kleinmann (1980, 1995) has proposed to interpret the illness, not as an objective entity within the physical world, but as an explanatory model which, through precise cultural and social interactions, brings together symptoms and gives them a collective name. In this conceptual framework, the disease is knowable, both the patient and the doctor, only through a series of interpretative actions which require particular mode of interaction between biology, social practices and cultural systems of meaning. In this perspective fits the conceptual separation, operated by medical anthropology between “disease”, “illness” and “sickness”.

If on one hand, the ethnomedicine has developed valuable analysis of linkages between the treatment strategies to the broader cultural context of the people that practice, on the other hand, through the use of related sciences such as ethnobotany, the ethnozoology and ethnopharmacology, allowed to highlight how many "remedies", as well as a symbolic value, also effective pharmaco-chemical and medical.

Odd beliefs and unusual therapies

There are many therapeutic practices (or prophylactic) implemented by traditional populations that, after careful analysis free from prejudices, even attract our attention today. Any we only remember some, the result of careful observations by Antonio Scarpa.

Water Therapy

In the course of a scientific mission promoted by Scarpa in Bali in 1939, Dr. Scarpacould saw that the water of a particular source of the island, was recommended by local therapists to heal those in the West would be generally defined as psychopathology. An analysis of the water subsequently conducted in Italy revealed the presence, in high quantity of lithium. Futile attempts were made to to stimulate the interest the scientific community towards this particular item. Over three decades were needed to prove the usefulness of the lithium salts in some of psychiatric pathologies.

Many are the observations and Scarpa's original research that have attracted the attention of researchers and laboratories in several countries of the world. We recall, among the many: the processes of immunization against bites of venomous snakes; the use of Ricinus communis in many therapeutic practices world; weaning addicts (in Burma) through traditional local medicine; condoms proceedings against dystocia birth and appendages; the lactatio mascula; equivalents in Chinese acupuncture medicine and historical European folk; the use of plant Kwao-kua in Asia; the "operations" of the surgeons-healers Philippines; the plants used as anthelmintics in the indigenous medicine of some populations Africa; some ignored behavior of cerulean congenital blemish; the etiology of

hystero-coreomanie (Madagascar); the importance of the dream in Traditional medicine of the current Maya.

To conclude this list is certainly not exhaustive, we recall some of the theoretical considerations such as the importance social medicine on the physio-pathological behavior of Ethni, the contribution of the study of animal behavior to the knowledge of new drugs by man, and his deep interest towards the instinctive search for the drug. A key element is, however, known by anthropologists: at the traditional populations ingestion of a "Drug" is always accompanied by a complex and encoded therapeutic ritual. This aims to build an act of faith and confidence in the substance taken: the certainty that what is ingested is definitely good. If, to this phenomenon, we associate the role of the supernatural that the therapist has in these cultures as depositary of knowledge, traditions, catalyst with the world of the ancestors and spirits, responsible the harmony of the group, owner of land, cattle and sheep, we can certainly think the intervention of important psycho-somatic factors and, if necessary, the placebo effect in the eventual healing process.

The Museum of Ethno-medicine at the University of Genoa

The Museum of Ethno-medicine "A. Scarpa" at the University of Genoa is currently hosted in the Area of Anthropology at the Department of Anthropological Sciences. Opened with the first 9 windows in October 1972 and terminated in May 1996, it became the only museum of its kind.

It summarizes the travel and over 55 years of research activities the medical doctor Antonio Scarpa, interested to learn how to treat people in the the five continents following their own traditional medicines. The objects of the exhibition are often complemented by extensive captions, bibliographic references, the all in an attempt to build an educational exhibition. The visitor can receive use useful ideas to get an idea of what the ethnomedicine, the subject expert will find many tracks and suggestions to address and develop new research topics. Objects, tools, drugs, photographs (with references to the circumstances of time and place) are currently documenting, from the point of Western biomedical observation, health strategies or individual practices prophylactic and curative, taken from several different ethnic groups. The result is a precious

testimony of an endangered medical knowledge, a universe itinerary in the humanity's health.

The UNESCO Chair "Health Anthropology, Biosphere and care systems"

The UNESCO Chair project stems from a cultural need and a heritage asset. The cultural need takes into account of contemporary trends in scientific research, aiming towards a recognition of a link between the concepts of health, environment and nursing. This approach overcomes the traditional separation between fields of knowledge - science, culture, nature - towards a new and integrated system. The concept of health and treatment methods do not have universal value: universal is the scientific quality of the survey.

The Chair shall develop a way of acquiring knowledge which starts from different origins, traditions, disciplines and cultures and learn to standardize scientifically etnomediche and indigenous notions not yet decoded. The Chair has a base of investigation the hypothesis that knowledge is unitary, but with multiple origins, methods and expressions. This difference is essential to preserve a culture system not only from the information it contains, but especially in the way in which acquires in its territory. Strengthen a link between this cultural dimension and knowledge transfer in universities or higher education is a primary necessity for the proper functioning of the Chair.

The long-term goal is to train a generation of multidisciplinary researchers, Western and not able to translate the second integrated sets scientific methods of knowledge of Ethnomedical world, capable of reaching a very knowledge in different ways.

This approach considers the economic and social development since the strength of the traditional community economies points.

The coexistence of multiple domains guarantees the necessary dialogue between different knowledge to fully preserve the tangible and intangible assets cannot be classified into one unit specification.

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THE POSSIBLE ROLE OF MENTAL INFLUENCE IN EVIDENCE-BASED MEDICINE

Jessica Utts [*]

Randomized controlled clinical trials have advanced our understanding of medicine tremendously, including research on placebos. Two key components of these studies are appropriate design, and appropriate use of basic statistical methods to analyze the results. Both the design and analysis phases rely on certain assumptions about how nature operates. These assumptions are reasonable under our current understanding of biology and physics. However, research in parapsychology (defined below) over the past few decades calls some of them into question, and thus the design and statistical analysis methods that require the assumptions, and the subsequent results, are also called into question.

There are two consequences of questioning the standard assumptions underlying the design and analysis of clinical trials. One consequence is that some of the results of earlier clinical trials may not be as sound as previously thought. The second consequence is that future clinical trials may need to be designed differently to account for different conjectures about how nature operates.

This paper begins with a review of standard study design used in medical research. Next, a review of findings from parapsychology research is given, with emphasis on how these findings challenge the traditional assumptions used in statistical experiments and analyses. Finally, suggestions are given for incorporating these research findings into the design and analysis of future clinical trials.

Randomized experiments and design issues

Randomized double-blind clinical trials are the "gold standard" in medical research because they attempt to control for all factors that

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might explain a difference in outcomes except the factor being tested. For instance, the Physicians' Health Study, led by The Steering Committee of the Physicians' Health Study Research Group (1988) and famous for the conclusion that taking low-dose aspirin may help prevent heart attacks, divided the participants into similar groups, and treated them in similar ways except for the contents of the pill they took (aspirin or placebo).

There are a number of elements that are necessary for a well-designed experiment. We discuss them next.

Placebos and Control Groups

Other than research on the placebo effect, described elsewhere in these proceedings, most clinical research is designed to compare the effectiveness of an active treatment with either a placebo or no treatment at all. Depending on the treatment, it is important to include either a placebo group or a control group in these experiments. A control group is a group of participants who are treated in the same way as those receiving the active treatment, except that they do not receive an active treatment. For instance, in a study designed to measure the effect of magnets to reduce pain, a control group might have pieces of metal of similar size and weight attached to them for the same amount of time. When the treatment is a medication, the control group typically receives a placebo in the form of an identical medication that simply lacks the active ingredient(s) being tested. For instance, in the Physicians Health Study, the pharmaceutical company that provided the aspirin also provided placebos that looked identical to the aspirin.

Control groups or placebos are important because comparisons can be made between the active treatment and the control, rather than the active treatment and nothing. Effects due to the special attention of being in an experiment, the expectation that a drug will work (placebo effect), and so on, should apply to both groups, so any remaining differences are attributed to the treatment.

Randomization

If possible, treatments (active versus placebo, treated versus control group, etc.) should be randomly assigned to participants. Random assignment is not the same thing as haphazard assignment, and should

be done carefully, using computer random number generators or other methods specifically designed for this purpose. If the experimenters were to decide which participants received which treatment, they could obviously choose the healthier ones to receive the preferred treatment. If all treatments are given to all participants, the order should be randomly assigned. (This may become more of an issue with the ethical debate about using placebos.)

One benefit of random assignment is that it tends to balance out differences such as age, general health and so on, across treatment groups. Sometimes, especially in smaller studies, partial randomization is used but groups are adjusted to be similar in age, gender and so on.

If all treatments are used on all participants, random order is necessary to rule out learning, habituation, preferences, etc. as the cause of differences. For example, in a study to compare two sunscreen lotions, participants may be asked to apply one to each arm. If lotion A was always applied to the right arm and lotion B to the left arm, perhaps lotion A would wear off sooner because the right arm tends to be used more than the left by most people. Frequency of use of the arm would be a confounding variable. Instead, which lotion to apply to which arm should be randomly assigned for each participant.

Matched Pairs, Blocks, Repeated Measures

Matched pairs, blocks and repeated measures are all methods used to match treated and control (or placebo) participants one-for-one on extraneous but important variables, such as age, sex and health. Pairs of similar participants are created, and then random assignment is done within each pair. The term "block" is used when more than two participants are matched, for instance if there are three treatments and they are randomly assigned to triples of similar individuals. The term "repeated measures" is used when the participants are each given multiple treatments.

Pairs and blocks are often used because, especially in small studies, it is possible that random assignment will leave the treatment groups unequal in terms of important factors like age and health. Even in larger studies, pairing or blocking reduces extraneous variability and allows for more direct and efficient comparisons.

Blinding (Masking)

Participants, and if possible evaluators, should not be told who is receiving which treatment because that could bias the outcome. "Double-blind" means neither group knows, while single-blind means only one group (participants or evaluators) is blind. Blinding helps to avoid self-fulfilling prophesies, expectations and experimenter effects.

Observational studies

In *observational studies*, researchers measure but do not intervene. For example, *USA Today* reported on a study showing that elderly people who regularly pray and attend church had lower blood pressure than those who did not do those things (Davis, 1998). Participants were obviously not randomly assigned to pray and attend church or not, they were simply observed to see whether they did so.

The problem with observational studies is that there are too many possible *confounding variables* for a *cause and effect* conclusion to be reached. A confounding variable is one that is related to the treatment and that is likely to have an effect on the outcome. For instance, when taking aspirin, drinking an extra glass of water may be a confounding variable if placebos were not used. Those taking aspirin would consume an extra glass of water each day, and that may help improve their health. In the prayer and blood pressure example, confounding variables are social support, ability to get out on Sundays and go to church (due to good health), possible depression, and so on. For instance, people who are in general ill health may stay home on Sundays, and it may be the ill health and not the lack of church attendance that causes higher blood pressure.

Research results from Parapsychology

Parapsychology is the scientific study of phenomena known in common language by terms including precognition, telepathy, clairvoyance, or the more general extrasensory perception (ESP). In the past few decades the accumulating evidence has been overwhelming for non-chance results in experiments designed to test these potential abilities See, for example, Bem et al (2015), Mossbridge et al (2012), Storm et

al (2010) and Radin, (1997). Anomalous cognition is a generic term used in parapsychology, for the ability to obtain information that could not have been obtained by normal means. The term does not indicate a mechanism, and could be telepathy, clairvoyance, precognition or some other ability that has not yet been suggested. The most common types of studies in anomalous cognition have focused on two methods, called "remote viewing" and "Ganzfeld" studies.

There is also accumulating evidence for anomalous interaction between living systems; see Radin (1997) and sources therein, and for presentiment, the potential ability for physiological changes in anticipation of a disturbing or emotional event; see Mossbridge et al (2007, 2012). And there is evidence that the results of some double-blind experiments in these areas depend on the experimenter, even though the experimenter should not be able to influence the results; e.g. Wiseman & Schlitz, 1997.

In addition to studies of anomalous access to information, numerous studies have been done on the influence of humans on physical systems; see Radin (1997) or Utts (1991). May et al (1995a, 1995b) have used these same studies to propose an alternative explanation. They have suggested that humans may have an ability to augment decisions by gaining information from the future about the probable results of making a particular decision. They suggest that this "decision augmentation" may be used routinely to help people make better decisions in the present about what actions to take, based on information about the consequences of those decisions in the future. If true, this kind of anomalous information about the future could include knowing when a favorable sequence is about to be generated by a random number generator, and that information could be used (unconsciously) in the randomization phase of clinical trials.

There are thousands of additional studies that could be cited from the research in parapsychology, and dozens of possible explanations that have been proposed for their results. Given that we do not know what mechanism is operating in these experiments, I will use the generic terms such as "anomalous cognition," "mental interaction" or simply "parapsychology research" in the remainder of this paper.

The studies quoted and other parapsychology research studies indicate that communication may be possible through unknown means, that time may not behave as we have assumed, and that humans may be able to interact with distant living and non-living systems. If these preliminary indications are correct, the assumptions upon which most medical (and other) research is based may not be accurate.

Rethinking traditional assumptions

Traditional design and analyses of medical studies are based on the following assumptions, all of which are in question based on recent studies discussed in the previous section.

The causal arrow of time is past → present → future

Interactions/agreements between individuals are not possible without known means of communication

Physical influence of individuals on living systems (or non-living systems) is only possible with direct physical contact.

The physical world (non-biological) stays constant, at least in a short timeframe

If these assumptions are indeed erroneous, the implications for past and future medical research are enormous. Both the design and the analysis phases of experiments would need to be revised to accommodate the implications of a world that behaves differently from what has been previously assumed.

Challenges in the design phase

Challenges to Randomization, Control Groups and Placebos:

There are numerous challenges to the efficacy of random assignment to treatments and controls that emerge from the combined results of the research in parapsychology:

Some participants may know when to sign up to get the desired treatment, based on information gained through anomalous cognition.

Experimenters may be able to influence the randomization device.

Randomization requires decisions by the experimenter, such as what computer program to use and when to activate it, and "decision

augmentation" could be used to help the experimenter make advantageous random assignments.

It is well-established that participants try to please experimenters. Experimenters could envision the desired outcome and communicate it to the participants, who in turn respond differently based on which treatment they are receiving.

Experimenters could directly influence the biology of participants, differently for different treatments.

In repeated measures, the order of "outcomes" could influence the order of random assignment (future outcome → past randomization).

Challenges to Double-Blind:

It may be impossible to conduct single or double-blind experiments, based on the results of mental interaction research. For example:

Feedback about who received which treatment is eventually given, or results published. It could be that the *future* knowledge of who got which treatment affects *past* performance.

Information about who had which treatment is known by someone, even if coded, so could be transmitted to participants or evaluators. For instance, in the Physicians' Health Study, someone had to provide the aspirin or placebo tablets to the physicians, so someone knew who was receiving aspirin and who was receiving placebos.

Depending on the treatments, participants could "know" which treatment they had, and communicate this information to the evaluator.

In single-blind studies, either the participant or the evaluator knows what treatment each participant has, and could communicate it to the other party.

Challenges in the analysis phase

Two basic assumptions accompany almost most for hypothesis testing and confidence intervals:

Observations are *independent* across participants. In other words, results for participants are uncorrelated with each other.

Each participant is considered to be representative of a larger population with a *fixed* mean, fixed variability, and so on. Generally it is the mean and not the variability that is compared for different treatments.

Challenges to Assumptions Commonly Used In Analyzing Experiments:

Based on the parapsychology research results, the statistical models generally employed may be much too simplistic. For instance:

Interconnected participants do not allow for independent observations. Perhaps a "group mind" cooperation makes an entire experiment succeed or fail.

"Reality" may not be fixed in time. Perhaps aspirin worked in the 1990s to prevent heart attacks, but a "group habituation" lessens the effect over time.

The interesting effects may be in the change (variability) and patterns, and not in the mean. In that case, different questions need to be asked. For instance, research has suggested that the position of the earth, measured by local sidereal time may influence the amount of "noise" in experimental results (Spottiswoode, 1997).

Conclusions and suggestions for research design

The results of research in parapsychology provide challenges to the methods currently used in medical research. In general, the challenges fall into three broad categories:

It may be impossible to hide information (no "blind" experiments)

It may be impossible to randomly assign participants to treatments conditions

It may be impossible to separate individual influences, such as the influence of the healer versus the desire of patients to be in the "treated" group, leading to decision to enter study at just the right time.

Challenges also present opportunities. The following recommendations are particularly relevant for randomized clinical trials. Some of the recommendations are based on ordinary statistical principles, and some are the steps that the parapsychology research suggests can enhance the results of experiments:

If "decision augmentation" works, it is better to randomize at multiple decision points, to increase the chances that the random assignments will result in favorable outcomes.

If experimenters can convey desired results, motivate everyone involved in the experiment to expect a positive outcome.

Don't design experiments with small effect sizes and low power by adding a treatment that can only have a small incremental effect. For instance, for studies of the placebo effect, don't chose participants who are already taking several other medications.

Based on past results of medical studies, the patients with the most severe illness tend to improve the most within a group, whether they are in the treatment group or the placebo group. For this reason, it is wise to use serious illnesses to test the efficacy of placebos.

Design experiments in ways that will allow possible causes to be separated.

More complex statistical models may be needed to accommodate new assumptions. Current assumptions of independence and fixed constants (such as relative risk, probability of a successful outcome, etc.) may need to be revised. For instance, in many parapsychology studies each participant is tested only once, and it is difficult to tell the difference between a fixed probability of success for each participant, and a perfect chance of success for some participants, but only chance for others. New designs, models and methods of analysis could help distinguish different possible mechanisms. As an example, see May et al (1995a, 1995b) for methods to distinguish between decision augmentation and remote influence in experiments designed to test remote influence.

The good news for medical research is that although results in parapsychology have been consistent in showing highly statistically significant deviations from chance, the effect sizes are small. So for clinical research studies that obtain large effects, it is likely that the contributions due to anomalous cognition are at most a small part of the observed results.

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HEALING THROUGH MEANING: PLACEBO, MEDITATION AND DISTANT INTENTIONS

Stefan Schmidt [*]

Defining the placebo effect as the meaning response

Placebo and placebo effects do challenge the biochemical model of medical science. This model cannot explain why an inert pill or an inert injection results in physiological changes as it is documented in placebo research so often. As such, the placebo effect relates directly to the mind-matter problem. That is, we do not know how the mental and the physical relate to and interact with each other. Within placebo research this hard problem of modern science is often circumvented by just remaining on one side of the mind-matter divide. That is, placebo research usually starts directly at that point where the first physiological trace of the placebo response can be found and is then following up its physiological and neurochemical pathways. By doing so the interesting question on how this causal chain started in the first place is ignored. In this contribution I will take a look at placebo effects and its implications beyond the biochemical model of medical science and address the issue how mental aspects relate to health and healing.

Placebo is often defined as an inert substance or inactive procedure within a medical context. The placebo effect is usually seen as the response following the placebo application. It is the contribution of the anthropologist Dan Moerman to point to the fact that this is a rather inappropriate conception of the placebo effect since one can be sure that the placebo response is not elicited by the placebo itself, as there is no active ingredient (Moerman, 2013; Moerman & Jonas, 2002). Rather than by the placebo itself the placebo response is elicited by the context and information related to the placebo administration. This applies for example to the color and size of the pill, the information given regarding

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the effect of the placebo procedure and of course the relationship and interaction with the person administering the placebo (Benedetti, 2013). The crucial point here is that all these contextual factors responsible for the placebo response are consciously processed. The information that some inert pill is a new, expensive and very powerful drug might result in a larger placebo response but only if the person is listening to this message and may get the pragmatic information out of it. If the patient is unconscious or the message is in a language the patient does not understand it won't unfold its effect. Thus, the placebo response will only be present if the message unfolds *meaning* in the patient. Therefore, Moerman suggests calling the placebo effect as a *meaning response*.

Meaning in the biochemical model

The interesting point of this definition is that it demonstrates the incompleteness of the present biochemical model of human functioning. Based on this model the human body including the brain work according to biochemical and physiological principles. This concept entails that all changes are due to mechanical causal effects and can be analyzed in an analytical mode. Due to its mechanistic conception, this model does not make any difference whether the person is conscious or unconscious. All neurophysiological processes in the brain and all biochemical processes in the cells will work in the same way independent of the conscious state of the respective organism. It is obvious that the placebo response, which relates to the application of an inert substance, cannot be explained sufficiently within such a framework. And if the placebo response is related to consciousness and meaning creation in a mental space the situation gets even more difficult.

What can we conclude from this analysis? There are two important messages to note: 1. If the results of placebo research during the last 25 years are taken serious then a biochemical description of the human organism is incomplete, because it cannot sufficiently explain placebo effects. 2. Obviously, mental processes like the creation of meaning, share a so far conceptually not defined relationship with the physiological and biochemical aspects of the human organism. Addressing this second aspect more directly, we can assume that there is a strong relationship between meaning and health and between meaning and healing.

The argument here is that placebo research has demonstrated many times that a change in meaning within a placebo context resulted in an improvement (or worsening) of the patients' condition. Thus, it can be assumed that world views, attitudes, meaning relating to someone's health and body have a relevant function for health. This model is rather obvious for lay persons not involved in medical research. But on the other hand it is hardly present within the most prestigious fields of health research.

The neglect of placebo effects in medicine

The reason why patients' meaning creation processes and individual world-views regarding their health and condition have been ignored so far in a large part of medical science is twofold. The first reason is the above-mentioned limitation of the biochemical model. This model is still largely dominating and it cannot account for effects, which relate to consciousness and meaning. Recently, we have suggested an alternative descriptive model which offers a solution how these categorical different concepts can be combined in one theoretical framework. This is the *biosemiotic model* first conceptualized by Thure von Uexküll (for more details see Schmidt & Walach, in press; Uexküll, 1982; Walach, 2011). The second reason is that the positive effects of placebo have been systematically kept out of scientific reasoning since the placebo was used as a controlled condition. This second argument is worth to be considered in detail.

Since the work of Beecher in The 1950s the randomized controlled trial has evolved as the gold standard for testing new medical procedures (Beecher, 1955). If the RCT is placebo controlled then the effect of the pharmacological substance in the verum condition is compared to the placebo condition where the drug is inert. The difference between these two study arms is considered to be the true effect of the pharmacological substance. This reasoning again makes perfectly sense within a mechanistic biochemical model of the human organism. Only those effects that can be causally tracked in the body are considered as real. All other improvements showing up in both study arms are considered to be placebo effects *only* and are not included in the development of medical procedures.

Let us make a simple example. An anti-depressant drug in an RCT reduces depressive symptoms in the verum condition by 10 points; the

respective placebo in the control condition reduces depressive symptoms by 6 points. Then the drug effect is estimated to be approximately a four-point reduction in depressive symptoms. The six-point reduction in the placebo arm is considered to be due to artifacts, e.g. by regression to the mean, placebo effects and other unspecific influences that cannot ruled out in clinical trials.

However, in the light of the recent placebo research it becomes obvious that also the six-point reduction is not a mere suggestive effect by the patient or artifact not present in real life but are related to sound neurobiological effects taking place in the organism. And these placebo effects can be traced and accounted for in the biochemical model. So the current practice in medicine to draw a sharp difference between placebo effects and pharmacological effects is deeply challenged.

Another reason why the impact of placebo effects is overlooked is misattribution. Let us consider an example in which a person takes a painkiller (e.g. aspirin) for her headache and is in a much-approved condition two hours later. This person will most likely attribute the reduction in headache to the pharmacological effect of acetylsalicylic acid. We have demonstrated elsewhere that based on an empirical study only approximately one quarter of the pain reduction can be explained by the pharmacological substance (for more details see Branthwaite & Cooper, 1981; Schmidt & Walach, in press). The other three quarters are due to the placebo effect, the natural course of the headache and other unspecific factors. Although these factors form the major part of the improvement they are usually not acknowledged, since the whole improvement is usually solely attributed to the pharmacological substance. If, after taking an aspirin, the headache ceases most people falsely interpret that the pharmacological substance is the single causal reason why the headache improved.

Walach has published a model called the *efficacy paradox* that demonstrates that by not considering placebo effects in medical reasoning patients in some cases will be withheld from more effective treatments in favor of weaker ones (Walach & Loef, 2015). The basic idea of the efficacy paradox is that a certain *treatment A* shows a large general effect (e.g. five points in pain reduction), but only a small specific effect compared to placebo (e.g. one point in pain reduction). The overall pain reduction in

the treatment condition will be six points. But since the treatment does not show a significant advantage over placebo, it will not be considered as evidence-based and it will not be offered to patients. A second *treatment B* might have just a small general effect (e.g. one point reduction), but a larger specific effect in comparison to placebo (two point reduction). This method will then most likely be offered to the patient, although its overall effect is with a three points total considerably weaker than in treatment A. A real-life example for such a situation is the effect of acupuncture on back pain compared to a pharmacological treatment (Haake et al., 2007).

Self-healing

Based on what was said so far, it is obvious that patients'world views, beliefs, attitudes, meaning creating processes and attributions are important factors for health. The logical next step would then be to consider the question of which types of attitudes and interpretations are beneficial and which are not? One can assume that there will be general factors applying to almost all persons, but that there will be also highly individual answers to this question. We know for example that openness and optimism are beneficial for health and this seems to be a rather general factor. But on a more individual level one might find beliefs and world views that are very much related to a specific person, her biography, prior experiences and socialization and are thus, not generalizable.

The interesting point here is that these beliefs and world views may depart from current scientific knowledge but still may have a positive effect. For example, a person may believe in the health effects of a certain amulet that was blessed by special shaman. From a scientific perspective, this would be seen as superstition and one could assume that a double blind trial with real vs. sham amulets will find no specific difference regarding health outcomes. Nevertheless, the person may benefit from her amulet due to her belief and the related placebo effect and this benefit will not only show up on subjective wellbeing but can also be traced on the biochemical and physiological level.

So any theory on self-healing effects has necessarily also to incorporate world views and belief systems of the patient, and in this case it will be irrelevant whether these beliefs are in accordance with a scientific world

view or not. Here the patients themselves are the experts for their world views. It is within their reference frame or mental space where certain beliefs are valued and unfold meaning while others don't.

Thus, a model describing self-healing effects will be, unlike other scientific models, less generalizable and more ideographic. It is the patient who decides what is meaningful to her, not to the doctor or the scientist.

From the perspective of medical interventions targeting such self-healing mechanisms one should ask the following questions: Which treatments have the potential to create meaning in the patient? Which interventions have a substantial effect on the way the patient looks at her illness? Which procedures are likely to induce positive changes in beliefs, interpretations and attitudes? One can assume that many treatment modalities from complementary and alternative medicine coming along with unorthodox explanations will fulfill such a function. Patients may be convinced by the idea that acupuncture activates energy in meridians which is then spread throughout the whole body. They may also subscribe to the idea that highly diluted and potentised homeopathic remedies contain specific information that can unfold positive effects on their condition. Of course this is not limited to alternative treatments. Within the pharmacological treatment of depression, for example, there is the long-held belief that serotonin-reuptake inhibitors (SSRI) make larger amounts of serotonin available in the synaptic cleft and thus will reduce depressive symptoms which are due to a lack of serotonin. Science has so far failed to prove this mechanism and there are many doubts about this explanation (Healy, 2015). Nevertheless, SSRI still perform as very powerful drugs in the treatment of depression. However, the major part of their effects are not specific but can be attributed to placebo effects (Kirsch et al., 2008). The latter example shows once more that regarding self-healing effects the persuasive power of theory is more important than its scientific correctness.

Meditation

But besides medical interventions and activities within the explicit context of health care patients will develop new world views or change their attitudes and beliefs also in daily life activities. We can think of many

instances that are capable of doing so, such as reading a book, discussing with friends or just having an insight while having a walk in in the forest. A more structured practice in order to generate meaningful insights is the Buddhist tradition of *Vipassana Meditation*. The word *Vipassana* translates to *insight* although the respective meditation technique is often referred to as *mindfulness meditation*. Meanwhile there is a large body of empirical literature describing the health benefits that can be gained through mindfulness meditation (Gotink et al., 2015; Khoury et al., 2013; Khoury, Sharma, Rush, & Fournier, 2015) and this evidence cannot be displayed in detail here. The interesting point here is, whether the practice of meditation can be linked to the concept of health impact by changing subjective meaning. There are already some models trying to identify the beneficial components and mechanism of mindfulness meditation (Bishop et al., 2004; Gu, Strauss, Bond, & Cavanagh, 2015; Hölzel et al., 2011; Shapiro, Carlson, Astin, & Freedman, 2006). Hölzel et al. (2011), for example, identify the four components of attention regulation, body awareness, emotion regulation and change in perspective of the self. Changes in these particular components are in part achieved by the very basic task of meditation, i.e. to maintain the focus of attention on a certain experience for an extended time-span (Schmidt, 2014). On the cognitive side meaning changes within mindfulness meditation are coming about by the repeated observation of the present moment experience from a detached perspective. Just seeing again and again how, for example, one's body reacts toward a particular sensation or how one's mind reacts to a particular thought might reveal a deeper understanding of one's own psychological functioning. This is what is meant by insight and especially these experience-based insights into general or personal mechanism underlying our functioning will generate strong meaning. Thus, these new insights will have governing effects on self-regulation within various areas. The components identified by Hölzel et al. describe the psychological mechanism resulting from such experience based insights, with 'changes of perspective of the self' coming close to the level of insight/meaning creation. Thus, the health effects of meditation can also be interpreted within the framework of meaning creation addressed here. In this context meditation can be reframed as structural and intentional method of insight creation and meaning changing.

Inter-subjectivity

It was argued so far that subjective world views, belief systems and especially the subjective meaning of experiences may play a fruitful role in self-healing processes. Thus, consciousness was identified as an important but so far neglected factor with respect to physiological and biological processes related to health. A crucial point in this argumentation is that these mind-body effects take place when certain experiences and information *make sense* within the individual reference frame of the respective person. This reference frame relates to a person's biography, personality, prior experiences, social environment and socialization. It will be different for every individual. We cannot expect for sure that some treatment or experiences that make sense to one person will also make sense to another person. Thus, if meaning is only created within subjective reference frames, and if these references frames are highly individual and unpredictable, then it will be difficult to find independent, inter-individual criteria in order to trigger such effects. This does not mean that it will be entirely impossible. What is meant here is that the balance between general criteria applying to all humans (or at least to a larger sample) and individual criteria being highly personal is shifted towards the personal. This is especially true, if these mind-body effects are compared to physiological or pharmacological interventions. The process of meaning creation cannot be enforced and thus there is no guarantee that these powerful effects can be triggered externally.

Such a model shares some commonalities with the epistemological approach of *constructivism*. Even here the balance is shifted by emphasizing more the subjective world view compared to an external objective truth, which according to constructivism, can never be revealed. What can be learned from that parallel is that by emphasizing the importance of an internal reference system this does not mean that everything is individual. Rather we have to acknowledge that the creation of world views and of meaning is a social process that can only take place in the close interaction with other individuals. Thus, according to the view of *social constructivism* we live in a co-created world and many aspects in our lives that we perceive as individual and personal may rather be due to our social interactions. Accordingly, our world views and meaning

creating process are at best neither be considered as entirely objective nor as entirely subjective but rather as inter-subjective.

Distant Intention

From what was said so far two conclusions can be drawn. At first, meaning effects are much more related to internal reference frames than to external conditions. Secondly, internal reference frames are predominately shaped by social interactions.

Taken these two conclusions together an interesting question can be formulated. Are physiological and biological effects that are due to consciousness and meaning creation process as described above limited only to one's own organism? Or, putting it the other way round, can meaning effects also reach other organisms?

This is what is researched in a group of parapsychological experiments subsumed under the term of *distant intention* research.

Distant intention experiments assess the basic hypothesis whether someone can only by intentional means interact with the physiology of a remote organism in the absence of any conventional communication channels. This is what is usually assumed to take place in distant healing or intercessory prayer but also in little rituals performed in daily life such as keeping fingers crossed for a friend or sending mentally wishes for recovery to a beloved person. The term intention is here defined as a mental state directed towards achieving a goal (Schlitz et al., 2003).

A distant intention experiment operationalizes this hypothesis by assessing whether there is a relationship between a directed intentional effort of a person to change a defined variable of a remote living system and the fluctuation of that variable. In these experiments, the intention functions as the independent variable manipulated systematically and the target variable of the remote organism is the dependent variable.

Regarding distant intentionality there is an empirical research tradition within parapsychology which spans approximately 40 years. This tradition is described in detail in Schmidt (2015). Here, I will give a comprehensive review of the most important paradigms and their results based on meta-analyses.

Distant Intention research was first started in 1977 by William Braud at the Mind Science Foundation in St. Austin Texas. Braud,

who was joined a few years later by medical anthropologist Marilyn Schlitz, made the groundbreaking work and developed many different experimental paradigms. Three of these paradigms received also major attention by other researchers and were replicated many times. These are the experimental set-ups known under the names of *EDA-DMILS, Remote Staring* and *Attention Focusing Facilitation*. These three paradigms will be described and reviewed in the subsequent sections.

EDA-DMILS

EDA stands for *electrodermal activity* and describes the dependent psychophysiological variable applied in this experiment. The acronym DMILS stands for *direct mental interaction in living systems* and this is another general description of this type of experiments. In an EDA-DMILS experiment two participants are invited into a laboratory. One person is assigned the role of an *agent* asked to provide intentional efforts, the other one is termed *receiver*, from whom the EDA is recorded as dependent variable. EDA is a psychophysiological indicator of autonomic arousal and reflects overall physiological activity. EDA is measured by electrodes attached to the receiver, who is then instructed to maintain a relaxed but wakeful state in a comfortable position for the rest of the session. Sessions usually last 20-30 min. The agent in the other room has a monitor that displays the task for the single intention epochs. They are usually either Activate or Calm and last 30-60 seconds. During an *Activate* epoch the agent is asked to activate the distant receiver by any means. During the *Calm* epochs the task is to calm the receiver. Usually 12-20 epochs of these epochs form a single session. Epochs are presented in a randomized and balanced fashion. In many experiments a feedback condition is added by displaying the real-time EDA activity of the receiver visually on a monitor to the agent. For the evaluation of the session, EDA data are sorted according to experimental conditions (Calm and Activate) and are then compared in order to assess a difference in the intended direction (Schmidt, 2015).

A meta-analysis of EDA-DMILS experiments was published in 2004 (Schmidt, Schneider, Utts, & Walach, 2004). It contained 40 experiments with 1045 single sessions that were conducted between 1977 and 2000.

Explicitly, this meta-analysis also assessed unpublished studies. Several tests regarding publication bias gave no indication of such a bias. Studies were assessed for several dimensions of study quality. Finally, four studies were removed from the data set since they showed severe methodological shortcomings. For the computation of an overall effect size single studies were weighted for sample size but as well as for study quality. The obtained overall effect size for k=36 studies with N=1015 session was d=0.106 (p=.001). This indicates a small but highly significant overall effect.

Remote Staring

The set-up of this experimental paradigm is quite similar to EDA-DMILS but it assesses a somewhat different question. In Remote Staring experiments it is investigated whether the remote receiver registers an intentional gaze by the agent. This protocol is very similar to that in studies on the feeling of being stared at (see e.g. Sheldrake, 2003). The difference is that in Remote Staring experiments the receivers are not asked to report verbally whether they believe someone is looking at them or not. Instead, their EDA is recorded and analyzed in the same fashion as in the EDA-DMILS setup. In such an experiment, receiver and agent are also separated in two different rooms. The EDA is recorded from the receiver and s/he is asked to rest in a wakeful but relaxed state for the duration of the experiment. The agent in the other room is seated in front of a monitor that either displays or does not display the receiver in real time by CCTV. The complete experimental session is randomly divided into staring and non-staring epochs that usually last 30-60 seconds. In staring epochs the agents are asked to gaze at the receiver; in non-staring epochs they are asked to busy their mind with other things. The data analysis is identical to that one for the EDA-DMILS protocol (Schmidt, 2015). It is assessed whether EDA activity during staring epochs differs from the activity during non-staring epochs.

A meta-analysis, also published in 2004 (Schmidt et al., 2004), combines the results of 15 such experiments conducted between 1990 and 2000 with overall 379 single sessions. It revealed an overall effect size weighted for study size of d=0.128 (p=.013). Similarly as in EDA-DMILS also this paradigm showed a small but significant effect in the meta-analysis.

Attention Focusing Facilitation

The third paradigm is an experiment that conceptualizes remote helping. In this set-up, the dependent variable is not physiological but a behavioral one. Here the receiver, also termed *helpee*, has the task of focusing her mind on a candle placed directly in front of her. Whenever s/he notices that her mind has wandered s/he is asked to bring her attention back to the candle and at the same time to press a button. The frequency of these button presses are used as a measure of distraction and, thus, as the dependent variable. The agent in the other room, also termed *remote helper*, has a similar candle in front of her so s/he can focus her mind in the same fashion as their experimental partner. The task of the agent is to either assist the helpee to focus on the candle, or not. Helping and non-helping epochs are indicated to them on a monitor and the sequence is in random order. For the analyses, the frequency of button presses during helping epochs is compared to that during non-helping (control) epochs. It is assessed whether there are fewer button presses during helping than during control epochs.

A meta-analysis of this paradigm included 11 studies with 576 sessions overall that were conducted between 1995 and 2006 (Schmidt, 2012)several clinical trials have assessed effects of distant healing. The basic question raised by these studies is whether a positive distant intention can be related to some outcome in a target person. There is a specific simple experimental setup that tests such a basic assumption. The task is to focus attention and to indicate unwanted mind wandering by a button press while at the same time a second remote person is either supporting this performance or not according to a randomized schedule. A meta-analysis was conducted to assess the overall effect of this experimental approach. Methods: A systematic literature search yielded 11 eligible studies, with 576 single sessions and almost identical design, that were conducted on three different continents. Study parameters were extracted and combined with a random-effects model. Results: The model yielded an overall effect size of d = 0.11 (p = 0.03. The statistical computation of the single effect-sizes weighted for study size yielded an overall effect size of d=0.114 (p=.029). Similar to the two other meta-analyses, also here a small but significant effect size in the size of approximately one tenth of the standard deviation is found.

Summary of distant intention experiments

In table 1 the results of the three meta-analyses are summarized. Overall, they form a data-set of more than 60 independent studies with close to 2000 single experimental sessions. The results of all three meta-analyses are surprisingly consistent, the effect sizes differ only in a range of d=0.022.

Experiment	*k*	*N*	*d*	*p*	*95 % CI*
EDA-DMILS	36	1015	0.106	.001	0.043 – 0.169
Remote Staring	15	379	0.128	.013	0.027 – 0.229
Attention Focusing Facilitation	11	576	0.114	.029	0.011 – 0.217
Sum	62	1970			

k = number of studies, *N* = number of sessions, *d* = mean effect size, *p* = according p-value, *95, CI* = 95% confidence interval of mean effect size.

Table 1. Results from three meta-analyses on distant intention effects

Overall, this research gives a clear indication of a small distant intention effect. However, there are a few limitations to these findings. First, there have been conducted more distant intention studies that are not displayed here. Braud and Schlitz, as well as other researchers, have tried many different paradigms, but most of them were either not replicated at all or received only one or two replications by the same lab (see Schmidt, 2015, for a more detailed review). Secondly, one has to take into account that if the here reported effect sizes are true, none of the single studies conducted so far, had an adequate statistical power in order to find the respective effect. Thirdly, all studies in these meta-analyses were conducted by researchers from the field of parapsychology who were either directly or indirectly introduced to this paradigm by William Braud (see Schmidt, 2015, for more details). What is lacking so far is an independent replication by a team or laboratory that had no prior connection with this line of research.

Finally, there is a recent debate in psychological science about a lack of replicability due to questionable research practices (John, Loewenstein, & Prelec, 2012; Open Science Collaboration, 2015). While it can be argued

that parapsychology research has different methodological approaches with respect to some of these questionable research practices (QRPs) (see Schmidt, S., in press, for more details) the presence of QRPs cannot be completely ruled out from parapsychological research. Bierman and colleagues (Bierman, Spottiswoode, & Bijl, 2016) made a reanalysis of another parapsychological data-base (Ganzfeld) and tried to simulate the effect of QRPs on this data base. Thus, it would be interesting also to reanalyze the distant intention data-base with respect to the likely presence of certain questionable research practices.

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BRAINS AND BEYOND: THE UNFOLDING VISION OF HEALTH AND HEALING

Larry Dossey *

> The notion of a separate organism is clearly an abstraction, as is also its boundary. Underlying all this is unbroken wholeness even though our civilization has developed in such a way as to strongly emphasize the separation into parts.[1]
>
> - David Bohm and Basil J. Hiley
> The Undivided Universe

"I suddenly developed a severe headache in the back of my head," the nurse said tearfully. "It was so painful I could not function and had to leave work. This was strange, because I never have headaches. When I reached home and was lying in bed, the phone rang. I learned that my beloved brother had been killed from a gunshot wound to the back of his head, the same place my terrible headache was located. My headache began at the same time the shooting occurred."

The woman was a prominent nurse leader at a major hospital in northern California. The occasion was a Q & A session following an address I had given to senior staff of the hospital consortium to which her hospital belonged. My topic was the importance of empathy, compassion, and caring in healing and healthcare. I had reviewed empirical evidence suggesting that empathy and compassion are more than vaporous emotions that float in our bodies somewhere above our clavicles. They are part of our biological makeup, I suggested. While empathy and compassion arise when we are in the presence of another person, as when a nurse or physician is at the bedside of a patient, evidence suggests their effects may also be felt between individuals at a distance, beyond the reach of the senses. Distant individuals often share feelings, sensations, and thoughts, particularly if they are emotionally close. These experiences, I

* New Mexico, USA.

explained, are often called *telesomatic events*. Hundreds of such cases have been reported over the years, but have been largely ignored.

This discussion had prompted the nurse to reveal her experience to several hundred of her colleagues in the audience. "Now I have a name for what happened between my brother and me," she said. "Now I can talk about it." Her story riveted the audience. When she finished, she was not the only person in the room in tears.

This woman's story is, of course, "only an anecdote." "Anecdote" comes from the Greek *anekdota,* "things unpublished." Our lives are comprised of anecdotes - stories, happenings, events, experiences that are all unpublished. Our existence does not unfold as a series of controlled, publishable scientific studies. It is when our experiences form patterns that are shared by others that we should pay attention to the possible messages they may convey.

LEVELS OF CONNECTEDNESS

Experiences such as these are not uncommon. They suggest a unity and connectedness between biological systems that transcend separation in space.

A growing body of evidence supports this invisible connectivity at several levels of biological complexity. This evidence goes beyond the etymology of "anecdote," for it has indeed been published in peer-reviewed journals and is now a part of the scientific record.

Distant Mental Interactions with Living Systems (DMILS)

Experiments generally known as DMILS-*d*istant *m*ental *i*nteractions with *l*iving *s*ystems involve a wide variety of entities such as whole humans, organs, cells, microbes, plants, and animals. In these studies individuals use their intentions to influence biological functions in humans, the growth rates of bacteria and fungi in test tubes and Petri dishes, the rate of wound healing in mice, the healing of transplanted cancers in mice, the function of cells in tissue cultures, the germination rates of seeds, the growth rates of seedlings; and many other phenomena. Two examples follow.

Gronowicz and colleagues assessed the effect of Therapeutic Touch

(TT) on the proliferation of normal human cells in culture, compared to sham and no-treatment controls. This non-touch technique, which emphasizes healing intentions, was administered twice a week for 2 weeks. Compared to untreated controls, TT significantly stimulated proliferation of fibroblasts (cells that produce collagen and are important in wound healing), tenocytes (tendon cells), and osteoblasts (bone cells) in culture ($P = 0.04$, 0.01, and 0.01, respectively). These data were obtained by sophisticated techniques such as immunocytochemical staining for proliferating cell nuclear antigen (PCNA). The researchers concluded, "A specific pattern of TT treatment produced a significant increase in proliferation of fibroblasts, osteoblasts, and tenocytes in culture. Therefore, TT may affect normal cells by stimulating cell proliferation."[2]

In 10 controlled experiments, researcher William Bengston tested the effect of "healing with intent" on laboratory mice. In 8 of these experiments, mice were injected with mammary adenocarcinoma (breast cancer) cells. In 2 experiments, mice with methylcholanthrene-induced sarcomas were used. The fatality rate for both cancers in mice, if untreated, is 100 percent. The healers were faculty and student volunteers. Although they had no previous experience or belief in healing with intent and were often skeptical of such, they were drilled extensively in the healing technique. Treatment length was from 30 to 60 minutes, delivered daily to weekly until the mice were cured or died. They were successful in producing full cures in approximately 90 percent of the mice. When mammary adenocarcinoma cells were re-injected into cured mice, the cancer would not take, suggesting that an immune response had been stimulated during treatment. The proximity of the volunteer healers to the cages of the mice varied from on site to approximately 600 miles. Thus Bengston notes, "[T]hese effects were at times brought about from a distance that defies conventional understanding," suggesting that a nonlocal process was at work. This series of studies, conducted at several academic centers, suggests that healing through intent can be predictable, reliable, and replicable.[3, 4, 5, 6]

However, the DMILS field is too extensive to be reviewed here. These studies are described and summarized in readily available sources.[7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18] A recent review must suffice. In a 2015 meta-analysis of this field, consciousness researcher Chris A. Roe and his colleagues at the

University of Northampton examined 106 "noncontact healing studies" - 57 involving whole humans and 49 involving non-whole humans (tissues, cells) and nonhumans (animals, plants, etc.). All the various healing methods employed in these experiments incorporated an intention to heal. The researchers concluded, "Results in the active condition exhibit a significant improvement in wellbeing relative to control subjects…. [Results] do not seem to be susceptible to placebo and expectancy effects. …The effect size is small, but statistically significant."[19]

To reiterate, nonhumans such as cells, plants, microbes and biochemical reactions presumably do not think positively or symbolically and are therefore not subject to suggestion and expectation. If in controlled experiments these entities respond to intentions, presumably the placebo response is not responsible, but the influence of the thoughts and intentions of the healer.

This generalization requires qualification. In humans, placebo effects are believed to be mediated by the empathy, compassion, likeability, and trustworthiness manifested by a physician. Thus, veterinarian and placebo researcher F. D. McMillan states, "To the extent that animals form such perceptions…it is reasonable to posit a similar influence of placebo effects in animal health care."[20] There is evidence that certain nonhuman animals can manifest placebo effects through operant conditioning. For example, Ader and Cohen paired an immunosuppressive drug (cyclophosphamide) with a neutral stimulus (a saccharine solution) in mice with a lupus-like disease. When only the neutral stimulus was later given, the result was immunosuppression, suggestive of a placebo response.[21, 22] Moreover, a body of research demonstrates healthy effects in animals from visual and tactile contact from a human, involving rabbits, dogs, horses, dairy cows, and sows.

How, then, can placebo responses be differentiated from our hypothesized effects of healing intentionality? The reasons are straightforward. Many of the relevant studies do not involve animals at all, but cells, tissues, plants, microbes, and chemical reactions. Moreover, intentionality effects do not depend on proximity to a subject. Many of the experiments suggesting distant healing effects have been done remotely, beyond sensory contact. This suggests that a *nonlocal* phenomenon is at play, as opposed to the *local*, sensory-mediated mechanisms believed to

underlie placebo responses in humans and higher animals. Therefore, if animals are not involved as test subjects, and if sensory-mediated contact is bypassed, placebo effects would appear to have been eliminated.[23]

Cell-to-Cell Connections

In 2009, a team of Italian researchers led by neuroscientist Rita Pizzi repeatedly demonstrated that, when one batch of human neurons was stimulated by a laser beam, a distant batch of neurons registered similar changes, although the two were completely shielded from each other. The researchers concluded, "[O]ur experimental data seem to strongly suggest that biological systems present non-local properties not explainable by classical models."[24]

In 2007 researcher Ashkan Farhadi and colleagues at Rush University Medical Center in Chicago examined whether cells in separate containers could communicate with each other. They exposed one container of intestinal epithelial "inducer" cells to hydrogen peroxide and assessed the damage done to them. Another batch of "detector" cells was placed in a separate container and was not exposed to hydrogen peroxide. Even though there was no obvious way the two batches of cells could communicate, the detector cells demonstrated damage similar to the inducer cells. "These findings," the researchers said, "provide evidence in support of a non-chemical, non-electrical communication."[25]

In 2013 researcher Victor B. Chaban and his colleagues at UCLA School of Medicine, demonstrated "physically disconnected non-diffusable cell-to-cell communication" between neuroblastoma cancer cells and normal neurons, when both are shielded, preventing any known means of communication.[26]

Brain-to-Brain Connections

In 1965 researchers T. D. Duane and Thomas Behrendt decided to test anecdotal reports that identical twins share feelings and physical sensations even when far apart. In two of fifteen pairs of twins tested, eye closure in one twin produced not only an immediate alpha rhythm in his own brain, but also in the brain of the other twin, even though he kept his eyes open and sat in a lighted room.[27]

The publication of this study in the prestigious journal *Science* evoked enormous interest. Ten attempted replications soon followed, by eight different research groups around the world. Of the ten studies, eight reported positive findings, published in mainstream journals such as *Nature* and *Behavioral Neuroscience*.[28, 29, 30, 31, 32, 33, 34,35, 36, 37]

In the late 1980s and 1990s, a team headed by psychophysiologist Jacobo Grinberg-Zylberbaum at the University of Mexico published experiments that, like most of the previous studies, demonstrated correlations in the EEGs of separated pairs of individuals who had no sensory contact with each other. [38, 39, 40] Two of the studies were published in the prominent journals *Physics Essays* and *International Journal of Neuroscience*, drawing further attention to this area.[41, 42, 43]

Experiments in this field became increasingly sophisticated. In 2003 Jiri Wackerman, an EEG expert from Germany's University of Freiberg, attempted to eliminate all possible weaknesses in earlier studies and applied a refined method of analysis. Following his successful experiment he concluded, "We are facing a phenomenon which is neither easy to dismiss as a methodological failure or a technical artifact nor understood as to its nature. No biophysical mechanism is presently known that could be responsible for the observed correlations between EEGs of two separated subjects."[44]

As fMRI brain-scanning techniques matured, these began to be employed, with intriguing results. Psychologist Leanna Standish at Seattle's Bastyr University found that when one individual in one room was visually stimulated by a flickering light, there was a significant increase in brain activity in a person in a distant room.[45]

In 2004, three new independent replications were reported, all successful -from Standish's group at Bastyr University,[46] from the University of Edinburgh,[47] and from researcher Dean Radin and his team at the Institute of Noetic Sciences.[48]

Person-to-Person Connections

Evidence that our thoughts, emotions, and behaviors may influence someone remotely has surfaced in recent analyses of social networks. The precise mechanism of these phenomena is currently unknown. James H.

Fowler, a political scientist at the University of California, San Diego, and Nicholas A. Christakis, a physician and social scientist at Harvard Medical School, published a provocative article in 2008 in the *British Medical Journal,* titled "Dynamic Spread of Happiness in a Large Social Network."[49] Christakis states, "[H]appiness is more contagious than previously thought…. Your happiness depends not just on your choices and actions, but also on the choices and actions of people you don't even know who are one, two and three degrees removed from you. … Emotions have a collective existence - they are not just an individual phenomenon."[50]

From 1983 to 2003, Fowler and Christakis collected information from 4,739 people enrolled in the well-known Framingham Heart Study and from several thousand other individuals with whom they were connected - spouses, relatives, close friends, neighbors and co-workers. They found, says Fowler, that, "[I]f your friend's friend's friend becomes happy, that has a bigger impact on you being happy than putting an extra $5,000 in your pocket." The idea that the emotional state of your friend's friend's friend could profoundly affect your psyche created a sensation in the popular media. As a *Washington Post* journalist put it, "[E]motion can ripple through clusters of people who may not even know each other."[51]

It's not just happiness that gets around. The team also found that depression, sadness, obesity, drinking and smoking habits, ill-health, the inclination to turn out and vote in elections, a taste for certain music or food, a preference for online privacy, and the tendency to think about suicide are also contagious.[52, 53]

Christakis and Fowler published their findings about the spread of obesity in large social networks in the influential *New England Journal of Medicine*. They showed that obesity in people you don't know and have never heard of could ricochet through you. They attributed the contagiousness of obesity to a "social network phenomenon" without proposing any specific physiological or psychological mechanism.[54] To label something, however, is not to explain it, and to merely call this sort of thing a "social network phenomenon" has all the explanatory value of saying "what happens happens." In the commentary that accompanied their *NEJM* article, the experts who weighed in took the same tack. They discussed the genetic factors that influence obesity and the connections

within and between cells in an individual that may contribute to overweight, but they too were mute about how distant humans might influence one another when they are beyond sensory contact.

Some suggest that the ripples work through the action of mirror neurons, which are brain cells believed to fire both when we perform an action ourselves and when we watch someone else doing it. But when people are remote from each other, there is no one to watch, and therefore no stimulus for the mirror neurons to fire. Others suggest that the spread is through mimicry, as when people unconsciously copy the facial expressions, body language, posture, and speech of those around them. There is a hint of desperation in these attempts to find some sneaky physical factor that mediates changes between distant individuals. But when all is said and done, Fowler and Christakis say they don't really know how happiness, obesity, etc. spread.[55]

The fact that your friend's friend's friend, someone you've neither seen nor heard of, is affecting your health has begun to rattle many of the gatekeepers in medicine. This field may be a bomb with a delayed fuse that is getting ready to explode in the very heart of materialistic medicine. A few medical insiders are raising the possibility that something heretofore unthinkable may be going on, such as a nonlocal, collective aspect of consciousness that links distant individuals. Among them is Dr. Robert S. Bobrow, a courageous clinical associate professor in the Department of Family Medicine at New York's Stony Brook University. In discussing the spread of obesity in his article "Evidence for a Communal Consciousness" in *Explore* in 2011, he says, "Frankly, obesity that develops from social connection, without face-to-face interaction, suggests emotional telepathy."[56]

If these experiments don't take your breath away, they should. They suggest that human isolation is a myth, and that human consciousness can manifest in the world beyond the brain. We are linked, united, entangled.

Do these person-to-person connections represent genuinely nonlocal phenomena? Are they on the same order as the cell-to-cell events demonstrated in the experiments of Pizzi, Farhadi, and Chaban? Currently no one knows for certain, as mentioned, and further research will hopefully clarify these important questions. On balance, however, as Bohm and Hiley state in the epigraph, "The notion of a separate organism is clearly an abstraction, as is also its boundary."

Telesomatic Events

> But if you stop clinging to coincidence and try explaining this trumpery affair, you might shatter one kind of world.[57]
>
> - J. B. Priestley
> *Man & Time*

Almost forgotten amid this flurry of research are hundreds of case reports such as the experience of the nurse above, which suggest a person-to-person form of communication that appears genuinely nonlocal. In them, individuals experience similar sensations or actual physical changes, even though they may be separated by great distances. Berthold E. Schwarz, an American neuropsychiatrist, documented many of these instances. In the 1960s he coined the term *telesomatic* to describe these events, from Greek words meaning "distant body."[58] The term is apt, because these events suggest that a shared mind is bridging two bodies. Most cases go unreported, however, because there is no accepted explanatory mechanism for them, and because of the social stigma that can result from discussing them publicly.

These happenings have an interesting pedigree. A typical example was described by the English social critic John Ruskin (1819-1900). It involved Arthur Severn, a famous landscape painter who was married to Ruskin's cousin Joan. Severn awoke early one morning and went to a nearby lake for a sail, while Joan remained in bed. She was suddenly awakened by the sensation of a severe, painful blow to the mouth, of no apparent cause. Shortly thereafter her husband Arthur returned, holding a cloth to his bleeding mouth. He reported that the wind had freshened abruptly and caused the boom to hit him in the mouth, almost knocking him from the boat, at the estimated time his wife felt the blow.[59]

A similar instance was reported in 2002 by mathematician-statistician Douglas Stokes. When he was teaching at the University of Michigan, one of his students reported that his father was knocked off a bench one day by an "invisible blow to the jaw." Five minutes later his dad received a call from a local gymnasium where his wife was exercising, informing him that she had broken her jaw on a piece of fitness equipment.

David Lorimer, a shrewd analyst of consciousness and a leader of the Scientific and Medical Network, an international organization based in the U.K., has collected many telesomatic cases in his wise book *Whole in One.* [60] Lorimer is struck by the fact that these events occur mainly between people who are emotionally close. He makes a strong case for what he calls "empathic resonance," which he believes links individuals across space and time.

The late psychiatrist lan Stevenson (1918-2007), of the University of Virginia, investigated scores of instances in which distant individuals experience similar physical symptoms. Most involve parents and children, spouses, siblings, twins, lovers, and very close friends.[61] Again, the common thread is the emotional closeness and empathy experienced by the separated persons.

In a typical example reported by Stevenson, a mother was writing a letter to her daughter, who had recently gone away to college. For no obvious reason her right hand began to burn so severely she had to put down her pen. She received a phone call less than an hour later informing her that her daughter's right hand had been severely burned by acid in a laboratory accident at the same time that she, the mother, had felt the burning pain.[62]

In a case reported by researcher Louisa E. Rhine, a woman suddenly doubled over, clutching her chest in severe pain, saying, "Something has happened to Nell, she has been hurt." Two hours later the sheriff arrived to inform her that her daughter Nell had been involved in an auto accident, and that a piece of the steering wheel had penetrated her chest.[63]

Level of Nonlocal Communication	Manifestation of Nonlocal Communication	Significance
Neuron to neuron	When one group of human brain neurons are stimulated, simultaneous changes are seen in distant neurons that are shielded from all incoming stimuli.	According to conventional science, nonlocal communication between groups of neurons that are isolated and shielded from each other should not be possible. Yet they behave as a unified, single entity, although far apart. A nonlocal form of connectedness and unity is implied.
Brain to brain	When one person's brain is stimulated, simultaneous changes are registered in a distant brain, as seen on EEG or fMRI brain scan.	These events should not be possible from the perspective of conventional science. A nonlocal form of connectedness and unity is implied.
Person to person	Telepathic communication, remote viewing, telesomatic events, remote healing, social network phenomena	A nonlocal form of connectedness and unity is implied - oneness not as metaphor but as empirical fact.

Table 1. A Brief Taxonomy of Nonlocal Communication

Twin Connections

Guy Lyon Playfair, a consciousness researcher in Great Britain, is the author of the important book *Twin Telepathy*.[64] He has collected a variety of documented telesomatic cases involving twins and non-twin siblings.

One case involved the identical twins Ross and Norris McWhirter, who were well known in Britain as co-editors of the *Guinness Book of Records.* On November 27, 1975, Ross was fatally shot in the head and chest by two gunmen on the doorstep of his north London home. According to an individual who was with his twin brother Norris, Norris reacted in a dramatic way at the time of the shooting, almost as if he had been shot by an invisible bullet.[65]

Skeptics invariably dismiss cases such as these as coincidence, but many are hard to squeeze into this category. An example reported by Playfair concerns four-year-old identical twins Silvia and Marta Landa, who lived in the village of Murillo de Río Leza in northern Spain. The Landa twins became celebrities in 1976 after being featured in the local

newspaper following a bizarre event. Marta had burned her hand on a hot clothes iron. As a large red blister was forming, an identical one developed on the hand of Silvia, who was away visiting her grandparents at the time. Silvia was taken to the doctor, unaware of what had happened to her sister Marta. When the two little girls were united, their parents saw that the blisters were the same size and on the same part of the hand.

It wasn't the first time this sort of thing had happened. If one twin had an accident, the other twin seemed to know about it, even though they were nowhere near each other. Once, when they arrived home in their car, Marta hopped out and ran inside the house, but suddenly complained that she could not move her foot. While this was happening, Silvia had got tangled up with the seat belt and her foot was stuck in it. On another occasion when one of them had misbehaved and was given a smack, the other one, out of sight, immediately burst into tears.

Members of the Madrid office of the Spanish Parapsychological Society got wind of the burned-hand incident, and decided to investigate. Their team of nine psychologists, psychiatrists, and physicians descended on the Landa house, with the full cooperation and approval of the twins' parents. They had hardly arrived when a typical trade-off incident happened to the little twins. When Marta accidentally banged her head on something, it was her sister Silvia who began to cry. The researchers got to work with a series of tests disguised as fun games for the twins. This meant the little girls had no idea they were involved in an experiment.

While Marta stayed on the ground floor with her mother and some of the researchers, Silvia went with her father and the rest of the team to the second floor. Everything that happened on both floors was filmed and tape-recorded. One of the psychologists played a game with Marta, using a glove puppet. Silvia was given an identical puppet, but no game was played. Downstairs, Marta grabbed the puppet and threw it at the investigator. Upstairs, at the same time, Silvia did the same.

One of the team's physicians next shined a bright light into Marta's left eye, as part of a simple physical check-up. When she did this four times, Silvia began to blink rapidly as if trying to avoid a bright light. Then the doctor did a knee-jerk reflex test by tapping her left knee tendon three times. At the same time, Silvia began to jerk her leg so dramatically that her father, unaware the test was going on downstairs on Marta, had to

hold it still. Then Marta was given some very aromatic perfume to smell. As she did so, Silvia shook her head and put her hand over her nose. Next, still in different rooms, the twins were given seven colored discs and were asked to arrange them in any order they liked. They arranged them in exactly the same order.

There were other tests as well. The team rated all but one of them as "highly positive" or "positive."

The Landa tests confirmed what many researchers have found - that children are more prone than adults to this sort of thing, and that results are more likely to be positive when experiments are done not in sterile, impersonal labs, but in the natural habitat of the subjects and in a relaxed, supportive environment. This latter lesson has often been flagrantly ignored in consciousness research by experimenters who should know better. Researchers have had to learn repeatedly the importance of *ecological validity* - the principle that what is being tested should be allowed to unfold as it does in real life.

Although telesomatic exchanges are by no means limited to twins, they are frequent among them. As Playfair states, in twins we see "the telepathic signal at full volume, as it were, at which not only information is transmitted at a distance but so are emotions, physical sensations and even symptoms such as burns and bruises."[66] Even so, he has found that only around 30 percent of identical twins have these experiences, but in those who do the phenomena can be mind-boggling.[67] Emotional closeness is an essential factor in the twin connection. Also, having an extraverted, outgoing personality has been shown to facilitate the link. And, as we see in the above examples, what twins seem to communicate best is bad news - depression, illness, accidents or death.

ERA III MEDICINE: THE NEXT STEP FOR THE MIND-BODY FIELD

We can take a socio-historical approach in sorting out the panoply of therapies currently available in the health professions.[68] Let's begin this perspective with the advent of modern, scientific medicine, which medical historians date to around the decade of the 1860s. About this time medicine began gradually to take on the complexion we see today.

We can designate this as Era I medicine or physical medicine, because of its overwhelming reliance on physical measures such as drugs and surgical procedures, which continues to this day. In Era I, the mind is assumed to play a nonexistent or negligible role in health and illness.

Space-Time Characteristic	Era I Local	Era Ill Local	Era III Nonlocal
Synonym	Mechanical, material, or physical medicine	Mind-body medicine	Nonlocal or transpersonal medicine
Description	Elements of Era I are causal, deterministic, and describable by classical concepts of space-time and matter-energy.	Mind is a major factor in healing *within* the single person.	Mind is a factor in healing both *within* and *between* persons.
	Mind is not a factor; "mind" is a result of brain mechanisms.	Mind has causal power and is thus not fully explainable by classical concepts in physics.	Mind is not completely localized to points in space (brains or bodies) or time (present moment or single lifetimes).
		Era II includes, but goes beyond, Era I.	Mind is unbounded and infinite in space and time, thus omnipresent, eternal, and ultimately unitary or one.
			Healing at a distance is possible.
			Elements of Era III are not describable by classical concepts of space-time or matter-energy.
			Era III includes, but goes beyond, Era II
Examples	Any form of therapy focusing solely on the effects of *things* on the body are Era I approaches, including techniques such as acupuncture and homeopathy, the use of herbs, etc.	Any therapy emphasizing the effects of consciousness solely within the individual body is an Era II approach.	Any therapy in which effects of consciousness bridge between different persons is an Era III approach.
	Almost all forms of "modern" medicine-drugs, surgery, irradiation, CPR, etc-are included.	Biofeedback, relaxation, self-hypnosis, imagery, visualization, and placebo effects are included in Era II.	All forms of distant healing, intercessory prayer, some types of shamanic healing, diagnosis at a distance, telesomatic events, and probably noncontact therapeutic touch are included in Era III.

Table 2. Medical Eras

Shortly after World War II, Era II medicine or mind-body medicine began to unfold. This was a radical departure from Era I, because in Era II the various expression of consciousness, such as thought and emotions, were acknowledged as causal factors in health within single individuals. These factors were not trivial; they might sometimes make the difference in life and death. The mind-body perspective did not negate or displace the physical focus of Era I, however, but overlapped with the drugs-and-surgery emphasis.

We are now seeing the birth of Era III medicine, the next great step in healing. Era III medicine acknowledges the intrapersonal effects of thoughts and emotions of Era II, but recognizes interpersonal effects as well. In other words, in Era III medicine one's thoughts, emotions, beliefs, and intentions can affect not just one's own body, but other individuals as well.

The premise underlying Era III is that minds at some level are connected and unitary. I've called Era III *nonlocal* medicine, leaning on the concept of nonlocality in modern physics. According to experimental evidence that is practically unchallenged, distant particles that were originally in contact behave as if they are a single particle, even though they may be widely separated at arbitrary distances.[69] When one changes they both change, instantly and to the same degree.[70]

That's not to say that the nonlocality of physical particles such as electrons or photons can account for the remote connectedness of minds, or that mental phenomena can be reduced to the behavior of subatomic particles, but that both particles and people display a kind of connectedness that defies separation in space and time. "Nonlocal" is a fitting description not only for particles but for minds as well, because "nonlocal" literally means "not in a place." Yet we should not equate the two phenomena; we may be dealing with accidental correlations of terminology - analogies, not homologies. Further scientific investigation may clarify this important issue.

The evidence that consciousness is "not in a place" in space and time is overwhelming and is too vast to review here. For over a hundred years this research has accumulated in painstaking experiments numbering in the thousands. I've repeatedly explored this evidence in several books including *One Mind: How Our Individual Mind Is Part of a Greater*

Consciousness and Why It Matters[71] and *The Power of Premonitions: How Knowing the Future Can Shape Our Lives.*[72] For an overview of this field, I also recommend two books by consciousness researchers Dean Radin, *The Conscious Universe*[73] and *Entangled Mind*;[74] and *Opening to the Infinite* by Stephan A. Schwartz.[75]

NONLOCAL MIND AND HEALTH

Nonlocal expressions of consciousness are frequently concerned with survival and therefore health. When information is shared between humans remotely, it is commonly about health risks, such as impending physical dangers, as we've seen. The quintessential example is a mother who "just knows" her child is in danger and takes measures to prevent harm, as in the following example from the archives of the Rhine Research Center in Durham, North Carolina.

Amanda, a young mother living in Washington State, awoke one night at 2:30 A.M. from a nightmare. She dreamed that a large chandelier that hung above their baby's bed in the next room fell into the crib and crushed the infant. In the dream, as she and her husband stood amid the wreckage, she saw that a clock on the baby's dresser read 4:35 A.M. The weather in the dream was violent; rain hammered the window and the wind was blowing a gale. The dream was so terrifying she roused her husband and told him about it. He laughed, told her the dream was silly, and urged her to go back to sleep, which he promptly did. But the dream was so frightening that Amanda went to the baby's room and brought the child back to bed with her. She noted that the weather was calm, not stormy as in the dream.

Amanda felt foolish - until around two hours later, when she and her husband were awakened by a loud crash. They dashed into the nursery and found the crib demolished by the chandelier, which had fallen directly into it. Amanda noted that the clock on the dresser read 4:35 A.M. and that the weather had changed. Now there was howling wind and rain. This time, her husband was not laughing.

Amanda's dream was a snapshot of the future - down to the specific event, the precise time it would happen, and a change in the weather.[76]

The image of consciousness flowing from this and thousands of similar cases is a *nonlocal* one, in which some aspect of consciousness appears unconfined to specific points in space, such as brains and bodies, or time, such as the present.

Unlike Amanda's experience, however, the information we gain nonlocally is often unconscious. The information may be nonlocal with respect not only to space, but to time as well, as mentioned. For example, an individual may cancel a travel reservation because of a vague gut feeling that something is not right, or that something ominous is going to happen, not because he actually foresees a specific event. This may be one reason why occupancy rates are statistically lower on the day of train wrecks compared to non-accident days.[77] Nonlocal awareness of dire future events may also account for why the overall vacancy rate on the four doomed planes on September 11 was nearly 80 percent.

From a survival perspective, it may be an advantage for information that is nonlocally acquired to be unconscious. Thinking, analyzing, and reasoning take time. In emergencies, instant reflexive action can save a life.

If minds are nonlocal in space and time, they are unbounded. This implies that at some level they come together with other minds and form a collective or universal mind. Nobel physicist Erwin Schrödinger, whose wave equation lies at the heart of quantum physics, was interested in this possibility and believed it to be true. As he put it, "To divide or multiply consciousness is something meaningless.[78] There is obviously only one alternative, namely the unification of minds or consciousness…. [I]n truth there is only one mind."[79]

A similar premise has emerged from the work of researcher Roger Nelson, of the Princeton Engineering Anomalies Research (PEAR) lab, and his colleagues. They have examined the function of scores of random number generators situated around the globe. These electronic devices normally spit out patternless, equal numbers of ones and zeroes. But during moments when the attention of the world is riveted on a singular event, such as the death of Princess Diana or September 11, these mechanical devices deviate from their normally chaotic, random patterns and become more orderly. Nelson suggests that when the psyche of humans behaves collectively, it can impart order into situations where there was none.[80]

WHITHER?

It is easy enough to focus only on experimental findings that point to fundamental separations between biological entities. That is what our science has done for centuries, while denying any "unbroken wholeness" that may exist, as physicists Bohm and Hiley state in the epigraph.

A recurring rebuttal from the separateness camp is that any indication of unbroken wholeness is a temporary aberration based in faulty empiricism at best and fantasy at worst. When science is complete, this reasoning has it, any "science of connectedness" will yield to "science as usual" - the view of separate phenomena interacting through the customary local, physical forces recognized in contemporary physics and chemistry. Yet this is a faith-based view, because no one knows for certain what future developments may reveal. Science is open-ended and its accounts are never foreclosed. That is its strength, and that is what separates it from ideology. Nobel neurophysiologist Sir John Eccles and philosopher of science Karl Popper have called this ideology "promissory materialism" - the promise that one day science will give a complete description of the material basis for the whole of reality, including consciousness. Eccles: "Promissory materialism [is] a superstition without a rational foundation. [It] is simply a religious belief held by dogmatic materialists…who confuse their religion with their science. It has all the features of a messianic prophecy."[81]

If the emerging science of unbroken wholeness and nonlocal connectivity are incomplete, what of it? Incompleteness is a characteristic of the entire canon of science. All of science comes with a warning: "Until further notice." Uncertainty and incompleteness are necessary ingredients for better science. As mathematician and theoretical physicist Henri Poincaré stated, "Guessing before proving! Need I remind you that it is [through guessing] that all important discoveries have been made?"[82] In the same spirit, consciousness researcher Ian Stevenson, already mentioned, stated, "I believe it is better to learn what is probable about important matters than to be certain about trivial ones."[83]

THE GHASTLY SILENCE

For many individuals, the materialistic, intellectual formulations of science are not enough, because they omit too much of the juice of life. This deficiency in a purely scientific approach has long been noted by some of the greatest individuals in the history of science. Among them was Gottfried Wilhelm Leibniz (1646-1716), the German philosopher and mathematician. Leibniz, who invented the infinitesimal calculus independently of Isaac Newton, was considered one of the greatest minds of the eighteenth century. He refined the binary number system, which underlies virtually all digital computers, and invented mechanical calculators that were a marvel for their time. His intellectual reach touched all the major domains of learning of his day. Even so, Leibniz could not find within science the satisfaction he was looking for. In a letter two years before his death, he wrote:

> But when I looked for the ultimate reasons for mechanism, and even for the laws of motion, I was greatly surprised to see that they could not be found in mathematics but that I should have to return to metaphysics.[84]

Three centuries later, Nobel physicist Erwin Schrödinger would come close to the same conclusion:

> The scientific picture of the real world around me is very deficient. It gives a lot of factual information, puts all our experience in a magnificently consistent order, but it is ghastly silent about all and sundry that is really near to our heart, that really matters to us. It cannot tell us a word about red and blue, bitter and sweet, physical pain and physical delight; it knows nothing of beautiful and ugly, good or bad, God and eternity. Science sometimes pretends to answer questions in these domains, but the answers are very often so silly that we are not inclined to take them seriously.[85]

The great Darwin also encountered the effects of the "ghastly silence" Schrödinger spoke of. Late in life he lamented, "My mind seems to have become a machine for grinding general laws out of large collections of facts…. The loss of [the emotional] tastes is a loss of happiness, and may possibly be injurious to the intellect, and more probably to the moral character, by enfeebling the emotional part of our nature." ….The loss of these tastes is a loss of happiness." His solution: "[I]f I had to live my life again, I would have made a rule to read some poetry and listen to some music at least once every week…."[86]

Something more is needed - something that can marshal not only an intellectual appreciation of the wholeness implied in biological entanglement and nonlocality, but also something that can quicken the pulse and stir an ethic toward the earth that can counter the unbridled greed, selfishness and plunder that threaten us.

Currently there are excellent exemplars of this awakening, including numerous scientists. But many scientists, it must be said, are reluctant to speak out in favor of wholeness, unity, and oneness because they fear being labeled as having "gone mystic." It's as if there are hooded inquisitors lurking within science who are keeping score, and who are continually oiling the rack and heating the pincers, just waiting for a scientist to step out of line.

Fear has never silenced the greatest poets and artists, however. Poets have been yammering away about wholeness for centuries. As author Philip Goldberg points out in his important book *American Veda,*[87] there are superb examples among the Romantic poets, particularly William Blake, Percy Bysshe Shelley, William Wordsworth, and Samuel Taylor Coleridge. These poets sensed the interconnectedness and unity that are a feature of an entangled, nonlocal world. Thus Blake, in "Augeries of Innocence": "To see a world in a grain of sand / And a heaven in a wild flower, / Hold infinity in the palm of your hand / And eternity in an hour."[88] Shelley, in "Adonais": "The One remains, the many change and pass…."[89] Wordsworth, in "Tintern Abbey": "A motion and a spirit, that impels / All thinking things, all objects of all thought, / And rolls through all things."[90] And Coleridge, who wrote of "the translucence of the eternal through and in the temporal."[91]

In his book *Opening to the Infinite,* consciousness researcher Stephan A. Schwartz describes how the personal experience of a nonlocal event can carry the emotional wallop of an epiphany. Schwartz, who practically invented the science of remote viewing, has taught thousands of individuals in workshops to have these experiences. He concludes that nonlocal experiences, of which remote viewing is only one example, bestow an "ineffable sense of connection" and a "sense of empowerment" that is so profound it can permanently and radically alter one's worldview and conduct.[92]

The felt experience of being nonlocally connected - all tangled up with all there is - may be a way out of the mess created by self-centered, greed-obsessed individuals who have no sense of wholeness and no concern for the integrity of the earth. As Goldberg puts it, when we realize the unitary nature of consciousness,

> …one's sense of "I" and "we" opens out from the narrow identification with family, tribe, race, political affiliation, religion, and so on, to encompass a broader swath of humanity. With that comes a corresponding expansion of the moral compass. This not a fanciful imagining of "we are the world" harmony but a living experience of unity with other humans, with nature, and ultimately with the cosmos.[93]

Straight-laced, paid-up scientists often deny the empirical findings pointing to an "unbroken wholeness" and unity between biological systems and humans, fearing the contamination of modern science by "the occult," one of their favorite epithets for nonlocal human experiences. But science desperately *needs* contamination by several factors that are missing from its equations, if we are to survive in any meaningful way. Some sort of connectivity is required for a moral center, an earth ethic, a sense of responsibility for all of life. The absence of these qualities has led to an abyss that is becoming impossible to ignore. A one-sided science is not only incomplete, it can be deadly. As Dr. Samuel Johnson put it nearly three centuries ago, "Integrity without knowledge is weak and useless, and knowledge without integrity is dangerous and dreadful."[94]

Dr. Johnson also observed, "When a man knows he is to be hanged in a fortnight, it concentrates his mind wonderfully."[95] Perhaps our sense of impending global disasters - I won't enumerate them - is concentrating our collective mind as a species, resulting in the return of ancient wisdom in the form of modern scientific insights, of which biological entanglement and nonlocality are an urgent example.

What we commonly call empathy, compassion, and love may be human entanglement banging on the doors of consciousness to gain entry. Albert Schweitzer, the legendary physician, missionary, priest, philanthropist, theologian, pacifist, musicologist, and winner of the 1952 Nobel Peace Prize, is an example of someone who opened those doors, and in so doing made the world a better place. In a kind of manifesto of wholeness, he wrote:

> What we call love is in its essence Reverence for Life[96]…. Profound love demands a deep conception and out of this develops reverence for the mystery of life. It brings us close to all beings. To the poorest and smallest, as well as all others….[T]he idea of Reverence for Life gives us something more profound and mightier than the idea of humanism. It includes all living beings.[97]

At this stage of humankind's existence, perhaps the best we can wish for one another is not that we achieve success, clarity of purpose, or even happiness in life, but that we each simply realize that we're intimately united with each other and everything, and that we find the courage to allow this realization to make a difference in how we live our life. On this recognition our future may depend.

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POSTER APRESENTADO PELA FUNDAÇÃO BIAL

POSTER PRESENTED BY THE BIAL FOUNDATION

Resumo do poster apresentado pela Fundação Bial
Abstract of the poster presented by the Bial Foundation

BIAL FOUNDATION GRANTS IN NUMBERS: A BIBLIOMETRIC STUDY

Marinho, S.*, Guedes, P.* & Sousa, N.*

Aim:

To analyze and measure the quantity and quality of papers published in the scope of research projects funded by the Bial Foundation from 1994 until today.

Method:

The research projects' productivity was measured by counting the number of full papers published from 1995 to 2015 (inclusive) and indexed in Scopus or Web of Science (WoS). The quality of publications was indirectly evaluated by the journal impact factor and by the quartile score (provided by the Journal Citation Reports), to mitigate differences between research fields. When a journal was associated to more than one subject category and as a result had a different position in the quartile ranking (Q1, Q2, Q3 or Q4), the best one was chosen. The publications' impact in scientific community was evaluated by the number of citations retrieved from Web of Science™ Core Collection in March 2016.

Results:

The Bial Foundation has funded 537 projects since 1994, in the areas of Psychophysiology (266 grants, 49.5%), Parapsychology (194 grants, 36.1%) and both areas (77 grants, 14.4%). These projects have been developed in universities and research centers from 25 different countries.

In the scope of the aforementioned projects, 696 indexed papers (conference paper, journal article, review, letter and book chapter) were published, from 1995 to 2015. Excluding the projects of the last

* Bial Foundation, Portugal.

edition (2014/2015), which have recently started, the ratio of indexed publications by funded projects per area, was on average 2 indexed papers per project in Psychophysiology and on average 1 indexed paper per project in Parapsychology and in both areas.

539 papers were published in journals with an average impact factor of 3.3, out of which 93 published in journals with an impact factor above 5. It is noteworthy that the majority of papers was published in top-ranked journals of quartile 1 (n = 259, 47%) and quartile 2 (n = 119, 22%).

A total of 7883 citations were computed, with 501 papers being cited on average 16 times (M = 15.74), ranging from 1 to 232 times and 102 papers being cited more than 20 times. The poster highlights the 10 most cited papers.

Conclusion:

The productivity, the quality and impact of the scientific publications are being systematically monitored supplying a basis for evaluating, orienting and stimulating current and future research projects funded by the Bial Foundation. Along the years, there has been a progressive increase of papers published in high impact journals and the Bial Foundation aims to reinforce this trend.

Keywords: Bial Foundation grants, Bibliometric indicators, Journal impact factors, Number of citations

LISTA DE POSTERS
POSTERS

Posters com resultados finais apresentados pelos bolseiros da Fundação Bial e/ou disponíveis em www.fundacaobial.com

Posters with final results presented by the Bial Foundation Fellows and/or available at www.fundacaobial.com

Resumos dos posters disponíveis em / *Posters' abstracts available at www.fundacaobial.com*

2008

119/08 - Comparison between false memories and subliminal stimulation in DRM paradigm - only abstract available
Investigadores/*Researchers*: Maria de Fátima de Jesus Simões, Isabel Maria Barbas dos Santos, Paulo Joaquim Fonseca da Silva Farinha Rodrigues
Instituição/*Institution*: Centro de Investigação em Educação e Ciências do Comportamento, Departamento de Ciências da Educação, Universidade de Aveiro (Portugal)
Duração/*Duration*: 2009/02 – 2015/09

2010

61/10 - Translation of neuron-glia interactions in complex cognitive functions
Investigadores/*Researchers*: João Filipe Pedreira de Oliveira, Nuno Sérgio Mendes Dias, Luis Ricardo Monteiro Jacinto
Instituição/*Institution*: Instituto de Investigação em Ciências da Vida e da Saúde (ICVS), Escola de Ciências da Saúde, Universidade do Minho, Braga (Portugal)
Duração/*Duration*: 2011/05 – 2015/07

144/10 - Nonlinear Processing of Emotional Information: behavioral evidence and neurophysiological correlates
Investigadores/*Researchers*: Manuel Fernando Santos Barbosa, João Eduardo Marques Teixeira, Fernando Ricardo Ferreira-Santos, Joana Maria Barbosa Vieira, Ana Cristina Basto Abreu
Instituição/*Institution*: Laboratório de Neuropsicofisiologia da Faculdade de Psicologia e Ciências da Educação, Universidade do Porto (Portugal)
Duração/*Duration*: 2011/10 – 2015/01

166/10 - Judgements of Moral Wrongdoings and Emotions: A Neuropsychophysiological study - only abstract available
Investigadores/*Researchers*: Paulo Sousa, João Eduardo Marques-Teixeira, Carlos Eduardo Evangelisti Mauro, Fernando Ricardo Ferreira-Santos
Instituição/*Institution*: Faculdade de Economia e Gestão, Universidade Católica Portuguesa, Centro Regional do Porto (Portugal)
Duração/*Duration*: 2012/01 – 2015/09

167/10 - Elucidating the molecular mechanisms mediating feeding behavior
Investigadores/*Researchers*: Carlos Vidal Ribeiro, Maria Teresa Montez, Laura Belmonte, Samantha Herbert
Instituição/*Institution*: Champalimaud Foundation, Lisboa (Portugal)
Duração/*Duration*: 2011/05 – 2014/09

172/10 - Attitudes sensitivity to context: presence of other and physiological evidences
Investigadores/*Researchers*: Teresa Maria Morais Garcia-Marques, Ricardo Fonseca, Marília Prada, Alexandre Fernandes
Instituição/*Institution*: Unidade de Investigação em Psicologia Cognitiva, do Desenvolvimento e da Educação (UIPCDE), ISPA - Instituto Universitário, Lisboa (Portugal)
Duração/*Duration*: 2011/05 – 2015/10

176/10 - Dopaminergic regulation of dietary learning in humans and rodents
Investigadores/*Researchers*: Albino Jorge Carvalho de Sousa Oliveira Maia, Rui M. Costa
Instituição/*Institution*: Champalimaud Foundation, Lisboa (Portugal)
Duração/*Duration*: 2011/07 – 2014/09

193/10 - Attachment and exceptional experiences amongst twins reporting "exceptional experiences"
Investigadores/*Researchers*: Göran Brusewitz, Adrian Parker, Lynn Cherkas
Instituição/*Institution*: Greenwich University (UK), Department of Psychology, University of Gothenburg (Sweden), Department of Twin Research and Genetic Epidemiology, King's College, London (UK)
Duração estimada/*Estimated Duration*: 2013/10 – 2016/04

226/10 - Brain decoding of spontaneous memory processes
Investigadores/*Researchers*: Pierre Maquet, Christophe Phillips, Jessica Schrouffs, Caroline Kussé
Instituição/*Institution*: Cyclotron Research Centre, University of Liège (Belgium)
Duração/*Duration*: 2011/10 – 2016/01

227/10 - Evaluation of alterations of consciousness and the model of pragmatic information in a ganzfeld protocol
Investigadores/*Researchers*: Etzel Cardeña, David Marcusson-Clavertz
Instituição/*Institution*: CERCAP, Dept. of Psychology, Lund University (Sweden)
Duração/*Duration*: 2011/04 – 2015/07

2012

10/12 - Enhancing Psychokinesis Task Performance Through the Practice of Imagery Strategies: New Psychophysiological Approach (Stage 2)
Investigadores/*Researchers*: Alejandro Parra, Juan Corbetta
Instituição/*Institution*: Instituto de Psicología Paranormal, Asoc. Civil, Buenos Aires (Argentina)
Duração/*Duration*: 2013/02 – 2015/02

21/12 - The depersonalized brain: Psychophysiological correlates of cortical hyperexcitability associated with signs of depersonalization, derealization and dissociation, in non-clinical samples
Investigador/*Researcher*: Jason John Braithwaite
Instituição/*Institution*: Behavioural Brain Sciences Centre, School of Psychology, University of Birmingham (UK)
Duração/*Duration*: 2013/06 – 2015/09

28/12 - A Test of Thermodynamic Entropy Effects in Anomalous Cognition
Investigadores/*Researchers*: Edwin May, Sonali Bhatt Marwaha
Instituição/*Institution*: Laboratories for Fundamental Research, Palo Alto, California (USA)
Duração/*Duration*: 2013/03 – 2016/01

30/12 - Regularity encoding and deviance detection in the human auditory brainstem - only abstract available
Investigadores/*Researchers*: Carles Escera, Katarzina Żarnowiec, Lilla Náfrádi
Instituição/*Institution*: Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona (Spain)
Duração/*Duration*: 2013/07 – 2015/06

38/12 - Testing a Methodological Formula for Consistent Hit Rates: Matching Psi Ability to Task Difficulty
Investigadores/*Researchers*: James Houran, Rense Lange
Instituição/*Institution*: Integrated Knowledge Systems, Inc., Illinois (USA)
Duração/*Duration*: 2013/02 – 2014/09

52/12 - The embodied experience of time: modulations of mindfulness meditation
Investigadores/*Researchers*: Marc Christoph Wittmann, Karin Meissner, Stefan Schmidt
Instituição/*Institution*: Institute for Frontier Areas of Psychology and Mental Health, Freiburg, Institute of Medical Psychology, University of Munich - LMU (Germany)
Duração/*Duration*: 2013/05 – 2015/01

53/12 - Libet revisited - The effects of mindfulness meditation training on voluntary action and on time perception: a controlled study with experienced meditators
Investigadores/*Researchers*: Stefan Schmidt, Han-Gue Jo, Marc Christoph Wittmann
Instituição/*Institution*: Dep. of Psychosomatic Medicine, University Medical Center Freiburg (Germany)
Duração/*Duration*: 2013/05 – 2015/03

56/12 - Psychophysical interactions with a single-photon double-slit optical system - only abstract available
Investigadores/*Researchers*: Dean Radin, Arnaud Delorme, Leena Michel
Instituição/*Institution*: Institute of Noetic Sciences, Petaluma (USA)
Duração/*Duration*: 2013/06 – 2015/02

57/12 - Neurophysiological mechanisms of aging: novel view of old concepts - only abstract available
Investigadores/*Researchers*: Maria José de Oliveira Diógenes Nogueira, Alexandre de Mendoça, Antonina Pereira, Bruno Teixeira da Silva, Raquel Dias
Instituição/*Institution*: Instituto de Medicina Molecular, Lisboa (Portugal)
Duração prevista/*Estimated Duration*: 2014/03 – 2016/04

63/12 - Forefeeling guilty knowledge - An innovative approach in presentiment research
Investigadores/*Researchers*: Wolfgang Ambach, Alexander Siller
Instituição/*Institution*: Institute for Frontier Areas of Psychology and Mental Health (IGPP), Freiburg (Germany)
Duração/*Duration*: 2013/03 – 2016/02

64/12 - Hematological and Psychophysiological Correlates of Anomalous Information Reception in Mediums Perspective - only abstract available
Investigadores/*Researchers*: Julie Beischel, Shawn Tassone, Mark Boccuzzi
Instituição/*Institution*: The Windbridge Institute for Applied Research in Human Potential, Tucson (USA)
Duração/*Duration*: 2013/05 – 2015/06

66/12 - Body and soul: A computational neurophysiological and qualitative investigation of Ganzfeld-induced imagery
Investigadores/*Researchers*: Alexander Sumich, Daniel Wilson, Nicholas Blagden
Instituição/*Institution*: Nottingham Trent University (NTU), Division of Psychology (UK)
Duração prevista/*Estimated Duration*: 2013/04 – 2016/04

72/12 - The psychophysiology of human attachment and stress
Investigadores/*Researchers*: Angela Clow, Lisa Thorn, Andrea Oskis, Nina Smyth
Instituição/*Institution*: Department of Psychology, University of Westminster, London (UK)
Duração/*Duration*: 2013/10 – 2015/09

77/12 - Human motor re-learning – the use of sensor information fusion
Investigadores/*Researchers*: Sandra Maria Caldas da Silva Mouta, Miguel Velhote Correia, Carolina Vila-Chã, Cláudia Silva, Mariana Silva, Carla Borges, António Salazar, Dominic Noy
Instituição/*Institution*: INESC - Porto (Portugal)
Duração/*Duration*: 2013/06 – 2015/09

83/12 - The Impact of Future Relevance on Dream Content and Sleep-Dependent Memory Processing - only abstract available
Investigadores/*Researchers*: Erin J. Wamsley, Robert Stickgold, Nam Nguyen
Instituição/*Institution*: Furman University, Greenville (USA)
Duração prevista/*Estimated Duration*: 2013/05 – 2016/05

84/12 - Neural bases of time processing: combining neuroimaging techniques and clinical evidence
Investigadores/*Researchers*: Patrizia Bisiacchi, Gianna Maria Toffolo, Vincenza Tarantino, Elias Casula, Giovanni Mento, Demis Basso
Instituição/*Institution*: Dipartimento di Psicologia Generale, Università di Padova (Italy)
Duração prevista/*Estimated Duration*: 2013/03 – 2016/03

89/12 - Interaction of medial and lateral temporal lobe in memory expression: insights from patient and fMRI data - only abstract available
Investigadores/*Researchers*: Ana Luísa Nunes Raposo, José Frederico Henzler Ferreira Marques, José Guilherme Cortez Pimentel
Instituição/*Institution*: Faculdade de Psicologia, Universidade de Lisboa (Portugal)
Duração/*Duration*: 2013/04 – 2016/01

91/12 - Psychophysiological studies into task-set inertia in switching paradigms - only abstract available
Investigadores/*Researchers*: Lisa Evans, Edward Wilding
Instituição/*Institution*: School of Psychology, Cardiff University (UK)
Duração/*Duration*: 2013/04 – 2014/12

92/12 - Dissociating familiarity and conceptual priming with event-related potentials - only abstract available
Investigadores/*Researchers*: Edward Wilding, Lisa Evans
Instituição/*Institution*: School of Psychology, Cardiff University (UK)
Duração/*Duration*: 2013/04 – 2015/01

103/12 - Psychological and psychophysiological factors in sexual desire and behaviour
Investigadores/*Researchers*: Rui Miguel dos Santos Amaro da Costa, Tânia F. Oliveira
Instituição/*Institution*: ISPA, CRL, Lisboa (Portugal)
Duração/*Duration*: 2013/04 – 2015/06

108/12 - Clinical parapsychology: Counselling experiences of clients who report anomalous experiences and the training needs of therapists
Investigador/*Researcher*: Elizabeth Roxburgh
Instituição/*Institution*: Centre for the Study of Anomalous Psychological Processes (CSAPP), Division of Psychology, School of Social Sciences, The University of Northampton (UK)
Duração/*Duration*: 2013/07 – 2015/10

112/12 – Retinotopic reorganization of the auditory cortex of congenitally deaf individuals due to neuroplasticity
Investigadores/*Researchers*: Jorge Manuel Castelo Branco de Albuquerque Almeida, Bradford Zack Mahon, Yanchao Bi, Óscar Filipe Coelho Neves Gonçalves
Instituição/*Institution*: Faculdade de Psicologia e Ciências da Educação, Universidade de Coimbra (Portugal)
Duração/*Duration*: 2013/05 – 2015/11

119/12 - Dynamic cortical and nucleus accumbens networks in humans: combining intracranial and MEG recordings
Investigadores/*Researchers*: Bryan Strange, Javier J. Gonzalez-Rosa, Juan A. Barcia, Stephan Moratti, Raffael Kaplan, Marijn Kroe
Instituição/*Institution*: Laboratory for Clinical Neuroscience, Centre for Biomedical Technology (CTB), Technology University of Madrid (UPM) and Fundación para la Investigación Biomédica del Hospital Clínico San Carlos - Universidad Complutense de Madrid. Instituto de Investigación Sanitario IdISSC (Spain)
Duração prevista/*Estimated Duration*: 2013/06 – 2016/06

122/12 - EEG Analysis of Auditory and Visual Stimuli in Normal Controls
Investigadores/*Researchers*: William Bunney, Blynn Bunney, James Fallon, Julie Patterson, Steven G. Potkin, Richard Stein, Joseph Wu
Instituição/*Institution*: Department of Psychiatry & Human Behavior, The Regents of the University of California, Irvine (USA)
Duração prevista/*Estimated Duration*: 2013/05 – 2016/07

124/12 - EEG correlates of mental entanglement at distance - only abstract available
Investigadores/*Researchers*: Patrizio Tressoldi, Francesco Salvadori, Patrizio Caini, Simone Melloni, Giorgio Gagliardi, Mirko de Vita, Alessandro Ferrini
Instituição/*Institution*: Dipartimento di Psicologia Generale, Università di Padova and Laboratorio Interdisciplinare di Ricerca Biopsicocibernetica, Bologna (Italy)
Duração prevista/*Estimated Duration*: 2013/03 – 2016/03

126/12 - Implicit and explicit processing of emotion in healthy adult ageing - only abstract available
Investigador/*Researcher*: Sarah MacPherson
Instituição/*Institution*: Human Cognitive Neuroscience Unit, Department of Psychology, PPLS, The University of Edinburgh (UK)
Duração/*Duration*: 2013/08 – 2014/10

132/12 - A direct test of the binding by synchrony hypothesis in humans: the neural correlates of coherent object perception
Investigadores/*Researchers*: Miguel Castelo-Branco, Maria Ribeiro, João Duarte, Gabriel Costa
Instituição/*Institution*: IBILI, Faculdade de Medicina, Universidade de Coimbra (Portugal)
Duração/*Duration*: 2013/11 – 2016/01

133/12 - The role of the core and extended face networks in visual perception and high level social cognition
Investigadores/*Researchers*: Miguel Castelo-Branco, Marco Simões, Carlos Amaral, Gregor Philipiak, José Rebola, João Castelhano
Instituição/*Institution*: IBILI, Faculdade de Medicina, Universidade de Coimbra (Portugal)
Duração/*Duration*: 2013/11 – 2016/01

167/12 - Impact of body image related variables on the psychophysiological indicators of human sexual response: comparative study with a clinical and non clinical sample
Investigadores/*Researchers*: Maria João Alvarez Martins, Pedro Nobre, Ellen Laan, Sandra Byers, Lisa Vicente, Nuno Monteiro Pereira, Patrícia Pascoal
Instituição/*Institution*: Faculdade de Psicologia da Universidade Lisboa and SEXLAB (Laboratórios de Investigação em Sexualidade Humana), Faculdade de Psicologia e Ciências da Educação da Universidade do Porto (Portugal)
Duração prevista/*Estimated Duration*: 2013/03 – 2016/04

191/12 - Defining the functional architecture of motion vision sensitive visual-motor circuits
Investigadores/*Researchers*: Eugenia Chiappe, Tomás Cruz
Instituição/*Institution*: Fundação Champalimaud, Lisboa (Portugal)
Duração prevista/*Estimated Duration*: 2013/08 – 2016/07

198/12 - Enhancing hypnotic suggestibility with transcranial direct current stimulation
Investigador/*Researcher*: Devin Blair Terhune
Instituição/*Institution*: The Chancellor, Masters and Scholars of the University of Oxford, Experimental Psychology (UK)
Duração/*Duration*: 2014/03 – 2015/02

199/12 - Brain-to-Brain Communication Enabled with Intracortical Microstimulation
Investigadores/*Researchers*: Miguel Angelo Laporta Nicolelis, Miguel Santos Pais Vieira
Instituição/*Institution*: Duke University, Durham (USA)
Duração/*Duration*: 2013/04 – 2015/10

209/12 - Predicting your decision while you make up your mind – an intracranial human study of the neural underpinning of decision making - only abstract available
Investigadores/*Researchers*: Uri Muz Maoz, Liad Mudrik, Ian Ross, Adam Mamelak, Ralph Adolphs
Instituição/*Institution*: California Institute of Technology, Pasadena and Cedars-Sinai Medical Center, Los Angeles (USA)
Duração/*Duration*: 2013/05 – 2015/02

217/12 - Temporal modulation of the subventricular zone neural stem cell niche by choroid plexus-cerebrospinal fluid derived factors
Investigadores/*Researchers*: João Carlos Cruz de Sousa, Fernanda Marques, Joana Palha, Ana Luísa Falcão, Ashley Novais
Instituição/*Institution*: ICVS/3B's - Laboratório Associado (ICVS/3B's), Universidade do Minho, Braga (Portugal)
Duração prevista/*Estimated Duration*: 2013/08 – 2016/04

220/12 - Consciousness Disconnects During Sleep - only abstract available
Investigador/*Researcher*: Giovanni Piantoni
Instituição/*Institution*: Cortical Physiology Lab, Massachusets General Hospital, Harvard Medical School (USA) and Netherlands Institute for Neuroscience, Amsterdam (The Netherlands)
Duração prevista/*Estimated Duration*: 2013/09 – 2016/04

222/12 - EEG functional connectivity in post-hypnotic amnesia - only abstract available
Investigadores/*Researchers*: Marios Kittenis, Graham Jamieson
Instituição/*Institution*: Koestler Parapsychology Unit, The University of Edinburgh (UK) and Neuropsychology Lab, School of Behavioural, Cognitive, and Social Sciences, The University of New England, Armindale (Australia)
Duração prevista/*Estimated Duration*: 2013/06 – 2016/04

224/12 - The magic of perception: Investigating misdirection and change blindness in magic using the novel combination of gaze behaviour and ERPs - only abstract available
Investigadores/*Researchers*: Tim J. Smith, Rebecca Nako
Instituição/*Institution*: Dynamic Visual Cognition (DVC) Lab, Dept. of Psychology, Birkbeck, University of London (UK)
Duração prevista/*Estimated Duration*: 2013/04 – 2016/03

225/12 - Roles of the reward system in sleep, dreaming, and the consolidation of emotional memories - only abstract available
Investigadores/*Researchers*: Sophie Schwartz, Lampros Perogamvros, Kristoffer Aberg, Virginie Sterpenich
Instituição/*Institution*: Geneva Neuroscience Center, University of Geneva (Switzerland)
Duração/*Duration*: 2013/10 – 2016/02

227/12 - System mechanisms of attention: toward the nature of hypnotizability
Investigadores/*Researchers*: Zinaida I. Storozheva, A. V.Kirenskaya, V. Y. Novototsky-Vlaso, A. N. Chistyakov, V. V. Myamlin, S. V. Solntseva
Instituição/*Institution*: P. K. Anokhin Institute of Normal Physiology and Serbsky National Research Centre for Social and Forensic Psychiatry, Moscow (Russia)
Duração prevista/*Estimated Duration*: 2013/04 – 2016/04

233/12 - The Study of Experimenter Effects in the Replication of Psi Experiments: A Global Initiative
Investigadores/*Researchers*: Marilyn Schlitz, Daryl Bem, Arnaud Delorme
Instituição/*Institution*: Institute of Noetic Sciences, Petaluma (USA)
Duração/*Duration*: 2013/07 – 2015/04

234/12 - Visual categorization of images of live and deceased individuals
Investigadores/*Researchers*: Arnaud Delorme, Dean Radin
Instituição/*Institution*: Centre de Recherche Cerveau et Cognition, Toulouse (France) and Institute of Noetic Sciences, Petaluma (USA)
Duração/*Duration*: 2014/02 – 2015/06

248/12 - Using hypnosis to distinguish between cognitive and metacognitive conscious experience
Investigadores/*Researchers*: Pedro Alexandre Magalhães de Saldanha da Gama, Axel Cleeremans, Zoltan Dienes, Amir Raz
Instituição/*Institution*: Université Libre de Bruxelles (Belgium)
Duração/*Duration*: 2013/11 – 2015/05

252/12 - Sleep state misperception mispercieved
Investigadores/*Researchers*: Eus J. W. Van Someren, J. Ramautar
Instituição/*Institution*: Netherlands Institute for Neuroscience, Dept. Sleep & Cognition, Amsterdam (The Netherlands)
Duração prevista/*Estimated Duration*: 2014/06 – 2016/04

256/12 - Contemplative Development Mapping Project
Investigadores/*Researchers*: Willoughby Britton, Catherine Kerr, Harold Roth, Jared Lindahl, Jake Davis, Chris Kaplan, Nathan Fisher
Instituição/*Institution*: The Clinical and Affective Neuroscience Laboratory, Brown University and Department of Psychiatry and Human Behavior, Brown University Medical School, Providence (USA)
Duração prevista/*Estimated Duration*: 2013/07 – 2017/04

270/12 - Synchronicity and Psi: A Controlled Comparison
Investigadores/*Researchers*: John Palmer, Nick Edington
Instituição/*Institution*: Rhine Research Center, Durham (USA)
Duração/*Duration*: 2013/03 – 2015/01

272/12 - Exploring the interactions between paranormal belief and disbelief and subjective experiences with the Shakti helmet
Investigadores/*Researchers*: Christine Simmonds-Moore, Don Rice, Ron Hopkins, Richard LaFleur, Chase O'Gwin
Instituição/*Institution*: Psychology Department, University of West Georgia, Carrollton (USA)
Duração prevista/*Estimated Duration*: 2013/09 – 2016/04

2014

282/14 - The Mindful Eye: Smooth Pursuit and Saccadic Eye Movements in Meditators and Non-meditators
Investigadores/*Researchers*: Veena Kumari, Elena Antonova
Instituição/*Institution*: Institute of Psychiatry, King's College London (UK)
Duração prevista/*Estimated Duration*: 2015/04 – 2016/08

PALESTRANTES E MODERADORES
SPEAKERS AND MODERATORS

FABRIZIO BENEDETTI Professor de Neurofisiologia e Fisiologia Humana na *University of Turin - Medical School*, Itália. Membro do *European Working Group on Pain and Impaired Cognition* e do *European Dana Alliance for the Brain*. Recebeu o prémio *Seymour Solomon Award*, da *American Headache Society* e o "Helitzka Prize", da *Academy of Sciences*, Turim. Membro do Conselho Editorial da revista *Pain* e da *Current Neuropharmacology*. Interesses científicos: neurofisiologia, efeito placebo, dor, nocebo.

Professor of Neurophysiology and Human Physiology, University of Turin Medical School, Italy. Member of the European Working Group on Pain and Impaired Cognition. Member of the European Dana Alliance for the Brain. Awarded the "Seymour Solomon Award" of the American Headache Society and the "Helitzka Prize", Academy of Sciences, Turin. Member of the Editorial Board of Pain and Current Neuropharmacology. Research interests: neurophysiology, placebo effect, pain, nocebo.

DICK BIERMAN Regente (Jubilado) da Cadeira *Heymans* de Experiências Excecionais, Universidade de Humanísticas, Utrecht, Holanda. Doutorado em Física Experimental, Universidade de Amesterdão, Holanda. Interesses científicos: estudos da consciência, inteligência artificial, aprendizagem sob estados alterados de consciência (em especial durante o sono), papel das emoções não conscientes na tomada (intuitiva) de decisão, pré-sentimento (excitação corporal anómala, que precede acontecimentos emocionais), relação entre a física quântica e consciência.

Heymans Chair of Exceptional Experiences, University for Humanistics, Utrecht, Netherlands (Emeritus). PhD in Experimental Physics, University of Amsterdam, Netherlands. Research interests: consciousness studies, artificial intelligence, learning during altered states of consciousness (especially during sleep), non-conscious emotions and their role in (intuitive) decision-making, pre-sentiment (anomalous body arousal preceding emotional events), relation between quantum physics and consciousness.

MIGUEL CASTELO-BRANCO Professor de Biofísica e Matemática e Ciências da Visão e Diretor do IBILI e ICNAS, Universidade de Coimbra. Vários prémios na área das Neurociências. Dezenas de artigos publicados na área da Bioengenharia, Neurociência da Visão e Neurociência Clínica. Consultor (*peer-reviewer*) de várias revistas científicas nas áreas de Neurociências e Ciências da Visão. Secretário científico da Sociedade Europeia EVER (Ciências da Visão). Interesses científicos: neurociências sensoriais e cognitivas em populações saudáveis e doentes.

Professor of Biophysics and Mathematics and Visual Sciences and Director of IBILI and ICNAS, University of Coimbra. Several awards on Neuroscience. Dozens of papers published on Bioengineering, Visual Neuroscience and Clinical Neuroscience. Consultant (peer-reviewer) for several journals on Neuroscience and Visual Sciences. Scientific Secretary of the European Society EVER (Visual Sciences). Research interests: sensory and cognitive neuroscience in healthy and ill populations.

AXEL CLEEREMANS Diretor de Investigação, Grupo da Consciência, Cognição e Computação, Universidade Livre de Bruxelas, Bélgica. Autor de múltiplos artigos científicos sobre aprendizagem implícita e consciência e editor dos livros *"The Unity of Consciousness: Binding, Integration and Dissociation"* e *"The Oxford Companion to Consciousness".* Membro da Real Academia da Bélgica. Interesses científicos: consciência e aprendizagem implícita, modelos de cognição consciente e não consciente, rede neuronal de processos cognitivos.

Research Director, Consciousness, Cognition & Computation Group, Université Libre de Bruxelles, Belgium. Author of numerous papers on implicit learning and consciousness and editor of the books "The Unity of Consciousness: Binding, Integration and Dissociation" and "The Oxford Companion to Consciousness". Member of the Royal Academy of Belgium. Research interests: consciousness and implicit learning, models of conscious and unconscious cognition, neural network of cognitive processes.

LARRY DOSSEY Médico de Medicina Interna, autor, consultor e docente. Cofundador e editor-executivo da revista, *com revisão por pares, Explore: The Journal of Science and Healing* e foi fundador e editor-executivo da revista *Alternative Therapies in Health and Medicine*. Foi presidente do *The Isthmus Institute of Dallas*. Anterior co-presidente do painel sobre Intervenções Mente/Corpo, do *National Centre for Complementary and Alternative Medicine, National Institutes of Health*. Publicou numerosos artigos e é autor de doze livros, entre os quais *One Mind: How Our Individual Mind Is Part of a Greater Consciousness and Why lt Matters* (2013), *The Power of Premonitions: How Knowing the Future Can Shape Our Lives* (2009). Interesses científicos: sustentar o chamado movimento de saúde holística num modelo que seja cientificamente respeitado e que, ao mesmo tempo, responda às necessidades espirituais íntimas do ser humano.

Physician of Internal Medicine, author, consultant and lecturer. Co-Founder and executive editor of the peer-reviewed journal Explore: The Journal of Science and Healing and was founder and executive editor of the journal Alternative Therapies in Health and Medicine. Past president of The Isthmus Institute of Dallas. Former co-chairman of the Panel on Mind/Body Interventions, National Centre for Complementary and Alternative Medicine, National Institutes of Health. Published numerous articles and is the author

of twelve books, including One Mind: How Our Individual Mind Is Part of a Greater Consciousness and Why lt Matters (2013), The Power of Premonitions: How Knowing the Future Can Shape Our Lives (2009). Scientific interests: to anchor the so-called holistic health movement in a model that is scientifically respectable and which, at the same time, answers to humankind's inner spiritual needs.

PAUL ENCK Diretor de Investigação e Professor no Departamento de Medicina Interna VI/ Medicina Psicossomática e Psicoterapia dos *University Hospitals Tübingen*, Alemanha. Possui mais de 190 artigos publicados com dados originais em revistas científicas com revisão por pares principalmente em neurogastroenterologia. É Presidente Honorário da *German Neurogastro Society*. É revisor em diversas agências de financiamento e consultor de numerosas empresas farmacêuticas e de tecnologia médica. Interesses científicos: medicina psicossomática, psicoterapia e neurogastroenterologia.

Director of Research and Professor, Department of Internal Medicine VI/ Psychosomatic Medicine and Psychotherapy, University Hospitals Tübingen, Germany. More than 190 original data paper in scientific, peer-reviewed journals mainly in neurogastroenterology. Honorary President of the German Neurogastro Society. Reviewer for several grant agencies and consultant for numerous companies in pharma and medical technology. Research interests: psychosomatic medicine, psychotherapy and neurogastroenterology.

DAMIEN FINNISS Professor Associado, investigador e médico na *University of Sydney Pain Management Research Institute, Royal North Shore Hospital*, e *Griffith University School of Rehabilitation Sciences*, Australia. Presidente da *International Association for the Study of Pain* (IASP), grupo do Placebo. Tem um *background* clínico ímpar, com formação clínica inicial e experiência em fisioterapia, tendo-se especializado em gestão da dor e trabalhado num grande centro multidisciplinar de gestão da dor crónica. Continuou depois com formação clínica em medicina, trabalhando tanto em doenças agudas como crónicas, antes de regressar à prática da Anestesia e da Medicina da Dor. Publicou múltiplos artigos e capítulos de livros sobre o tema do Placebo. Interesses científicos: papel do contexto terapêutico e como este pode modular a dor e os resultados dos tratamentos, efeitos de placebo e implicações clínicas da investigação acerca do placebo.

Associate Professor, researcher and clinician, University of Sydney Pain Management Research Institute, Royal North Shore Hospital, and Griffith University School of Rehabilitation Sciences, Australia. Chairman of the International Association for the Study of Pain (IASP) group on Placebo. He has a unique clinical background with initial clinical training and experience in Physiotherapy, where he specialised in Pain Management working in a large multidisciplinary chronic pain management centre. He then proceeded to clinical training in medicine, working in both general acute and chronic medicine, before returning to current

roles in Anaesthesia and Pain Medicine practice. Published multiple papers and textbook chapters on the topic Placebo. Scientific interests: role of the therapeutic context and how this can modulate pain and treatment outcomes, placebo effects and clinical implications of the research on placebo.

RAINER GOEBEL Professor Catedrático de Neurociência Cognitiva, Faculdade de Psicologia e Neurociência, Universidade de Maastricht, Holanda. Diretor fundador do *Maastricht Brain Imaging Centre* (M-BIC) e líder de equipa do grupo "*Neuromodeling and Neuroimaging*", *Netherlands Institute for Neuroscience (NIN), Royal Netherlands Academy of Arts and Sciences (KNAW).* Interesses científicos: representações neuronais no cérebro e o modo como estas são processadas para permitir funções percetivas e cognitivas específicas, correlatos neuronais de perceção visual, aplicações clínicas nas interfaces cérebro-computador (ICC) e estudos de *neurofeedback*.

Full professor for Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands. Founding director of the Maastricht Brain Imaging Centre (M-BIC) and team leader of the "Neuromodeling and Neuroimaging" group, Netherlands Institute for Neuroscience (NIN), Royal Netherlands Academy of Arts and Sciences (KNAW). Research interests: neuronal representations in the brain and how they are processed to enable specific perceptual and cognitive functions, neural correlates of visual awareness, clinical applications in brain computer interfaces (BCls) and neurofeedback studies.

ANTONIO GUERCI Professor de Antropologia, Diretor do Departamento de Ciências Antropológicas, Diretor do Museu de Etnomedicina " A. Scarpa", e Diretor da cadeira da UNESCO "Antropologia da saúde. Biosfera e sistemas de cura", *University of Genoa*, Itália. Consultor especializado na *Chinese University of Hong Kong*, China, no "Programa de Medicinas Tradicionais", e na *University of Toluca*, México, no programa "Antropologia e Dor". Professor Honorário na *Universidad Cientifica del Sur*, Lima, Perú. Vice-presidente da *European Society of Ethnopharmacology*. Publicou mais de 380 títulos incluindo livros, monografias, artigos e comunicações científicas. Interesses científicos: antropologia médica, etnomedicina, biotipologia humana e adaptação ambiental, cultural e biológica de diferentes populações humanas.

Full Professor of Anthropology, Head, Department of Anthropological Sciences, Head of the Museum of Ethnomedicine "A. Scarpa", and Head of UNESCO Chair "Anthropology of health. Biosphere and care systems", University of Genoa, ltaly. Expert Adviser of the Chinese University of Hong Kong, China, in "Traditional Medicines Programme", and of the University of Toluca, Mexico, in the programme "Anthropology and Pain". Honorary Professor in Universidad Cientifica del Sur, Lima, Peru. Vice President of the European Society of Ethnopharmacology. Published over 380 titles including books, monographs, articles

and scientific communications. Research interests: medical anthropology, ethnomedicine, human biotypology and environmental, cultural and biological adaptation of different human populations.

TED KAPTCHUK Professor de Medicina na *Harvard Medical School*, Boston; Professor Adjunto na *School of Public Health, University of Alabama*, Birmingham, e Diretor do *Harvard-wide Program in Placebo Studies & Therapeutic Encounter* sedeado no *Beth Israel Deaconess Medical Centre*, Boston, EUA. Membro do Conselho Editorial e revisor em revistas de excelência em Medicina e Medicina Alternativa e Complementar. Interesses científicos: investigação multidisciplinar dos efeitos placebo, controlos placebo e a relação paciente-médico como integradora de conceitos, desenhos de investigação e métodos analíticos provenientes das ciências clínicas, básicas e sociais, bem como das humanidades, Medicina Tradicional Chinesa, experiências fisiológicas, neuroimagem, investigação antropológica e medicina integrativa orientada para o paciente.

Professor of Medicine, Harvard Medical School, Boston, Adjunct Professor, School of Public Health, University of Alabama, Birmingham, and Director of the Harvard-wide Program in Placebo Studies & Therapeutic Encounter hosted at the Beth Israel Deaconess Medical Centre, Boston, USA. Member of the Editorial and Peer-Review Board of outstanding Journals in Medicine and Alternative and Complementary Medicine. Research interests: multi-disciplinary investigation of placebo effects, placebo controls and the patient-physician relationship that integrates concepts, research designs and analytic methods drawn from the clinical, basic, and social sciences as well as the humanities, Traditional Chinese Medicine, physiological experiments, neuroimaging, anthropological investigations, patient-oriented integrative medicine.

IRVING KIRSCH Diretor Associado do Programa em Estudos de Placebo no *Beth Deaconess Israel Medical Center*, EUA, Professor em Medicina, na *Harvard Medical School*, Professor Jubilado das Universidades de Plymouth, Hull e Connecticut. Editor Associado: *National Library for Health, Complementary and Alternative Medicine Specialist Library, NHS,* e de *Contemporary Hypnosis & lntegrative Therapy, Hypnosis lnternational Monographs.* Publicou mais de 240 artigos em revistas de excelência e dez livros, entre os quais *Handbook of clinical hypnosis (2010)* e *The emperor's new drugs: Exploding the antidepressant myth (2010).* Interesses científicos: efeito placebo, depressão, antidepressivos, acupuntura, sugestão, sugestionabilidade, automatismo, memória, psicoterapia cognitivo-comportamental, hipnose, ansiedade, história e filosofia da psicologia.

Associate Director Program in Placebo Studies, Beth Deaconess Israel Medical Center, USA, Lecturer in Medicine, Harvard Medical School, Professor Emeritus, Universities of Plymouth, Hull and Connecticut. Associate Editor: National Library for Health, Complementary and Alternative Medicine Specialist Library, NHS, and of Contemporary Hypnosis & lntegrative Therapy, Hypnosis lnternational Monographs. Published more than 240 papers in outstanding scientific journals and ten books, among them Handbook of clinical hypnosis (2010) and The emperor's new drugs: Exploding the antidepressant myth (2010). Research interests: placebo effects, depression, antidepressants, acupuncture, suggestion, suggestibility, automaticity, memory, cognitive-behavioral psychotherapy, hypnosis, anxiety, history and philosophy of psychology.

FERNANDO LOPES DA SILVA Professor Jubilado de Fisiologia Geral, Universidade de Amesterdão, Holanda, e *Investigador Coordenador do* Instituto Superior Técnico (IST) de Lisboa. Interesses científicos: eletrofisiologia do cérebro, origens do fenómeno epilético, redes neuronais em relação com a memória, atenção e consciência.

Emeritus Professor of General Physiology, University of Amsterdam, The Netherlands, and Head researcher of the Higher Technical Institute (IST) of Lisbon, Portugal. Research interests: electrophysiology of the brain, origin of epileptic phenomena, neuronal networks in relation to memory, attention and consciousness.

AMIR RAZ Professor Associado, Neurociências e Psicologia, *Canada Research Chair* em Neurociência Cognitiva da Atenção, Departamento de Psiquiatria, Faculdade de Medicina, *McGill University*, Montréal, Canadá. Comunicador ativo sobre ciência popular com documentários sobre tópicos específicos da neurociência (por ex. na BBC, National Geographic e CBC). Autor de mais de uma centena de publicações com revisão por pares em revistas de excelência e dos dois recentes livros *Talking Placebos: Modern perspectives on placebos in society* e *Hypnosis and Meditation: Towards an Integrative Science of Conscious Planes*. Interesses científicos: psicologia, neurociências (processos automáticos e controlo voluntário), filosofia, pensamento crítico, neuropsicologia, hipnose, ciência do placebo.

Associate Professor, Neuroscience and Psychology, Canada Research Chair in the Cognitive Neuroscience of Attention, Department of Psychiatry, Faculty of Medicine, McGill University, Montréal, Canada. Active communicator of popular science with documentaries on specific neuroscience topics (e.g., with the BBC, National Geographic, and CBC). Authored more than a hundred peer-reviewed publications in outstanding journals as well as the two recent books "Talking Placebos: Modern perspectives on placebos in society" and "Hypnosis and Meditation: Towards an Integrative Science of Conscious Planes". Research interests: psychology, neuroscience (automatic processes and voluntary control), philosophy, critical thinking, neuropsychology, hypnosis, placebo science.

TANIA RE Professora Assistente de Etnomedicina e Etnopsicologia, na Faculdade de Medicina, Turim, *University of Florence*, Itália. Psicóloga, Antropologista Médica, Fundadora e membro da Direção da cadeira da UNESCO "Antropologia da saúde, Biosfera e sistemas de cura" *University of Genoa*, Itália. Investigadora e bolseira no Centro Regional de Fitoterapia (CERFIT) no Hospital Careggi, Florença, Itália. Interesses científicos: investigação no Perú no âmbito da medicina tradicional, antropologia médica, processos de cura tradicionais interligando a mente, o corpo e o espírito e Plantas Mestras e os Estados de Consciência.

Assistant Professor of Ethnomedicine and Ethnopsychology, Faculty of Medicine, Torino, and University of Florence, Italy. Psychologist, Medical Anthropologist, Founder and Board Member of the UNESCO Chair "Health Anthropology, Biosphere and Healing systems", University of Genoa, Italy. Researcher and fellow at the Regional Centre for Phytotherapy (CERFIT) in Careggi Hospital, Florence, Italy. Research interests: field research in Peru on traditional medicine, medical anthropology, traditional healing systems processes connecting mind, body and spirit and Teaching Plants and States of Consciousness.

MANFRED SCHEDLOWSKI Professor e Diretor do Instituto de Psicologia Médica e Imunobiologia Comportamental da Faculdade de Medicina, *University of Duisburg-Essen*, Alemanha, com uma interrupção para investigação como Professor de Psicologia e Imunobiologia comportamental no *Swiss Federal lnstitute of Technology (ETH)*, Zurique, Suíça (2004-2007). Interesses científicos: neurobiologia das respostas placebo e nocebo, em particular os mecanismos e a relevância clínica do comportamento ou condicionamento Pavloviano das funções imunes e neuro-endócrinas.

Professor and Director of the lnstitute of Medical Psychology and Behavioural lmmunobiology, Medical Faculty, University of Duisburg-Essen, Germany, interrupted by a research stay as Professor of Psychology and Behavioural lmmunobiology, Swiss Federal lnstitute of Technology (ETH), Zürich, Switzerland (2004-2007). Research interests: neurobiology of placebo and nocebo responses, in particular the mechanisms and clinical relevance of behavioural or Pavlovian conditioning of immune and neuroendocrine functions.

STEFAN SCHMIDT Investigador e Diretor da Secção Académica do Grupo de Avaliação de Medicina Complementar, Departamento de Medicina Psicossomática e Psicoterapia, do *University Medical Centre*, Freiburg, Alemanha. Professor de Estudos Transculturais da Saúde na *Europa University Viadrina*, Frankfurt (Oder), Alemanha. Interesses científicos: medicina complementar e alternativa, psicofisiologia, investigação em consciência, meditação atencional consciente ("*mindfulness*"), parapsicologia experimental, experiências excecionais, investigação sobre placebo e interface cérebro-computador.

Research Fellow and Head of the Academic Section at the Evaluation Group for Complementary Medicine, Department of Psychosomatic Medicine and Psychotherapy, University Medical Centre, Freiburg, Germany. Professor of Transcultural Health Studies, Europa University Viadrina, Frankfurt (Oder), Germany. Research interests: complementary and alternative medicine, psychophysiology, consciousness research, mindfulness meditation, experimental parapsychology, exceptional experiences, placebo research and brain-computer interface.

MÁRIO SIMÕES Professor de Psiquiatria e de Ciências da Consciência, Faculdade de Medicina de Lisboa. Diretor do Curso de Pós-Graduação em Hipnose Clínica e Experimental da Faculdade de Medicina de Lisboa. Interesses científicos: psicologia e psicofisiologia dos estados alterados de consciência, etnomedicina, experiências excecionais humanas e psicologia e espiritualidade.

Professor of Psychiatry and Consciousness Sciences, Faculty of Medicine of Lisbon, Portugal. Director of the Post-Graduation Course in Clinical and Experimental Hypnosis, Faculty of Medicine of Lisbon. Research interests: psychology and psychophysiology of altered states of consciousness, ethnomedicine, human exceptional experiences and psychology and spirituality.

JESSICA UTTS Professora e Regente do Departamento de Estatística, *University of California*, Irvine, EUA. Diretora de avaliação no *Advancement Placement Statistics in the Educational Testing Service*. Presidente da Direção do *Consortium for the Advancement of Undergraduate Statistics Education* (CAUSE) e membro da Direção do *Institute of Statistical Sciences* (NISS). Publicou artigos científicos sobre questões estatísticas na parapsicologia e na medicina alternativa. Editora do livro *Seeing Through Statistics,* 4ª edição *(2014)* e coeditora do livro *Mind On Statistics, 5ª Edição (2015)* e *Statistical ldeas and Methods (2006).* Interesses científicos: estatística aplicada.

Professor and Chair, Department of Statistics, University of California, Irvine, USA. Chief Reader, Advancement Placement Statistics in the Educational Testing Service. Chair of the Board of the Consortium for the Advancement of Undergraduate Statistics Education (CAUSE) and member of the Board of National Institute of Statistical Sciences (NISS). Published scientific papers on statistics of parapsychological and alternative medicine issues. Editor of the book Seeing Through Statistics, 4th Edition (2014) and co-editor of Mind On Statistics, 5th Edition (2015) and of Statistical Ideas and Methods (2006). Research interests: applied statistics.

TOR WAGER Professor de Psicologia e Neurociências e docente no *Institute for Cognitive Science, University of Colorado*, Boulder, EUA. Membro do Conselho Editorial e revisor em revistas de excelência em psiquiatria e neurociências. Interesses científicos: a influência do pensamento em experiências afetivas, comunicação cérebro-corpo e *software*/ferramentas para análise fMRI.

Professor of Psychology and Neuroscience and faculty member in the Institute for Cognitive Science, University of Colorado, Boulder, USA. Member of the Editorial and Peer-Review Board of outstanding Journals in Psychiatry and Neurosciences. Research interests: influence of thought in affective experiences, brain-body communication and software toolboxes for fMRI analysis.

CAROLINE WATT Membro fundador do *Koestler Parapsychology Unit* e Docente Sénior, Departamento de Psicologia, Universidade de Edimburgo, Escócia. Foi Investigadora Sénior *Perrott-Warrick* e Presidente da *Parapsychological Association*. É coautora do livro "*An Introduction to Parapsychology*" e autora de artigos em livros e revistas científicas na área da parapsicologia e de crenças paranormais. Interesses científicos: questões de replicabilidade em parapsicologia, a psicologia e a parapsicologia de experiências de sonhos pré-cognitivos.

A founder member of the Koestler Parapsychology Unit, and Senior Lecturer, Psychology Department, University of Edinburgh, Scotland. Former Perrott-Warrick Senior Researcher and Past President of the Parapsychological Association, co-author of the book "An Introduction to Parapsychology" and author of journal articles on parapsychology and paranormal beliefs. Research interests: replication issues in parapsychology, the psychology and parapsychology of precognitive dream experiences.

JON-KAR ZUBIETA Professor de Psiquiatria e Radiologia na *University of Michigan* e Professor de Investigação no *Molecular and Behavioural Neuroscience Institute*, *University of Michigan*, Ann Arbor, EUA. Revisor *ad hoc* para mais de sessenta revistas de excelência, principalmente em Psiquiatria e Neurociências e membro do conselho editorial de revistas em neurociências. Publicou mais de 160 artigos originais em revistas científicas com revisão por pares. Interesses científicos: Neuroimagem Funcional, mecanismos reguladores do *stress* e da emoção no cérebro humano, patofisiologia do humor e dos distúrbios da utilização de substâncias, integração de mecanismos genético-neurobiológicos nas perturbações de humor e de uso de substâncias e mecanismos neurobiológicos dos efeitos placebo.

Professor of Psychiatry and Radiology, University of Michigan, and Research Professor, Molecular and Behavioural Neuroscience Institute, University of Michigan, Ann Arbor, USA. Ad-hoc reviewer in more than sixty outstanding Journals, mainly in Psychiatry and Neurosciences and member of the editorial board of Journals in Neurosciences. Published more than 160 original papers in scientific, peer-reviewed journals. Research interests: functional neuroimaging, stress and emotion regulatory mechanisms in the human brain, pathophysiology of mood and substance use disorders, integration of genetic-neurobiological mechanisms in mood and substance use disorders and neurobiological mechanisms of placebo effects.

Posters com resultados finais apresentados pelos bolseiros da Fundação Bial
Posters with final results presented by the Bial Foundation Fellows

2008

119/08 - "Comparison between false memories and subliminal stimulation in DRM paradigm"
Investigadores/*Researchers*: Maria de Fátima de Jesus Simões, Isabel Maria Barbas dos Santos, Paulo Joaquim Fonseca da Silva Farinha Rodrigues
Instituição/*Institution*: Centro de Investigação em Educação e Ciências do Comportamento, Departamento de Ciências da Educação, Universidade de Aveiro (Portugal)
Duração/*Duration*: 2009/02 – 2015/09

Abstract: The DRM paradigm is very robust and provides results consistently producing false memories. We review the concepts associated with memory as well as the main theories that attempt to explain the process of formation of false memories in this paradigm. We proposed that the modification of the visual cues of stimuli between the stages of study and recovery may increase the formation of false memories. To test this hypothesis we planned 3 experiments. In the **first experiment**, a behavioral assessment comparing two groups was performed. The first group received the items in the traditional way, with no differences in the presentation of items between the study phase and the recognition phase. For the second group, the items were displayed in uppercase letters in the study phase, and lowercase letters in the recovery phase. **The results** show an increase in the production of false memories. We concluded that this was due to the removal of visual cues promoting decisions based on familiarity and concepts of words. In the **second experiment**, we assessed the skin conductance response to the DRM paradigm and the amendment referred above. **The results** points out to the conclusion that the skin conductance response is closely associated with the orientation response to the items previously studied. In the **third study**, we explored the differences between the evoked potential of the recovery process occurring in the presence and absence of physical cues of the perceptive aspects. **The results** indicate greater activity related to the familiarity in the group that observe the change of visual cues from the study phase to the recovery phase. We found further novel effects that have inverse response relationships in the group where the items differ in terms of the physical cues from the study phase and the recovery phase.
We also present the validation of an automated quotation system for skin conductance data.

Keywords: Memory, DRM paradigm, Electrodermal activity, Evoked potentials

2010

61/10 - "Translation of neuron-glia interactions in complex cognitive functions"
Investigadores/*Researchers*: João Filipe Pedreira de Oliveira, Nuno Sérgio Mendes Dias, Luis Ricardo Monteiro Jacinto
Instituição/*Institution*: Instituto de Investigação em Ciências da Vida e da Saúde (ICVS), Escola de Ciências da Saúde, Universidade do Minho, Braga (Portugal)
Duração/*Duration*: 2011/05 – 2015/07

Objectives: The classical paradigm that cognitive processing is exclusively neuronal has been challenged in the past 2 decades by an exciting body of evidence. Indeed, the importance of glial cells is rising due to emerging data supporting dynamic neuron-glia interactions, in which a cross-talk between astrocytes and neurons complements and modulates the communication between pre- and post-synaptic structures. The main research objective of this project was to assess the interplay between astrocytes and neurons underlying cognitive function in the brain.

Method: We have used dnSNARE mice in which we interfere with the release of neurotransmitters by astrocytes. This way, we have blocked the astrocyte-to-neuron dialogue. We have used complementary state-of-the-art techniques such as in vivo electrophysiology, innovative behavior, anatomical and molecular analysis, to characterize, monitor and rescue that astrocyte component in the computation of cognitive functions.

Results: The disruption of the astrocyte-to-neuron dialogue led a decrease in performance in behavior tasks dependent on the function of the cortico-limbic circuitry. Interestingly, the electrophysiological performance of those brain areas was critically affected and correlated with cellular and molecular alterations.

Conclusion: Astrocytes are critical elements of the neuroglial network, and the release of neurotransmitters by astrocytes is required for the normal hippocampal function. This information accounts for new knowledge on the cognitive computation and this new player may account also for the cognitive decline observed for instance in ageing or pathological processes, arising as a possible therapeutic target for the treatment of prevention of cognitive deficits in psychiatric disorders.

Keywords: Astrocyte, Electrophysiology, Spatial memory, Hippocampus, Prefrontal cortex

Publications:
Oliveira JF, Sardinha VM, Guerra-Gomes S, Araque A, Sousa N (2015). Do stars govern our actions? Astrocyte involvement in rodents' behavior. *Trends in Neurosciences 38*:535–549.

144/10 - "Nonlinear Processing of Emotional Information: behavioral evidence and neurophysiological correlates"

Investigadores/*Researchers*: Manuel Fernando Santos Barbosa, João Eduardo Marques Teixeira, Fernando Ricardo Ferreira-Santos, Joana Maria Barbosa Vieira, Ana Cristina Basto Abreu
Instituição/*Institution*: Laboratório de Neuropsicofisiologia da Faculdade de Psicologia e Ciências da Educação, Universidade do Porto (Portugal)
Duração/*Duration*: 2011/10 – 2015/01

Objectives: Little is known about how continuously changing emotional expressions are perceived, but it has been hypothesized that specific characteristics of emotional processing can be profitably explored within the framework of the non-linear dynamic systems theory. Recent studies based on such framework report perceptive "jumps" when continua of morphed facial expressions of emotion are presented. Specifically, emotions displayed in the middle of the continua seem to be more frequently decoded accordingly to the initial emotion, being consistent with a Hysteresis effect. In this study we further explore the non-linear properties of emotional processing and examine its EEG correlates.

Method: We developed six continua of 11 frames each, of morphed expressions between pairs of emotions (anger, fear, sadness, happiness). During an EEG recording session, 55 healthy participants observed these continua, from emotion X to Y, Y to X and in random order, and were asked to identify the emotion being presented in each frame.

Results: Behavioral data revealed a remanence effect, with participants still perceiving the initial emotion beyond the mid-point of the continua, resulting in perceptual bimodality of the morphed expressions that are in the vicinity of the turning point between emotional categories. Different N170 mean amplitudes were found for mid-point frames of the continua Anger-Sadness and Sadness-Happiness, while for Fear-Sadness such difference was found for the LPP of the frame-related brain potentials.

Conclusion: Results suggest a generalized hysteresis effect in the processing of facial expressions of emotion, and the same expression seems to induce different brain responses, depending on preceding stimuli.

Keywords: Hysteresis, Emotions, ERP, EEG

Publications:

Barbosa, F., Almeida, P. R., Barreiros, A., Ferreira-Santos, F., Vieira, J., Reis, C., Paiva, T., & Marques-Teixeira, J. (2013). *Hysteresis effect in the processing of facial expressions of emotion and its neurophysiological correlates* [abstract]. Psychophysiology, 50(S1), 132-132.

Barbosa, F., Almeida, P. R., Ferreira-Santos, F., Vieira, J. B., & Marques-Teixeira, J (2014). *Hysteresis effects in the processing of facial expressions of emotion: Behavioral and electrophysiological (N170) evidence.* Abstracts from the International Conference of the European Society for Cognitive and Affective Neuroscience. Dortmund: ESCAN/IFADO.

Barreiros, R. (2012). *Processamento não-linear de informação emocional facial - Correlatos Neurofisiológicos* (dissertação de mestrado). Faculdade de Psicologia e C.E. da UP, Porto.

Barreiros, A., Barbosa, F. Almeida, P., Vieira, J., & Marques-Teixeira, J. (2013). Dinâmica não linear no processamento de informação emocional facial. In M. Calheiros et al. (Eds.), *VIII Simpósio Nacional de Investigação em Psicologia* (p. 44-51). Lisboa: APP.

Pereira, M. (2014). *Psychopathy and non-linearity of facial expressions of emotion processing* (Master dissertation). Faculdade de Psicologia e C.E. da UP, Porto.

166/10 - "Judgements of Moral Wrongdoings and Emotions: A Neuropsychophysiological study" - only abstract available

Investigadores/*Researchers*: Paulo Sousa, João Eduardo Marques-Teixeira, Carlos Eduardo Evangelisti Mauro, Fernando Ricardo Ferreira-Santos

Instituição/*Institution*: Faculdade de Economia e Gestão, Universidade Católica Portuguesa, Centro Regional do Porto (Portugal)

Duração/*Duration*: 2012/01 – 2015/09

Objectives: The aim of this project was to study the role of emotional processes in judgements of moral wrongdoings, while at the same time addressing the conceptual and methodological limitations present in the empirical studies of moral judgements.

Methods: In order to achieve our goals, we have implemented the moral-conventional task (Turiel, 1983) to distinguish moral from conventional judgments. Different scenarios were created/adapted to fit Haidt's moral domains classification (2007). In a phase 1, a survey was implemented, which also asked participants about the content of the scenario that leads it to being judged as a transgression. At the same time, it was measured the valence and arousal elicited in the participants while reading the scenarios, as well as other discrete emotions. In a phase 2, participants read the scenarios while the electrodermal activity and the heart rate variability was registered, which are associated with arousal and valence, respectively. In a phase 3 an electroencephalogram was recorded instead, in order to find event-related potentials (ERP) of interest; some of these potentials are modulated by emotions.

Results: About the phase 1, we found evidences that the moralization of the studied domains can be predicted strongly by the perception of injustice. Moreover, wrongful scenarios were reported has less pleasant, more arousing, disgusting, and upsetting than not-wrongful scenarios. Regarding the phase 2, we found no differences between participants in terms of the physiological responses. The phase 3 yielded as main results a correlation with the self-reported affect and the mean amplitudes of the N400 and LPP during the time windows. We did not find differences between these later ERP components for different domains.

Conclusions: Phases 1 and 3 yielded successful results, showing that moral judgments have systematic emotional properties, and that they seem to be related to specific neural correlates. This finding is, to our knowledge, the first electrophysiological evidence to directly show the affective properties of moral scenarios. The absence of evidences for the later ERP components in different moral domains may suggest that these potentials are capturing general properties of the moral scenarios, namely their affective contents. Phase 2, on the other hand, led to null findings, possibly revealing the limitations of verbally presented moral scenarios in eliciting sufficiently strong responses of the autonomous nervous system.

Keywords: Moral domains, Arousal, Valence, EEG/ERP, Psychophysiology

Publications:

Pipa, F., Sousa, P., Ferreira-Santos, F., & Mauro, C. (in preparation). The scope of morality: examination of the moral-conventional distinction across moral-domains.

Ferreira-Santos, F., Pipa, F., Sousa, P., Mauro, C., & Marques-Teixeira, J. (in preparation). Affect and the moral domain: The emotional properties of moral and conventional transgressions.

Pipa, F., Sousa, P., Ferreira-Santos, F., & Mauro, C. (2013). Juízos morais e emoções: Um estudo através da Tarefa Moral Convencional revista e ampliada In A. Pereira, M. Calheiros, P. Vagos, I. Direito, S. Monteiro, C. F. Silva & A. A. Gomes (Eds.), *Livro de Atas: VIII Simpósio Nacional de Investigação em Psicologia* (pp. 205-215). Aveiro: Associação Portuguesa de Psicologia. Retrieved from http://www.viiisnip2013.com/livro_atas.pdf.

167/10 - "Elucidating the molecular mechanisms mediating feeding behavior"
Investigadores/*Researchers*: Carlos Vidal Ribeiro, Maria Teresa Montez, Laura Belmonte, Samantha Herbert
Instituição/*Institution*: Champalimaud Foundation, Lisboa (Portugal)
Duração/*Duration*: 2011/05 – 2014/09

Objectives: The nervous system plays a key role in coordinating an animal's intake of food, and in matching both the quality and quantity to the organisms needs. In *Drosophila*, a diet lacking amino acids induces a feeding preference for yeast. However, the neuronal molecular mechanisms underlying the behavioural response to changes in dietary amino acids remain poorly understood. Here we aim at showing that the nervous system of adult *Drosophila* is able to react and respond directly to changes in the availability of dietary amino acids.

Methods: To use a novel holidic medium that is adequate for fly development as well as adult traits, such as behavior to manipulate specific nutrients in the fly diet. Furthermore to determine whether amino acids are an important input governing nutrient decisions, acting directly on the nervous system we have used a combination of genetic and molecular nutrient-sensitive readouts to monitor and modify the responses of the nervous system of *Drosophila* to changes in dietary conditions. Finally we used a novel automated, quantitative, high throughput feeding assay to identify the specific aspects of the microstructure of feeding affected by the nutritional and molecular manipulations.

Results: We first asked whether the nervous system reacts to dietary amino acid content by assaying the nutrient sensitive pathway, autophagy. Quantification of Atg8a indicates that dietary depletion of amino acids induces neuronal autophagy. Remarkably, we found that removal of one essential amino acid from the diet is sufficient to induce this increase. Furthermore, we identified a gene with sequence similarity to the Solute Carrier group of membrane transporters that seems to be required in the nervous system to maintain homeostatic yeast feeding in adult flies.

Conclusions: All together, these results suggest a model where the nervous system is able to directly sense the availability of amino acids to regulate yeast feeding behaviour and maintain physiological amino acid levels.

Keywords: behaviour, feeding, nutrition, nutrient sensing, molecular mechanisms

172/10 - "Attitudes sensitivity to context: presence of other and physiological evidences"
Investigadores/*Researchers*: Teresa Maria Morais Garcia-Marques, Ricardo Fonseca, Marília Prada, Alexandre Fernandes
Instituição/*Institution*: Unidade de Investigação em Psicologia Cognitiva, do Desenvolvimento e da Educação (UIPCDE), ISPA - Instituto Universitário, Lisboa (Portugal)
Duração/*Duration*: 2011/05 – 2015/10

Objectives: In our research project, we investigated the role of social presence in how we process information. We directly tested the impact that others exert in our mental and physiological activity, namely an increase in task involvement, context-sensitivity reactions and brain central executive functions.

Method: In this talk, we summarize our research that addressed the hypothesis by showing 1) how the presence of others increases task engagement, indexed by sympathetic neural and adrenal medullary (SAM) axis activation, increases heart rate and ventricular contractility, and how this engagement modulates levels of challenge and threat associated with context processing features; 2) how the presence of others increases context sensitivity, indexed by an increase in face holistic processing and vision illusions, such as in the Ebbinghaus task, in quicker responses directly determined by earlier attentional processes; and 3) how the presence of others activates central executive functions, indexed by a better performance in Stroop tasks documented by behavioral responses and facial electromyography activity (EMG).

Results and Conclusion: Consistently across all these methodological approaches, it is turned clear that others' presence modulates our physiological and psychological responses to the environment, influencing our behavior.

Keywords: Social facilitation, Context-sensitivity, Executive control functions, Task engagement

Publications:
Garcia-Marques, T., Fernandes, A., Fonseca, R., & Prada, M. (2015). Social presence and the composite face effect. *Acta Psychologica*, *158*, 61-66.
Fonseca, R., Blascovich, J., & Garcia-Marques, T. (2014). Challenge and threat motivation: Effects on superficial and elaborative information processing. *Frontiers in Psychology*, *5*, 1170.
Garcia-Marques, T., Fonseca, R., & Blascovich, J., (in press). Familiarity challenge and processing of persuasive messages. *Social Cognition*
Garcia-Marques, T., Fernandes, A., Fonseca, R., & Prada, M., (in press). Seeing the big picture: Size perception is more context-sensitive in the presence of others. *PLoS ONE*.

176/10 - "Dopaminergic regulation of dietary learning in humans and rodents"
Investigadores/*Researchers*: Albino Jorge Carvalho de Sousa Oliveira Maia, Rui M. Costa
Instituição/*Institution*: Champalimaud Foundation, Lisboa (Portugal)
Duração/*Duration*: 2011/07 – 2014/09

Objectives: Here we proposed to explore the role of dopaminergic signalling in postingestive-dependent reward learning, in humans and rodents.

Method: A protocol to condition flavour-nutrient associations in human subjects was developed, using natural yoghurt with two different flavours. While one of the flavours was enriched with maltodextrin to increase the caloric value, the two yoghurts were not distinguishable according to the presence of maltodextrin. In mice, we tested if instrumental behaviours are sustained by postingestive reinforcement, using direct intra-gastric administration of sucrose contingent upon lever pressing, and a transgenic model with deficits in sweet taste processing. Finally, mice with NR1 receptor deletion in ventral tegmental area (VTA) dopamine neurons and mice with lesions of the hepatic branch of the vagus nerve were tested in the same paradigm.

Results: When comparing pleasantness ratings before and after the flavour-nutrient conditioning protocol we found that, in healthy human volunteers, there are no significant conditioning-induced differences in flavour pleasantness, in either flavour. However, subjects increased the intake of both flavours, with a greater post-conditioning volume consumption increase for the flavour paired with maltodextrin than for the alternate yoghurt. Results of instrumental conditioning experiments in mice demonstrate that the postingestive effects of sucrose are sufficient to sustain lever-pressing behaviour, both in mice with gastric catheters and sweet-blind mice working to obtain sucrose. Furthermore, such behaviours are abolished or significantly reduced, specifically in regards to postingestive, but not oral, reinforcers, in mice with hepatic-vagal nerve lesions or disrupted dopaminergic activity in the VTA.

Discussion: The results described here suggest that, in humans, the impact of caloric postingestive reinforcement occurs mostly in regard to implicit consumption decisions, rather than explicit hedonic evaluations of stimuli. Accordingly, we found that, in mice, postingestive reinforcement is able to sustain instrumental behaviours. Furthermore, dopamine-producing neurons in VTA, as well as integrity of the hepatic branch of the vagus nerve, are necessary for this postingestive-dependent behaviour.

Conclusion: Overall, these findings suggest the presence of a liver-brain neural axis that is sensitive to the caloric content of simple carbohydrates, modulating behaviour to optimize their consumption.

Keywords: Postingestive, Dopamine, VTA, Vagus nerve, Reinforcement

Publications:
Bugalho, P., & Oliveira-Maia, A. J. (2013). Impulse control disorders in Parkinson's disease: crossroads between neurology, psychiatry and neuroscience. *Behavioural Neurology*, *27*(4), 547-557. doi: 10.3233/BEN-129019

Castro-Rodrigues, P., & Oliveira-Maia, A. J. (2013). Exploring the effects of depression and treatment of depression in reinforcement learning. *Frontiers in Integrative Neuroscience*, *7*: 72. doi: 10.3389/fnint.2013.00072

Ribeiro, G., Santos, O., Camacho, M., Torres, S., Vieira, F., Sampaio, D., Oliveira-Maia, A.J. Validation of the Power of Food Scale in a Portuguese-speaking adult population. Submitted (in press).

193/10 - "Attachment and exceptional experiences amongst twins reporting "exceptional experiences"

Investigadores/*Researchers*: Göran Brusewitz, Adrian Parker, Lynn Cherkas
Instituição/*Institution*: Greenwich University (UK), Department of Psychology, University of Gothenburg (Sweden), Department of Twin Research and Genetic Epidemiology, King's College, London (UK)
Duração estimada/*Estimated Duration*: 2013/10 – 2016/04

Introduction: Attachment theory is a basic theory in psychology, dealing with a bond that one individual has to another individual, primarily being between a child and its caregiver(s). For attachment between twins, there are very few, if any studies being reported.

Objectives: The objectives for the study are: a) to find pairs of twins who can demonstrate having a telepathic contact with each other in a controlled experiment, b) to evaluate if their degree of attachment relates to this performance.

Method: Psychophysiological equipment measuring Electrodermal Activity, EDA was used to indicate a potential (telepathic) connectedness. A self-report questionnaire (*Experiences in Close Relationships Revised, ECR),* was used to get scores on the two subscales "avoidance" and "anxiety", as was the *Exceptional Experiences Questionnaire*, EEQ, prefilled by the twins. The study took place in May 2014 at the Department of Psychology and Counselling, The University of Greenwich, London. Each pair of the 8 UK twins participated in two runs, in one being sender, then being receiver. Each run had five trials, each one with eight possible windows. In one of these, randomly chosen, a surprise stimulus was exposed for the sender that hopefully was to be picked up with telepathy by the receiver with a distinct peak on the EDA graph. The twin being 'receiver' was connected to the equipment. Synchronization between sender and receiver was cared for. AP carried out the randomizations to choose the window of exposure. After five minutes, the run started. After the second run, the twins separately filled the questionnaire on attachment. As surprise stimuli, a balloon burst was e. g. used.

Results: With 19 trials, each one having a one in eight expectancy to have the correct window of exposure and with four correct placements of the window (and MCE=2.38), the result was above chance, but not significant. There was no relationship between the number of hits and the reported attachment on the questionnaire EEQ, neither with the scores on anxiety and avoidance, due to these having a lack of variance.

Conclusion: The result in the present study was above chance, but didn't reach significance. Since all the twins reported a high degree of attachment on the EEQ, and the low scores on anxiety and avoidance showed little variation, the second hypothesis could not be evaluated. More confirmatory experiments are needed, one already carried out and some more planned, with other support.

Keywords: Attachment, Telepathy, Electrodermal activity, Synchronous reaction

Publications:

Brusewitz, G., Parker, A., Luke, D., & Puhle, AK (2015). An experimental study of physiological connectedness among twins in relation to attachment, *Book of Abstracts*, 58th Annual Convention of the Parapsychological Association & 39th SPR International Annual Conference, University of Greenwich, UK, July 16-19, 2015.

Acknowledgements:

Thanks to dr Annekatrin Puhle, to the Dutch Fund J. Kleijne-Frankfort Foundation, and to BIAL Foundation.

226/10 - "Brain decoding of spontaneous memory processes"
Investigadores/*Researcherss*: Pierre Maquet, Christophe Phillips, Jessica Schrouffs, Caroline Kussé
Instituição/*Institution*: Cyclotron Research Centre, University of Liège (Belgium)
Duração/*Duration*: 2011/10 – 2016/01

Objectives: The objective of this project is to develop a research strategy for examining spontaneous memory offline processing in human volunteers in order to characterize in a direct manner the neuronal correlates of a recently formed memory trace.

Method: We developed our own specific experimental protocol in order to create a controlled environment to assess memory and its organization. Multivariate pattern analysis methods were then used and expanded to characterize elicited and pre-/post-learning resting state brain activity in fMRI. With ECoG we had to resort to a simpler protocol and worked on sparse "multi kernel learning" approach to select the relevant features.

Results: With fMRI data, (semi-)constrained brain activity can readily be decoded and we found that activity patterns spontaneously emerge in unimodal associative areas of the visual ventral stream during resting wakefulness. These results provide evidence that memories are maintained during resting wakefulness by spatially-organised repetitions of regional brain activity. With ECoG data, a subject's mental state ('math' versus 'non-math') could be decoded from the combination of frequency band activity.

Conclusion: The new methodological tools developed rely on advanced machine learning techniques, to model brain activity. To some extent, one can also track the spontaneous replay of activity linked to learned material, i.e. mnesic traces, in rest fMRI data but the temporal resolution is too low to capture its dynamics. With ECoG data, it is also possible to decode the quality of a subject's mentation. This might bring further insights on how the information is coded in the human brain.

Keywords: fMRI, EEG, Brain decoding, Spontaneous activity, Memory

Publications:
J. Schrouff, et al., "Decoding semi-constrained brain activity from fMRI using support vector machines and Gaussian processes." *PLoS ONE* 2012, 4:e35860.
J. Schrouff, et al., "Decoding spontaneous brain activity from fMRI using Gaussian processes: Tracking brain reactivation." Int. Works. on *PRNI*, 2012.
J. Schrouff, et al., "Localizing and comparing weight maps generated from linear kernel machine learning models." Int. Works. on *PRNI*, 2013.
J. Schrouff, et al., "Decoding memory processing from electro-corticography in human posteromedial cortex." Int. Works. on *PRNI*, 2014.
J. Schrouff, et al., "Using multiple kernel learning to automatically select features for the decoding of electro-corticographic signals." *J. of Neurosci. Meth.*, 2016, 261:19-28
Open-source "Pattern Recognition for Neuroimaging Toolbox" (http://www.mlnl.cs.ucl.ac.uk/pronto/)

227/10 - "Evaluation of alterations of consciousness and the model of pragmatic information in a ganzfeld protocol"

Investigadores/*Researchers*: Etzel Cardeña, David Marcusson-Clavertz
Instituição/*Institution*: CERCAP, Dept. of Psychology, Lund University (Sweden)
Duração/*Duration*: 2011/04 – 2015/07

Objectives: Evaluate**:** 1) if individuals likely to be successful in a ganzfeld test perform better than chance; 2) if a ganzfeld condition is superior to a hypnotic one; 3) an association between altered consciousness and psi scores; 4) the Model of Pragmatic Information; 5) if the first third of trials would produce better results than the second third; 6) if task related re-appraisals/interferences (e.g., " I thought about the purpose of the experiment") during mentation correlate with lower psi scores; 7) if psi scores correlate with confidence in ratings.

Method: 35 high hypnotizable with some belief that they would succeed in the experiment and previous psi experience took part. They had two sessions, in which they were asked to "see" a film clip being seen by the PI in another building; the clips were randomly chosen with an automated protocol. One session was carried out with ganzfeld following a hypnotic induction; in the other participants only listened to the induction. The manipulations lasted 10 min. At the end of the session volunteers saw the target and 3 decoys arranged randomly and gave their ratings for each clip. Alterations of consciousness were assessed after a 2 minutes baseline and at the end of the session. Volunteers got feedback of the targets at the end of the 2nd session Significance was set at $p < .05$. The study was preregistered with the KPU depository.

Results: Hypothesis 1 was not supported, and there was no difference between conditions. For the third hypothesis, although the psi *z*-scores did not correlate with Altered State, they correlated positively with the Attention and negatively with the Arousal scales; they also correlated with a *shift* for Altered State between baseline and the ganzfeld condition. The fourth hypothesis was supported: the same number of correlations was found as in our previous study although referring to two different variables. Hypotheses 5, 6, and 7 were not supported.

Conclusions: Three alternative explanations might explain why the first hypothesis was not supported: 1) there is no psi to begin with (although this would go against previous studies and the results for the 3rd hypothesis), 2) there was a negative experimenter effect, 3) something in the procedure went against it (we found later that a previous meta-analysis suggests that 10 min is insufficient exposure). We found support for a link between altered consciousness and psi scoring, and for the Model of Pragmatic Information.

Keywords: Ganzfeld, telepathy, alterations of consciousness, model of pragmatic information

2012

10/12 - "Enhancing Psychokiness Task Performance Through the Practice of Imagery Strategies: New Psychophysiological Approach (Stage 2)"
Investigadores/*Researchers*: Alejandro Parra, Juan Corbetta
Instituição/*Institution*: Instituto de Psicología Paranormal, Asoc. Civil, Buenos Aires (Argentina)
Duração/*Duration*: 2013/02 – 2015/02

Objectives: Two studies were done exploring the effectiveness of two PK imagery strategies derived from a survey of popular writings on how to develop psychic skills. Goal-oriented imagery involves visualizing only the final outcome or desired goal; process-oriented imagery involves visualizing some sort of process gradually leading up to the desired final outcome.

Method: Three volitional (imagery) strategies were examined: (1) goal oriented, (2) process oriented, and (3) end oriented (final result) strategies. A number of participants practiced each one of the three strategies on six occasions. In both studies, the three strategies was carried out in order to enhance the PK scoring or increase PK scores over a period of time (as we predict), thus to confirm earlier findings with imagery strategies and PK.

Results and Conclusions: In the first study, 62 subjects were asked to bias the behavior of a visual display controlled by a random number generator (Psyleron v.2011), using each imagery strategy half the time (8 runs of 16 trials for each strategy). There was significantly positive overall evidence for PK ($p < .02$) and for PK during goal-oriented imagery ($p < .01$). In a second study, 20 subjects attempted the same PK task, using each imagery strategy half the time. An analysis of variance revealed that goal-oriented imagery scores were significantly greater than process-oriented scores, that prior training was not itself a significant factor, but that imagery strategy and prior training interacted significantly ($p < .02$). Subjects in this study were asked to practice concentration enhancement exercises and return in two weeks to repeat the PK procedure, this time using their preferred imagery strategy for all 16 runs. Eight subjects chose the goal-oriented strategy; their scores were significantly above chance ($p < .01$). Eleven subjects chose the process-oriented strategy; their results were at chance. The difference between the two groups was significant ($p < .02$). Thus the goal-oriented imagery strategy appears to be more effective than the process-oriented Strategy, at least for those with no prior exposure to mental development training.

Keywords: Goal/process oriented, Psychokinesis, Imagery strategies, Feedback/ nonfeedback conditions

Researcher's Contacts:
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21/12 - "The depersonalized brain: Psychophysiological correlates of cortical hyperexcitability associated with signs of depersonalization, derealization and dissociation, in non-clinical samples"

Investigador/*Researcher*: Jason John Braithwaite
Instituição/*Institution*: Behavioural Brain Sciences Centre, School of Psychology, University of Birmingham (UK)
Duração/*Duration*: 2013/06 – 2015/09

Objectives: Striped patterns (i.e., gratings) with a spatial frequency of 3 cycles-per-degree of visual angle are known to produce visual discomfort, induce phantom visual distortions and somatic sensations in susceptible observers. These phenomena have been termed *'pattern-glare'* and are thought to reflect increased degrees of cortical hyperexcitability and be associated with visual distortions and hallucinations. This study explored the role of cortical hyperexcitability underlying the aberrant perceptions reported by those predisposed to sub-clinical levels of dissociation, depersonaliztion and derealization experiences. The anomalous perceptions experienced in these conditions range from perceptual distortions in relation to ones own body, to an altered experience of ones surroundings. The neurocognitive underpinnings of these distortions in conscious experience remain unclear.

Method: Participants were screened on a variety of questionnaire measures that sought to quantify predisposition to anomalous visual and multi-sensory perceptions. A revised version of the pattern-glare task was devised to examine the degree of visual distortions experienced from viewing irritable visual gratings presented on a computer screen. Baseline gratings (non-irritable) were also presented. Interactions between perceptual (associated visual distotions from viewing the gratings) and emotional (facial EMG reactions from the corrugator supercillius muscle group) factors were explored to provide as indicative perceptual / emotional concomitants of dissociative states in the non-clinical population.

Results: Those showing an increased predisposition to anomalous dissociative experiences reported significantly more perceptual distortions from viewing the irritable gratings relative to those scorring low on such measures. There were do reliable differences between the groups for baseline gratings. There were no effects from psychophysiological recordings from emotional facial regions.

Conclusion: Cortical hyperexcitability is reliably associated with the presence of anomalous perceptions reported by some experiencing distorted and dissociative conscious experiences of the self. These effects may be mediated more in 'perceptual' rather than 'emotional' brain processes.

Keywords: Dissociation, Depersonalization, Aberrant perceptions, Cortical hyperexcitability

Publications:

Braithwaite, J.J., Mevorach, C., & Takahashi, C (2015). Stimulating the aberrant brain: Evidence for increased cortical hyperexcitability from a transcranial Direct Current Stimulation (tDCS) study of individuals predisposed to anomalous perceptions. *Cortex*, *69*, doi:10.1016/j.cortex.2015.03.023.

Braithwaite, J.J., Marchant, R., Takahashi, C., Dewe, H., & Watson, D (2015). The Cortical Hyperexcitability Index (*CHi*): A new measure for quantifying correlates of visually driven cortical hyperexcitability. *Cognitive Neuropsychiatry(20), 4, 330-348*. doi:10.1080/13546805.2015.1040152

Braithwaite, J.J., & Dewe, H (2015). Neurocognitive correlates of anomalous body experiences: Aberrations of self-consciousness in non-clinical populations. Presentation given at the conference launch of the *Aberrant Experience & Belief* research theme, University of Birmingham.

Takahashi, C. & Braithwaite, J. J. (2015). Stimulating the aberrant brain: Predisposition to anomalous visual distortions reflects increased cortical hyperexcitability in those prone to Hallucinations: Evidence from a tDCS brain stimulation study. A presentation given at *The European Conference of Visual Perception (ECVP)*, Liverpool, UK. August, 23-27, 2015.

Takahashi, C. & Braithwaite, J. J. (2015). Predisposition to aberrant perceptions is related to A hyperexcitable visual cortex even in non-clinical groups: A presentation given at the *European Brain and Behaviour Society (EBBS) & European Behavioural Pharmacology Society (EBPS)* Joint Meeting, Verona, Italy. September, 12-15, 2015.

Takahashi, C., Marchant, R., Dewe, H., Watson, D.G., & Braithwaite, J.J (2015). The Cortical Hyperexcitability Index (CHi): A new measure for quantifying correlates of visually-driven cortical hyperexcitability. A presentation given at the *Experimental Psychology Society (EPS), Lincoln, UK. July, 8-10*.

Braithwaite, J.J (2014). The dark side of the mind: Inducing anomalous bodily experiences in those predisposed to hallucinatory experiences. Presentation given at the Annual scientific meeting of the Psychobiology section of the *British Psychological Society*, Sept 2014, Windermere, UK.

Braithwaite, J.J (2014). The dark side of the mind: Inducing anomalous bodily experiences in those predisposed to hallucinatory experiences. Presentation given at the Annual scientific meeting of the *British Psychological Society*, May 2014, Birmingham, UK.

Takahashi, C., & Braithwaite, J.J (2014). Neuroscience and anomalous experience: Cortical hyperexcitability and the out-of-body experience. Presentation given at the Annual conference of the *British Psychological Society*, May 2014, Birmingham, UK.

Work in preparation:

Braithwaite, J.J., & Dewe, H., (in final stages of preparation). The depersonalized brain. New evidence for cortical hyperexcitability underlying aberrant perceptions associated with depersonalization and dissociation.

28/12 - "A Test of Thermodynamic Entropy Effects in Anomalous Cognition"
Investigadores/*Researchers*: Edwin May, Sonali Bhatt Marwaha
Instituição/*Institution*: Laboratories for Fundamental Research, Palo Alto, California (USA)
Duração/*Duration*: 2013/03 – 2016/01

Objectives: The object is to determine whether or not changes of thermodynamic entropy at a remote stimulus site influences the quality and accuracy of the resulting anomalous cognition (AC).

Method: Develop 22 outdoors stimulus sites and encode them into fuzzy sets. Three participants contributed 24 sessions each - half when a 3-l pour of liquid nitrogen (LN) at a remote site and half not. A single session proceeds as follows.

- 10:00: One participant and a monitor (E1) are sequestered in the laboratory.
  They conduct an anomalous cognition (AC) session typically lasting 5-15 minutes. Then E1 enters the data into a fuzzy set.
- 10:20: The word "done" is atomically sent via SMA to the second experimenter (E2).
- 10:25: E2 generates five targets chosen one each from the five orthogonal categories and randomly assigns one of them as the stimulus site for the session and randomly determines the entropy condition. The stimulus numbers are sent as a CSV file to E1. The stimuli set and entropy condition are also uploaded to a secure cloud folder maintained by E3 in India.
- 10:30: The CSV file is used to compute a Figure of Merit - a fuzzy set metric for AC quality - for each of the five sites, and all results are sent to a different secure cloud folder. "Finished" is automatically to E2 who sends the target stimulus number by phone to E1
- 11:15: E2 sends and SMS note, "leaving site" to E1.
- 11:16: E1 blindfolds the participant as the drive to the intended site.
- 11:45: E1 guides the participant to the site and orients the participant to a predefined direction. The blindfold is removed as feedback for the session.

Results: The effect size for the observed distribution difference between LN pour and not was 0.251 ± 0.167 leading to a *z*-score of 1.503 and an associated *p*-value of .066

- Performance declined between the first and second half of the study for all three participants.
- The difference between the means of the Figures of Merit distribution for just the first half of the study was significant (z_{diff} = 1.80, p = .036, ES = 0.425 ± 0.236).
- One participant exhibited a statistically significant result (z_{diff} = 2.23, p = .013, ES = 0.909 ± 0.408).

Conclusion: The first half supported the primary objective: thermodynamic entropy changes at a remote site significantly improve the quality of the resulting AC of that site.

Keywords: AC, Entropy, Fuzzy sets

Publications:
We will place this experiment into the *Journal of Parapsychology*

30/12 - "Regularity encoding and deviance detection in the human auditory brainstem" - only abstract available

Investigadores/*Researchers*: Carles Escera, Katarzina Żarnowiec, Lilla Náfrádi
Instituição/*Institution*: Institute for Brain, Cognition and Behavior (IR3C), University of Barcelona (Spain)
Duração/*Duration*: 2013/07 – 2015/06

Objectives: Neural activity is reduced after the presentation of a repeated stimulus, a phenomenon known as repetition suppression (RS). In the auditory domain, this reduction was widely studied in animal cortical and subcortical structures as well as in the human auditory cortex. However, investigation of repetition suppression in the human subcortical auditory pathway has not been addresses systematically so far, with only one functional magnetic resonance study reporting attenuated responses with repetition in the inferior colliculus. Furthermore, in the human auditory cortex, it has been demonstrated that the timing regularity of the upcoming stimulus influences the encoding of this repetitive environment. However, before the auditory information reaches the cortex, it is deeply processed in the auditory brainstem, which has the ability to encode context–dependent information. The present study was set out to investigate repetition suppression in the human auditory brainstem and ascertain whether stimulus timing predictability influences the brainstem response to repetitive sounds.

Method: Here we recorded the human auditory brainstem frequency–following response (FFR), on a sample of 30 healthy volunteers, to consonant–vowel stimuli (/wa/) delivered in predictable (rhythmic) and unpredictable (non-rhythmic) timing conditions among a six–talker babble background. The predictable timing used a constant stimulus-onset asynchrony (SOA) of 366 ms, whereas in the unpredictable condition the SOA varied from 183 and 549 ms randomly (mean 366 ms). We recorded brain responses to 8 blocks of 1000 stimuli each, and averaged the responses as 8 consecutive subgroups of 100 stimuli across the 8 blocks, so that the effects of cumulative repetitions could be assessed. From the FFR, we extracted a pitch strength derivative, which measures the fidelity with which the periodic components of sound are encoded in inferior colliculus.

Results: Results revealed a significant effect of condition (with stronger phase locking for constant versus random) and an interaction between repetition and timing.

Conclusion: Our findings confirm that repetition suppression is a phenomenon that occurs at the human auditory brainstem and demonstrate, for the first time, that timing predictability of the incoming stimulation influences the brainstem response to repetitive sounds, eliciting a better and faster encoding of regularities.

Keywords: Regularity encoding, Repetition Suppression, Timing predictability, Auditory–evoked potentials, Frequency–following response (FFR), Auditory brainstem, Human

38/12 - "Testing a Methodological Formula for Consistent Hit Rates: Matching Psi Ability to Task Difficulty"

Investigadores/*Researchers*: James Houran, Rense Lange
Instituição/*Institution*: Integrated Knowledge Systems, Inc., Illinois (USA)
Duração/*Duration*: 2013/02 – 2014/09

Objectives: We conducted two studies to investigate whether "task difficulty" was a moderator variable in experimental psi research, similar to its mediating role in educational psychology and traditional learning theory.

Method: In Study 1, 124 hospitality professionals completed measures of Transliminality, Paranormal Belief (New Age Philosophy), Intuitive Thinking, and self-reported paranormal abilities and experiences (Anomalous Experiences Inventory), along with one run of 25 trials of a previously published computerized intuition (psi) task (Houran & Lange, 2013). Rasch scaling revealed that the perceptual-personality variables (except intuitive thinking) conformed to a probabilistic hierarchy, which subsequently corresponded to a probabilistic hierarchy of self-reported paranormal abilities, experiences, and hit rate on the computerized task. Those scoring above mean-chance expectations on the computer task also scored suggestively higher on the Rasch perceptual-personality measure of psi ability than those scoring at or below mean-chance expectations. This suggests that manifestations of psi involve an inherent trait ability matched to task difficulty. Study 2 tested the predictive validity of these conclusions in a convenience sample of 153 hospitality professionals who were independent from Study 1. Participants completed the same measures from Study 1 and then took the computerized intuition (psi) task.

Results: Those with expected trait ability as inferred from the Rasch perceptual-personality measure ("targets") scored significantly higher on hit rate on the computer task than did "controls," those with non-expected trait ability as inferred from the Rasch perceptual-personality measure. Furthermore, overall hit rate of the "targets" on the computer task was suggestive and in the predicted direction, albeit non-significant.

Conclusion: The methodological approaches introduced here hold promise for better refinement and stronger effect sizes, but the cumulative results appear to validate "task difficulty" as a potentially important mediating variable neither previously considered nor controlled for in experimental psi studies. Researchers should refine future studies in order to better understand and apply classic learning theory to experimental research. By matching participants' inferred trait/state abilities for psi to the estimated difficulty level of specific psi-oriented tasks, replication issues in parapsychology may be overcome.

Keywords: Rasch scaling, Assessment, Learning theory, Task difficulty, Psi-conducive variables

Publications:

Houran, J., & Lange, R. (2012). Reflections on paranormal beliefs as informed vs. pseudo beliefs: comment on Jinks (2012). *Australian Journal of Parapsychology, 12*, 159-167.

Houran, J. (2013). Anomalous experiences as transliminal drama: the case of Wasney De Almeida Ferreira. *Australian Journal of Parapsychology, 13*, 169-185.

Houran, J., & Lange, R. (2014). *Technical Report. Matching Psi Ability to Task Difficulty: A Methodological Proposal and Pilot Study*. Chatham, IL: Integrated Knowledge Systems.

Lange, R., & Houran, J. (2015). "A picture is worth a thousand words:" perceptual-personality profiling via a free-response imagery task. *North American Journal of Psychology, 17*, 387-402.

52/12 - "The embodied experience of time: modulations of mindfulness meditation"
Investigadores/*Researchers*: Marc Christoph Wittmann, Karin Meissner, Stefan Schmidt
Instituição/*Institution*: Institute for Frontier Areas of Psychology and Mental Health, Freiburg, Institute of Medical Psychology, University of Munich - LMU (Germany)
Duração/*Duration*: 2013/05 – 2015/01

Objectives: Experienced meditators typically report that they experience time slowing down in meditation practice as well as in everyday life. Conceptually this phenomenon may be understood through functional states of mindfulness, i.e. by more efficient attention regulation and enhanced body awareness.

Method: In this cross-sectional study, we investigated whether 42 experienced mindfulness meditators (on average 10 years of experience) showed differences in the experience of time as compared to 42 controls without any meditation experience. The perception of time was assessed with a battery of psychophysical tasks assessing the accuracy of prospective time judgments in the milliseconds to minutes range as well with several psychometric instruments related to subjective time. In a subgroup of 22 meditators and matched controls heart rate and skin conductance during duration reproduction were assessed. Participants also performed in a heart-beat perception task.

Results: Regarding subjective time, mindfulness meditators experienced less time pressure, more time dilation, and a general slower passage of time. Moreover, they felt that the last week and the last month passed more slowly. Regarding psychophysical tasks, no differences in duration estimates were detected. Psychophysiological results revealed only few differences between meditators and controls with respect to psychophysiological correlates of duration reproduction performance. Across all subjects, correlational analyses revealed several associations between performance in the duration reproduction tasks and psychophysiological changes, the latter being also related to heart beat perception scores.

Conclusion: Overall, although no intergroup differences in psychophysical tasks were detected and only a few regarding psychophysiological indices, the reported findings demonstrate a close association between mindfulness meditation and the subjective feeling of the passage of time captured by psychometric instruments. Moreover, the results across all subjects support the notion that bodily processes and the experience of time are related.

Keywords: Time perception, Body awareness, Heart-beat, Mindfulness, Meditation

Publications:
Wittmann M, Otten S, Schötz E, Sarikaya A, Lehnen H, Jo H-G, Kohls N, Schmidt S, Meissner K (2015). Subjective expansion of extended time-spans in experienced meditators. *Frontiers in Psychology*, 5 (1586).
Otten S, Schötz E, Wittmann M, Kohls N, Schmidt S, Meissner K (2015). Psychophysiology of duration estimation in experienced mindfulness meditators and matched controls. *Frontiers in Psychology*, 6 (1215).

53/12 - "Libet revisited - The effects of mindfulness meditation training on voluntary action and on time perception: a controlled study with experienced meditators

Investigadores/*Researchers*: Stefan Schmidt, Han-Gue Jo, Marc Christoph Wittmann
Instituição/*Institution*: Dep. of Psychosomatic Medicine, University Medical Center Freiburg (Germany)
Duração/*Duration*: 2013/05 – 2015/03

Objectives: Intuitively, being aware of one's inner processes to move should be crucial for the control of voluntary movements. However, research findings suggest that we are not always aware of the processes leading to movement execution. The present study investigated induced first-person access to inner processes of movement initiation and the underlying brain activities which contribute to the emergence of voluntary movement. Moreover, we investigated differences in task performance between mindfulness meditators and non-meditators while assuming that meditators are more experienced in attending to their inner processes.

Method: Two Libet-type tasks were performed; one in which participants were asked to press a button at a moment of their own decision, and the other one in which participants' attention was directed towards their inner processes of decision making regarding the intended movement which lead them to press the button.

Results: Meditators revealed a consistent readiness potential (RP) between the two tasks with correlations between the subjective intention time to act and the slope of the early RP. However, non-meditators did not show this consistency. Instead, elicited introspection of inner processes of movement initiation changed early brain activity that is related to voluntary movement processes.

Conclusion: Our findings suggest that compared to non-meditators, meditators are more able to access the emergence of negative deflections of slow cortical potentials (SCPs), which could have fundamental effects on initiating a voluntary movement with awareness.

Keywords: Meditation, Slow cortical potential, Libet experiment, Volition

Publications:

Jo, H.-G., Hinterberger, T., Wittmann, M., & Schmidt, S. (2015). Do meditators have higher awareness of their intentions to act? *Cortex*, *65*, 149–158. http://doi.org/10.1016/j.cortex.2014.12.015

Jo, H.-G., Wittmann, M., Hinterberger, T., & Schmidt, S. (2014). Brain Correlates of Intentional Binding: An EEG Study in Mindfulness Meditators. *Procedia - Social and Behavioral Sciences*, *126*, 240. http://doi.org/10.1016/j.sbspro.2014.02.394

56/12 - "Psychophysical interactions with a single-photon double-slit optical system" - only abstract available
Investigadores/*Researchers*: Dean Radin, Arnaud Delorme, Leena Michel
Instituição/*Institution*: Institute of Noetic Sciences, Petaluma (USA)
Duração/*Duration*: 2013/06 – 2015/02

Objective: Six experiments were conducted using a single-photon double-slit apparatus to test von Neumann's proposal that the quantum wavefunction collapses into classical particles through what he termed an "extra-physical" interaction.

Method: Participants were invited to direct their attention toward or away from the optical system while receiving information about the number of photons arriving per second at an interference fringe minimum.

Result: Overall, there was no evidence of a systematic mean-shift in photon counts while attending toward vs. away ($z = -0.58$, $p = 0.56$), but there was a significant variance shift ($z = 3.95$, $p = 3.8 \times 10^{-5}$). This suggests the presence of an interaction that "steered" the quantum wavefunction to become either more wave-like or more particle-like, depending on the specific task.

Conclusion: This outcome is consistent with prior experiments the authors have conducted using continuous-beam double-slit optical systems. Together these experiments support von Neumann's concept of a psychophysical interaction. Such an effect can be interpreted in two main ways: It either reflects a form of mind-matter interaction at the quantum scale, suggestive of dualism, or it suggests a correlation arising from a common source, suggestive of monism. Further research is required to rigorously discriminate between these two possibilities.

Keywords: Quantum measurement problem, Single photon interferometer

Publication:
Radin, D., Michel, L., Pierce, A., Delorme, A. (in press, 2015). Psychophysical interactions with a single-photon double-slit optical system. *Quantum Biosystems.*
Note: This publication won the 2015 Nascent Systems Innovative Research Prize, for an article published in *Quantum Biosystems.*

57/12 - "Neurophysiological mechanisms of aging: novel view of old concepts" - only abstract available

Investigadores/*Researchers*: Maria José de Oliveira Diógenes Nogueira, Alexandre de Mendoça, Antonina Pereira, Bruno Teixeira da Silva, Raquel Dias
Instituição/*Institution*: Instituto de Medicina Molecular, Lisboa (Portugal)
Duração prevista/*Estimated Duration*: 2014/03 – 2016/04

Objectives: Hippocampal long-term potentiation (LTP) is considered the neurophysiological basis of memory. In ageing, there is a well documented age-dependent decay of memory which have been repeateadly associated with LTP impairments. We have shown that hippocampal LTP magnitude is enhanced in aged animals. However, this increased LTP is not accompanied by cognitive enhancements. NMDA glutamate receptors are crucial for CA1 hippocampal LTP. Curiously, in spite of being an antagonist of NMDA receptors, memantine, is a drug widely used in the treatment of Alzheimer's disease with cognitive enhancing properties. Through the use of memantine, as a pharmacological tool, our objectives were to study whether changes in NMDA receptor activation were related to an increase in the magnitude of LTP in aging and whether this enhanced LTP could be considred as a compensatory effect or a dysfunctional phenomena.

Method: Field-excitatory post-synaptic potentials were recorded from the CA1 area of hippocampal slices from young (10-14week old) and aged rats (70-80week old). LTP was induced by a θ-burst protocol. Morris water maze was used to evaluate hippocampal dependent learning and memory in the aged animals blindly treated with memantine (1,5,10 mg/Kg/day, for 14 days) or saline vehicle given intraperitoneally (i.p).

Results: A smaller LTP (20±4.9%, n=8, $P<0.05$) was recorded in hippocampal slices from young rats when compared to LTP obtained in aged (68±10.1%, n=5). A pre-incubation of slices with memantine (1μM) for 4 hours significantly decreased the larger LTP observed in aged rats (29±3.7%, n=7, $P<0.05$), without compromising the LTP in slices taken from younger rats (16±2.6%, n=7). When administered via i.p., memantine, induced a dose dependent effect in old animals: the higher dose (10mg/kg/day) decreased LTP by approximately 59% (memantine:28±6.2%; vehicle:69±3.7%, n=4-9, $P<0.05$), and leads to hippocampal dependent memory impairments ($P<0.05$); the intermediate dose (5mg/kg/day) decreased LTP by approximately 32% (48±4.8%, n=9, $P<0.05$), whereas learning remained unchanged. The lower dose (1mg/Kg /day) did not affect neither LTP nor the learning of the animals.

Conclusion: The blockade of NMDA receptors by memantine can reverse the increased LTP recorded in aged animals either administered *in vivo* or *ex vivo*. Moreover, the dose (10mg/kg/day) of memantine responsible to the blockade of the higher LTP leads to learning deficits suggesting that this LTP observed in old animals is probably a compensatory phenomenon.

Keywords: LTP, Hippocampus, NMDA, Aging

63/12 - "Forefeeling guilty knowledge - An innovative approach in presentiment research"
Investigadores/*Researchers*: Wolfgang Ambach, Alexander Siller
Instituição/*Institution*: Institute for Frontier Areas of Psychology and Mental Health (IGPP), Freiburg (Germany)
Duração/*Duration*: 2013/03 – 2016/02

Objectives: The objective of this project was to replicate anticipatory activity (AA) ("presentiment") under different methodological conditions. In our first study we wanted to understand possible underlying expectation effects and tested different types of randomization. For our second study we selected the randomization less compromised by expectation effects and tested if participants with an affinity to paranormal beliefs performed better in AA than participants with less such affinity.

Method: In the both studies (n=154; n=80 respectively) participants performed a mock crime followed by a Concealed Information Test (CIT), which allowed us to manipulate the personal relevance of stimuli individually within subject. We measured electrodermal activity, respiration, finger pulse, heart rate and reaction time. The first study compared four different types of randomization, some reducing and others increasing expectation. For the second study, we preselected high-scorers and low-scorers in the Tellegen Absorption Scale; items were now presented with replacement and without categories.

Results: Anticipatory activity was not found in these studies. The first study showed that the more cues the participant gets about an upcoming item, the more expectation is built. Groups with unpredictable item sequences did not show this relationship and did not show any "presentiment" effect. Still participants could be influenced by ongoing cognitive processing (based on objective probabilities) or a bias like the gambler's fallacy. In the second study, believers and non-believers in the paranormal did not respond differently in anticipatory activity.

Conclusion: In neither study we found significant effect for "presentiment". Even after preselection, participants with proneness to the paranormal did not outperform the other participants.

Keywords: Psychophysiology, Expectation, Presentiment, Consciousness, Concealed information test

Publications:
Siller, A., Ambach, W., & Vaitl, D. (2015). Investigating expectation effects using multiple physiological measures. *Frontiers in Psychology, 6*. http://doi.org/10.3389/fpsyg.2015.01553

64/12 - "Hematological and Psychophysiological Correlates of Anomalous Information Reception in Mediums Perspective" - only abstract available

Investigadores/*Researchers*: Julie Beischel, Shawn Tassone, Mark Boccuzzi
Instituição/*Institution*: The Windbridge Institute for Applied Research in Human Potential, Tucson (USA)
Duração/*Duration*: 2013/05 – 2015/06

Background: Mediumship research at the Windbridge Institute includes a three-tiered approach to investigations of secular, American mediums. The Information, Operation, and Application research programs examine (i) the accuracy of the mediums' information; (ii) the mediums' phenomenology, physiology, and psychology, and (iii) the social applications of mediumship readings, respectively. Studying mediums' physiology as part of the Operation research program may help in managing medical issues in mediums. An informal survey of Windbridge Certified Research Mediums (WCRMs) demonstrated that chronic medical problems may be a serious concern for this population. For example, this sample has seven times the incidence of autoimmune disorders compared to the incidence in the general US population. And the incidence of migraines in female WCRMs is nearly two and a half times the prevalence in women in the US.

Objectives: The purpose of this study was to systematically investigate the biological components of anomalous information reception (AIR; the reporting of accurate and specific information about the deceased in the absence of prior knowledge, feedback, or deceptive means) in these mediums.

Methods: General physiological measures and 28 hematological elements during mediumship readings and a control task were examined.

Results: Data collected do not demonstrate any significant changes in these measures when pre- and post-condition comparisons were made for the counter-balanced sessions.

Conclusions: These results imply that the mediumship process itself may not responsible for the increased health issues in this population. We propose an alternative model addressing the relationship between childhood trauma and physical illness.

Keywords: mediums, physiology, hematology, anomalous information reception, trauma

Publications:

Beischel, J. Assessing hematological and psychophysiological correlates of anomalous information reception in mediums. 34th Annual Meeting of the Society for Scientific Exploration, Rockville, Maryland, USA. 2015, May.

Beischel, J., Boccuzzi, M., Tassone, S. (in preparation). Assessing hematological and psychophysiological correlates of anomalous information reception in mediums. *Explore: Journal of Science and Healing*.

66/12 - "Body and soul: A computational neurophysiological and qualitative investigation of Ganzfeld-induced imagery"

Investigadores/*Researchers*: Alexander Sumich, Daniel Wilson, Nicholas Blagden
Instituição/*Institution*: Nottingham Trent University (NTU), Division of Psychology (UK)
Duração prevista/*Estimated Duration*: 2013/04 – 2016/04

Objectives: Degraded and/or random sensory input facilitates imagery production and might, in part, underpin the experience of hallucinations. Experimentally, this can be investigated using Ganzfeld conditions: a homogeneous sensory field. Individual difference is seen in the extent to which simple (e.g. pukunje-type spirals, tunnels, zig-zags) and more complex (e.g. faces, cartoons) images are produced under Ganzfeld conditions. The current study investigated whether such differences are associated with trait mental imagery and/or psychometric risk for psychosis.

Method: Thirty six healthy participants (aged 18-57; n=14 men) completed self-report scales for mental imagery and psychosis proneness. They also completed a Ganzfeld task in which whiteout goggles were used to create a homogeneous visual field and LED lights were used to generate random sensory noise (flicker= 8-24Hz). Participants indicated with a button press whenever they experienced simple or complex images across several blocks.

Results: Multiple linear regression analysis suggested independent positive contributions by mental imagery and psychosis proneness in predicting simple (R2=.33) and complex (R2=.30) imagery. Sex explained a further 8% of the variance for complex images (higher in men), but was not associated with the production of simple imagery.

Conclusion: Although previous studies have explored predictors of the psi response under Ganzfeld conditions, to our knowledge this is the first study to show that mental imagery, psychosis proneness and sex make independent contributions to the imagery response during Ganzfeld. Future studies will investigate the neurobiological underpinnings of these associations.

Keywords: Ganzfeld, Individual difference, Mental imagery, Psychosis proneness

72/12 - "The psychophysiology of human attachment and stress"
Investigadores/*Researchers*: Angela Clow, Lisa Thorn, Andrea Oskis, Nina Smyth
Instituição/*Institution*: Department of Psychology, University of Westminster, London (UK)
Duração/*Duration*: 2013/10 – 2015/09

Objectives: Insecure attachment style is associated with poor health outcomes. A proposed pathway implicates the hypothalamic-pituitary-adrenal axis (HPA-axis), dysregulation of which is associated with a wide range of mental and physical ill-health. However data on stress reactivity in relation to attachment style is contradictory. This relationship was examined using the novel Trier Social Stress Test for groups (TSST-G): a group-based acute psychosocial stressor.

Method: Each participant, in the presence of other group members, individually performed public speaking and mental arithmetic tasks. Seventy-eight healthy young females (20.2 ± 3.2 years), in groups of up to 6 participants completed demographic information and the Vulnerable Attachment Style Questionnaire (VASQ), and were then exposed to the TSST-G. Physiological stress reactivity was assessed using salivary cortisol concentrations, measured on 7 occasions at 10-minute intervals.

Results: Vulnerable attachment predicted greater cortisol reactivity independent of age, smoking status, menstrual phase and BMI. Supplementary analysis indicated that insecure anxious attachment style (high scores on the insecurity and proximity seeking sub-scales of the VASQ) showed greater cortisol reactivity than participants with secure attachment style. Avoidant attachment style (high scores for insecurity and low scores for proximity seeking) was not significantly different from the secure attachment style. Attachment style was not associated with the timing of the cortisol peak or post-stress recovery in cortisol concentrations.

Conclusion: These findings in healthy young females indicate subtle underlying changes in HPA axis function in relation to attachment style and may be important for future mental health and well-being.

Keywords: Group stressor, HPA axis, Healthy females, Stress reactivity, Saliva, Trier social stress test

Publications:
Smyth, N., Thorn, L., Oskis, A., Hucklebridge, F., Evans, P., & Clow, A. (2015). Anxious attachment style predicts an enhanced cortisol response to group psychosocial stress. *Stress, 18*(2),143-148.

77/12 - "Human motor re-learning – the use of sensor information fusion"
Investigadores/*Researchers*: Sandra Maria Caldas da Silva Mouta, Miguel Velhote Correia, Carolina Vila-Chã, Cláudia Silva, Mariana Silva, Carla Borges, António Salazar, Dominic Noy
Instituição/*Institution*: INESC - Porto (Portugal)
Duração/*Duration*: 2013/06 – 2015/09

Objectives: A greater understanding of the mechanisms underlying normal and impaired upper-limb movement is required, in order to improve sensory–motor control, and subsequently to develop adequate interventions and to assess their effectiveness. The main goals of the project were:
(1) characterization of motor skills of the upper limbs;
(2) characterization of the upper limbs' functional tasks;
(3) parameterization of the healthy and pathological pattern of human movement;
(4) study of the influence of perceptual feedback in motor control;
(5) protocols' assessment with healthy participants and stroke patients.

Method: A sample of voluntary participants was selected and divided in two groups: healthy and post-stroke. In the first phase of the project, during the experimental sessions the participants performed 3 tasks: functional task (C1), non-functional task with intentional object (C2) and non-functional task with non-intentional object (C3). In the second phase of the project, psychophysical tasks were conducted in an immersive virtual environment in order to understand the role of sensorial feedback in motor control.

Results: Movement was segmented for every condition, from the velocity profile of hand segment, into a series of events providing the analysis of movement onset and the time until reaching the target as well as the distribution of time spent in each event. Temporal analysis of these events was informative regarding the type of target manipulated and instruction given. The tangential velocity profile of the hand segment was generated in order to extract the number of movement units, which access movement smoothness. EMG analysis was obtained from the time of muscle activation regarding the correspondent event.

Conclusion: Within the scope of this project a methodology was designed with the purpose of assessing functional daily tasks in several complexity degrees and with different instructions and intentions. A database was constructed for the healthy upper-limb movement contemplating the biomechanical parameters and spatiotemporal variables extracted. With this setup it could be possible to characterize upper-limb movements, to identify parameters that categorize healthy and pathological movement patterns (post-stroke) and to develop guidelines to an applied-to-daily-living intervention program.

Keywords: Upper-limb, Functional tasks, Stroke rehabilitation, Kinematics

Publications:
Silva, R.M., Lamas, J., Silva, CC., López-Moliner, J., Coello, Y., Mouta, S., & Santos, J. (submitted). Temporal Estimation of Looming sounds. PlosOne.
Silva, R.M., Fonseca, P., Pinheiro, A.R., Sousa, E., Ferreira, J.P., Silva, C., Vila-Chã, C. & Correia, M.V., Mouta, S., (in preparation). Upper limb functional tasks: Comparison between healthy and post-stroke samples.
Mouta, S., Silva, C., Silva, R.M., Fonseca, P., Pinheiro, A.R., Vila-Chã, C. & Correia, M.V. (2015). Upper limb functional tasks: the effect of location, instruction and object. 6º Congresso Nacional de Biomecânica, Leiria.

83/12 - "The Impact of Future Relevance on Dream Content and Sleep-Dependent Memory Processing" - only abstract available
Investigadores/*Researchers*: Erin J. Wamsley, Robert Stickgold, Nam Nguyen
Instituição/*Institution*: Furman University, Greenville (USA)
Duração prevista/*Estimated Duration*: 2013/05 – 2016/05

Objectives: Recent studies have suggested that sleep preferentially consolidates information that is relevant to an individuals' future. Here, we examined the effect of test expectation on memory consolidation across sleep and wakefulness. Following prior reports (*e.g.* Wilhelm et al. 2010), we hypothesized that test expectation would enhance memory consolidation across a period of sleep, but not across wakefulness. We also hypothesized that test expectation would increase incorporation of the learning task into dreaming.

Method: Immediately following encoding of a Virtual Maze Task (VMT) and Motor Sequence Task (MST), participants in "Expected" groups (n=39) were instructed that they would later be tested again on the same material. Participants in "Unexpected" groups (n=58) were instructed that the tasks were complete. "Sleep" participants trained in the evening and were tested the following morning, 11hr later. "Wake" participants trained in the morning and were tested after 11hr of wakefulness.

Results: Those assigned to the "Expected" groups were much more likely to report that they had expected or suspected the delayed retrieval test (p=.001). In line with our hypotheses, test expectation significantly enhanced memory at delayed test for the MST (p=.04) and VMT (p=.01). But contrary to our hypotheses, this effect of test expectation was strongly equivalent across sleep and waking retention intervals. There was also no evidence that test expectation increased incorporation of the learning tasks into dream content.

Conclusion: We found that expectation of a future test enhanced memory for both spatial and motor learning, even though the test instruction was not introduced until after encoding was complete. However, this effect was equivalently present across both sleep and wakefulness. This observation contradicts those of at least two prior reports, and fails to support the hypothesis that the "future relevance" of learned material selectively influences consolidation during sleep. Instead, our data are consistent with the hypothesis that information important to an individuals' future is preferentially consolidated during both sleep and wakefulness. Thus, future-oriented processing may be a general feature of the brain across states of consciousness.

Publications:
We are currently in the final stages of preparing a manuscript for submission to PLOSOne, and have also submitted an abstract for presentation at the annual SLEEP conference.

84/12 - "Neural bases of time processing: combining neuroimaging techniques and clinical evidence"

Investigadores/*Researchers*: Patrizia Bisiacchi, Gianna Maria Toffolo, Vincenza Tarantino, Elias Casula, Giovanni Mento, Demis Basso

Instituição/*Institution*: Dipartimento di Psicologia Generale, Università di Padova (Italy)

Duração prevista/*Estimated Duration*: 2013/03 – 2016/03

Objectives: The present project aimed at identifying whether there is a core mechanism for timing processes. Specifically, will we investigate which brain areas subserve such mechanism, and their functional role.

Method:

1. High-density EEG study
2. rTMS study
3. EEG-TMS study
4. Clinical studies

Results:

1. High-density EEG study - Brain source analysis of S1- and ISI-related ERP activity revealed activation of sensorial cortical areas and the supplementary motor area (SMA), respectively. We suggest that this area is the major cortical generator of the temporal CNV reflecting an automatic, action-independent mechanism underlying temporal expectancy.
2. rTMS tudy - The results showed that frontal TMS produced differential effects as a function of type of cuing. In symbolic cuing, TMS on either left or right frontal site (vs. sham) increased temporal orienting effects by reducing reaction times invalid trials. In rhythmic cuing, however, frontal TMS did not influence performance
3. EEG-TMS study - Our results confirm the reliability of the TMS-evoked N100 as a marker of cortical inhibition and provide insight into the neuromodulatory effects of 1-Hz rTMS.
4. Clinical studies - On-line comparison process between the two time intervals, reflected by the P1-P2 and LPCt amplitude and morphology, was impaired in patients with Parkinson's disease and support the presence of a deficit of memory for time in such clinical population.

Conclusion: Specific ERP components were shown to index processing of short interval durations. Our findings support the involvement of contingent negative variation (CNV) observed in frontal regions in time processing. Remarkably, the neural generators of the temporal CNV have been located in the SMA. We may consider the CNV as an index of memory and decision. Furthermore our researches show a role of both left and right DLPFC in the ability for temporal orienting. In patients with Parkinson's disease ERPs results suggest that the on-line comparison process between two different time intervals was distorted. This result support the presence of a deficit of memory for time in such clinical population.

Keywords: Time processing, High-density EEG, TMS, Parkinson Disease

Publications:

BISIACCHI P, CONA G, TARANTINO V, SCHIFF S, MONTAGNESE S, AMODIO P, & CAPIZZI G. (2014) Assessing inter- and intra-individual cognitive variability in patients at risk for cognitive impairment: the case of minimal hepatic encephalopathy Metab Brain Dis 29:945–953 DOI 10.1007/s11011-014-9529-0

SCHIFF S., D'AVANZO C., CONA G., GOLJAHANI A., MONTAGNESE S., VOLPATO C., GATTA, A., SPARACINO G., AMODIO P., & BISIACCHI P. (2014) Insight into the relationship between brain/behavioral speed and variability in patients with minimal hepatic encephalopathy. Clinical Neurophysiology 125, 287–297 http://dx.doi.org/10.1016/j.clinph.2013.08.004

CASULA EP, TARANTINO V, BASSO D, ARCARA G, MARINO G, TOFFOLO GM, ROTHWELL JC, & BISIACCHI PS. (2014) Low-frequency rTMS inhibitory effects in the primary motor cortex: insights from TMS-evoked potentials. Neuroimage. (98) 225-232 2014 May 1. pii: S1053-8119(14)00345-0. doi: 10.1016/j.neuroimage.2014.04.065

CAVAZZANA A, BEGLIOMINI C, & BISIACCHI PS (2014) Intentional Binding effect in children: insights from a new paradigm Frontiers in Human Neuroscience 8, 651 DOI: 10.3389/fnhum.2014.00651

CORREA A., CONA G., ARBULA S., VALLESI A., & BISIACCHI P. (2014). Neural dissociation of automatic and controlled temporal preparation by transcranial magnetic stimulation Neuropsychologia 65(2014)131–136

MENTO G, TARANTINO V, VALLESI A, & BISIACCHI PS (2014) Spatiotemporal Neurodynamics Underlying Internally and Externally Driven Temporal Prediction: A High Spatial Resolution ERP Study. J Cogn Neurosci. 2014 Sep 9:1-15. [Epub ahead of print]

CONA G, KLIEGEL M, & BISIACCHI P (2015). Differential effects of emotional cues on components of prospective memory: An ERP study. Frontiers in Human Neuroscience, 9:10. doi: 10.3389/fnhum.2015.00010

CONA G., ARCARA G, TARANTINO V, & BISIACCHI P. (2015). Does predictability matter? Effects of cue predictability on neurocognitive mechanisms underlying prospective memory. Frontiers in Human Neurosciences, 9:188. doi: 10.3389/fnhum.2015.00188

CAVAZZANA A, PENOLAZZI B, BEGLIOMINI C, & BISIACCHI PS (2015). Neural underpinnings of the "agent brain": new evidence from transcranial direct current stimulation. European Journal of neuroscience Accepted manuscript online: 4 MAY 2015 09:21AM EST | DOI: 10.1111/ejn.12937

CONA, G., SCARPAZZA C, SARTORI G., MOSKOVITCH M., & BISIACCHI PS (2015). Neural bases of prospective memory: A meta-analysis and the "Attention to Delayed Intention" (AtoDI) model. NEUROSCI. BIOBEHAV. REV, 52, 21-37 http://dx.doi.org/10.1016/j.neubiorev.2015.02.007

89/12 - "Interaction of medial and lateral temporal lobe in memory expression: insights from patient and fMRI data" - only abstract available

Investigadores/*Researchers*: Ana Luísa Nunes Raposo, José Frederico Henzler Ferreira Marques, José Guilherme Cortez Pimentel
Instituição/*Institution*: Faculdade de Psicologia, Universidade de Lisboa (Portugal)
Duração/*Duration*: 2013/04 – 2016/01

Objectives: While a dog is a good example of a mammal, a bat is less so. Concept typicality is a key dimension of semantic memory that reflects the degree to which a concept belongs to a category. For decades, typicality has been recognized as critical to structuring conceptual knowledge, and more recently, it has also been identified as important in episodic memory. We aimed at clarifying how typicality shapes the neurocognitive bases of semantic and episodic memory.

Method: We carried out a behavioural and an fMRI study that explored concept typicality effects on both semantic and episodic decisions. In a semantic task, participants saw a category (e.g., mammal) followed by typical (e.g., dog) or atypical (e.g., bat) exemplars and had to decide if the exemplar belonged to the category. In a subsequent item memory retrieval task, previously seen exemplars and new ones were presented and participants decided if the item was old or new.

Results: We found a typicality effect in the semantic task, such that participants were faster and more accurate to categorize typical than atypical concepts. Interestingly, the item memory task revealed the opposite effect with better retrieval of atypical than typical items. At a neural level, retrieval of atypical items (relative to new ones) involved an extensive network including lateral temporal cortices bilaterally, left ventrolateral prefrontal cortex, medial frontopolar cortex and bilateral angular gyrus. In contrast, retrieval of typical items showed restricted activation in posterior regions, namely posterior cingulate and superior parietal cortex.

Conclusion: The findings suggest that during retrieval of atypical items, the lateral temporal cortex, important in the storage of semantic features, interplays with frontal areas, involved in controlled semantic elaboration and monitoring. Atypical items carry unique, distinctive features (e.g., a bat is a flying mammal) that are more diagnostic to the memory decision. We argue that distinctive events induce greater semantic elaboration, via fronto-temporal interactions, which in turn promote episodic memory retrieval.

Keywords: Concept typicality, Semantic memory, Episodic retrieval, Fronto-temporal network

Publications:

Alves, M. & Raposo, A. (in press). Is it a bird? Differential effects of concept typicality on semantic memory and episodic recollection. *Revista Portuguesa de Psicologia*.

Santi, A., Raposo, A. & Marques, J.F. (in press). Superordinate and domain category structure: evidence from typicality ratings. *Revista Portuguesa de Psicologia*.

91/12 - "Psychophysiological studies into task-set inertia in switching paradigms" - only abstract available

Investigadores/*Researchers*: Lisa Evans, Edward Wilding
Instituição/*Institution*: School of Psychology, Cardiff University (UK)
Duração/*Duration*: 2013/04 – 2014/12

Background: We switch between tasks multiple times every day. A robust finding is that switching results in poorer task performance, because people usually take longer to complete tasks and they are more subject to errors. These outcomes are known as switch costs. One influential explanation for them is that they reflect interference arising from completing a previous task - known as task-set

Objectives: In this program of work we used a novel approach for assessing task-set inertia in memory experiments using Event-Related Potentials (ERPs). Our aim was to examine how task properties affect task-set inertia, which in turn will give insight into the mechanisms which underlie this phenomenon.

Method: Healthy volunteers completed an initial study phase followed by a switching task, during which ERPs were acquired. In this task participants switched between completing a memory task (retrieving information from the study phase) and a perceptual task. These tasks alternated every two trials.

Results: An ERP index of the retrieval of study information was evident in the memory task. It was also present on the first trial of the perceptual task but was markedly attenuated on the second. Moreover, this task-irrelevant ERP activity was positively correlated with the behavioural cost associated with switching between tasks.

Conclusion: These findings indicate that in the perceptual task irrelevant information was more active on the first trial compared to the second. This provides direct neural evidence of task-set inertia, its duration, and the functional role it plays in switch costs.

Keywords: Task switching, Episodic memory, Task-set inertia, Event-Related Potentials (ERPs)

Publications:

Evans L.H., Williams, A.N. and Wilding, E.L. (2015). Electrophysiological evidence for retrieval mode immediately after a task switch. *NeuroImage, 108*, 435-440.

Evans L.H., Herron, J.E. and Wilding, E.L. (2015). Direct real-time neural evidence for task-set inertia. *Psychological Science, 26*, 284-290.

92/12 - "Dissociating familiarity and conceptual priming with event-related potentials" - only abstract available
Investigadores/*Researchers*: Edward Wilding, Lisa Evans
Instituição/*Institution*: School of Psychology, Cardiff University (UK)
Duração/*Duration*: 2013/04 – 2015/01

Objectives: The objective in two experiments was to contribute to an understanding of the sensitivities of ERPs to memory processes. This is an important objective, because understanding their sensitivity is critical if ERPs are to be used to investigate how and when different memory processes are used, and how they are compromised during healthy and pathological ageing and in other disease states.
The specific objective here was to investigate whether the mid-frontal ERP old/new effect indexes familiarity or conceptual priming. The mid-frontal ERP old/new effect has two accounts: it indexes *familiarity* – a graded memory strength signal supporting old/new judgments, or it indexes *conceptual prim*ing - a performance facilitation for events due to pre-exposure to semantically related events.

Method: Participants saw words one at a time. All were repeated twice. In Experiment 1 participants made a living/non-living judgment to words. In Experiment 2 they did this for half of them, making old/new judgments to the remainder. ERPs were acquired locked to word onset and analysed for first presentations and repetitions (both experiments) and for words attracting correct old/new judgments (Exp2 only).

Results: Priming - faster reaction times for repetitions than first presentations - was similar for both repetitions in both experiments. Old/new recognition was better for the second than the first repetition. The mid-frontal effect was similar for both repeats in Exp2 for words with correct old/new judgments. At the same sites the repetition effect for both repeats was also similar.

Conclusion: Mid-frontal activity from 300-500ms mirrored the priming data: there was little change between first and second repetitions. Because of this, and because this activity did not track old/new accuracy in Exp2, the data are consistent with a priming account of the mid-frontal effect. In subsequent work we will increase the difference in old/new recognition accuracies between first and second repeats to rule out a lack of sensitivity as an explanation for the lack of correspondence between the ERP and recognition memory data.

Keywords: Familiarity, Conceptual Priming, Event-Related Potentials (ERPs), FN400

103/12 - "Psychological and psychophysiological factors in sexual desire and behaviour"
Investigadores/*Researchers*: Rui Miguel dos Santos Amaro da Costa, Tânia F. Oliveira
Instituição/*Institution*: ISPA, CRL, Lisboa (Portugal)
Duração/*Duration*: 2013/04 – 2015/06

Introduction: Spirituality as a human personality trait has various facets; one consists in a sense of connectedness with human life transcending one's lifetime (henceforth, Connectedness). Spirituality and sexuality are often thought as very distinct realms, but there are crossroads between them; in previous research, women's coital frequency was related to greater Connectedness.

Objectives: To explore associations of Connectedness with sexual desire, frequency of sexual behaviours, basal testosterone (T), T elicited by sexual stimuli, and concordance between T and reported sexual desire (a putative index of awareness of T-induced sex drives). Mediating effects of variables related to health, sexuality and spirituality were explored – alexithymia, defense mechanisms, tactile sensitivity, heart rate variability, blood pressure, interoception, depressive symptoms, subjective sleep quality, waist circumference, religiousness, conscientiousness, openness to experience, and creative self-forgetfulness (a personality trait consisting in tendency for absorption in sensations and imagination, and feelings of eternity and unity with all things).

Method: Before and after sexual stimuli, 251 Portuguese (149 women) provided saliva samples for T determination by luminescence immunoassays. Interoception was measured by a heartbeat detection task and tactile sensitivity by von Frey microfilaments.

Results: Female Connectedness correlated with higher desire in the past month, higher T response to a romantic movie scene, and greater concordance between basal T and past month desire. Results were partly explained by creative self-forgetfulness, interoception and low alexithymia. Male Connectedness correlated with concordance between desire elicited by visual erotica and both basal T and post-stimulus T.

Conclusion: The results confirm that Connectedness relates to greater sexual responsiveness. For women, that was mainly explained by indices of emotional awareness and creative self-forgetfulness, a personality trait reflecting tendency to altered states of consciousness. Both men and women higher in Connectedness appear to be more aware of the sexual effects of T.

Keywords: Spirituality, Sexual desire, Sexual behaviours, Testosterone, Emotional awareness

Publications:
Costa R. M., & Oliveira T. F. (2014). Interoceptive awareness and resting heart rate variability in women. In Proceedings of EAPM 2014: Care and Cure: An Integrated Approach to Psychosomatic Medicine, pp. 64-66. D. L. Dimitrascu, W., Soellner, Eds. Medimond International Proceedings.

108/12 - "Clinical parapsychology: Counselling experiences of clients who report anomalous experiences and the training needs of therapists"

Investigador/*Researcher*: Elizabeth Roxburgh
Instituição/*Institution*: Centre for the Study of Anomalous Psychological Processes (CSAPP), Division of Psychology, School of Social Sciences,The University of Northampton (UK)
Duração/*Duration*: 2013/07 – 2015/10

Objectives: To investigate 1) the experiences of clients who have reported anomalous experiences (AEs) in secular counselling services, 2) the experiences of therapists who work with such clients, and 3) the training needs of students.

Method: A mixed method design was adopted. Questionnaires were used to investigate the range and incidence of AEs, interviews were conducted with clients and therapists, and an online survey and focus groups explored the training needs of students.

Results: Few clients reported AEs in a secular counselling service over a one-year period (N= 8). Consequently, an additional study was undertaken on help-seeking for AEs (i.e., if individuals do not seek support from counselling services, where do they seek support or do they not seek support?).When clients did seek counselling the majority of participants we interviewed said that they felt dismissed when they tried to discuss AEs or reported that their counsellor did not take into account their worldview. Therapists reflected on how clients are often reluctant to disclose AEs to them for fear of being seen as 'mad'. They emphasised the importance of exploring the meaning with clients rather than imposing an explanation or making a judgement as to the authenticity of AEs. Most of the students that took part in the focus groups felt that they were unequipped to work with clients who reported AEs and stated that they had not received any training on these issues.

Conclusion: Findings have implications for clients in terms of accessibility of services, engagement with therapy, and psychological adjustment following AEs. It would be useful for therapists to have reliable and accurate information about AEs and/or for students to be introduced to the topic whilst undertaking training.

Keywords: Anomalous experiences, Clinical parapsychology, Counselling, Therapy, Training

Publications:

Roxburgh, E. C., & Evenden, R. E. (under review). "Most people think you're a fruit loop": An exploratory study of clients' experiences of seeking support for anomalous experiences.

Roxburgh, E. C., & Evenden, R. E. (under review). "They daren't tell people": Therapists experiences of working with clients who report anomalous experiences.

Roxburgh, E. C., & Evenden, R. E. (in preparation). "It's about having exposure to this": Investigating the training needs of therapists in relation to the issue of anomalous experiences.

Roxburgh, E. C., & Evenden, R. E. (in preparation). Help-seeking for anomalous experiences.

112/12 – "Retinotopic reorganization of the auditory cortex of congenitally deaf individuals due to neuroplascticity"

Investigadores/*Researchers*: Jorge Manuel Castelo Branco de Albuquerque Almeida, Bradford Zack Mahon, Yanchao Bi, Óscar Filipe Coelho Neves Gonçalves
Instituição/*Institution*: Faculdade de Psicologia e Ciências da Educação, Universidade de Coimbra (Portugal)
Duração/*Duration*: 2013/05 – 2015/11

Objectives: Sensory cortices of individuals who are congenitally deprived of a sense can undergo considerable plasticity and be recruited to process information from the senses that remain intact. How information that is rerouted to the neuroplastically changed cortex is still under debate. Here we explore the volumetric changes in auditory and visual subcortical areas of the congenitally deaf, when compared to the hearing, to uncover the circuitry involved in relaying visual information to the auditory cortex (AC).

Methods: We used MRI to perform volumetric analysis. Individual brain images were manual segmented to determinate the regions of interest (ROIs). The ROIs were the inferior colliculi, superior colliculi, and the thalamus. Within the thalamus we further defined the pulvinar, the lateral geniculate nucleus (LGN) and the medial geniculate nucleus. Each ROI was traced based on its anatomical borders, and the total volume of ROIs was calculated. These volumes were compared, within-subjects, in order to investigate the volumetric differences between left and right hemisphere per ROI and per group (deaf and hearing), because of the known right hemisphere AC biases in neuroplasticity.

Preliminary results: We show hemispheric asymmetries in the deaf but not in the hearing for the Thalamus and the Inferior Colliculus, such that the right counterpart was larger than the left. Since the Thalamus can be divided in different nucleus we also analyze the volume of different thalamic nuclei. We show a marginally significant difference between the right and left LGN for the deaf participants, such that the right counterpart was also larger than the left.

Conclusion/discussion: These results suggest that subcortical regions like the Thalamus and Inferior Colliculi can be responsible for neuroplastically rerouting visual information to the AC. That is, visual information may reach the AC from an auditory structure – the inferior colliculi – and/or from a visual structure – the LGN.

Keywords: Congenital deafness, Neuroplasticity, Volumetric analysis

119/12 - "Dynamic cortical and nucleus accumbens networks in humans: combining intracranial and MEG recordings"

Investigadores/*Researchers*: Bryan Strange, Javier J. Gonzalez-Rosa, Juan A. Barcia, Stephan Moratti, Raffael Kaplan, Marijn Kroe

Instituição/*Institution*: Laboratory for Clinical Neuroscience, Centre for Biomedical Technology (CTB), Technology University of Madrid (UPM) and Fundación para la Investigación Biomédica del Hospital Clínico San Carlos - Universidad Complutense de Madrid. Instituto de Investigación Sanitario IdISSC (Spain)

Duração prevista/*Estimated Duration*: 2013/06 – 2016/06

Objectives: We studied the effects of deep-brain stimulation (DBS) of the human nucleus accumbens on decision making. Real-world decisions about reward often involve a complex counterbalance of risk and value. Although the nucleus accumbens has been implicated in the underlying neural substrate, its criticality to human behaviour remains an open question, best addressed with interventional methodology – such as DBS – that probes the behavioural consequences of focal neural modulation.

Methods: In four patients with treatment-resistant psychiatric disease, we combined a psychometric index of risky decision-making with transient electrical modulation of the nucleus accumbens.

Results: We observed profound, highly dynamic alteration of the relation between probability of reward and choice during therapeutic deep brain stimulation in all patients tested. Short-lived phasic electrical stimulation of the region of the nucleus accumbens dynamically altered risk behaviour, transiently shifting the psychometric function towards more risky decisions only for the duration of stimulation.

Conclusions: A critical, on-line role of human nucleus accumbens in dynamic risk control is thereby established.

Keywords. Decision-making, deep-brain stimulation, nucleus accumbens, risk taking

Publications:

P Nachev, F Lopez-Sosa, JJ Gonzalez-Rosa, A Galarza, J Avecillas, JA Pineda-Pardo, JJ Lopez-Ibor, B Reneses, JA Barcia, BA Strange (2015) Dynamic risk control by human nucleus accumbens. *Brain (in press)*

122/12 - "EEG Analysis of Auditory and Visual Stimuli in Normal Controls"

Investigadores/*Researchers*: William Bunney, Blynn Bunney, James Fallon, Julie Patterson, Steven G. Potkin, Richard Stein, Joseph Wu
Instituição/*Institution*: Department of Psychiatry & Human Behavior, The Regents of the University of California, Irvine (USA)
Duração prevista/*Estimated Duration*: 2013/05 – 2016/07

Objectives: A number of EEG studies on randomly presented visual and auditory stimuli have been reported, and although not analyzed, have collected data before and after stimulus onset. The objective was to determine if brain activity could differentiate between pleasant and unpleasant visual stimuli and loud and soft auditory stimuli.

Method: Forty, right-handed female subjects aged 18-55 were studied. Established ratings of pictures from the International Affective Picture System were screened for 80 in each category for the most highly pleasant, unpleasant or emotionally neutral properties. Stimuli were selected at random in real time immediately before presentation using a true random number generator circuit with the provision that an equal number of unpleasant, pleasant and neutral stimuli were selected. EEG data were collected from 64 recording sites using an Easy Cap from Brain Vision, Inc. and Neuroscan amplifiers After eye blink artifact correction, averaged evoked potentials to both visual and auditory stimuli began 1200 msec prior to stimulus onset and continued 1000 msec after the auditory or visual stimulus onset. Traditional post-stimulus effects for these stimulus types were evaluated. A visual cue was presented at a randomized time prior to the subject seeing the visual stimulus. Following the anlaysis of the EEG post-stimulus, the pre-stimulus period was analyzed.

Results: Post-stimulus late positivity effects for visual stimuli ($p<.0001$) and late negativity effects for auditory ($p=.0012$) were found. The channels with the strongest post-stimulus differential responses were grouped for pre-stimulus analysis to minimize the statistical issue of multiple testing. Statistically signficant pre-stimulus visual ($p=0.015$) and auditory effects ($p=0.034$) were also observed.

Conclusion: Consistent with previous reports, post-stimuli slow potentials differentiated pleasant and unpleasant pictures as well as loud and soft auditory tones. Since we recorded EEG in the pre-stimulus period, its analysis also differentiated pleasant vs. unpleasant pictures and simple loud vs. soft auditory tones.

Keywords: EEG, Pre-stimulus, Visual, Auditory

124/12 - "EEG correlates of mental entanglement at distance" - only abstract available
Investigadores/*Researchers*: Patrizio Tressoldi, Francesco Salvadori, Patrizio Caini, Simone Melloni, Giorgio Gagliardi, Mirko de Vita, Alessandro Ferrini
Instituição/*Institution*: Dipartimento di Psicologia Generale, Università di Padova and Laboratorio Interdisciplinare di Ricerca Biopsicocibernetica, Bologna (Italy)
Duração prevista/*Estimated Duration*: 2013/03 – 2016/03

Objectives: To identify EEG correlates of personal interaction (mental entanglement) between individual participants in pairs, when all conventional forms of communication are absent.

Method: The participants were selected on the basis of their advanced ability to control their minds and for their longstanding mutual friendships. In a first pre-registered confirmation study with individuals of each pair placed 190 Km apart, the EEG activity of one member from each pair was analyzed before, during, and after being presented with an expressive image accompanied by a sound (a newborn crying), for a total of twenty sessions. In a second exploratory study, twenty-five sessions were analyzed in which the members of each pair were 5 metres apart; their EEG activities were studied before, during, and after the simultaneous visual and auditory stimulations (one-second stimulation from a light signal produced by an arrangement of red LEDs, and a simultaneous 500 Hz sinusoidal audio signal of the same length).

Results: Regarding the first study, EEG analysis of the member of each pair who was not shown the image allowed us to correctly identify 76.4% of cases in which this member's partner received the image. In the second study we used an innovative analytical method for correlating recorded EEG activity in different electrodes, and discovered a statistically significant correlation exclusively concomitant with each stimulation period.

Conclusion: These results clearly show EEG correlates in distant mind interactions (mental entanglement) which can be identified through various methods, thus leading to the possibility of future applications in mental telecommunications.

Keywords: Mental entanglement, Interaction at distance, EEG

Publications:
Tressoldi P, Pederzoli L, Bilucaglia M et al. Brain-to-Brain (mind-to-mind) interaction at distance: a confirmatory study [v3; ref status: approved 1, not approved 1, http://f1000r.es/4ka] F1000Research 2014, 3:1(doi:10.12688/f1000research.4336.3)

Giroldini W, Pederzoli L, Bilucaglia M et al. EEG correlates of social interaction at distance [v1; ref status: awaiting peer review, http://f1000r.es/5ll] F1000Research 2015, 4:457 (doi: 10.12688/f1000research.6755.1)

Giroldini, W, Pederzoli, L, Bilucaglia, M, Melloni, S. and Tressoldi, P. E., (2015). A New Method to Detect Event-Related Potentials Based on Pearson's Correlation (May 21, 2015). Available at SSRN: http://ssrn.com/abstract=2609008 or http://dx.doi.org/10.2139/ssrn.2609008

126/12 - "Implicit and explicit processing of emotion in healthy adult ageing" - only abstract available

Investigador/*Researcher*: Sarah MacPherson
Instituição/*Institution*: Human Cognitive Neuroscience Unit, Department of Psychology, PPLS, The University of Edinburgh (UK)
Duração/*Duration*: 2013/08 – 2014/10

Objectives: While the aging literature contains a large number of studies demonstrating age-related differences in the ability to explicitly recognise emotions portrayed through facial expressions, there do not appear to be studies that have compared the ability of younger and older adults to implicitly identify facial expressions of emotion. Eye tracking during explicit emotion recognition studies has shown that older adults gaze less at the eye region of faces than younger adults which may explain their poorer ability to judge certain emotions. Yet, the fixation patterns of younger and older adults during implicit emotional processing remains unclear. Given that previous work in other research areas such as memory has shown that implicit processes are often spared in aging, it is hypothesised that older adults will not differ in their ability to implicitly process emotions compared to younger adults.

Method: In Experiment 1, 24 younger and 24 older adults performed explicit emotion and age categorisation tasks. In Experiment 2, 24 younger and 24 older adults performed implicit emotion and identity matching tasks.

Results: Older adults were significantly poorer at explicitly but not implicitly identifying emotions compared to the younger adults. In terms of eye gaze patterns, older adults showed a reduced bias to inspect the top half of faces than younger adults across all tasks except the implicit emotion matching task. During implicit emotion matching, older adults showed a negative bias towards the lower half of faces compared to younger adults whose bias was towards the top half.

Conclusion: These results suggest that explicit but not implicit emotion processing declines with age and the fewer fixations towards the top of a face in older adults may explain the age differences found in the explicit but not implicit processing of emotional faces.

Keywords: Emotion, Explicit processing, Implicit processing, Aging

Publications:

Hirose, Y., & MacPherson, S.E. (under review). Implicit and explicit processing of emotion from faces: An eye tracking study. *Emotion.*

Hirose, Y., & MacPherson, S.E. (in prep). The influence of full and divided attention on implicit and explicit emotion processing.

132/12 - "A direct test of the binding by synchrony hypothesis in humans: the neural correlates of coherent object perception"

Investigadores/*Researchers*: Miguel Castelo-Branco, Maria Ribeiro, João Duarte, Gabriel Costa
Instituição/*Institution*: IBILI, Faculdade de Medicina, Universidade de Coimbra (Portugal)
Duração/*Duration*: 2013/11 – 2016/01

Objectives: This project had 3 main goals: 1. to investigate the coupling between perception and oscillatory neural synchrony. 2. Neurophysiological correlates and temporal dynamics of perceptual decision. An important goal was to provide a critical test to the binding by synchrony hypothesis in humans.

Methods: We have developed a set of paradigms involving long-range perceptual spatial integration. Some of these paradigms included stimuli requiring interhemispheric integration (roof shaped patterns), and holistic integration for perceptual decision.

Results: We found that oscillation amplitude and phase coherence can be uncoupled when related with the emergence of perceptual decision. Moreover we identified that perception related different gamma band sub components that be traced to distinct neural modules within the perceptual decision network, as also tested by simultaneous EEG/fMRI.
Concerning the roof-shaped patterns, by analyzing the EEG signal resulting from coherent object perception of ambiguous/unambiguous stimuli we were surprised to identify common features of oscillatory activity in the beta-gamma frequency range. This particular subband seems to be involved in perception related changes in oscillatory patterning. The topography of EEG synchronization is this band seems to be not directly related to the emergence or disruption of bilateral synchronization and the areas involved in bilateral integration of such roof-shaped patterns.
Importantly, we were able to also implement data-driven approaches to test the hypothesis of binding by synchrony in humans which are critical to test model driven approaches.

Conclusions: In sum our data highlight a complex network o regions involved in perceptual decision making and seem to support a functional role for spatiotemporal patterns in the beta and gamma frequency range for perceptual integration, but do not support a direct role for the binding by synchrony hypothesis.

Keywords: EEG, fMRI, holistic perception, synchrony

Publications:

Castelhano, J., Duarte, I. C., Wibral, M., Rodriguez, E., and Castelo-Branco, M. (2014). The dual facet of gamma oscillations: separate visual and decision making circuits as revealed by simultaneous EEG/fMRI. Human Brain Mapping, Oct;35(10):5219-35. doi: 10.1002/hbm.22545.

Castelo-Branco M. and Castelhano J Perceptual Decision Making Book: Brain Mapping: An Encyclopedic Reference (BRNM) (Ed. A. Toga) Chapter: 00261 2015 Elsevier Inc.

133/12 - "The role of the core and extended face networks in visual perception and high level social cognition"

Investigadores/*Researchers*: Miguel Castelo-Branco, Marco Simões, Carlos Amaral, Gregor Philipiak, José Rebola, João Castelhano
Instituição/*Institution*: IBILI, Faculdade de Medicina, Universidade de Coimbra (Portugal)
Duração/*Duration*: 2013/11 – 2016/01

Objectives: This project had 3 main goals: 1. To study of selectivity dynamics of mapped category-preferring visual networks, in particular the Superior Temporal Sulcus (STS) before, during and after perceptual closure (perceptual "Eureka" under ambiguous conditions). 2. To identify the neural correlates of face perception when facial /head signals are used as social attention cues to other objects or human-like agents. 3. To study reward and decision making processes in the highly naturalistic setting of a social interaction (a trust game).

Methods: We used mooney stimuli in which the observer suddenly becomes aware of the emergence of a holistic face percept for EEG and EEG/fMRI experiments. We also investigated if stimuli of increasing hierarchical social complexity, generate identifiable neurophysiological correlates of 3D human faces and agents as targets for focus of social attention. We attempted single trial classification of P300-like markers of detection of "social" events. Finally, we used fMRI to study how face and social cognition network, are modulated by face- to-face interaction and how they are modulated by eye contact the payoff values of the interaction.

Results: Using EEG and fMRI we found that distinct gamma frequency sub-bands reflect different neural substrates and cognitive mechanisms when comparing object perception states vs. no categorical perception. We found a neural correlate of complex social signals and single-trial detection of this signal reached a balanced accuracy of 79%. We found a specific right lateralization only for more complex social scenes. We also found evidence for interaction of social variables such as behavioural trust and neural responses in the face and social cognition networks.

Conclusions: We found evidence for functional parcellation of general and specific perceptual and affective decision making circuits in relation to face perception and social cognition

Keywords: Social cognition, EEG, fMRI, face perception

Publications:

Rebola J, Castelo-Branco M. Visual areas PPA and pSTS diverge from other processing modules during perceptual closure: Functional dichotomies within category selective networks. Neuropsychologia. 2014 Jun 17;61C:135-142. doi: 10.1016/j.neuropsychologia.2014.06.010.

Amaral CP, Simões MA, Castelo-Branco MS. Neural signals evoked by stimuli of increasing social scene complexity are detectable at the single-trial level and right lateralized. PLoS One. 2015 Mar 25;10(3):e0121970. doi: 10.1371/journal.pone.0121970. eCollection 2015.

167/12 - "Impact of body image related variables on the psychophysiological indicators of human sexual response: comparative study with a clinical and non clinical sample"

Investigadores/*Researchers*: Maria João Alvarez Martins, Pedro Nobre, Ellen Laan, Sandra Byers, Lisa Vicente, Nuno Monteiro Pereira, Patrícia Pascoal

Instituição/*Institution*: Faculdade de Psicologia da Universidade Lisboa and SEXLAB (Laboratórios de Investigação em Sexualidade Humana), Faculdade de Psicologia e Ciências da Educação da Universidade do Porto (Portugal)

Duração prevista/*Estimated Duration*: 2013/03 – 2016/04

Objectives: This project aimed to take a dyadic perspective and demonstrates the role of beliefs and body image dimensions as predictors of self-reported and psychophysiological sexual functioning among heterosexual couples. It sets out specifically to: develop a new measure of sexual beliefs about sexual functioning, to adapt the Beliefs About Appearance Scale in a sample of heterosexual couples; to understand the impact of sexual functioning on sexual satisfaction from a dyadic perspective; to establish the role of cognitive distraction with body appearance as a mediator between beliefs and sexual response, and to test a dyadic model of the impact of sexual beliefs and body image on psychophysiological sexual outcomes.

Method: Using a cross-sectional, correlational design, data was collected from single informants as well as amorous dyads using mixed methodology of data collection (self-report and psychophysiological data) and different data analysis methodologies, such as the Actor Partner Interdependence model.

Results: The studied measures proved to be reliable and valid and beliefs about appearance were shown to be interdependent in couples and explanatory of sexual outcomes related to dysfunctional sexual response. Furthermore, it was also established that the impact of sexual functioning on sexual satisfaction is better explained from a dyadic perspective, establishing that men's, but not women's, sexual satisfaction is partner dependent. Furthermore, it was verified that after controlling for relationship satisfaction, cognitive distraction mediated the impact of sexual beliefs and body appearance on sexual functioning. Psychophysiological data is currently under analysis.

Conclusion: Our results are supportive of a relational cognitive model of sexual response.

Keywords: Body image, Psychophysiological sexual response, Dyadic approach, Sexual beliefs

Publications:

Pascoal, P. M., Alvarez, M.-J., Pereira, C., & Nobre, P. Development and validation of the Beliefs About Sexual Function Scale (submitted).

Pascoal, P. M., Alvarez, M.-J., Pereira, C., Nobre, P., Byers, S. E., & Laan, E. The impact of sexual function on sexual satisfaction: A dyadic study using the APIM model (submitted).

Pascoal, P. M., Alvarez, M.-J., Pereira, C., Nobre, P., Byers, S. E., & Laan, E. Dyadic effects of the beliefs about appearance on cognitive distraction with body appearance during sexual activity: A study using the APIM model (in preparation).

191/12 - "Defining the functional architecture of motion vision sensitive visual-motor circuits"
Investigadores/*Researchers*: Eugenia Chiappe, Tomás Cruz
Instituição/*Institution*: Fundação Champalimaud, Lisboa (Portugal)
Duração prevista/*Estimated Duration*: 2013/08 – 2016/07

Objectives: Animal behavior, including our own, depends on the neural processes that happen between sensation and action. In order to understand our behaviors, we need an explicit explanation of how neural circuits transform sensory information into action selection. Because of its powerful genetic toolkit, we argue that Drosophila melanogaster is a legitimate model to study —at a mechanistic level, integrative functions of the brain to understand how ours may work. Specifically, we are interested in how neural circuits dynamics control the fly's oriented behaviors, from the detection of to the successful approach towards an attractive target.

Method: We use quantitative analysis of behavior, systematic manipulations of the activity of genetically identified neuronal populations, and modern labeling techniques to identify candidate neurons and their postsynaptic partners involved in oriented behaviors. We also record neural activity in simultaneous with behavior to correlate the neural circuit dynamics with the spatial orientation capacity of the fly.

Results: We developed behavioral assays to find visual interneurons involved in the detection of attractive targets to the fly. Using the Gal4/UAS expression system we targeted and identified circuit components that are important in visual-spatial processing. Different populations of neurons show restricted projections to specific and distinct visual areas of the brain. Targeted expression of synaptic-specific proteins revealed the flow of information of the identified neurons. Using this information, we are searching for post-synaptic partners. We have also developed a system to adapt the oriented behaviors in the real world to virtual worlds. Using this virtual reality set-up, we are characterizing the activity dynamics of the identified neurons as the fly approaches virtual targets.

Discussion: Our data shows that the fly's successful oriented locomotion depends on the interaction among sensory signals, self-generated sensory feedback, and motor related signals, in striking similarity to many spatially oriented behaviors in humans and non-human primates. We have applied a systematic approach that leaded us to identify populations of visual interneurons involved in different aspects of the behavior. These neurons serve as entrance points to uncover visuomotor circuits involved in the transformation of visual motion signals into oriented locomotion.

Keywords: Visuomotor transformation, Spatial orientation

198/12 - "Enhancing hypnotic suggestibility with transcranial direct current stimulation"
Investigador/*Researcher*: Devin Blair Terhune
Instituição/*Institution*: The Chancellor, Masters and Scholars of the University of Oxford, Experimental Psychology (UK)
Duração/*Duration*: 2014/03 – 2015/02

Objectives: The primary phenomenological feature of response to a hypnotic suggestion is the perception that one is not the author of one's action or experience (the classic suggestion effect). Theoretical accounts of hypnosis converge on the hypothesis that hypnotic responding is characterized by a disruption in meta-awareness and in particular awareness of intentions underlying the implementation of hypnotic responses. One possible corollary of this hypothesis is that highly suggestible individuals will exhibit impaired or reduced metacognition pertaining to their sense of agency over their actions, but retain otherwise normal metacognition more broadly.

Method: Seventy-four healthy participants, 16 of whom displayed high hypnotic suggestibility, completed the Metacognition of Agency Task (Metcalfe & Green, 2007, JEP: General), which requires one to move a cursor to "catch" particular stimuli and avoid others. Motor control was surreptitiously manipulated through changes in stimulus speed and cursor lag and participants were asked to make metacognitive judgments regarding their performance and their sense of agency.

Results: Across participants, task performance (d´ and hit rates) and metacognitive judgments of performance and agency declined when speed and cursor lag were altered. Highly suggestible participants did not differ from controls in task performance or in judgments of performance, indicating preserved metacognition. However, they displayed greater judgments of agency than controls selectively when motor control was impaired most strongly through the cursor lag manipulation, but not through the speed manipulation. Further analyses indicated that this effect was independent of associations between task performance and judgments of performance and judgments of agency.

Conclusion: These results indicate that highly suggestible individuals display a selective reduction in metacognition of agency. Accordingly, they provide an important corroboration of the hypothesis that hypnotic responding is characterized by a disruption or reduction in awareness of mental representations pertaining to agency.

Keywords: Agency, Hypnosis, Hypnotizability, Meta-awareness, Metacognition, Suggestion

199/12 - "Brain-to-Brain Communication Enabled with Intracortical Microstimulation"
Investigadores/*Researchers*: Miguel Angelo Laporta Nicolelis, Miguel Santos Pais Vieira
Instituição/*Institution*: Duke University, Durham (USA)
Duração/*Duration*: 2013/04 – 2015/10

Introduction: Recently, we proposed that Brainets, i.e. networks formed by multiple animal brains, cooperating and exchanging information in real time through direct brain-to-brain interfaces, could provide the core for a new type of computing device: an organic computer.

Objectives: To develop a proof of concept of an organic computing device that uses multiple interconnected brains.

Method: Brainets worked by concurrently recording the extracellular electrical activity generated by populations of cortical neurons distributed across multiple rats chronically implanted with multi-electrode arrays. Cortical neuronal activity was recorded and analyzed in real time, and then delivered to the somatosensory cortices of other animals that participated in the Brainet using intracortical microstimulation (ICMS).

Results: Different Brainet architectures solved a number of useful computational problems, such as discrete classification, image processing, storage and retrieval of tactile information, and even weather forecasting. Brainets consistently performed at the same or higher levels than single rats in these tasks.

Conclusion: Based on these findings, we propose that Brainets could be used to investigate animal social behaviors as well as a test bed for exploring the properties and potential applications of organic computers.

Keywords: Tactile, information, Brainet

Publications:
Pais-Vieira M, Lebedev M, Kunicki C, Wang J, Nicolelis MA. (2013) A brain-to-brain interface for real-time sharing of sensorimotor information. Sci Rep. 3:1319.
Pais-Vieira M, Chiuffa G, Lebedev M, Yadav A, Nicolelis MA.(2015) Building an organic computing device with multiple interconnected brains. Sci Rep. 5:11869.

209/12 - "Predicting your decision while you make up your mind – an intracranial human study of the neural underpinning of decision making" - only abstract available

Investigadores/*Researchers*: Uri Muz Maoz, Liad Mudrik, Ian Ross, Adam Mamelak, Ralph Adolphs
Instituição/*Institution*: California Institute of Technology, Pasadena and Cedars-Sinai Medical Center, Los Angeles (USA)
Duração/*Duration*: 2013/05 – 2015/02

Objectives: Humans strongly experience deciding freely. Yet decision-related neural activity before subjects report deciding led some to deny a causal role for consciousness in decision-making and designate free will and moral responsibility illusions. However, our Bial work, among others, challenges this conclusion. In particular, preconscious neural activity was typically recorded before purposeless, unreasoned, arbitrary actions, less important for free will. We wanted to test whether such early activations also occur before deliberate decisions.

Method: We used electroencephalography (EEG) to compare the role of consciousness in both decision types. Subjects indicated their choices between donations to two Non-Profit Organizations (NPOs) by pressing the left or right button with the corresponding hand. In deliberate-decision trials, they selected which NPO should receive $1000; in arbitrary-decision trials, both NPOs received $500.

Results: We found predictive differences in EEG waveforms about 1 s before left/right button presses for arbitrary decisions, but only much smaller and later ones for deliberate decisions.

Conclusions: Viewing decisions as dynamic processes that converge to the alternative with the higher value, we hypothesize that random neural fluctuations also weakly bias decisions. In arbitrary decisions, the alternatives' values are similar to identical, so decisions are typically driven by bias activity. For deliberate choice, in contrast, this bias activity is generally weaker than the divergence of the values, so it little affects the decision. We postulate that the early, predictive activations in arbitrary decisions reflect bias activity rather than decision activity.

Keywords: Decision-making, Free will, Consciousness, Bias

Publications:

Maoz U et al., What Does Recent Neuroscience Tell Us About Criminal Responsibility? *Journal of Law and the Biosciences*, In Press

Mudrik L and Maoz U (2015) "Me & my brain": Exposing neuroscience's closet dualism in studies of consciousness and free will. *Journal of Cognitive Neuroscience*, *27*(2): 211-221

Maoz U, et al. (2015) On reporting the onset of the intention to move, in Alfred R. Mele, (Ed). *Surrounding Free Will: Philosophy, Psychology, Neuroscience*. Oxford University Press, 184-202

Maoz U et al., Neuroscience and the Law (2013), in Gazzaniga et al. (Eds.), *Cognitive Neuroscience*, The Biology of Mind 4th Edition, Norton & Company, 1025-1033.

217/12 - "Temporal modulation of the subventricular zone neural stem cell niche by choroid plexus-cerebrospinal fluid derived factors"

Investigadores/*Researchers*: João Carlos Cruz de Sousa, Fernanda Marques, Joana Palha, Ana Luísa Falcão, Ashley Novais

Instituição/*Institution*: ICVS/3B's - Laboratório Associado (ICVS/3B's), Universidade do Minho, Braga (Portugal)

Duração prevista/*Estimated Duration*: 2013/08 – 2016/04

Background: The choroid plexus (CP) is part of the barriers of the brain, and it limits and regulates the passage of blood-born molecules towards the cerebrospinal fluid (CSF). The CSF fills the brain ventricles and baths the brain parenchyma modulating brain cells activity. The neurogenic niches, namely the subventricular zone (SVZ) is in close contact with the CSF. Thus any changes in the transcriptome/secretome of the CP will reflect in CSF composition and ultimately affect the SVZ neural stem cells.

Objectives: To determine temporal changes in the CP transcriptome and CSF content that impact the brain neural stem cell niches.

Method: Microarray profiling of the CP transcriptome and protein quantification in the CSF. In vitro cultures of CP cells and SVZ neurospheres.

Results: In the CP we observed a global shift in the gene expression pattern with age. Namely, during adult aging an increase in the expression of IFN alpha in the CP and the protein levels in the CSF. This changes correlated with poor performance in a cognitive task.

Conclusion: Physiological changes at the CP-CSF interface are key to brain functioning and impact neural cells which is of relevance in pathological conditions.

Keywords: Choroid plexus, Cerebrospinal fluid, Neural stem cells, Subventricular zone

Publications:

Marques F, Sousa JC. The choroid plexus is modulated by various peripheral stimuli: implications to diseases of the central nervous system. Front Cell Neurosci. 2015. 9:136

Mesquita SD, Ferreira AC, Gao F, Coppola G, Geschwind DH, Sousa JC, Correia-Neves M, Sousa N, Palha JA, Marques F. The choroid plexus transcriptome reveals changes in type I and II interferon responses in a mouse model of Alzheimer's disease. Brain Behav Immun. 2015. 49:280-92.

Salgado AJ, Sousa JC, Costa BM, Pires AO, Mateus-Pinheiro A, Teixeira FG, Pinto L, Sousa N. Mesenchymal stem cells secretome as a modulator of the neurogenic niche: basic insights and therapeutic opportunities. Front Cell Neurosci. 2015. 9:249.

220/12 - "Consciousness Disconnects During Sleep" - only abstract available
Investigador/*Researcher*: Giovanni Piantoni
Instituição/*Institution*: Cortical Physiology Lab, Massachusets General Hospital, Harvard Medical School (USA) and Netherlands Institute for Neuroscience, Amsterdam (The Netherlands)
Duração prevista/*Estimated Duration*: 2013/09 – 2016/04

Objectives: Brain activity is the result of a dynamic interplay between cortical and thalamic neuronal populations and this interplay is thought to underlie conscious and unconscious neuronal processing. A characteristic phenomenon that is generated by the thalamocortical network associated with the unconscious state of sleep is the spindle, a 0.5-2 s long burst of oscillations between 11 and 16 Hz. While animal and computational studies have highlighted the importance of the reciprocal connections between cortex and thalamus, the spatio-temporal properties of the spindle on the cortex remain largely unexplored. We here investigated the evolution of the spindle oscillations over large cortical areas, measured on the human neocortex.

Method: Spindles were described by their instantaneous amplitude and phase over neighboring electrodes. We collected recordings from NREM sleep stage 2, using electrocorticography in eight patients undergoing evaluation for intractable epilepsy. Electrodes covered large parts of one hemisphere and were spaced 1 cm apart. The research was approved by the local institutional review board and electrode placement was determined solely by clinical criteria.

Results: Based on the instantaneous amplitude in the spindle frequency band for each electrode, we computed the covariance on overlapping 1s long intervals of these time-series. We observed recurring patterns of spatio-temporal organization, which include focal, widespread and global spindling activities. Spindles were more likely to synchronize over multiple cortical areas if they included the lateral prefrontal cortex, a putative pivot of spindle activity. In addition, we observed a drastic phase reset at the beginning of the sleep spindle. We interpret this phase reset as the putative thalamic input to the cortical mantle. The spatial extent of this phenomenon was compatible with the two anatomically defined thalamocortical pathways: the spatially diffuse matrix pathway and the locally selective core pathway.

Conclusion: These results highlight the importance of thalamocortical projections in shaping the spindle evolution and define the spatial extent of the functional influence of these projections. These findings will help elucidate the mechanisms underlying spindle generation and the functional role of thalamocortical loops in maintaining a stable state of conscious or unconscious activity during wakefulness and sleep, respectively.

Keywords: Sleep, brain rhythms, oscillations, spindles, synchronization

Publications:
Synchronization of Spindle Activity over Prefrontal Regions, *Under Review*

222/12 - "EEG functional connectivity in post-hypnotic amnesia"

Investigadores/*Researchers*: Marios Kittenis, Graham Jamieson
Instituição/*Institution*: Koestler Parapsychology Unit, The University of Edinburgh (UK) and Neuropsychology Lab, School of Behavioural, Cognitive, and Social Sciences, The University of New England, Armindale (Australia)
Duração prevista/*Estimated Duration*: 2013/06 – 2016/04

Objectives: Hypnotic amnesia (HA) presents an opportunity to uncover the mechanisms of hypnotic dissociation and similar phenomena found in many psychological conditions. Dissociation, considered as the temporary unavailability of information from one neuropsychological process to another, may arise from many mechanisms. Here we test the proposal that dynamic changes in topographic patterns of cortical oscillations in the upper-alpha band (Uα: 10-12Hz) may underlie the selective inhibition of recall during HA, by blocking the availability of processed information at specific points in the retrieval process.

Method: Participants were nine high (>9) and seven low (<3) susceptibles, doubly screened with the HGSHS:A and SHSS:C scales. Following hypnotic induction participants were presented with a series of 60 face stimuli and required to identify their affective expression. Later participants received a HA suggestion for these faces. They were then presented with a mixed set of 30 old and 30 new faces and identified each as new or old. HA suggestion was lifted and participants tested again using the remaining 30 old faces and another 30 new faces. 64 channel EEG was recorded on a Biosemi system at the University of Edinburgh. eLORETA source analysis is reported on highs showing reversible amnesia response to old faces.

Results and Conclusion: For old faces wrongly identified (OW) compared to new faces correctly identified, late evoked Uα is significantly higher in OW in right (R) BA7, a region independently implicated in top down executive control to assist recall of visual information. Lagged nonlinear connectivity analysis of Uα in the same condition shows significantly increased connectivity in Uα between R BA34 (parahippocampal gyrus) and R BAs 7, 20 and 22 respectively. The integration of information between these functional regions is essential for successful recall of recent faces. In HA response spatial and temporal coordination of Uα appears to suppress the integrated functioning of these regions (and hence recall). These patterns were not found after reversal of HA suggestion.

Keywords: Hypnotic amnesia, Upper alpha, Dissociation

Publications:

Tivadar, R. (2014). *Towards a profile of the hypnotic state: Continuing the search for a state marker*. Master of Science thesis, School of Philosophy, Psychology and Language Sciences, University of Edinburgh.

224/12 - "The magic of perception: Investigating misdirection and change blindness in magic using the novel combination of gaze behaviour and ERPs" - only abstract available

Investigadores/*Researchers*: Tim J. Smith, Rebecca Nako
Instituição/*Institution*: Dynamic Visual Cognition (DVC) Lab, Dept. of Psychology, Birkbeck, University of London (UK)
Duração prevista/*Estimated Duration*: 2013/04 – 2016/03

Objectives: The main objective of this project is to investigate how magicians manipulate overt (eye movements) and covert attention (processing resources) during magic tricks. Investigating both aspects of visual attention during naturalistic dynamic scenes such as magic tricks entails several technical and methodological challenges.

Methods: During this project two parallel lines of research have a) investigated how real-time overt attentional allocation occurs during an interactive magic trick using eyetracking and, b) how covert attentional selection can be shaped by the expectation of the relevance of certain object features such as colour or category, expectations that are often manipulated by magicians.

Results: Our findings indicate that attention can be rapidly guided to naturalistic objects via abstract features such as object categories (e.g. clothing, number or card suit) and that the perceived relevance of such categorical features can not only alter the allocation of attention to particular objects but also awareness of a change made to this feature when the object is fixated.

Conclusions: These studies demonstrate the power of magic technique for manipulating awareness using basic principles of visual attention and perception.

Keywords: Magic, Change blindness, Eyetracking, EEG

Publications:

Smith, T. J. (2015) The role of audience participation and task relevance on change detection during a card trick. Frontiers in Psychology, 6:13.

Nako, R., Smith, T.J., & Eimer, M. (under review). The role of color search templates for real-world target objects. Journal of Cognitive Neuroscience.

Nako, R., Smith, T.J., & Eimer, M. (2015). Activation of New Attentional Templates for Real-world Objects in Visual Search. Journal of Cognitive Neuroscience, 27(5), 902-912.

Nako, R., Wu, R., Smith, T. J., & Eimer, M. (2014). Item and Category-Based Attentional Control During Search for Real-World Objects: Can You Find the Pants Among the Pans? Journal of Experimental Psychology: Human Perception and Performance. 40, 1283-1288.

225/12 - "Roles of the reward system in sleep, dreaming, and the consolidation of emotional memories" - only abstract available

Investigadores/*Researchers*: Sophie Schwartz, Lampros Perogamvros, Kristoffer Aberg, Virginie Sterpenich

Instituição/*Institution*: Geneva Neuroscience Center, University of Geneva (Switzerland)

Duração/*Duration*: 2013/10 – 2016/02

Objectives: The present project aimed at providing new data concerning the role of the dopaminergic-reward system in the regulation of sleep, dreaming, and daytime emotional functions. We previously suggested that abnormal sleep behaviors, i.e., as found in parasomnias, may relate to an increased activity of the reward system during sleep. Because nightmares and sleepwalking predominate during REM and NREM sleep respectively, here we tested whether exploratory excitability, a waking personality trait reflecting high activity within the mesolimbic dopaminergic (ML-DA) system, may be associated with specific changes in REM and NREM sleep patterns in these two sleep disorders.

Methods: 24 unmedicated patients with parasomnia (12 with chronic sleepwalking and 12 with idiopathic nightmares) and no psychiatric comorbidities were studied. Each patient spent one night of sleep monitored by polysomnography. The Temperament and Character Inventory (TCI) was administered to all patients and healthy controls from the Geneva population (n = 293).

Results: Sleepwalkers were more anxious than patients with idiopathic nightmares (Spielberger Trait anxiety/STAI-T), but the patient groups did not differ on any personality dimension as estimated by the TCI. Compared to controls, all parasomnia patients scored higher on the Novelty Seeking (NS) TCI scale and in particular on the exploratory excitability/curiosity (NS1) subscale, and lower on the Self-directedness (SD) TCI scale, suggesting a general increase in reward sensitivity and impulsivity. Furthermore, parasomnia patients tended to worry about social separation persistently, as indicated by greater anticipatory worry (HA1) and dependence on social attachment (RD3). Moreover, exploratory excitability (NS1) correlated positively with the severity of parasomnia (i.e., the frequency of self-reported occurrences of nightmares and sleepwalking), and with time spent in REM sleep in patients with nightmares.

Conclusions: These results suggest that patients with parasomnia share common waking personality traits associated to reward-related brain functions. Our findings have important theoretical implications, as they support the hypothesis that reward networks are activated during human sleep, and clinical implications pertaining to the pathophysiology of parasomnias, as they reveal specific personality characteristics of patients with parasomnias, which could potentially be targeted by psychotherapy.

Publications:

Main publication of the project

Perogamvros L., Aberg K., Gex-Fabry M., Perrig S., Cloninger CR., Schwartz S. 'Increased reward-related behaviors during sleep and wakefulness in idiopathic nightmares and sleepwalking'. *PLOS ONE* 2015 Aug 19; 10(8): e0134504. (IF: 4.2)

Related reviews

Perogamvros L., Schwartz S. 'Sleep and emotional functions'. *Curr Top in Behav Neurosci.* 2015; 25:411-31.

Perogamvros L., Desseilles M., Dang-Vu TT., Schwartz S. 'Sleep and dreaming are for important matters'. *Frontiers in Consciousness Research*. 2013; 4:474.

Book Chapters

Perogamvros L., Schwartz S. 'Emotion, Motivation, and Reward in Relation to Dreaming' *Principles and Practice of Sleep Medicine*, 6th edition, 2015.

Perogamvros L., Schwartz S. 'The neural basis of dreaming'. *International Encyclopedia of Social and Behavioral Sciences*, 2nd edition, 2015.

227/12 - "System mechanisms of attention: toward the nature of hypnotizability"

Investigadores/*Researchers*: Zinaida I. Storozheva, A. V.Kirenskaya, V. Y. Novototsky-Vlaso, A. N. Chistyakov, V. V. Myamlin, S. V. Solntseva
Instituição/*Institution*: P. K. Anokhin Institute of Normal Physiology and Serbsky National Research Centre for Social and Forensic Psychiatry, Moscow (Russia)
Duração prevista/*Estimated Duration*: 2013/04 – 2016/04

Objectives: The current study was designed to investigate the neurophysiological, and genetic underpinnings of attentional abilities in subjects with high (HH) and low (LH) hypnotizability.

Methods: Evaluation of the hypnotizability level was performed using a modified version of the Stanford Hypnotic Susceptibility Scale for the small group. 19 HH subjects (10 women and 9 men, mean hypnotizability - 3.78±0.11) and 17 LH (4 women and 13 men, mean hypnotizability - 1.79±0.09) subjects were selected for the study. Val158Met *COMT* polymorphism was detected using real-time PCR. The measures of P50 suppression and prepulse inhibition (PPI) of the acoustic startle response (ASR) were used to estimate involuntary attentive processes; the odd-ball task performance with concurrent estimation of P300 amplitude and latency were determined as voluntary attention measures. The Immediate Memory Task (IMT, Dougherty et al., 1999) was used to test the sustained voluntary attention and its selectivity.

Results: Met/Met homozygosity of *COMT* was found to be associated with high hypnotizability. Comparison of attentional measures in HH and LH groups revealed: (1) independent of gender better performance of odd-ball task and increased frontal p300 amplitude in HH group; (2) gender-dependent influence of hypnotizability on IMT performance: increase of commission errors in HH men compared to LH ones, and increase of correct responses in HH women compared to LH ones; (3) no difference in P50 suppression between HH and LH groups was found; (4) an increase of baseline ASR amplitude and longer baseline ASR latency in HH relative to LH group; (5) impaired PPI at prepulse latency of 120 ms in HH men relative to LH men; (6) increased prepulse facilitation of ASR at prepulse latency of 2500 ms in LH relative to HH women, (7) the specific patterns of correlations between IMT and neurophysiologic measures found in HH and LH groups

Conclusion: The data obtained indicate the existence of gender- and hypnotizability-dependent differences in the cognitive strategy and organization of the mechanisms of attention.

Keywords: Hypnotizability, *COMT*, Sensorimotor gating, P300, Immediate memory test

233/12 - "The Study of Experimenter Effects in the Replication of Psi Experiments: A Global Initiative"
Investigadores/*Researchers*: Marilyn Schlitz, Daryl Bem, Arnaud Delorme
Instituição/*Institution*: Institute of Noetic Sciences, Petaluma (USA)
Duração/*Duration*: 2013/07 – 2015/04

Objectives: This study addressed the replication problem in parapsychology through the examination of experimenter and participant belief in psi and their impact on the outcome of a psi task.

Methods: The meta study involved an international collaboration of teachers, student experimenters, and experimental volunteers, who made use of a standardized psi protocol that has been the focus of a number of replication attempts and that allows for a systematic collection of data under well controlled conditions (Bem, 2011). It included 12 different laboratories across 32 experimenters and 512 participants.

Results: While the preregistered hypothesis that was assessed on a participant basis did not show a significant psi effect, when the statistical power was increased by using a single trial analysis, the primary hypothesis was highly significant. The results did not support a correlation between study outcome and experimenter expectancy.

Conclusions: While the preregistered hypothesis that was assessed on a participant basis did not show a significant psi effect, when the statistical power was increased by using a single trial analysis, the primary hypothesis was highly significant. The results did not support a correlation between study outcome and experimenter expectancy. Overall, these results support the feasibility of a multi laboratory collaboration and show that single trial analysis might be more appropriate and powerful to process these types of data. An extension of this study is now underway.

Keywords: Experimenter effects, Belief, Priming, Precognition

234/12 - "Visual categorization of images of live and deceased individuals"
Investigadores/*Researchers*: Arnaud Delorme, Dean Radin
Instituição/*Institution*: Centre de Recherche Cerveau et Cognition, Toulouse (France) and Institute of Noetic Sciences, Petaluma (USA)
Duração/*Duration*: 2014/02 – 2015/06

Objectives: Anomalous psychological phenomena have been documented which involve apparent reception of accurate intuition about future events or spontaneous telepathic communications. A subset of the population, called mediums in English, seem particularly sensitive to this type of phenomenon.
In a previous BIAL project (94/10), we analysed brain activity and physiology of mediums when they were performing readings in a double blind condition. We have obtained significant results, which have been published in Delorme et al., 2013, Frontiers in Psychology, 4:834. However, it appears that we need a more automated and less subjective task on a larger number of stimuli to obtain unequivocal results and to improve the power of our statistical analysis. Several mediums during our initial experiment mentioned that they were most easily able to connect to a deceased individual if they could see their photograph. This connection usually happened instantaneously. They also mentioned that they would be able to determine if an individual was alive or dead based on that photo.

Methods: In the proposed research project, we will first select mediums based on a double blind protocol run online. We will then record the brain activity and body responses of 12 mediums while they view photos of people, some of whom are living and some of whom are deceased.
For both the online and the laboratory experiment, we will present subjects 200 photos of faces, half of which will be from deceased individuals. All of the photos are standardized in size, luminance as well as 7 different features (age, gender, face orientation, gase orientation, hair color, glasses, resolution, presence of smile). The task of the subject is press a button to indicate if they feel that a given person is alive or has passed (see http://intuitiontest.org).

Results: Behavioral data collected both online and in the laboratory appear to indicate that some individuals are capable of correctly classifying photos of alive vs. deceased people under conditions where the photos are balanced across 8 dimensions, reducing possible visual cues about the health status of the individuals in the photos (online: accuracy tested against chance detection level – 50% – using one-tailed t-test; $p < 0.007$; in laboratory: average combined performance was 53.6%, resulting in $p = 0.005$ with 11 degrees of freedom).
EEG data from 12 professional mediums tested in the laboratory suggests that there is a biological basis for the behavioral data at a latency of about 100 ms, which occurs prior to the mediums' conscious assessment of the photo. These results appear to be promising, and further research and data analysis are warranted to assess if these results are robust.

Conclusion: Our current results support the hypothesis that it is possible for some people to detect deceased individual in photographs.

Keywords: Intuition, Visual categorization, Electro-encephalography, Mediumship

248/12 - "Using hypnosis to distinguish between cognitive and metacognitive conscious experience"
Investigadores/*Researchers*: Pedro Alexandre Magalhães de Saldanha da Gama, Axel Cleeremans, Zoltan Dienes, Amir Raz
Instituição/*Institution*: Université Libre de Bruxelles (Belgium)
Duração/*Duration*: 2013/11 – 2015/05

Objectives: Hypnosis is characterized by a lost of volition, in the sense that hypntized volunteers generally report their movements as involuntary under hypnosis. Volition and the sense of agency are two concepts closely related. Indeed, the sense of agency is the experience that one is responsible for a voluntary action and its outcome (i.e., active condition). According to the reduction of volition experienced under hypnotic suggestion, a reduced sense of agency should also be observed. However, to our knowledge no one has tried to assess whether hypnotic suggestion could modify the perception of volitionality associated with passive movements. In passive movements (e.g., the experimenter presses on the participants' finger), the sense of agency is reduced. The question adressed in the current experiment was to understand wether or not passive movements could be experienced as active under hypnotic suggestion involving a enhanced feeling of control. This question is important because it could help to understand the role of actions for the sense of agency and to assess which of hierarchical and dual-channel models best captures metacognition.

Methods: To measure the sense of agency, we used both explicit and implicit measures. Explicit measures of agency consist in asking participants how much they felt in control during each condition while implicit measures of agency use time perception between an action and its effect (i.e., intentional binding method). In our experiment, we recruited participants based on their scores at the Waterloo-Stanford Group C (WSGC) scale in order to screen highly and low hypnotizable participants. Indeed, results could change according to the hypnosis succeptibility (i.e., hypnotizability) of our participants. During the experiments, participants passed four conditions, two controls without suggestion and two experimental with suggestion. In the active condition with suggestion, participants were told that their movements were not under their control even if they were moving their fingers. In the passive condition with suggestion, participants were told that they were totally in control of their movements even if they could feel a pression on their fingers at the moment of the actions.

Results: Data are discussed based on theories on the sense of agency, hypnotizability and metacognition.

Conclusions: Participants hypnotizability is intimatly related to the sense of agency.

Keywords: Agency, Hypnosis, Hypnotizability, Intentional Binding, Metacognition

252/12 - "Sleep state misperception mispercieved"
Investigadores/*Researchers*: Eus J. W. Van Someren, J. Ramautar
Instituição/*Institution*: Netherlands Institute for Neuroscience, Dept. Sleep & Cognition, Amsterdam (The Netherlands)
Duração prevista/*Estimated Duration*: 2014/06 – 2016/04

Objectives: Insomnia is characterized by fragmented sleep and sleep state misperception - experiencing wake in spite of electroencephalographic (EEG) signs of sleep. Whereas diagnostic criteria include daytime complaints, studies mostly focused on sleep EEG. We systematically evaluated wake high-density (HD) EEG signatures of insomnia during resting state and in response to external (auditory) and internal (heartbeat) stimuli.

Methods: Fifty-four people with insomnia were compared to 48 controls without sleep complaints, recruited from www.sleepregistry.nl. During the evening hours, HD-EEG was assessed using a 256-electrode system during an active auditory oddball task and during 5 minutes of eyes open and 5 minutes of eyes closed resting-state. Simultaneous electrocardiography allowed for heartbeat evoked potentials (HEP) analyses.

Results: During adaptation to frequent tones, the auditory N100 amplitude decreased in controls but not in people with insomnia. Moreover, they showed a larger P300 amplitude to infrequent tones. Heartbeat evoked potential analysis indicated that eye closure attenuated the frontal HEP amplitude in a late (372–492 ms) time window. In people with insomnia, eye closure attenuated this late part of the HEP amplitude significantly less (Wei et al., submitted). Resting-state spectral power analyses indicated that insomnia is characterized by low power in the upper alpha range (11-12.7 Hz during eyes open over restricted bilateral frontal and left temporal regions. During eyes closed, people with insomnia show high power in the beta-gamma range (16.3 to 40 Hz over extended prefrontal, central and parieto-occipital regions (Colombo et al., submitted).

Conclusions: Increased high-frequency power in insomnia is not limited to sleep-EEG, suggesting a 24-hr deficiency to suppress cortical activation. This interpretation is also supported by the attenuated power in the upper alpha band, given the inhibitory role of alpha. Auditory ERP findings suggest that people with insomnia show an exaggerated response to infrequent stimuli and insufficiently adapt to frequent stimuli. The lack of adaptation is also supported by the enhanced late HEP amplitude. Current analyses investigate the role of these findings in the degree of sleep state misperception.

Keywords: Insomnia, Sleep state misperception, High-density EEG, Heartbeat evoked potential, Resting state.

Publications:
Colombo M, Ramautar JR, Wei Y et al. (submitted) Wake high-density EEG spatiospectral signatures of insomnia.
Wei Y, Ramautar JR, Gomez-Herrero G et al. (submitted) I keep a close watch on this heart of mine: increased interoception in insomnia.

256/12 - "Contemplative Development Mapping Project"
Investigadores/*Researchers*: Willoughby Britton, Catherine Kerr, Harold Roth, Jared Lindahl, Jake Davis, Chris Kaplan, Nathan Fisher
Instituição/*Institution*: The Clinical and Affective Neuroscience Laboratory, Brown University and Department of Psychiatry and Human Behavior, Brown University Medical School, Providence (USA)
Duração prevista/*Estimated Duration*: 2013/07 – 2017/04

Objectives: To investigate the full range of possible experiences associated wtih contemplative practices, including those considered anomalous, challenging, or impairing to functioning.

Method: The range of experiences associated with contemplative practice were investigated through qualitative interviews with meditation practitioners and teachers from Buddhist and Abrahamic traditions (n=160). Interview questions probed phenomenology, influencing factors, and remedies. Based on thematic content analysis of phenomenology, a Meditation Experiences Scale (MES) was created and administered to participants in a randomized controlled trial of three different types of contemplative practices (n=100).

Results: Fifty-eight categories of experiences clustered into seven higher order domains: *Cognitive* (change in cognitive processing, vivid imagery, paranormal beliefs), *Perceptual* (hypersensitivity, visions and hallucinations, space-time alterations), *Affective* (emotional lability or quiescence, euphoria, terror, de-repression of psychological material), *Conative* (changes in motivation, goal-directed behavior, or effort), *Somatic* (sensations of "energy", releases of tension, involuntary movements), *Sense of self* (changes in sense of embodiment, agency, and self-other boundaries), *Social* (social withdrawal). In the clinical trial, more than 60% of respondents endorsed one or more experiences on the MES, with 21% reporting two experiences, and 13% reporting three or more.
While all traditions, practice types, and samples reported unexpected experiences, the type, frequency, duration, and reaction were impacted by four sets of influencing factors: practioner-level (psychiatric comorbidity, worldviews and expectations), practice-level (dose/type), relationships (teachers, social support), and health behaviors (diet, exercise, psychotherapy).

Conclusion: Contemplative practices across multiple traditions, styles and contexts produce a wide range of anomalous, challenging and sometimes impairing experiences beyond the oft reported health benefits. The frequency, type, duration and impact of resultant experiences is influenced by multiple intersecting factors including tradition, practice type, intensity, context, and interpretation.

Keywords: Meditation, Transformation, Anomalous experiences

Publications:
Lindahl, J.R., Kaplan, C., Winget, E., & Britton, W.B. (2014). A Phenomenology of Meditation-Induced Light Experiences: Traditional Buddhist and Neurobiological Perspectives. *Frontiers in Psychology*, *4*(973) 1-16.

270/12 - "Synchronicity and Psi: A Controlled Comparison"
Investigadores/*Researchers*: John Palmer, Nick Edington
Instituição/*Institution*: Rhine Research Center, Durham (USA)
Duração/*Duration*: 2013/03 – 2015/01

Objectives: Aims of the study were to compare (a) performance on two similar tasks structured and introduced as tests of synchronicity and psi respectively and (b) psi vs. synchronicity as interpretations of the "synchronicity" scores.

Method: 60 volunteers completed each of the two forced-choice tasks in counterbalanced order; 1 of 4 rectangles was randomly assigned as the target for each of 40 trials. In the synchronicity task, participants (Ps) were asked to choose which of 4 I-Ching-like messages inside the rectangles was most personally meaningful. In the ESP task, the messages were invisible and Ps were asked to use ESP to select the target rectangle. Mean scores on both tasks were n.s. below chance.

Results: A sig. decline in paranormality scores with declining confidence in task success was attributed to increasing doubt in the capacity of the tasks to capture a paranormal effect. Among Ps who did the synchronicity task first, a sig. negative correlation of average meaningfulness rating of all the messages with synchronicity scores was attributed to frustration in having to choose a target from a set of uniformly meaningful messages; a sig. reversal for ESP scores was attributed to the ESP task being a relief in comparison, engendering a more positive mood. Meaningfulness ratings correlated sig. positively with posttest confidence on both tasks, interpreted as Ps who perceived high meaningfulness in the messages becoming convinced that "something paranormal was going on." A sig. positive correlation between synchronicity hits and the average difference between the hit and miss trials in how long Ps waited for the "right time" to access the target message on the synchronicity task was interpreted as some Ps became impatient when the internal signal to click the mouse to access the target did not come quickly, this negative mood causing them to miss the target. ESP scores correlated sig. negatively with combined subscale scores on Levenson's Multilevel Locus of Control (LOC) Scale; Ps with high internal locus of control scored high on the ESP task, a mirror image of the expected positive external LOC correlation with synchronicity scores.

Conclusion: The evidence for a real paranormal effect, based on post-hoc analyses, is marginal. If there is such, the sig. correlations of psychological variables with synchronicity scores tend to favor a psi interpretation, because psi is a personal ability whereas synchronicity is a principle of nature.

Keywords: Synchronicity, Psi, Confidence, Locus of control, Frustration

272/12 - "Exploring the interactions between paranormal belief and disbelief and subjective experiences with the Shakti helmet"

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Duração prevista/*Estimated Duration*: 2013/09 – 2016/04

Objectives: Previous studies have found that some participants report anomalous experiences whilst wearing a head device that emits mild electromagnetic pulses. It is noteworthy that a significant proportion (30%) report anomalous experiences under a sham condition. This current study systematically explored the contributing roles of psychological variables (wearing a head device; strong belief and disbelief in the paranormal; time of day; hyperaesthesia; synesthesia; locus of control) in the aetiology of subjective anomalous experiences under a sham condition.

Method: Participants completed a survey, and those scoring 2 standard deviations above and below the mean on Tobacyk's revised Paranormal Belief Scale were invited to take part in a laboratory investigation. All participants attended an orientation session where they completed a battery of questionnaires (hyperaesthesia, synesthesia and locus of control and an open-ended question about their expectations). Each participant completed 3 laboratory sessions, two of which took place in the morning (10.00 AM) and one in the afternoon (5PM). Participants wore a sham head device during one of the morning sessions and the afternoon session. Study order was counterbalanced across study participants. During each session, participants relaxed in a reclining chair in a faraday chamber and were encouraged to observe any thoughts, feelings, images or experiences which they could verbalize if they wanted to do. A voice recorder was on throughout the study. At the end of a 30 minute period, participants were interviewed about their experiences and then completed a Phenomenology of Consciousness Inventory (PCI). All participants were fully debriefed and paid $100.

Results: This study is currently in progress. Comparisons will be made between believers and disbelievers; time of day and wearing versus not wearing a head device in terms of PCI dimensions of consciousness and the number of anomalous experiences reported (by content analysis).

Conclusion: This study is currently in progress.

Keywords: Paranormal belief, Skepticism, Anomalous experiences, Time of day, Placebo

2014

282/14 - "The Mindful Eye: Smooth Pursuit and Saccadic Eye Movements in Meditators and Non-meditators"

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Duração prevista/*Estimated Duration*: 2015/04 – 2016/08

Objectives: The objective was to explore the relationship between mindfulness practice within Buddhist tradition and schizotypy dimensions in two independent samples. Some of the Buddhist beliefs and experiences that can arise through meditation practice closely resemble Out of Ordinary Experiences (OOEs) and Psychotic Like Experiences (PLEs) that are considered to be a core feature of high-risk or prodromal state. Despite growing evidence for demonstrated efficacy of mindfulness in various mental and physical disorders, particularly in reducing depression and anxiety, there are limited data examining the efficacy of mindfulness interventions for people with psychosis. Furthermore, there is a concern (based on the single case studies) that mindfulness practice might trigger psychotic symptoms in vulnerable individuals. We hypothesised that individuals practicing mindfulness meditation within Buddhist tradition will hold unusual beliefs pertaining to the dimension of schizotypy, but this will not be accompanied by any increases in paranoid ideations or social anxiety.

Method: Sample 1 included 48 healthy participants: 24 meditators and 24 meditation-naïve; and sample 2 included 56 healthy participants: 28 meditators and 28 meditation-naïve. Meditators had at least 2 years of consistent mmindfulness practice defined as a minimum of 45 min per day, at least 6 days a week. All participants completed the Schizotypal Personality Questionnaire (SPQ, Raine, 1991, Schiz Bull), a self-report scale containing 9 subscales: ideas of reference, excessive social anxiety, magical thinking, unusual perceptual experiences, odd/eccentric behaviour, no close friends, odd speech, constricted affect, and suspiciousness.

Results: Experienced mindfulness practitioners scored higher on magical thinking ($P<0.05$), but lower on suspiciousness ($P<0.05$) and social anxiety (trend level effect) compared to meditation-naïve individuals in both samples. The two groups did not differ significantly on other SPQ subscales or the total SPQ score.

Conclusion: Mindfulness practice does not result in an overall schizotypal profile and may help to reduce suspiciousness and excessive social anxiety in people with psychosis.

Keywords: Mindfulness, Psychosis, Schizotypy, Suspiciousness

Publications:

Antonova E, Hamid A, Wright B, Kumari V. (2015). Mindfulness and Schizotypy: Magical Thinking without Suspiciousness Characterises Mindfulness Meditators. *European Archives of Psychiatry and Clinical Neuroscience 265*, s71.

11º Simpósio da Fundação Bial

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