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ECNP DAILY NEWS

Keynote lecture starts congress with a bang

Colin Blakemore

The Keynote Session on Saturday evening was filled with awards, speeches and live entertainment that served as a befitting tribute to the opening of the landmark 25th ECNP Congress. Of course, a crowning moment of the session was the keynote lecture, 'The plastic brain', delivered by prestigious and renowned expert Colin Blakemore (Department of Physiology, Anatomy and Genetics, University of Oxford, UK).

Though likely needing no introduction to most in attendance, Professor Blakemore has been, and continues to be, involved in groundbreaking developments in our understanding of fundamental phenomena in the brain. During his keynote lecture he led us on a journey through the history of brain experimentation and of the mammalian brain itself.

History has a curious way of slipping from our consciousness, and Professor Blakemore reminded us of just how far we had come over the past several decades: "Certainly when I was a student, I learned that every neuron in the brain is created before birth, that many of them die shortly after birth and that the loss of neurons is progressive. The mammalian nervous system can never change and reorganise, can never regenerate, can never adapt from damage, and that no neurons are created after birth: all of these ideas have gone, and there has been a revolutionary change in our concept of the brain.

"We see it now as the most dynamic, adaptable and plastic organ in the body and indeed so many of its functions depend on that plasticity. The sorts of problems that we are interested in – behavioural disorders – are probably due to aberrations in plasticity in the brain, and paradoxically the plasticity of the brain might therefore hold a route to new treatments for many disorders."

Continuing with an interesting perspective of the evolutionary underpinnings of the growth of the hominid brain, Professor Blakemore said: "I think that many of the problems we suffer, particularly neurological and psychiatric disorder, are a consequence of two things: our brains are too big, and we live too long. Having a big brain obviously has its advantages, and these advantages were spotted during the evolutionary process. The brain size of hominids has increased enormously in size, particularly about 200,000 years ago with a rapid doubling in cerebral volume.

"The standard argument is a Darwinian one: that there must have been some kind of advantage for a very large brain, which led to the conservation of these changes. These changes of course carry disadvantages: the brain is a metabolically hungry organ, it is consuming about 20% of the oxygen in your blood at the moment. So there is a big disadvantage in having a big brain, but there must have been compensating advantages."

It has been shown in mice that it is possible to double the size of the brain, either by reducing developmental neuronal death or by inducing a greater proportion of stem cells to reenter mitosis. Although this demonstrated that this process could be trivially achieved, it is not sufficient simply to have an increased number of brain cells; they need to be organised in a more sophisticated manner as well.

Professor Blakemore continued: "How could the enlargement of the brain make it more useful? What kind of processes would the brain have to go through in order to be better, simply as a result of being larger? If you look at the way in which the brain changed during the mammalian evolution by extant species representative of different points in the mammalian line, what we see is that the sensory areas – the audio, visual, somatic sensory areas – maintain their relative positions throughout evolution, but they occupy a relatively smaller proportion of the cortex in more advanced species. It's not simply that the brain has uniformly increased in size, but it is that it has introduced more space in between the primary sensory areas and the motor areas. That has generated space for more specialised areas and we now know that the whole of the cerebral cortex is a mosaic of specialised areas."

How this was achieved throughout the course of mammalian evolution is difficult to ascertain. Using the example of language, Professor Blakemore proposed: "It is interesting that the major language areas occupying the association cortex are strategically placed in between the primary sensory areas – auditory and visual – and the part of the motor cortex responsible for the tongue and the laryngeal movements. It is as if these areas might have been created because of the additional availability of brain space and their strategic location in relation to existing functions.

"And I'd like to suggest that this might have been the way in which much of the modular organisation of the cerebral cortex developed, simply being in the right place at the right time, with sufficient extra brain to utilise the normal connectivity and plasticity to begin the process of evolving new functional structures. There are so many examples of specialisation, particularly in visual parts of the brain. Our cortex has come up with 35 specialised areas responsible for ever more refined processing of the

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Keynote lecture

Keynote lecture starts congress with a bang

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visual image. And that seems to have been a hallmark of human sensory evolution: that we just found new ways of reprocessing, again and again, the same information that enters the primary visual cortex."

Professor Blakemore tested the role of plasticity as a critical factor in the evolution of cortical growth in mammals by addressing whether that intrinsic process would be plastic enough to be able to utilise increases in cortex size that have occurred during evolution. With evidence of cortical reorganisation following the removal of half of one brain hemisphere during a critical developmental phase in experimental animals, it is clear that this may well be the case, as he explained: "If this sort of adaptive relationship is utilised in normal development, it could easily have been used in the evolutionary process, because additional brain would automatically be filled by this adaptive process of projection. If there were projections, then that pattern of connections between neurons might turn out to be useful to the individual.

"After birth, very different forms of plasticity begin to happen. There are two main phases: an early stage, usually called the sensitive period (although there are many, many sensitive periods) in which sensory areas of the brain seem to be programmed by their own sensory input. It starts at birth (even before birth in the case of the auditory system) and it's completed quite quickly – in weeks in monkeys and perhaps a year in humans, with sensory areas learning about the statistics of the outside world, and changing their properties – their receptive field characteristics to match the outside world."

Further experiments in sensory deprivation in cats identified that the development of sensory areas depended largely on the nature of sensory stimuli that kittens were exposed to during development; kittens that were only exposed to vertical lines had denser, more active and larger areas relating to those vertical sensory phenomena than areas devoted to other orientations. Professor Blakemore described the significance of these findings with regard to the classic dichotomy of genes and environment, saying: "So the cortex is adapting itself for its own world. This is a sophisticated physiological property; it cannot be accidental.

"So that leads to the conclusion that although this form of plasticity has an environmental dependence, it is nurture at work, it must depend on nature, on the genetics of the neurons. There must be something special about the neurons of the visual and other sensory cortices early in life that make those cells capable of regulating their connections as a result of activity: that's genetics. Genetics endows neurons with the ability to acquire new properties and new connections as a result of activity in the environment. So there isn't a sharp distinction between nature and nurture; nature provides the capacity for nurture to influence the brain."

> *"I have tried to remind you of how important plasticity is, to reinforce the view that what we are has depended completely on the fact that our brains are plastic, and can be reorganised during our evolution as well as during our individual development."*
>
> *Colin Blakemore (Department of Physiology, Anatomy and Genetics, University of Oxford, UK)*

This naturally led to the identification of several genes involved in the regulation of developmental plasticity using knock-out mice. However, plasticity continues throughout life, and Professor Blakemore acknowledged the many different forms it may take: "There are now so many examples of the ways in which the adult cortex can change dramatically as a result of learning – of attentive learning of particular tasks." A dramatic demonstration of this was the representation of the somatic sensory cortex and the neighbouring motor cortex in the brains of individuals that had started to learn a stringed instrument, starting at different ages. By measuring the difference in the degree of reorganisation between controls and those who had started to learn, Professor Blakemore explained that the earlier learning starts, the more dramatic the reorganisation of the cortex. He said: "Changes like this are being demonstrated even after a few days of practice."

He concluded his keynote presentation by marking out the potential therapeutic uses of these fascinating discoveries, saying: "Cortical plasticity continues throughout life, but it is not necessarily always adaptive. However, we know that during early development, the rapid plasticity of sensory areas can actually make the brain vulnerable. Children who have unequal stimulation of their two eyes can suffer in cortical organisation by losing input from both eyes. Language disorders, which develop from insufficient exposure to language, seem to be due to the fact that there is a language-sensitive period – perhaps up to seven or eight years of age.

"If it is not utilised, the cortex can never fully develop language function. Dyslexia too: perhaps some forms could be explained by disorders in the plasticity that lead to the formation of structures that come to acquire the computational capacity for reading. And also in learning: IQ is dependent on stimulation: as much as a 30 IQ point difference can be produced in children who have been very socially deprived in early life compared with normal children. Perhaps in conditions like PTSD and reactive depression, because there is very good evidence of a gene-environment interaction in individual depressive episodes, these may be examples of plasticity gone wrong.

> *"Perhaps utilising plasticity, developing methods to capture and reapply plasticity in the brain might be a route to prevention or therapy."*
>
> *Colin Blakemore (Department of Physiology, Anatomy and Genetics, University of Oxford, UK)*

"If this is the case, perhaps utilising plasticity, developing methods to capture and reapply plasticity in the brain might be a route to prevention or therapy. There are very early but promising developments in that area, using transcranial magnetic stimulation, or transcranial direct current stimulation, to try to reactivate developmental or normal plastic mechanisms to try to reorganise damaged or disordered brains in order for them to recover. I have tried to remind you of how important plasticity is, to reinforce the view that what we are has depended completely on the fact that our brains are plastic, and can be reorganised during our evolution as well as during our individual development. Aberrant plasticity might be at the heart of many disorders. Utilising and enhancing plasticity might lead us to new forms of remediation and prevention."

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Immunotherapy in neurodegenerative disorders Monday October 15 14.30 **Hall D**

Thinking ahead: Immunotherapy in the brain

The use of antibody-based treatments to combat neurodegenerative disorders is a promising avenue of research that needs more focus, and financial support, delegates will hear this afternoon during a session that will explore the cutting-edge status of immunotherapy in the brain.

Co-chairing the session will be Thomas Bayer (Department for Psychiatry, Göttingen University, Germany) a biologist by training who found himself fascinated by the discovery of the first mutation in a gene related to Alzheimer's pathology. That a single gene could have such tremendously devastating consequences in the brain inspired him to develop transgenic model systems to mimic the disorder.

Speaking to *ECNP Daily News* ahead of the congress, Professor Bayer summarised the commonalities between different neurodegenerative disorders, referring to the developments in his own area of expertise and offering insight into the current state, and future promises, that the field of immunotherapy offers.

He began by giving a brief overview of the symposium's speakers and their progress in developing different kinds of immunotherapies for proteinopathies – a term used to describe disease in the brain with protein aggregation.

"There are several speakers with hands-on experience on different proteinopathies, presenting ideas about preventing ALS amytrophic lateral sclerosis and other 'tauopathies', a generic term for brain disorders where the tau protein is affected," he said.

"Einar Sigurdsson has shown that active or passive immunisation works, even for proteins inside cells, and this approach has also been tried for prion diseases – the only infectious disease in this symposium – with unfortunately less success."

"We need to bring antibodies into the brain, and technical improvements are needed there... There is no lack of information; everything is available. There is a lack of money to perform all of the experiments that need to be done."

Thomas Bayer (Department for Psychiatry, Göttingen University, Germany)

Elaborating on the results in ALS that pave the way for similar research, Professor Bayer continued: "Dr Julien has several approaches that target ALS, using active and passive immunisation with single chain antibodies. He has also cloned these antibodies into viruses and then injected the virus into the brain. This is a gene therapy approach that requires only a single injection, not a series of them."

Thomas Bayer

These developments present a clear future for addressing the causes of many age-related diseases and, along with improvements in diagnostics, show immense promise for treating them effectively in their very early stages. "This body of research clearly opens up a new research line: how to tackle proteinopathies, and not just Alzheimer's; it has a very broad application," added Professor Bayer.

Distinguishing immunotherapies from existing drugs for Alzheimer's disease, he also emphasised that there is much work yet to be done. He said: "Existing drugs are not really causally active, they only treat the symptoms. We need to develop these drugs to show that we can really intervene – this is open at the moment."

Regarding the course that Alzheimer's research has taken, Professor Bayer cautioned: "With Alzheimer's, a big disadvantage has been that one or two big pharmaceutical companies jumped into development too early, basing studies on unpromising scientific grounds."

Referring to the recent data that suggests soluble oligomers of Aß, not Aß plaques, are the toxic species that form a key therapeutic target in Alzheimer's pathology, he continued: "Now there is a strong paradigm shift, and the big companies are aware that removing plaques is not a good idea."

Professor Bayer concluded with a positive yet realistic summary about what is yet to be achieved in proteinopathy therapies: "We need to bring antibodies into the brain, and technical improvements are needed there. Alternatively, there are antibodies that work in the peripheral blood system in Alzheimer's, which apparently is sufficient to remove Aß in the brain. There is no lack of information; everything is available. There is a lack of money to perform all of the experiments that need to be done, and to carry out clinical trials at least until phase II."

Professor Bayer will co-chair the session 'Immunotherapy in neurodegenerative disorders' at 14.30 this afternoon in Hall D. The session will be immediately followed by a scientific café on neurodegenerative disorders at 16.10 in the foyer GH.

Live from ECNP

ECNP Neuropsychopharmacology Award 2012

Sunday's keynote session featured the ECNP Neuropsychopharmacology Award – an honour that recognises innovative and distinguished research achievements in neuropsychopharmacology and closely related disciplines. Amongst other prizes, the recipients of the award are invited to present a plenary lecture at the 25th ECNP Congress, as well as the submission of a review article for publication in *European Neuropsychopharmacology*.

Guy Goodwin (Department of Psychiatry, University of Oxford, UK) hosted during the award ceremony which, for this year, would see two recipients take the stage. "We have had a difficult time in the committee because we ended up not being able to make up our minds," said Professor Goodwin.

"Those of you that have sat in committees will know that this is not uncommon. But in the case of this kind of award, it is rather critical one does reach a decision. I observed deliberations which eventually came to the right answer: invite two people to accept, and therefore divide the prize."

Guy Goodwin

Introducing the first recipient Paul Harrison (Department of Psychiatry, University of Oxford, UK), Professor Goodwin said: "The first is my colleague from Oxford, he is Professor of psychiatry, and he has been working in Oxford now for quite a number of years. Probably more than he wants to remember!

"He originally trained there and did research in London, and he made his reputation initially by working in what was described as the 'graveyard of pathology' which was the post-mortem studies of the schizophrenic brain. Paul is one of the very few people who has been able to make sense and produce sensible results from those kinds of studies which greatly influence our field.

"He's moved on from that to look the consequences of the abnormal kinds of gene expression that one sees

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Schizophrenia: from pathophysiological understanding to novel treatments Monday 15 October 11.00 **Hall D**

2012 ECNP Neuropsychopharmacology Award Lecture

A combined approach to schizophrenia therapy

Pathophysiological understanding should take centre stage alongside preclinical data and experiential animal models in the quest for novel schizophrenia treatments, delegates will hear on Monday morning in the second of two plenary lectures delivered by the 2012 ECNP Neuropsychopharmacology Award winners at the congress.

"The central theme of the lecture is the extent to which findings in schizophrenia itself can or should contribute in deciding what treatment targets to investigate," joint 2012 award winner Paul Harrison (Department of Psychiatry, University of Oxford, UK) explained to *ECNP Daily News*.

Expanding on this idea, Professor Harrison explained that there is now great interest in ascertaining to what extent the differences exhibited between patients and controls (for a certain parameter) will be useful in developing novel therapeutics.

"Now, to me that seems fairly obvious, but I think it's been, in some ways, a relatively neglected or difficult area to contribute fully to," continued Professor Harrison. "So the lecture is going to explore those issues."

One recent finding that has been placed under the spotlight is Neuregulin 1, a growth factor involved in neurodevelopment and plasticity that has been identified as a schizophrenia candidate gene.[1] "Neuregulin is a good example – it became of interest to schizophrenia because of genetic association to the illness," said Professor Harrison.

"That was an example of a finding in the illness that might be relevant therapeutically. In other words, it's a gene that at least some studies show is associated genetically. Then the question is what is it that is different in the form of the gene that is associated with the illness? How does that affect the biology of Neuregulin?

"So we and others did studies suggesting that what is different is that you express different amounts of isoforms or variants of the Neuregulin gene, so the balance of signalling that different forms of Neuregulin are carrying out in the brain are probably altered, and that may be one of the mechanisms. And then you can say 'ok, well is directing that, or normalising it, likely to be therapeutically useful?'"

> *"Neuregulin was an example of a finding in the illness that might be relevant therapeutically. In other words, it's a gene that at least some studies show is associated genetically. Then the question is what is it that is different in the form of the gene that is associated with the illness?"*
>
> *Paul Harrison (Department of Psychiatry, University of Oxford, UK)*

However, despite the identification of genes such as Neuregulin, does Professor Harrison agree that while new genes are actively being discovered, they are still largely elusive in their function or effect? "Yes – and whether something is a gene that puts you at risk of the illness or not – whether that in itself is therapeutically relevant – is a matter of some debate," he said.

"Clearly I think, other things being equal, it is a good thing – because you can then sort of think that you are targeting one of the causes of the illness. However, it is not necessary. There are plenty of effective treatments in medicine that are not targeting causative genes. And secondly there are plenty of causative genes that don't turn out to be effective therapeutic targets for one reason or another. But yes I think that is one example of a role that the genetics of schizophrenia may be able to play in advancing treatments.

He continued: "Just to take the Neuregulin story further, Neuregulin sets off a particular signalling pathway, and following up on the original observations about Neuregulin and schizophrenia from former colleagues of mine that now work in the States, they have traced this pathway down to three or four components further downstream and they found again an abnormality in patients with schizophrenia in this signalling pathway, and they've then used a drug that corrects that change in an animal model, and it corrects some of the animal behaviours that are considered to be like behaviours seen in schizophrenia.

Paul Harrison

"Now, that drug has never been tested in people in this regard, so there is a lot of work to be done, but it is an example of where therapeutics developments can come based upon the dissection of genetic pathways and the biochemistry that they contribute to."

Continuing in his discussion of novel treatment pathways, Professor Harrison also referred to the comparative measurement of enzyme activity in post-mortem brains of both patients and controls. "One example is an enzyme called D-amino acid oxidase, or DAO," he said.

"We and a number of other groups have studies that enzyme, and it turns out that that enzyme's activity in increased in patients with schizophrenia (when compared to control subjects). A number of drug companies are studying DAO inhibitors for schizophrenia, and so the argument there is: well that might be a good thing because the inhibitors could then bring down the excessive activity back to normal."

ECNP Neuropsychopharmacology Award lecture: 'Schizophrenia: from pathophysiological understanding to novel treatments'; 11.00, Monday 15 October, Hall D

Reference

1 H Deakin et al. Transgenic Overexpression of the Type I Isoform of Neuregulin 1 Affects Working Memory and Hippocampal Oscillations but not Long-term Potentiation. Cereb. Cortex. 2011 (In press: Accessed August 30, 2011)

The immune–brain axis: a concept gaining momentum Monday October 15 14:30 **Hall IK**

Taking a journey from immunity to psychology

The influence of the immune system over the brain's emergent characteristics has long been appreciated, yet much remains to be understood about this intricate relationship, not least when it comes to complex psychiatric disorders. Speaking to *ECNP Daily News*, Martin Schäfer, Director of the Department of Psychiatry, Psychotherapy and Addiction Medicine and associated Professor for Psychiatry at the Charité-University Berlin, Germany, described the intriguing findings that drive this thriving research area, drawing together the immune interactions of current therapies with the future of psychoimmunological treatments.

The innate immune response is related to the maintenance of enteric flora within the gut lining, and Professor Schäfer described how these effects might be transmitted to the brain: "There are a variety of proposed mechanisms, including humoral and neural routes, through which microbiota can modulate signalling along the brain-gut axis. For example, recent studies suggest a role for both the vagus nerve and the modulation of systemic tryptophan levels in relaying the influence of both resident and exogenous microflora along this bidirectional communication axis," he explained.

Stress in the gut can cause disturbances in the central nervous system (CNS), and vice-versa. He added: "Interestingly in most immune related disorders, an increased incidence of psychiatric problems such as depression, anxiety, fatigue and cognitive disturbance has been found. An increase of pro-inflammatory cytokines with secondary changes in the monoamine system has also been related to these mood changes."

Professor Schäfer moved on to describe three key mechanisms by which pro-inflammatory cytokines stimulate the brain: The humoral pathway, via activated monocytes and macrophages through 'leaky' areas of the blood-brain barrier; the neural pathway, via the vagus nerve; and the cellular pathway, via the stimulation of microglia, leading to the production of monocyte chemoattractant protein-1 (MCP-1) and the recruitment of monocytes into the brain.

He continued: "There has been an explosion in our knowledge of the pathways and mechanisms by which the immune system can influence the brain and behaviour. In the context of inflammation, pro-inflammatory cytokines can access the CNS and interact with a cytokine network in the brain to influence virtually every aspect of brain function relevant to behaviour, including neuro-

Martin Schäfer

Live from ECNP

A warm introduction to the 25th ECNP congress

The Keynote Session of the 25th ECNP congress was opened by its president, Joseph Zohar (Chaim Sheba Medical Center, Department of Psychiatry, Tel Hashomer, Israel) with a description of the exciting events marking out its 25th anniversary. Describing the workshops, educational events, national interactive seminars, and other sessions, Professor Zohar highlighted all ECNP initiatives that are working to achieve a borderless network of scientific communication throughout Europe.

The focus upon interaction is a key element in the knowledge-sharing process at ECNP, demonstrated by the workshops for young scientists held every March in Nice. Another step that ECNP has taken in ensuring equal opportunity, in light of the different economic situations in the broad range of European countries, is the reduction of membership fees for young scientists in developing economies. He said: "Its purpose is to make sure that the membership fee is not an obstacle for individuals that would like to join the college. And we also give grants and awards, including six Fellowship Awards, fifty Travel Awards, Poster Awards and Seminar Awards."

President Zohar went on to note the important reasons for supporting multi-centre European collaborations, which are designed to "standardise variables collected from different studies, and to build a platform to enable the network to support a joint grant proposal."

He also noted the importance of maintaining cross-industry relationships, saying: "We are an organisation busy in facilitating dialogue. We are doing this in the form of Consultation Meetings every year in March. This is an open dialogue between the scientific community, regulatory authorities, and the pharmacological industry, and the output is published in the journal *European Neuropsychopharmacology*."

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transmitter metabolism, neuroendocrine function, synaptic plasticity, and the neurocircuits that regulate mood, motor activity, motivation, anxiety and alarm."

On the possible outcomes of such disequilibrium, Professor Schäfer noted: "Behavioural consequences of these effects of the immune system on the brain include depression, anxiety, fatigue, psychomotor slowing, anorexia, cognitive dysfunction and sleep impairment; symptoms that overlap with those that characterise neuropsychiatric disorders, especially depression."

These immune changes seem to plug an aetiological gap in our understanding of CNS disorders, as Professor Schäfer explained: "Although many things remain unclear, immune changes have been shown in patients with acute or chronic schizophrenic, unipolar and bipolar affective disorders. Beside acute immunological changes possibly being involved in the development of psychiatric symptoms, there are also immune models of schizophrenia in animals that focus on possible early mother-child infection during pregnancy as a risk factor for later developing psychosis."

Citing a well-known immune-brain interaction, the hypothalamic-pituitary-adrenal axis, he remarked: "Stress is clearly associated with an increased risk for affective disorders or other psychiatric symptoms. Stress is linked to changes in the hormonal axis and the immune system and finally also with neurotransmitters."

Translating this fascinating knowledge into valuable clinical therapy is a challenge for research. Professor Schäfer illustrated that the present state of therapy leaves much room for improvement, saying: "Up to now, genetic research could not really explain the individual vulnerability to a psychiatric disorder or the dynamic course of the disease. Moreover, 30 to 60 percent of patients do not or only partially recover from depressive or psychotic symptoms after treatment with currently available drugs that primarily influence dopamine or serotonin neurotransmission."

However, there is encouraging evidence that further pursuit of immune therapies will bear fruit: "Antidepressants (SSRIs) have been shown to be effective in the treatment and prevention of depression caused by cytokine treatment with interferon-alpha. COX-2 inhibitors are known to influence the immune system, and recently the COX-2 inhibitor, celecoxib, has been tested as a possible adjunctive therapeutic approach in the treatment of depression and schizophrenia," he said.

Although the first trial of COX-2 in schizophrenia yielded positive results, additional studies have indicated that this may be limited to early-onset cases. While these findings point to the need for greater understanding of such immune interactions, there is a parallel necessity for aligning them with the diagnosis of disorder subtypes. Professor Schäfer added: "TNF-alpha or IL-2 receptor antagonists have also been discussed as possible targets for a psycho-immunological treatment. However, although the current available antidepressants, mood-stabilisers and antipsychotics have some effect on the immune system, it remains unknown if such an effect is involved in the clinical stabilisation of patients."

Professor Schäfer will co-chair the symposium 'The immune–brain axis: a concept gaining momentum' at 14:30 this afternoon in Hall IK. The session will be immediately followed by a scientific café on psychoneuroimmunology at 16:10 in foyer IK.

Plenary lecture: Disruptive innovations in clinical neuroscience Monday 15 October 13:30 **Hall D**

Blossoming future perspectives for mental health

More consideration of the whole gamut of therapeutic, diagnostic and cultural aspects in clinical neuroscience would offer significant benefits in the treatment of mental disorders, Thomas R Insel (Director of the National Institute of Mental Health in Bethesda, USA) will communicate to delegates in his plenary lecture this afternoon at the congress.

More consideration of the whole gamut of therapeutic, diagnostic and cultural aspects in clinical neuroscience would offer significant benefits in the treatment of mental disorders, Thomas R Insel (Director of the National Institute of Mental Health in Bethesda, USA) will communicate to delegates in his plenary lecture this afternoon at the congress.

Speaking to *ECNP Daily News*, Dr Insel began by noting that there is simply an enormous public health burden stemming from mental disorders: "The needs here are really very striking, very profound and very urgent," he said. "As an example, in the Unites States, the mortality defined here by suicide is really unchanged over the last two or three decades."

He added: "There's a suicide every 15 minutes in the United Sates, about 36,000 per year, so the actual suicide rate is higher than the rate of homicide and the rate of traffic fatalities."

However, this very significant mortality rate is only part of the puzzle in the poor prognosis for those suffering from serious mental health disorders. There is also a marked increase in the number of complicated medical problems that manifest alongside mental illness. "So on both scores we have problems with mortality," said Dr Insel.

"We also have evidence that the morbidities from these disorders have actually not gone down, as far as we can tell from any of the measures that we have (measured either as diagnosis or prevalence, or measures such as employment or completion of education)."

This, he added, was despite the incredible journey made in the field of neuropharmacology, with an "extraordinary" three-decade growth in the medications now available. But these improvements, even when coupled to the increased number of patients now being exposed to them, has made too little impact in Dr Insel's opinion: "The reality is that the public health outcomes don't seem to be much better," he said.

"And that tells me – and this is my first point – that we need a new generation of therapeutics, and what I will talk about is the likelihood of where those next generation of therapeutics could come from; where are the opportunities."

Moving on to discuss the second point he would like to communicate to those in attendance, Dr Insel stressed that we must rethink the way in which we even talk about these disorders, as he believes one of the reasons that we haven't reached our full potential is because we are somewhat hindered by the language that we use, particularly in the realms of diagnostics.

He explained: "The diagnostic categories we have are not biologically valid. They largely come about from consensus of subjective observations. And increasingly, when you look at the biological observations that are accumulating – both from genetics and from clinical neuroscience – it's becoming apparent that these are fictive categories that don't really help us to either identify the mechanisms of disease or identify the most effective treatments for the subgroups of people."

As such, Dr Insel highlighted that while the labelling of depression or autism (for example) as a single disorder has now been moved away from, diagnostically it is still often the case that we assign one antidepressant or one class of drug to cover a syndrome that is highly heterogeneous.

> *"In the new era the focus needs to be on understanding these disorders mechanistically. So not by thinking that the problem is chemical imbalance, or that the problem is a lack of Thorazine, but by understanding them the way we understand other diseases in medicine: at the level of molecular, cellular and system pathophysiology."*
>
> *Thomas R Insel (National Institute of Mental Health, Bethesda, USA)*

"We don't do this any longer for hypertension. We don't do it even for most forms of cancers, where we now understand much more precisely how to diagnose the subtypes," he added. "But because of the lack of biomarkers, and the lack of cognitive markers, and frankly the lack of insight we have about e disorders, and the way that we still talk about them precludes the progress that we need in many ways.

Thomas R Insel

"So point number two would be the importance of transforming our approach to prognosis using what we call the research domain criteria, and I'll talk about what those are and how we'll develop a new approach to nosology or diagnosis."

If Dr Insel's first and second points could be boiled down to the need for new therapeutics and new diagnostics, respectively, his third point could be concisely described as relating to the need for a change in the culture of how we operate. "It's not so much what we do but how we do it," he said.

Specifically, he stressed that we need to form better partnerships, i.e. nurturing patient advocacy groups and other organisations which will ultimately benefit in the quest for new cures, and in the resolution of unmet public need.

Dr Insel continued: "So what I'm going to talk about is the importance of standardisation in the way that data are collected. The integration of data across multiple platforms, and the importance of sharing. And I'll talk about how this culture – which is beginning to develop in other areas of medicine – needs to be quickly implemented in the space that we call neuropsychopharmacology."

In summation, Dr Insel added that we should be pulling together these therapeutic, diagnostic and cultural considerations with improved language and attribution. Explicitly, he believes we should now foster an era in which the terms 'psychiatry' and 'neuropharmacology' are better placed in the grand scheme of clinical neuroscience.

What's more, this should sit alongside a better diagnostic and therapeutic framework, as he described: "In the new era the focus needs to be on understanding these disorders mechanistically. So not by thinking that the problem is chemical imbalance, or that the problem is a lack of Thorazine, but by understanding them the way we understand other diseases in medicine: at the level of molecular, cellular and system pathophysiology."

Plenary lecture: 'Disruptive innovations in clinical neuroscience'; Monday 15 October, 13:30, Hall D.

Social anxiety disorder (SAD): from the clinic to the laboratory and backwards Monday 15 October 14:30 **Hall E**

The unmet needs of social phobia

Social anxiety disorder (SAD) will take centre stage this afternoon in a session that will see experts discuss a range of related issues all the way from clinic to laboratory. To that end, session presenter David Baldwin (Professor of Psychiatry, University of Southampton, UK) spoke to *ECNP Daily News* ahead of the congress to introduce the topic of social phobia, as well as describing the limits of our current knowledge and the problems that must be addressed.

Beginning with the distinction between social phobia and shyness, Professor Baldwin explained that although shyness may be a feature of social phobia, they are far from similar, noting: "Social phobia is an anxiety disorder – in which shyness is admittedly a prominent symptom – characterised by the fear and avoidance of social encounters and performance situations, in which people think they will humiliate or embarrass themselves or appear ridiculous to others."

Further defining social phobia subtypes, Professor Baldwin continued: "There are two main types of social phobia: generalised and non-generalised. In the generalised form, affected

David Baldwin

individuals have a fear and avoidance of most social and performance situations, and could be markedly disabled by these symptoms. In the non-generalised form, individuals may fear just a few situations, and so typically are less affected."

Early diagnosis and treatment is a target for many psychiatric disorders; however, perhaps because social phobia often has an early onset (in late childhood and early adolescence), evidence for the efficacy of earlier intervention is limited. This certainly does not negate the benefit of treatment, however, as Professor Baldwin explained: "Social phobia tends to run a chronic course, which explains the damaging effects on academic performance, relationships and employment. Left untreated, affected individuals can develop depression, and alcohol and other drug abuse, and have an increased risk of attempted suicide."

Clues from neuroimaging and psychological studies can offer targets for psychological intervention, and neurobiological evidence has an equal place in developing drug therapies. Professor Baldwin summarised the state of our knowledge, saying: "The neurobiology of social phobia is likely to be complex, with some involvement of serotonergic, noradrenergic and dopaminergic systems, and possibly contributions from neuropeptides such as oxytocin. The principal pharmacological treatments are the selective serotonin reuptake inhibitors and monoamine oxidase inhibitors."

> *"Many individuals with social phobia are probably unaware they have a potentially treatable condition, and that treatment could see improvements across many domains of their life"*
>
> *David Baldwin (Professor of Psychiatry, University of Southampton, UK)*

He continued on the topic of combinational therapies, saying: "Combining medication and psychological interventions is common in clinical practice, but the trial evidence suggesting this is more effective than drug treatment or psychotherapy alone is rather inconsistent." Whether this is due to inconsistencies in psychological treatment methods, disorder heterogeneity or external factors is clearly an important avenue of future study.

Professor Baldwin looked back over the past few decades of development in our understanding of social phobia. He said: "Even 25 years ago, social phobia could still be called 'the neglected anxiety disorder' and indeed it was, but the last few decades have seen great advances in understanding of the epidemiology, aetiology and treatment of social phobia."

That being said, there is still an enduring issue in the provision of effective treatment, with debilitating consequences for social phobia sufferers, as Professor Baldwin explained: "Many individuals with social phobia are probably unaware they have a potentially treatable condition, and that treatment could see improvements across many domains of their life."

Speaking of unmet needs, Professor Baldwin concluded: "The existing treatments for patients with social phobia cannot be considered ideal. Many patients do not respond, others relapse despite continuing treatment, and others soldier on with distressing side effects, so there is much room for improvement in developing novel interventions which are more effective and more acceptable than those which are currently available."

Professor Baldwin will discuss the efficacy, acceptability and unmet needs of a pharmacological approach to social phobia in the session 'Social anxiety disorder (SAD): from the clinic to the laboratory and backwards' held this afternoon at 14:30 in Hall E.

A clinician's perspective on the amygdala story

Speaking to *ECNP Daily News* ahead of this afternoon's session dedicated to the latest clinical and research insights in social anxiety disorder (SAD), psychiatrist Iulian Iancu (Director of the Yavne Community Clinic, Beer Yaakov Hospital, Tel Aviv University, Israel) described his great interest in the disorder and his intrigue at the role of the amygdala in fear and anxiety modulation. Illustrating the current understanding of SAD and citing interesting clinical examples, he suggests areas of research that could lead to the most promising novel targets.

Functional imaging studies have uncovered a great deal with regards to SAD emotional processing and behaviour, as Dr Iancu explained: "Individuals with SAD showed higher activation of the amygdala when they were shown angry or fearful faces, and they have also been shown to have a smaller amygdala. In normal people the size of the amygdala correlates with the size of social networks; this is logically correct with respect to SAD behavioural traits."

> *"SSRIs, CBT and mindfulness-based interventions reduce blood flow to the amygdala, among other regions. This attenuation is associated with clinical improvements at the one-year follow-up stage."*
>
> *Iulian Iancu (Yavne Community Clinic, Beer Yaakov Hospital, Tel Aviv University, Israel)*

Citing the rare genetic disorder, William's syndrome, in which the amygdala is hypoactive, Dr Iancu continued: "I will talk in my speech about the lack of stranger anxiety in William's syndrome. It seems that these individuals fail to recruit the amygdala, which may explain their disinhibited social behaviour and unusual friendliness. These individuals have large amygdalas, as opposed to a small overall brain volume.

"There is another disorder called Urbach–Wiethe Disorder, which exhibits calcification of the amygdala. In this disorder, there is probably a problem in fear response and evaluation of untrustworthy people that arises directly or indirectly from calcifications in the amygdala."

The over-activation of the amygdala that SAD patients experience has naturally led to therapies that work to reduce activation, as Dr Iancu described: "SSRIs, CBT and mindfulness-based interventions reduce blood flow to the amygdala, among other regions. This attenuation is associated with clinical improvements at the one-year follow-up stage."

The role of the neuromodulatory hormone oxytocin in pair bonding and social recognition has prompted its study in SAD as well as other disorders, such as depression and PTSD. Dr Iancu described its action, saying: "Acute oxytocin treatment reduces amygdala activity in generalised social anxiety disorder, which is very interesting. When patients see negative faces when they are on oxytocin, the amygdala shows reduced activation when compared to placebo."

Although there are certainly other brain regions involved in SAD mechanisms, there are clearly therapeutic benefits in targeting the amygdala. Dr Iancu concluded:

Iulian Iancu

"I cannot say that SAD is a primary problem in the amygdala, but I will suggest that oxytocin may prove to be a good agent for SAD in the long term. It will be interesting to see if oxytocin helps in social problems and also in amygdala hyperarousal."

'Social anxiety disorder (SAD): from the clinic to the laboratory and backwards'; Monday 15 October, 14:30, Hall E

The immune–brain axis: a concept gaining momentum Monday 15 October 14:30 **Hall IK**

Bridging the gap between gut and brain

Peter Holzer

While the process of reduction helps to understand psychiatric disorders in terms of their constituent aspects, it is nevertheless important to bear in mind that the brain is connected to and continually affected by the goings on in the rest of the body. Bridging this gap is one of the principle interests of Peter Holzer (Professor of Neurogastroenterology, Medical University of Graz, Austria), and he spoke to *ECNP Daily News* ahead of the congress to divulge a little about the gut-brain axis and the various ways in which the body and brain and intertwined.

Speaking of their specific mechanisms of communication, Professor Holzer said: "There is an important information channel between the gut and the brain, and this is not only facilitated via sensory neurons or gut hormones, but also via the immune system."

The interactions between the gut lining and the immune system are well established, and the effects on the brain are similarly intuitive as well as being evidenced by various clinical and microbiological observations. Professor Holzer explained: "At the ECNP conference in Amsterdam two years ago there was a symposium which in part covered similar areas. Michael Maes presented findings pertaining to some patients who apparently had a leaky gut, with antibodies circulating in the blood in an elevated manner against bacterial components such as LDS. He thinks leaky gut activation of the immune system, the flooding of the body with microbial chemicals, could somehow reach the brain and initiate processes that eventually lead to depression or other psychiatric conditions."

The development in understanding of the psychological effects of immune disruption on the brain demands a broadening of concepts of psychiatric treatment, and many data already support the notion of psychiatric risk due to birth complications and maternal illness during gestation. Citing a well known example of this phenomenon, Professor Holzer described how negative psychiatric effects might be ameliorated with immune therapy: "In schizophrenia the idea has been around for some time that infection early in life or during gestation could be a risk factor in developing schizophrenia later. However, I think the data, although mostly from animal studies, suggest that anxiety and depression-like behaviours can be changed if you perturb to the intestinal immune system balance," he said.

Citing his own research in this field that serves to strengthen this hypothesis, he continued: "We also have data showing that if you change the gut-hormone situation you may also end up with some mood disturbances in mice deficient in the hormone PYY. This peptide is really only present in the gut. The mice that lacked this peptide appeared to be somewhat depressed. So this system, and especially the PYY in the intestinal epithelium, probably does respond in some way to the changes in microbiota."

Professor Holzer went on to reason as to the underlying mechanisms that may explain these mood changes, saying: "Microbiota usually helps to digest indigestible carbohydrates, producing short chain fatty acids that act on PYY cells and release PYY. This gets into the circulation and reaches the brain, changing appetite and food intake but may also have an effect on other processes in the brain such as those that are relevant to depression."

One of the speakers of the symposium is Raz Yirmiya (Department of Psychology, The Hebrew University of Jerusalem, Israel), who will be talking about the interaction of the immune system with emotion and cognition. Professor Holzer highlighted Professor Yirmiya's contribution to the field, saying: "He was one of the first researchers to show that if you stimulate the peripheral immune system – not just the gut, but the entire thing – by giving animals LPS, which activates toll-like receptors (receptors of the innate immune system), then you do cause changes in behaviour."

> *"There is an important information channel between the gut and the brain, and this is not only facilitated via sensory neurons or gut hormones, but also via the immune system"*
>
> *Peter Holzer (Professor of Neurogastroenterology, Medical University of Graz, Austria)*

Analogous studies in humans since then have shown similar effects in inducing mood changes. Professor Holzer concluded: "So this is one of the ideas, the concept of cytokine-induced depression; this is still a hypothesis, but it has been used for some time in depression research."

The symposium will be addressing basic research questions relating to gut-brain interactions, as well as proposing psychiatric treatment strategies that could be used as adjuncts to more conventional therapies, particularly in depression and anxiety. Professor Holzer described the work of John F Cryan (Department of Anatomy & Neuroscience, University College Cork, Ireland) whose focus is stress-related disorders, saying: "He had very interesting data published recently showing that if the microbiota is changed – in this case using lactobacillus probiotics for a few weeks in mice – very surprising effects are seen in behaviour: these probiotics reduced anxiety, reduced depression-like behaviour and seemed to increase stress resilience.

"He also looked at some of the neurochemical changes that could explain these effects and found that the GABA system was altered by the probiotic." Changes in microbiota were not measured in this experiment, but documenting these changes would surely be a useful topic of study in order to understand the causal factors that emerge from the gut to affect the immune system and brain.

Professor Holzer also summarised other methods that may be applied to disrupt the microbiota-immune equilibrium, which could form a foundation of knowledge upon which human studies could be based. He said: "You can disturb the microbiota with antibiotic treatment, or use germ-free mice, which show differences in several phenotypes from normal mice. I am not really aware of studies in humans that the relationship between gut microbiota and the brain, but experimental studies really suggest that there is a relationship, which could have great use in psychiatric disorders."

Professor Holzer will co-chair the session 'The immune–brain axis: a concept gaining momentum'; Monday 15 October, 14:30, Hall IK.

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ECNP Neuropsychopharmacology Award 2012

Continued from page 3

in post-mortem brains to see whether one can model those kinds of abnormalities in animals and to link that to the potential for drugs and treatments to modify those problems. So he very much plays in the areas which is dear to the hearts of all of us in this society, which is to look for the science that can improve treatment, in this case particularly in schizophrenia and psychosis."

Continuing to introduce the next recipient, Andreas Meyer-Lindenberg (Director of the Central Institute of Mental Health, Mannheim, Germany), Professor Goodwin said: "His work has been groundbreaking in linking genetic variation with variation in brain structure and in function.

"This is work that he originally conducted with Daniel Weinberger in the United States, and mercifully his brain was not permanently drawn to that part of the world, and he returned to Europe some years ago. He has now set up independently in this part of the world and is doing fantastic work, related partly to initiatives – one of the key ways in which we see collaboration between academia and industry being pushed forward in Europe.

"And he has been at the cutting edge of developments again as to how we translate the new science that informs our understanding of psychosis and schizophrenia into new treatments.

Paul Harrison

Department of Psychiatry, University of Oxford, UK

"Thank you very much indeed Guy, and it is an honour to get this award. I mean that very sincerely – it is a particular pleasure of course to receive it from Guy, though I'm glad to hear he was conflicted with the decision! Guy actually appointed me to my present post and I have had the pleasure of working in his department for many years since then."

He added: "It's also a real honour to share it with Andreas Meyer-Lindenberg. I've always thought he was an absolutely outstanding scientist, so I'm very grateful to the committee that they consider me inseparable from Andreas. It's a great honour.

"Lastly, and most importantly I'd just like to thank all of the members of my research group past and present, as well as our collaborators in Oxford and beyond. The person receiving this award is really just a figurehead of a team effort, and this really has been exceptional in my case for a number of years so I am very, very grateful to all of those members who've had the ideas and done the hard work for the experimental data that allowed me to receive this award. Thank you very much to them, and thank you to the ECNP."

Andreas Meyer-Lindenberg

Director of the Central Institute of Mental Health, Mannheim, Germany

"Thank you very much, Guy, and thank you very much to the committee for giving me this award. I'm very honoured and I can give right back what Paul said: It's an enormous honour and pleasure to be sandwiched between Paul Harrison and Jules Angst – scientists who I very greatly admire. That's a bit humbling but is also a great pleasure to give thanks to many people who are really beyond the work that you mentioned.

"There is a conceptual debt to my colleagues at the National Institute of Mental Health especially Danny Weinberg and Karen Berman for their work on genetic variation, and there is a debt to my outstanding colleagues at the Central Institute of Mental Health who have made it a great pleasure to continue and extend that work here in Europe. And I would like to specially mention my group leaders in the imaging genetics work, Peter Kirsch and Heike Tost who have been supporting that work greatly. And finally of course all of that wouldn't be possible if you didn't have understanding families so I am very pleased that my wife is here to witness this award.

"So thank you to all of these people who are really the ones to whom the honour goes. Thank you very much to the committee and thank you to ECNP."

ECNP Lifetime Achievement Award

Jules Angst trained under the auspicious wing of Manfred Bleuler, son of Eugen Bleuler, in Zurich, Switzerland, where he now resides as Emeritus Professor of Psychiatry at Zurich University. His six-decade span of work in the field earned him the Lifetime Achievement Award on this special 25th anniversary ECNP Congress.

Professor Angst was introduced by Guy Goodwin (Department of Psychiatry, University of Oxford, UK) during the Keynote Session on Saturday evening, who said: "Lifetime achievement awards pose a delicate problem as to when one has achieved one's lifetime's work. And in the case of our recipient this evening, that has been a particular problem because he has not stopped producing fantastic work!"

Offering his gratitude for the honour, Professor Angst said: "I'd like to thank you for these wonderful words, and to the committee especially for giving me this honour. It is a wonderful and unexpected honour to receive this lifetime achievement award after my 60 years of activity in research in psychiatry."

Referring to how he has witnessed the field develop in his lifetime, Professor Angst added: "Progress was, and still is dramatic, and we have the pleasure to see our knowledge of the complexity and dynamics of our human nature expanded every day; the keynote lecture illustrated that again. The ECNP Lifetime Achievement Award will encourage and help me to continue work to follow these scientific developments as long as I possibly can, and I thank you once more immensely for this great honour."

"The ECNP Lifetime Achievement Award will encourage and help me to continue work to follow these scientific developments as long as I possibly can, and I thank you once more immensely for this great honour."

Jules Angst (Emeritus Professor of Psychiatry at Zurich University, Switzerland).

Jules Angst

Live from ECNP

Sunday brainstorming

The first Brainstorming Sessions yesterday morning at the 25th ECNP Congress were packed to full capacity as delegates joined each other for the chance to discuss, query and – of course – brainstorm issues in the field.

In the 'Neurogenesis, major depression and antidepressive action: a relevant link?' session, Eberhard Fuchs (Germany) was joined by Sebastien Couillard-Despres (Austria) and Paul John Lucassen (the Netherlands) to discuss with participants the obstacles and questions regarding the effects of antidepressants on neurogenesis, and what we have learned that could be significant for the treatment of depression. Recent findings regarding exercise and neurogeneration in rats, as well as the interesting effects of ketamine, suggest interesting directions for future research.

Decreasing hippocampal volume is a factor of many psychiatric disorders, including depression, and studies have shown the increases of neurogenesis by antidepressant administration in rats. But the relationship is not clear as of yet, and the significance of hippocampal neurogenesis unspecified, especially with regard to glial cells (although there is some evidence to support its role in learning and memory as well as in spatial orientation). Studying the condition presents familiar practical problems in this discipline, as Professor Fuchs described: "In humans, the field suffers from a major limitation in that it's difficult to detect neurogenesis. We are limited in markers of proliferation per se, and it's hard to get antibodies that work in human tissue. On top of that, it's quite hard to get these tissues of course."

> *"In humans, the field suffers from a major limitation in that it's difficult to detect neurogenesis. We are limited in markers of proliferation per se, and it's hard to get antibodies that work in human tissue. On top of that, it's quite hard to get these tissues of course."*
>
> *Eberhard Fuchs, (University of München, Germany)*

Experiments in rats have shown that exercise can increase hippocampal neurogenesis. During the brainstorming segment, Dr Couillard-Despres addressed the variability of the stress response, saying: "One point that is very interesting is the individual reaction to stress, the individual response to running. In the experiment where rats were put on a treadmill to look at how increased physical activity would increase neurogenesis, there were rats that were running voluntarily, really enjoying it, and their neurogenesis increased significantly. There was another cohort that didn't enjoy it at all however. They were trying to force them to run by bumping them in the back when they stopped running. These animals went through the experiment in a very stressful way because they didn't enjoy it at all, and in that experiment, neurogenesis actually decreased." Clearly, whether or not the stimulus is enjoyable plays a significant role in the animals' stress response, a finding that is surely relevant for studying the human population.

Another participant noted the acute effects of ketamine on depression, which is distinct from the effects of conventional antidepressants, which require around three weeks to take effect. Providing an explanation for this phenomenon, Dr Couillard-Despres said: "It was observed in the clinic that you do need a week to a month to increase neurogenesis for those cells to be integrated in the system. You had a very strong secretion of functional BDNF associated with these acute effects, which was linked to post-transcriptional maturation of the peptide."

This rapid onset of antidepressant action is certain useful clinically, but converting this to long-term antidepressant action is a key concern of clinicians. Dr Couillard-Despres said: "I definitely think this is a very good means of increasing BDNF for the synaptic plasticity that you need to kick-start the system, to stabilise it and improve the activation level. I think we should keep that in mind in the future, to develop a sequence of events in the future, to first kick start the system in an acute way, and then try to build up the system as a whole network by long term antidepressant action, to give the opportunity to change these connections in a long term fashion."

Poster and travel awards @ ECNP congress

Congratulations to all of the recipients of the poster award and travel award on Sunday.

Poster Award winners:

Pablo Leon-Ortiz, Mexico
Poster number: P.3.c.008

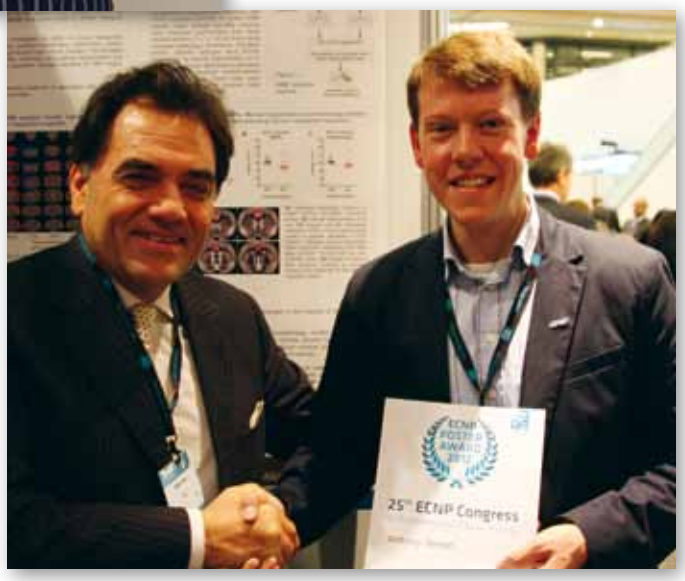
Anthony Vernon, United Kingdom
Poster number: P.3.d.007

Sinead E. Shortall, United Kingdom
Poster number: P.6.d.001

Laura Pina-Camacho, Spain
Poster number: P.7.a.009

Travel Award winners:

P.3.a.014 Marta Bosia, Italy
P.3.b.001 Suzanne Gage, United Kingdom
P.6.a.005 Daniele Stavros Hatzigiakoumis, Italy
P.6.b.005 Erika Comasco, Sweden
P.6.b.006 Magdalena Sikora, Poland
P.6.b.007 Francisco Navarrete Rueda, Spain
P.6.c.007 Tom Freeman, United Kingdom
P.6.c.011 Michael Bloomfield, United Kingdom
P.6.d.001 Sinead Shortall, United Kingdom
P.6.d.004 Jana Merhautová, Czech Republic
P.7.a.001 Marta Tyszkiewicz, Poland
P.7.a.009 Laura Pina-Camacho, Spain
P.7.a.014 Sara Carucci, Italy
P.7.c.005 Dragan Dronjak, Serbia
P.7.c.007 Covadonga Díaz-Caneja, Spain



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The neural mechanisms of pathological

A presentation that delved deeper into our understanding of brain activation associated with pathological gambling – and offered a comparison to other addictive and dependent disorders – took place on Sunday morning at ECNP congress.

Beginning her lecture, Anna E. Goudriaan (Department of Psychiatry, Academic Medical Center, University of Amsterdam, The Netherlands) recalled Nancy Petry and Marc Potenza's 2005/2006 work that discusssed whether pathological gambling should be classed as an addictive disorder.

"They started lots of research on the topic of whether gambling would actually be similar to substance dependence, or dissimilar," said Dr Goudriaan. "When you look at the diagnostic criteria for symptoms, the DSM-4 defines pathological gambling as 'persistent and recurrent maladaptive gambling behaviour'." Pre-occupation with gambling; loss of control... unable to stop gambling; gambling with increasing amounts to achieve the desired excitement (similar to tolerance).

As such, she added that almost all of the criteria resembled those of substance dependence. That is, apart from the persistence to keep gambling in order to regain lost money – a concept which cannot be analogous in areas such as alcohol dependence.

Moving on to show co-morbidity data of gamblers who also have alcohol or drug use disorders, Dr Goudriaan demonstrated that non-pathological gamblers have a significantly lower rate of alcohol or drug dependence when compared to those who are pathological.

To that end, within the new DSM-5 classification, pathological gambling has been moved from the 'impulsive control disorder' group to the 'addiction and related disorders' group, based upon similarities and core symptoms, co-morbidity patterns, shared heritability or genetics and functional imaging and neurocognitive profiles.

Offering her results in functional imaging and neurocognitive profiles specifically, Dr Goudriaan first posed the question of why people gamble, i.e. where does the "fun" come from?: "Is it the winning?" she said. "Or maybe it's not the winning but the excitement. You don't win as of yet, but there is a moment of anticipation or arousal where you don't know what is coming. Or maybe it is the rewarding effect."

She continued: "We know from brain studies that the reward circuitry gets activated when you win money. And also when you anticipate winning money. In substance dependence there is lots of evidence showing diminished activation of the reward circuitry... Is this similar in pathological gambling or not? Do these people also have diminished reward sensitivity?"

To try and answer this question, Dr Goudriaan designed a test paradigm based upon the established 'impaired response inhibition salience attribution model' by Goldstein & Volkow (2002/2006) in which people who have substance dependence exhibit a diminished reward sensitivity.

Genetic and functional dissection of dopaminergic pathway functions Wednesday 17 October 09:00 **Hall IK**

Analysing individual neuronal roles in motor co

An overview of cutting-edge research that has been illuminating the roles of the medium-sized spiny neurons (MSN) in locomotion, learning and dopaminergenic drug response will be delivered to delegates on Wednesday morning.

The MSN population is subdivided into striatonigral neurons and striatopallidal neurons, but to date the individual roles of each of the sub-populations in motor control and addiction has been under-exposed, leading to the genesis of new investigation : "One of the main points is the fact that these two populations are completely mixed in the striatum, and when we began this study there didn't exist a model or way to specifically target one of these two populations," Alban de Kerchove d' Exaerde (Laboratory of Neurophysiology, University of Brussels, Belgium) told *ECNP Daily News*.

To begin to understand more about the individual roles of each neuron in this setting, Dr de Kerchove d' Exaerde and his colleagues developed transgenic mice in which they were able to ablate each of these populations specifically. Expanding upon models of basal ganglia where striatopallidal neurons had an inhibitory action on locomotion – and striatonigral neurons had an activating effect – they first investigated the effect that ablating each of these neurons had on locomotion in mice.

In their results, full ablation of striatopallidal neurons led to hyperlocomotion, in contrast to the reduction of ambulation seen with ablation of striatonigral neurons.[1] As such, the data provided direct experimental evidence that striatopallidal and striatonigral neurons inhibit and stimulate motor activity, respectively.

In the second part of his work, Dr de Kerchove d' Exaerde investigated both of these neuronal populations in the dorsomedial striatum (DMS) and dorsolateral striatum (DLS). The dorsal striatum is primarily implicated in motor control and the learning of habits and skills[2], thus there was great interest in building on the rather limited knowledge in this arena: "We tried to understand the respective role of these two populations in these two different parts of the dorsal striatum because nothing was really known when we began our study," said Dr de Kerchove d' Exaerde.

In these tests, the neurons were found to be fundamental in motor learning, as observed during models in which mice were observed attempting a set task. "When they lost striatopallidal neurons in the whole striatum we saw an early impairment of the task, but with progressive improvement of learning of the task," said Dr de Kerchove d' Exaerde. "When we completely ablate striatonigral neurons the mice were absolutely unable to learn the task."

> *"These results highlight the reliance of striatopallidal neurons in the dorsomedial striatum for amphetamine sensitisation. This result was not predicted by models."*
>
> *Alban de Kerchove d' Exaerde (Laboratory of Neurophysiology, University of Brussels, Belgium)*

As such, these results suggest that striatonigral neurons are necessary for the undertaking of these types of motor-learning tasks, whereas striatopallidal neurons appear to be unnecessary once a task is already learnt.

Moving on to describe similar work exploring the reaction of the mice to

gambling

The test utilised visual cues of people drinking beer, for example, which in turn increase the action of the reward system owing to the memory of pleasant experience of having had an alcoholic drink before. This increased drive when confronted with cues diminishes cognitive function and lowers the ability to control behaviour.

"Dorsolateral prefrontal cortex function and anterior singlet functioning is related to a higher chance of a relapse in substance dependence," said Dr Goudriaan. "So how does this cognitive control centre function in pathological gamblers?"

To answer this question, she began by showing an example of the pioneering work by Reuter et al. (Nat Nuerosci, 2005) who designed a simple card game in which gamblers and controls lost money or gained money. In the study, the activity from both winning and losing was compared.

"What they found was that in healthy controls, you see an activation of the reward system after winning when compared to losing money, as you would expect, but in problem gamblers there is diminished activation of the reward circuitry," she said.

"That could mean two things: One, that they developed this diminished reward because they are gambling with increasing amounts of money. Or, they could have diminished reward system activity in the first place, before developing gambling problems which would make them prone."

In later studies, Dr Goudriaan incorporated a 'probabilistic reversal learning task' to investigate if there was a diminished effect of losing in pathological gamblers as well. Their results showed that problem gamblers had lower reactivity compared to healthy controls. Smokers also showed this trait.

"This shows that pathological gamblers are less sensitive to losses... less sensitive to negative consequences of addictive behaviour," said Dr Goudriaan.

Probing another aspect, her team then investigated the cue reactivity patterns of this gambling behaviour and compared it to that seen in cocaine and alcohol dependence. Specifically, they imaged the brains of subjects when exposed to pictorial cues of drugs, alcohol, gambling or, conversely, neutral picture controls.

"We saw an increased pattern of reactivity in the reward circuitry of pathological gamblers... so higher activation in the dorsal and ventral attentional routes, showing that pathological gamblers also process these stimuli with more attention," said Dr Goudriaan.

She added that there was still higher activity in controls observing gambling cues when compared to neutral cues. She postulated a reason, referencing the use of colours and lights etc found in gambling environments: "The gambling industry does a good job of attracting the attention of even healthy controls," she said.

Responsiveness was also examined closely, tested with the aid of simple left and right-facing drawings that required users to press a button corresponding to the appropriate direction they saw. Crucially, a number of images appeared intermittently that subjects were instructed not to respond to.

"Everyone made errors in the task because it is designed that way," said Dr Goudriaan. "Normally what happens is that you activate your cognitive control circuit in order to adapt your behaviour. So, in healthy controls we see that happens very well. Smokers we see there is less activity and gamblers even less."

She added that while similarities clearly exist between gambling and substance dependence, when purchasing alcohol or drugs, the user has a given expectation of the effect they will feel, whereas gamblers do not know if they will win or lose. Thus the anticipation may be a large factor.

"Does over-estimation of winning play a role?" Dr Goudriaan questioned, suggesting that gamblers have difficulty in assessing just how often they will win, and just how much they have done so already. In the initial interpretation of the data, there was no significant difference in the how often healthy controls or gamblers over-estimated their chances of winning.

However, when using functional magnetic resonance imaging to delve deeper, results showed there was higher activation in the bilateral ventral striatum, bilateral ventromedial prefrontal cortex and left insula in gamblers versus control patients. These differences were not apparent when subjects were confronted with losing.

Offering a summary of her work, Dr Goudriaan said: "Gamblers showed: less reactivity in reward areas during monetary gain outcomes... and when they experience losses; higher reactivity to gambling cues compared to healthy controls (and also this was related to gambling cravings); and diminished activity of the cognitive control network during response inhibition."

She continued: "The addiction is also in the anticipation: problem gamblers have heightened activity in their reward system during expectation of winning, and this is dissimilar from substance dependence, where there is a lower reward anticipation. There is this imbalance between control and motivation which can be crucial for continuation of problematic gambling.

"There is diminished ability for them to control their higher motivational drive to gamble."

> *"Problem gamblers have heightened activity in their reward system during expectation of winning, and this is dissimilar from substance dependence, where there is a lower reward anticipation. There is this imbalance between control and motivation which can be crucial for continuation of problematic gambling."*
>
> *Anna E. Goudriaan (Department of Psychiatry, Academic Medical Center, University of Amsterdam, The Netherlands)*

ntrol and addiction

novel objects, Dr de Kerchove d' Exaerde first explained the test methodology: decoupled delayed spontaneous object recognition. "It's not an automatic task – the mice have to recognise an object put in the middle of an open field," he said.

"Mice without striatopallidal neurons on the DMS had a dramatic increase of the exploration of the novel object, and mice without striatonigral neurons have a decrease of this exploration. Moreover, mice without striatopallidal neurons in the DMS are also unable to decrease this exploration when an object is frequently presented."

As such, these results point to the importance of the DMS in mediating novel reactivity: "This was not known before this experiment," said Dr de Kerchove d' Exaerde.

In addition to motor control and learning, the dorsal striatum is also critically involved in the motor response to pscyhostimulants and neuroleptic drugs.[1] As such, when one considers the cataleptic side effects of many neuroleptic drugs used to treat schizophrenia (haloperidol, for example), understanding more about the roles of these neurons in this setting in crucial.

"These [drugs] are often antagonists for dopamine D2 receptors," said Dr de Kerchove d' Exaerde, adding that the direct neuronal interaction involved in these side effects had previously remained elusive.

To that end, Dr de Kerchove d' Exaerde set out to investigate the individual striatal neuron roles in mediation of these side effects: "We tested four ablated

mice, and finally discovered that only in the ablation of the striatopallidal neurons of the DMS would we completely lose this haloperidol-induced immobility catalepsy," he said.

"Thus we have demonstrated that the dopamine D2 antagonism in the striatopallidal neurons of the DMS are responsible for the locomotory side effects of neuroleptics."

Logically, Dr de Kerchove d' Exaerde expanded this investigation to include the psychostimulant amphetamine – an agent associated with a potent increase in dopamine concentration – with particular focus on observing changes in sensitisation after ablation of either striatopallidal or striatonigral neurons.

"If we ablate striatopallidal neurons in the DMS we completely disrupt this amphetamine locomotor sensitisation," he said. In contrast, ablation of striatonigral neurons did not have an effect on amphetamine sensitisation.[1]

"Thus these results highlight the reliance of striatopallidal neurons in the dorsomedial striatum for amphetamine sensitisation. This result was not predicted by models," he said in closing.

Co-chair Dr de Kerchove d' Exaerde give his presentation 'The roles of specific neuronal populations of the striatum in addiction and motor control: a molecular and transgenic approach' in the session 'Genetic and functional dissection of dopaminergic pathway functions'; Wednesday 17 October, 09:00, Hall IK.

References

1) PF Durieux, SN Schiffmann and A de Kerchove d'Exaerde. Differential regulation of motor control and response to dopaminergic drugs by D1R and D2R neurons in distinct dorsal striatum subregions. The EMBO Journal, 2011; 1–14

2) P F Durieux et al. D2R striatopallidal neurons inhibit both locomotor and drug reward processes. Nature Neuroscience, 2009; 12 (4): 393-395

Glutamate co-transmission in brain: where, when, how and what for? Monday 15 October 09:00 **Hall IK**

Discussing the main messages in neuronal co-transmission

New understanding of the types of neuronal messengers at work in the dopamine, serotonin and other associated systems could have significant implications for combating a variety of brain diseases, delegates will hear this morning in a pre-clinical track symposium.

"In Parkinson's disease there are many dopamine-containing neurons in the brain that degenerate and die, and in diseases such as drug abuse and schizophrenia, there are some known perturbations of dopamine signalling in the brain," session co-chair Louis-Eric Trudeau (Department of pharmacology, University of Montreal, Canada) told *ECNP Daily News*.

As such, there is a lot of interest in understanding how these neurons function, and Professor Trudeau underlined that, in the last few years, much work has been carried out by both his centre, and others worldwide, to garner new perspectives. "Now we know they don't only use dopamine as a chemical messenger, they also use glutamate as an additional messenger," said Professor Trudeau.

This 'co-transmission' – describing neurons with more than one chemical messenger – has changed previous thinking of a 'main language' in the messaging mechanisms of neurons. "Now essentially what we have to do is understand why they do this and whether this has some relevance for brain diseases," he added.

With an already intricate network of synaptic transmission to comprehend, and the many, many neurons and circuits to consider, the concept of co-transmission adds a layer of complexity: not only do cells have multiple connections to their neighbours, but they also release different transmitters depending on the interacting cell.

Referring to the specific presentations within the ECNP session, Professor Trudeau continued: "Myself and Dr Wallén-Mackenzie will speak about this concept of co-transmission in the dopamine system, and there will be Dr El Mestikawy who will be talking about the same concept but in another subtype of neurons in the brain: the neurons that use serotonin and acetylcholine as chemical messengers.

"In the case of serotonin, this is also another transmitter that people are interested in because it is associated with diseases like depression and anxiety. And so, for example, the mechanism of action of anti-depressant drugs is to enhance the amount of serotonin in the brain that can activate some cells. And now with the same concept of co-transmission, we realised that the serotonin neurons also have this capacity to use glutamate as a second neurotransmitter."

To that end, while the serotonin system can be identified as dysfunctional in some patients with depression and anxiety, this realisation means that it is unclear whether it is a direct problem with serotonin or a perturbation of the second neurotransmitter that is at the helm.

"At this point there is no direct link that has been established, but this is really in the works, and I think this is why this is interesting for the people that will attend this meeting because it is alerting them to a new phenomenon that maybe will change the way that we think about these brain circuits," said Professor Trudeau.

The fourth presentation in the session will be delivered by Gudrun Ahnert-Hilger who will discuss the co-existence of GABA (gamma-aminobutyric acid) and glutamate in defined neurons: an issue that adds another level of complexity, as Professor Trudeau explained: "When we think about dopamine and glutamate or serotonin and glutamate, it's complicated but it's not that difficult to understand why one neuron could signal through two chemical messengers, especially as these chemical messengers use different types of receptors.

"But in the case of glutamate and GABA, they use completely opposite types of receptors in the brain. Glutamate typically has excitatory effects, and GABA typically has some inhibitory effects. And what they are linking this with functionally – and it's quite interesting – is they suggest that in epilepsy perhaps some neurons that typically use glutamate as a neurotransmitter will start gradually releasing more and more GABA, and this may be an attempt of the brain to compensate for the over-excitation."

Despite all of these observations, Professor Trudeau stressed that, while we have existing therapies that modulate GABA or excitatory signalling depending on therapeutic application, new drugs that can take full advantage of new understanding are "simply not there yet".

"It may be a question of, eventually, gene therapy rather than drugs," he said, adding that one problem is that drugs to increase GABA, for example, do so everywhere in the brain, not just specific targets.

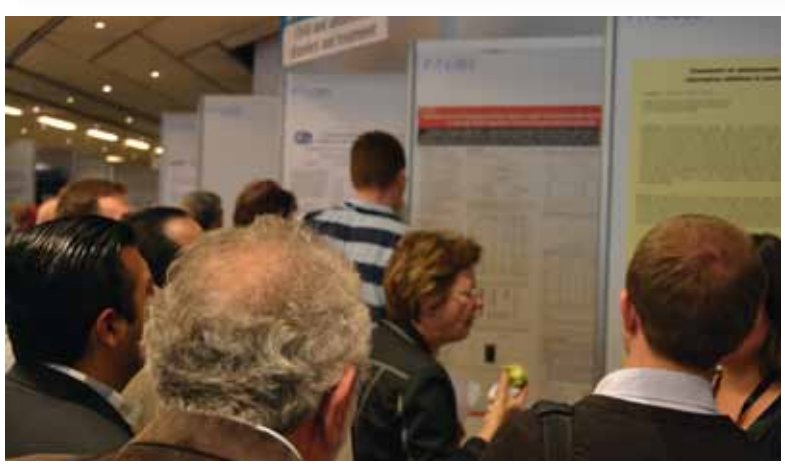
"This is a big problem obviously because it leads to sedation for example, and it is very difficult to reduce the drug doses so that people do not have too many side effects. If in this case we know that there is specific circuit in the brain that is over excited maybe we can actually modify these over-excited neurons and make them release more GABA instead.

"This could be a eventual therapeutic strategy, but I would see this as a more as a gene therapy approach rather than a pharmacological approach."

> *"At this point there is no direct link that has been established, but this is really in the works, and I think this is why this is interesting for the people that will attend this meeting because it is alerting them to a new phenomenon that maybe will change the way that we think about these brain circuits."*
>
> *Louis-Eric Trudeau (Department of pharmacology, University of Montreal, Canada)*

Louis-Eric Trudeau

'Glutamate co-transmission in brain: where, when, how and what for?'; Monday 15 October, 09:00, Hall IK.



Delegates enjoying a spot of lunch and browsing the posters.

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NEUROPSYCHOPHARMACOLOGY AWARD ECNP

GABA modulation of dopamine mesolimbic system in addiction Monday 15 October 14:30 **Hall F1**

The impulsivity of addiction

A 'bench to bedside' approach in understanding the gamma-aminobutyric acid (GABA) modulation of the dopamine system, including a detailed look at inhibitory pathways and the role of impulsivity in addiction will take centre stage this afternoon at ECNP congress.

Concentrating on the interplay between impulsivity and addiction during the session will be Tommy Pattij (VU University Medical Center, Amsterdam, The Netherlands). "The main topic that I'm going to talk about is, first, that impulsivity might be a vulnerability trait or predictor, if you will, of drug dependence," he told *ECNP Daily News*.

During his presentation, Dr Pattij hopes to discuss the evidence for this idea, while focussing on the neurobiology of impulsive behaviour as a way to perhaps intervene, prevent or help those suffering from drug dependence. "Not by targeting drug dependence itself, but by targeting impulsivity as a possible predictor," he clarified.

Dr Pattij added that, given we know that dopamine elevation increases impulsive behaviour, it follows that compounds that potently elevate dopamine levels, such as amphetamine, also have implications in impulsivity: "There is a clear overlap between the role of dopamine in impulsive behaviour and drug addiction," he said.

"The pathways I am going to talk about are primarily the opioid pathway and the cannabinoid pathway, and these are inhibitory pathways that are able to modulate dopamine action or dopamine function in the brain.

> *"Impulsivity might be a vulnerability trait or predictor, if you will, of drug dependence."*
>
> *Tommy Pattij (VU University Medical Center, Amsterdam, The Netherlands)*

Moving on to discuss how impulsivity is now linking psychiatric disorders such as drug addiction, Dr Pattij emphasised that, clinically, we are now able to better understand the role of dopamine in impulsive behaviour, and there is a huge amount of data emerging on the role of dopamine both in drug addiction and in attention deficit-hyperactivity disorder (ADHD).

Tommy Pattij

"The work I am doing is primarily pre-clinical work, and it looks like these different fields are now merging, and there is a lot of consistency between the pre-clinical – laboratory animal work – and clinical observations... there is a lot of cross talk now between the different fields," he said.

This unison of clinical and pre-clinical work mirrors a trend emerging in many different areas of research, but Dr Pattij was still keen to stress that there was much to be done in order to establish solid clinical support for this kind of work: "I think that is still a little bit soon to tell – as far as I am aware I don't know if there is solid clinical support for this," he said in closing.

Dr Pattij will delve into the topic of impulsivity in addiction in more detail during his presentation 'Role of impulsivity in addiction: dopamine and inhibitory pathways' during the session 'GABA modulation of dopamine mesolimbic system in addiction: from bench to bedside'; Monday 15 October, 14:30, Hall F1.

Fiona Fox and Claire Bithell recieve the ECNP Media Award for the Science Media Centre, United Kingdom

Musical entertainment in the Keynote Session on Saturday evening

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