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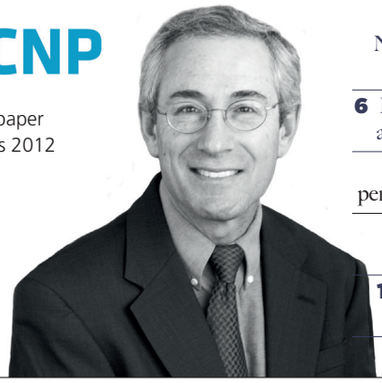

25th ECNP CONGRESS Special edition

A look back at a landmark congress

This year marks the quarter century milestone for ECNP. To that end, the 25th ECNP Congress offered both a look back – celebrating the college's exemplary journey so far – and a look forward, setting the scene for how it can continue its influential, cutting-edge exchange of expertise that will drive forward the field for a new generation.

Alongside the comprehensive and diverse range of sessions now synonymous with ECNP Congress, this special anniversary event contained a number of additional highlights. For the first time, the plenary lectures were increased to a total of six, offering the chance for even more insight from world-leading experts. Extra focus was also placed on collaboration, with the ECNP Plaza – a place for networking, sharing and exchangeand, for the first time, scientific cafés.

Furthermore, and with the next 25 years in mind, young scientists were also given more and more chance to interact with senior members, thanks to a varied and extended number of sessions that focussed on the work of more junior colleagues.

The anniversary congress also saw the first outing for the official congress newspaper, *ECNP Daily News*. Spread over three issues, it served as a forum for extra views, interviews and inside looks from the congress as a whole.

In a similar vein, within these pages we present a special edition of *ECNP Daily News* that brings together a compilation of articles from all three issues of the congress newspaper, thus offering a bite-size overview of the diverse and engaging programme, and providing a glimpse of this truly landmark year.

Keynote lecture: The plastic brain – Colin Blakemore

Keynote lecture sets ECNP Congress off with a bang

The Keynote Session was filled with awards, speeches and live entertainment that served as a befitting tribute to the opening of the landmark 25th ECNP Congress.

Perhaps its most anticipated segment was the keynote lecture, 'The plastic brain', delivered by the eminent neuroscientist Colin Blakemore (Department of Physiology, Anatomy and Genetics, University of Oxford, UK). Professor Blakemore continues to be involved in groundbreaking developments in our understanding of fundamental phenomena in the brain.

History has a curious way of slipping from our consciousness, and Professor Blakemore recounted just how far our understanding has come in recent times – how we are getting to grips with the dynamism and diversity 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 disorders, 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."

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,

Colin Blakemore

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Keynote lecture

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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 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.

Colin Blakemore

"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."

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 musical 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. Dyslexia too: perhaps some forms could be explained by disorders in 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.

"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."

'The plastic brain' webcast can be viewed at www.ecnp.eu

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Plenary lecture: Operational principles of inhibitory circuits in the cerebral cortex

Interview: **Tamás Freund**

Tamás Freund is the Director of the Institute of Experimental Medicine at the Hungarian Academy of Sciences, Budapest, Hungary. In 2011, his research into novel types of inhibitory nerve cells in the hippocampus, and their role in the regulation of rhythmic activity in the cerebral cortex, earned him the prestigious Brain Prize.


Tamás Freund

Professor Freund was one of the distinguished plenary lecturers featured at this special 25th anniversary congress, and *ECNP Daily News* spoke to him to catch a glimpse of his work in this exciting field.

What are core findings and messages from your research that you emphasised in your plenary lecture at the 25th ECNP Congress?

I believe my first significant piece of work in this field was published in the late eighties, and concerned the mechanism of how pacemaker neurons in the septal region induce hippocampal theta oscillation. In a paper published in *Nature*[1] we demonstrated that these pacemaker cells are GABAergic, inhibitory, and selectively innervate GABAergic interneurons in the hippocampus, thereby synchronising principal cell activity rhythmically at theta frequency.

This fundamental discovery was followed by a series of papers demonstrating that a similar GABAergic pathway with the same target selectivity extends from the basal forebrain to the neocortex, and that other subcortical pathways, such as the serotonergic raphe-hippocampal projection, use the same strategy, the innervation of local interneurons, to achieve control over population discharge patterns in various cortical regions. I developed a combined septalhippocampal slice preparation in which direct electrophysiological evidence has been provided – in collaboration with Richard Miles in Paris, and my student Katalin Tóth – that indeed, the mechanism of septal control of hippocampal theta oscillation is disinhibition.

Recently, with my former students (Zsolt Borhegyi and Viktor Varga) we fine-tuned these complex approaches, and carried out similar combined electrophysiological, pharmacological and morphological studies in the brain of living anaesthetised animals to investigate the interplay between identified septal pacemaker units and hippocampal activity patterns under various levels of sleep and anaesthesia. Our data explained why and how the firing of different interneuron types are coupled to different phases of hippocampal theta oscillations. We are using now a similar approach in combination with optogenetic techniques to study how serotonergic neurons in the raphe nuclei influence hippocampal populations discharge patterns via the innervation of local GABAergic interneurons.

Our interest in interneurons led us to a different field, the endocannabinoids. The first major breakthrough came when together with my group we demonstrated that CB1 cannabinoid receptors, which are the major targets of the psychoactive compound in the cannabis plant, are localised presynaptically on GABAergic axon terminals, and inhibit neurotransmitter release. These results paved the way to the discovery of a novel communication channel in the brain: retrograde synaptic signalling via endocannabinoids. We provided evidence for the existence of a molecular assembly called perisynaptic signaling machinery (PSM), a term we coined in a recent review in *Nature Medicine*[2]. This module is designed to detect spill over of the excitatory transmitter glutamate from the synaptic cleft upon hyperactivity on the presynaptic side, which will then trigger the synthesis and release of an endocannabinoid in the PSM that will act back on the axon terminal via CB1 receptors to inhibit further glutamate.

How have these discoveries changed our practises – or indeed, how do you think they will change our future perspectives and understanding? Will it pave the way to new approaches in pharmacotherapy for a variety of disorders?

We exploited the implications of these basic research findings from the point of clinical relevance. Using comparative expression profiling of the molecular components of the endocannabinoid system we demonstrated that the endocannabinoid signaling pathway is robustly downregulated in hippocampal glutamatergic synapses of temporal lobe epilepsy patients[3]. Thus, malfunctioning of the circuit breaker may partly explain excessive glutamate release and runaway excitation during seizures.

Since the loss of CB1 receptors from glutamatergic axon terminals preceded profound cell death in the vulnerable regions, this change is likely to be involved in early stages of epileptogenesis. On the other hand, CB1 receptors located on the GABAergic axon terminals of a select subset of interneurons was shown to be relevant for anxiety-like behaviour.

In collaboration with Jozsef Haller, we provided evidence that impaired CB1 receptor function plays a central role in anxiogenesis. We described the differences between major basket cell types, one operating as a clockwork for oscillations (the parvalbumin-containing cells), and the other as a fine tuning device (the CCK-containing neurons). The latter type was found to express several receptors and to receive afferent inputs that are all involved in anxiogenesis, which led to the conclusion that this cell type itself may represent a novel target for pharmacotherapy[4]. Thus, our most recent research can result in changes in rational drug design and drug development.

References

1) Freund TF and Antal F, GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. Nature, 1988; 336: 170-173

2) Katona I, Freund TF, Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. Nat Med. 2008; 14(9):923-30

3) A Ludanyi et al., Downregulation of the CB1 Can-nabinoid Receptor and Related Molecular Elements of the Endocannabinoid System in Epileptic Human Hippocampus. J. Neurosci., 2008; 28(12):2976–2990

4) Freund TF, Interneuron Diversity series: Rhythm and mood in perisomatic inhibition. Trends Neurosci. 2003; 26(9):489-95

Keynote Session: ECNP Neuropsychopharmacology Award 2012

ECNP Neuropsychopharmacology Award presentations

Saturday'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 were 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, left, (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

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Keynote Session: ECNP Neuropsychopharmacology Award 2012

ECNP Neuropsychopharmacology Award presentations

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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."

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 at the consequences of the abnormal kinds of gene expres-

ECNP Neuropsychopharmacology Award lecture: Neural mechanisms of risk for psychiatric disorders

Mechanisms of neural risk offer hope for therapy and prevention

Sunday afternoon's plenary lecture on the neural mechanisms of risk in psychiatric disorders was the first of two delivered by the 2012 ECNP Neuropsychopharmacology Award winners.

The ECNP Neuropsychopharmacology Award 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 ECNP Congress, as well as the submission of a review article for publication in *European Neuropsychopharmacology*.

Joint-recipient of the award Andreas Meyer-Lindenberg, Director of the Central Institute of Mental Health, Mannheim, Germany, spoke to *ECNP Daily News* about his lecture.

"There is a research tradition to look at patients with mental illness and try to figure out what's wrong in their brain – using a variety of technologies such as brain imaging, for example," he said. "What I propose to do in this talk instead is to not look at mental illness per se, but the things that increase your risk of having a mental illness. Or, if you flip it around, by their absence, those that decrease your risk."

Specifically, Professor Meyer-Lindenberg focussed his talk on both genetic and environmental risk factors – and their influence on psychiatric disorders. "Some are very heritable, such as schizophrenia, autism or bipolar disorder," he said. "In some the environment is a much bigger contribution, for example in depression and anxiety disorders."

He continued: "What I propose is that we can learn about the risk for illness by looking at how given genetic and environmental risk factors that have been identified work in the brain."

As such, this kind of strategy would involve shifting focus to look at control groups who carry a given genetic risk factor, or those that have been exposed to environmental risks. "What we try to get in the end is a neural risk architecture of mental illness, which we hope will then be a scaffold for better therapy and prevention," said Professor Meyer-Lindenberg.

> *"What I propose is that we can learn about the risk for illness by looking at how a given genetic risk factor that has been identified works in the brain, and how given environmental risk factors that have been identified work in the brain."*
>
> *Andreas Meyer-Lindenberg (Director of the Central Institute of Mental Health, Mannheim, Germany)*

"Many mental illnesses become symptomatic at a given point in time, but we know something is going on long before. By way of example, schizophrenia starts at around puberty usually (or in the decade thereafter), but we know abnormalities are discernible in retrospect since early childhood. So from the point of view of therapy, it may be that if we start treating schizophrenia only when people become psychotic, we're missing out all chance of primary intervention, and we also might be too late in treatment."

Drawing parallels to the treatment of cardiovascular disease, Professor Meyer-Lindenberg added that this kind of approach would be, in effect, like waiting for a myocardial infarction before treating the underlying cardiovascular risk factors that may have prevented the event from occurring at all. "We need to figure out what the psychiatric equivalent is… figure it out, and then devise treatment and prevention strategies that target these mechanisms before the illness manifests itself," he said.

As such, did Professor Meyer-Lindenberg see these strategies transposing to a more individualised, 'personalised medicine' approach for each patient? "I would take better therapies in whatever shape, size or form they come in," he replied.

"I would take a therapy that works well for a lot of people indiscriminately, but that is not necessarily on the horizon. I think many improved therapies, as you suggest, will come from better understanding and individual risk configuration. So that would be a way of arriving at personalised therapy."

Andreas Meyer-Lindenberg

Professor Meyer-Lindenberg stressed that, should we move into more preventative care, generalised strategies will also likely have their place. "To give you a specific example, we published a paper in *Nature* last year showing that city life, specifically a city birth, has an effect on brain function that can be linked to risks of schizophrenia," he said. "So the question is, how do we restructure city life to try and minimise that effect on brain function?"

He continued: "It might be something like reducing the density of people living in the city through urban planning, or increasing the amount of green space. And that would then be a preventive measure that would be rather general. But on the other side of the equation you could see a situation (and we will discuss this in the talk) in which we find some rare – but for those people who have them – very relevant genetic mutations.

"If you are one of the very few people who do carry one of these copy-number variant mutations your risk of schizophrenia is actually going to be quite elevated, and you might want to have a conversation with your physician about preventive drug treatment."

sion that one sees 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 that are 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."

ECNP Neuropsychopharmacology Award lecture: Schizophrenia: from pathophysiological understanding to novel treatment

A combined approach to schizophrenia therapy

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


Paul Harrison

Joint 2012 award winner Paul Harrison (Department of Psychiatry, University of Oxford, UK) explained to *ECNP Daily News*: "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."

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 (with respect to a given 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 'well, is directing that, or normalising it, likely to be therapeutically useful?'"

However, despite the identification of genes such as Neuregulin, did 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.

"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 studied that enzyme, and it turns out that that enzyme's activity is 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: that might be a good thing, because the inhibitors could then bring down the excessive activity back to normal."

> *"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)*

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)

How relevant are animal models to understand and treat psychiatric disorders?

'Invaluable' animal models in psychiatry

Bill Deakin (Professor of Psychiatry and Director of the Neuroscience and Psychiatry Unit, University of Manchester, UK) moderated Wednesday's educational update session on the relevance of animal models of psychiatric disorders. He spoke to *ECNP Daily News* to describe the historical backdrop behind animal models today, outlining the improvements that are being prompted by evolving techniques and hypotheses. The two speakers of the session were Kevin Fone, a preclinical expert in animal models, and Klaus-Peter Lesch, a clinician with expertise spanning clinical biological psychiatry and animal models.

Beginning with the value of models that employ genetic modification in order to study candidate genes, Professor Deakin said: "There's amazing ingenuity in the development of animal models. They are invaluable in providing an indication of drug efficacy, selecting candidate drugs for further testing that might be suitable for therapy. I think new genetics has made an impact particularly in terms of validating targets.

"If you see analogous changes in experimental animals when you modify a receptor that you think may be relevant, and it stacks up and parallels the disease, then that is an interesting way of modelling the disorder and validating the target, which then makes companies think about developing compounds to hit that target. That is the way it is today. Companies want target validation, which means parallel studies in animals and humans, identifying what the disease process is in humans; that is the ideal situation – backtracking that to animal models to see if it reproduces analogous behaviour."

Professor Deakin singled out psychosis and schizophrenia as perhaps the greatest challenges in animal modelling, given the need to target the symptoms that are not addressed by dopamine-targeting drugs. He explained: "Apart from dopamine, we don't really know what's going on. There is a huge interest in glutamate, and there are a number of experimental models of psychosis in genetically modified mice with, for example, knocked-out NMDA receptors. There are many things that impinge on this, producing behaviours that are reminiscent of schizophrenia, and produce its chronic symptoms: cognitive impairment and negative symptoms."

Speaking about the recent historical landmarks that demonstrate the power of animal experimentation in the understanding of disease mechanisms that can then identify candidate targets, Professor Deakin said: "Arvid Carlsson got the Nobel Prize for determining that dopamine was a neurotransmitter and for understanding that antipsychotics block the behavioural effects that are seen with amphetamines in animals. This suggested for the first time that antipsychotics might work in this way, in the 1960s. Proving that there was a problem with dopamine in humans, that this is how the drug works, came after that. So that was one forward translational approach."

The impact of this approach endures still, it constituting one of the primary methods of drug discovery today, at least in the search for antipsychotics. However, the fact that the whole spectrum of symptoms is not treated in conditions such as schizophrenia perhaps demands a different approach. Professor Deakin explained: "The problem remains that all standard antipsychotics don't do much for negative symptoms. Although people's hallucinations and delusions die down, they rarely disappear completely. People are left with a poor quality of life, keeping themselves to themselves and neglecting themselves, and they don't experience the normal range of emotions; that emotional blunting is a hard thing to model."

> *"There's amazing ingenuity in the development of animal models. They are invaluable in providing an indication of drug efficacy, selecting candidate drugs for further testing that might be suitable for therapy."*
>
> *Bill Deakin (Professor of Psychiatry and Director of the Neuroscience and Psychiatry Unit, University of Manchester, UK)*

Modelling aspects of social behaviour to study negative symptoms in mice has been achieved by modifying glutamate, but there still remains much to be learned, as Professor Deakin noted: "There can be substantial problems when you change non-specific aspects of the brain; you could be damping down everything including social behaviour. We don't have any drugs that definitely improve negative symptoms and that's closely related to the issue of cognitive impairment, although the association is not that strong. There could be different processes going on."

Bill Deakin

Citing some up-and-coming research into negative symptoms, Professor Deakin was hopeful that negative symptoms can be addressed with medication – at least in part. He said: "Those animal studies rather strongly suggest that doing things to glutamate transmission may be beneficial for the deficit syndrome – the negative symptoms and cognitive impairment. There are drugs that have come through that line of research; Roche have a compound that improves NMDA neurotransmission – it's a glycine transport inhibitor (glycine enhances the way that the NMDA receptor works). You can show in experimental animals that it improves behaviours by blocking NMDA receptors, and the clinical trials are looking pretty good in humans too, but it's very early days yet."

Modelling behavioural traits is, Professor Deakin said, the most complete way of addressing a drug's function. He explained: "We need studies in humans, mainly in drugs that mimic psychosis, so that then we can give those drugs to animals to induce psychosis and figure out how they work. The trouble with this approach is that you will keep getting the same compounds, because the model will always have the same, perhaps oversimplified biochemical action in terms of modelling the neurochemistry of complex disorders. So what we really need are behavioural models, because if you model the disease state in terms of neural systems and behaviour, it doesn't really matter how the compound works – if it works on the behaviour, you have a pretty good idea that it is going to work on the disorder."

Moving on to describe other approaches that might elucidate similar deficits, Professor Deakin continued: "There are drugs that are used in animal models that mimic development – giving drugs for a time to induce subtle brain dysfunction. Taking away the drug leaves you with social, behavioural and cognitive deficit – inducing a model that doesn't depend on the acute effects of the drug. This allows the development of drugs that could help to bridge this deficit, and in fact the glycine transport inhibitor model works in this fashion."

Schizophrenia is clearly a big target for behavioural models, and modelling individual traits might lead to more appropriate, more specific targets, as well as addressing adverse effects. Professor Deakin explained: "This is the other side of translational therapy. Why does a group of antipsychotics induce diabetes and obesity? There's not a lot of research going into modelling this in animals, but perhaps there ought to be."

In addition to schizophrenia, anxiety and depression were also addressed in the session. Professor Deakin said: "One criticism of the antidepressant model has been, for example, the behavioural despair tests, in which you put rodents in a beaker of water and see how long they swim for. Those that are 'depressed' will give up easily, whereas others are more resilient and keep swimming. I think there are quite a lot of false problems from this model. It's a simple screen, though, for detecting candidate drugs that might be useful for therapy. But there is no question that these sorts of tests could be improved in behavioural models."

Plenary lecture: Disruptive innovations in clinical neuroscience

Blossoming future perspectives for mental health

Greater 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) communicated to delegates in his plenary lecture on Monday at the congress.

Thomas Insel

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 United 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 States, 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 this next generation of therapeutics could come from; where are the opportunities."

Moving on to discuss his second point of communication to congress delegates, 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.

"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 psychiatric disorders, and the way that we still talk about them precludes the progress that we need in many ways.

"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.

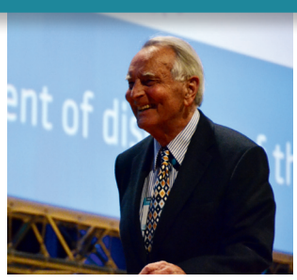
Dr Insel continued: "So what I'm going to talk about is the importance of standardisation in the way that data are collected, the integration of data across multiple platforms, and the importance of sharing. And I'll talk about how this culture – which is beginning to develop in other areas of medicine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

ECNP Lifetime Achievement Award 2012

Jules Angst awarded for his life's work



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, 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

The immune–brain axis: a concept gaining momentum

Bridging the gap between gut and brain

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.


Peter Holzer

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* to divulge a little about the gut-brain axis and the various ways in which the body and brain are 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 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, Raz Yirmiya (Department of Psychology, Hebrew University of Jerusalem, Israel) spoke 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."

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 addressed 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 on 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 of 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."

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."

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

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25 years of ECNP

An 'inspirational' 25-year journey for ECNP

As a former president of ECNP, David Nutt (Edmond J Safra Chair of Neuropsychopharmacology and Director of the Neuropsychopharmacology Unit in the Division of Brain Sciences at Imperial College London, UK) has witnessed the evolution of the organisation from a unique perspective that few others share. Current Chair of the Independent Scientific Committee on Drugs (ISCD), he is an outspoken and innovative thinker, his expertise spanning the diverse field of drug research, from laboratory to policy, bench to bedside.

Professor Nutt spoke to *ECNP Daily News* about the role ECNP has played in the evolution of neuropsychopharmacology over the past quarter of a century: "It really has been 25 years of uninterrupted success; it's a truly remarkable organisation," he said. "I think I went to the fifth meeting and it's been remarkable the way it has grown, and not just in numbers. It now has a broad portfolio, from its annual general meeting, with lots of science and educational tracts, to its international seminars and workshops; it is a stellar organisation. It has laid down a mark as to how these kinds of international organisations should try to deal with the present, but also how to build for the future."

The future of therapeutic development for the brain will surely encompass diverse disciplines working together to improve the understanding of brain mechanisms in good and ill health, but Professor Nutt remains certain that neuropsychopharmacology will remain at its centre:

David Nutt

"Neuropsychopharmacology as a term will always be with us – 'neuroscience' is a much broader term," he said. "Human beings have always used drugs, and we can be pretty certain that we will still be using them for another few centuries at least. Drugs are the most efficient way of targeting the brain because the brain has its own drugs – neurotransmitters. So, neuropsychopharmacology is one of the core disciplines of the brain and it is always going to be one of the key mediators of therapy – and perhaps will always be the key."

Highlighting the central importance of developing relevant novel medications, Professor Nutt further described the use of broader disciplines: "We will always have to embrace new technologies, like genetics and imaging, and I think we do that very well. However, these techniques are only really relevant when they translate into something applicable, and we must keep flying the flag for intervention through medication. "To give an example of this, during the genetics revolution people assumed, once the genome was cracked, that medicine would undergo a transformation. But, as it stands, the direct contribution of genetics has as yet been minimal when it comes to real therapies." Illustrating how genetics has played an invaluable, if backseat, role in drug discovery, he continued: "The brain is a complex organ, and when we use multiple drugs we know that they are going to work in complex ways.

"Genes can only ever really be part of the understanding, but we certainly take this information on board. Certainly from the aspect of drug metabolism, and therapeutically, genes are very important; genetic variance in metabolic enzymes is currently the only credible use of genetic knowledge. But it could be useful in the future – if we could learn more about slow and fast metabolisers, we could form better interventions. But this really illustrates how ECNP always has had the ability to accommodate and integrate these different disciplines."

Professor Nutt concluded by describing ECNP as a triumph of education, exchange and enthusiasm: "I have found working for ECNP quite inspirational – it has been extremely well managed," he said. "It has resources which you can use to do important scientific things, particularly in the field of education. It is very democratic in the sense that it represents the wide range of European countries.

"It's been very committed to excellence; there is a real sense that the people that work for ECNP are at the top of their field. So, the real strength of ECNP is that it encompasses multiple disciplines at a very high level, and that's why it's delivered so effectively and why it will survive such a tough period when companies are pulling out of brain research. It is at the top of the tree in terms of both people and delivery, and it has the highest integrity. And this is why I have continued to work with ECNP for so long, because it really has delivered what no other organisation has been able to."

ECNP@25: Celebrating a quarter-century at the cutting edge

Vulnerability and resilience in the development of anxiety

Rapid response shows promise in reducing traumatic stress

Intervention initiated within hours of a traumatic event is effective in reducing the onset of posttraumatic stress disorder (PTSD), delegates heard as part of a session that took a closer look at the susceptibility of patients to the development of anxiety. Delivering the message was Barbara Rothbaum (Emory School of Medicine, Atlanta, USA), who gave an overview of her recent study that focussed on early intervention for patients following a traumatic event.[1] "What we wanted to try to do in this study is prevent the development of PTSD from the start," she told *ECNP Daily News*.

Professor Rothbaum added that approximately 70% of people will be exposed to a traumatic event in their lifetime, with roughly 10% of those people developing full-blown PTSD. Thus the onset of such a disorder is dependent on the inherent vulnerability of each individual trauma patient. "For most of us, fear and anxiety is a natural response to trauma – it's almost universal," she said. "But for most people those fear responses do extinguish over time. And I think one of the ways that we do that is that we emotionally process it. So we're upset, we cry, we talk about it, we think about it, and then hopefully nothing bad happens again, and it is very similar to the grief process."

Following animal work that focussed on early extinction training to 'erase' fear memories, the human study was initialised with the goal of modifying the course of memory from trauma, reducing the chance of PTSD before the fear could be consolidated. "What we do in the immediate aftermath of trauma can become incorporated into that trauma memory, and we know that from rape victims all the time; what happens to them in the emergency room, what happens to them in the police, becomes part of that whole dialogue," she said. As such, the study team worked directly with the emergency room, identifying trauma patients as they came in and following them for a number of weeks.

"We assessed everybody right there in the emergency room, one month later when PTSD could be diagnosed,

Barbara Rothbaum

and three months later when chronic PTSD could be diagnosed, and then we randomly assigned them to have either just that assessment or to receive an intervention starting in the emergency room," said Professor Rothbaum. Patients were initially assessed an average of 11.79 hours post-trauma, with sessions then scheduled with each patient weekly up until the next assessment at 28 days.

"What we found was very exciting," continued Professor Rothbaum. "The people that received the early intervention, at 12 weeks post trauma they had half of the rate of PTSD of the people who just had the assessment only. And they had about a third less depression at that point too." With these impressive early results in mind, surely there will be rapid expansion of further trials with more and more people, with other centres following suite? "You would think wouldn't you!" replied Professor Rothbaum, adding that unfortunately a lack of funding is still a key issue in further testing.

That being said, she was keen to stress that there are a number of steps already planned for the future, the first being better predictive power in identifying those most at risk of PTSD. "My colleague who worked with me on that study, Kerry Ressler, has a big study looking at biomarkers in early trauma victims, and trying to predict over time who is going to get PTSD, so that is obviously a piece of the puzzle," she said.

Secondly, Professor Rothbaum added that more work was needed to identify whether delays in genetic analysis is limiting the efficacy of the treatment. She explained: "At this stage we can't get results back from genetic analyses fast enough, while folks are in the emergency room, to know who we should treat and who we should not, so who is at risk and who is not. We could probably get it back say a week later.

"So that is my next step to try and get funding for: Is it as effective if we give that first session say a week later, or does it really need to be in the emergency room before that memory is consolidated? Because if it can be at a later time that is obviously much more convenient. This is not a great time to be trying to treat people who've had a traumatic event. They've been in the emergency room for hours, they're usually tired and hurt and upset and they just want to go home. So if it was just as effective to do it a week later that would be important to know."

References

1) B Rothbaum et al. Early Intervention May Prevent the Development of Posttraumatic Stress Disorder: A Randomized Pilot Civilian Study with Modified Prolonged Exposure. Biol Psychiatry2012. (Ahead of print, accessed October 2012).

Social anxiety disorder (SAD): from the clinic to the laboratory and backwards

The unmet needs of social phobia

Social anxiety disorder (SAD) took centre stage on Monday afternoon at the congress in a session that saw 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* 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: "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, he continued: "There are two main types of social phobia: generalised and non-generalised. In the generalised form, affected 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.

However, this certainly does not negate the benefit of treatment, 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

Plenary Lecture: Pharma and the future of drug discovery

The future directions of pharma

The first day of ECNP Congress featured a plenary lecture that offered delegates the chance to witness expertise and insight from a speaker who is at the forefront of the current and future perspectives of the pharmaceutical industry. The lecture was given by Ruth McKernan, Senior Vice President of Pfizer and Chief Scientific officer at Pfizer's Research Unit Neusentis, Cambridge, UK.

Professor McKernan is a prolific contributor to the neuroscience field, both in journals and in non-science publishing, her book *Billy's Halo* earning her a nomination for the 2007 MIND awards. Speaking to *ECNP Daily News* before her lecture, Professor McKernan began by discussing the industry changes that have had to be made to move research into an area of biotechnological and academic excellence: "That is quite a major upheaval, and quite a major change in the way in which we operate," she said.

"That, I think, is an acknowledgement that most of the research really goes on in universities and small companies, and we operate very differently from the way we did before where we had really large sites with all of our research and development consolidated there, and in pharma we expect to do really the minimum of research ourselves, and much more of what we do is done via partnerships."

These partnerships form an important part of the pharmaceutical industry, especially for the challenging arena that is neuroscience: "Selective drugs that work in the brain are very difficult to make, and when safety hurdles are high, that challenge is much higher than making drugs that work only in the periphery," said Professor McKernan. She added that antibody-based therapeutics are not generally the first point of call for these types of applications, even though areas such as Alzheimer's disease have been exposed to a great deal of testing.

Professor McKernan continued to stress that, while somewhat of a revolution in genetics has been witnessed for cancer therapies, this kind of 'precision medicine' is only beginning to emerge in other areas. She said: "There is a tantalising hope that precision medicine based on mechanisms that are involved in neurotransmission might have value in different patient populations for psychiatric disease, but by and large I think we have to say that the human genome hasn't done a huge amount for new drugs for CNS (central nervous system) indications. Not yet."

One shortfall in this respect is that many genes only contribute a small amount in psychiatry, with neuroscience being at the 'tough' end of the spectrum. "What has neuroscience got going for it?" said Professor McKernan. "What are the opportunities where we can begin to get some leverage, because I'm not unoptimistic about the future for neuroscience, but we have to make the best of what's available."

Ruth McKernan

Professor McKernan added that she believed there was some potential value in using induced pluripotent stem (IPS) cells in understanding the biology in neurodegenerative (and possibly psychiatric) disease, because it would possibly allow some illumination as to the mechanisms in cells where we can get action potentials. "Really we're looking at targets in their much more natural functioning environment, and this has been very poor in neuroscience really up to this point," she said. In the lecture, Professor McKernan showed data on her own pain work in which embryonic cells were made into sensory neurons, as well as discussing the general concepts involved in making cells from patients with different genetic backgrounds.

Echoing a shift in thinking that many other speakers seem to share, Professor McKernan also emphasised that a move away from animal models should be encouraged. "The brain is so plastic, and animal models haven't helped us as much as we had hoped," she said. "There is a limit to what you can learn from the biology in a rodent or even a primate, but the quality of information that you can get from human volunteers is massive when compared to an animal model. So I think a lot more experimental medicine is called for, and understanding the spectrum of psychiatric disease, and what we can learn from people who may have some minor psychiatric indication but who manage very well with it."

In her closing remarks to *ECNP Daily News*, Professor McKernan accentuated the benefits that information technology (IT) and computer-based analysis could have in the exploration of the mind – an ace card which other areas of therapeutical discovery cannot play. "Our advances in IT could in fact enable development of new therapies for psychiatry, and we need to think quite differently about treating psychiatric and neurological patients," she said. "And maybe the small molecule or the antibody, or even the cell therapy isn't the right treatment, or isn't the only treatment."

David Baldwin

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."

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 then looked back over the past few decades of development in our understanding of social phobia, adding: "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."

The ECNP-NI Child and Adolescent Network: Recent advances

A bright future for children and adolescents

Alessandro Zuddas (University of Cagliari Center for Pharmacological Therapies in Child & Adolescent Neuropsychiatry, Italy) co-chaired the congress's update on the work of the ECNP Child and Adolescent Network.

Alessandro Zuddas

Much work has been done over the past decade to bring the Network into fruition, and it is carrying out major work, not only in uncovering the effects of medications that are specific to children and adolescents, but also in educating young clinicians about these data.

Using the example of depression, Professor Zuddas described the behavioural differences that distinguish child onset and adult onset conditions. He said: "One issue is that of diagnosis, and the other is of clinical presentation. The clinical presentation in children is not exactly the same as in adults. The adult will often be crying, sitting in the same place without moving, for example. In many cases of a child or young adult, the symptoms can be very positive – they can be very irritable, rather than crying."

Whilst behavioural expression of depression is distinct between children, adolescents and adults, we also know that their brains and bodies are at different stages of maturation, and this ought to be treated separately in order for therapies to be more specific. Explaining the demands of clinical diagnosis in separating young from old, Professor Zuddas added: "One year of illness in a twelve year old is completely different to one year in a forty year old. So you have to be able to verify the symptoms, and to appreciate that you are not only considering only for what is now but knowing that you can implement for the development of the child."

The safety concerns are growing for children and adolescents using medication that have only been studied in adults, as Professor Zuddas explained: "There are both efficacy and safety issues. So first of all there is not enough data. We need to implement methodologically, clinically and ethically well-performed studies, to have more information to get an idea for the efficacy. The main use for antipsychotics in treating adolescents is not psychosis, but behavioural disorders. For tricyclic antidepressants, there is not a single paper that shows any evidence, and there are even a few that show that it is no different from placebo.

"And the side effects are also different. There are antipsychotics that can increase prolactin, and if you have an increase in prolactin with amennorhea in a young girl, that is a problem. In an older woman, it is still a problem but it has a different impact at that stage of life." In light of such serious issues of health and safety of the child and adolescent patient population, the FDA and EMA are now encouraging clinical trials to bolster pediatric data.

Professor Zuddas continued: "ECNP supports clinicians to create networks to apply for these kinds of grants – to increase knowledge, to increase awareness about these types of problems. There are three projects in prevention founded by ECNP in suicidality induced by medication, in stimulant efficacy, and in safety.

"There are a lot of projects led by university researchers into the efficacy of antipsychotics in conduct disorder in normal developing children and adolescents. There is another important initiative which is the ECNP School of Child and Adolescent Neuropsychopharmacology in Venice. The first edition was very successful with 48 participants from perhaps 40 European countries. Again, that is showing that there is a big interest in the field, that there is a lot of new information coming out and that there is a lot of support for young clinicians.

"The knowledge is poor at the moment but definitely increasing, compared to what we knew five years ago. ECNP has played a huge role in that by supporting the network, but also on the educational front with the ECNP school. There is a great interest; ECNP is working on that in different directions, generating information, and communicating these new findings to young colleagues."

"The knowledge is poor at the moment but definitely increasing, compared to what we knew five years ago. ECNP has played a huge role in that by supporting the network, but also on the educational front with the ECNP school. There is a great interest; ECNP is working on that in different directions, generating information, and communicating these new findings to young colleagues."

Alessandro Zuddas (University of Cagliari Center for Pharmacological Therapies in Child & Adolescent Neuropsychiatry, Italy)

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Science and nomenclature Could infusion of neuroscience change an outdated psychotropic classification?

Dragging nomenclature out of the sixties

Nomenclature presents problems for clinicians, as well as being a source of much confusion for patients. To that end, Sunday at the congress played host to an interactive educational update session that explored this arena. Conducted by David Nutt (UK) and Stephen Stahl (US), moderator Joseph Zohar (Chaim Sheba Medical Center, Department of Psychiatry, Tel Hashomer, Israel) introduced the need to identify these problems, explaining how the audience would form a crucial element of the solution by voting on a variety of questions regarding drug action and the current system of nomenclature (their answers being transmitted via individual keypads). In this way, attendees were probed about their knowledge of the pharmacological significance of the array of drugs available for treatment, as well as their opinion as to the best approach to overhauling the present conventions in nomenclature.

Professor Zohar explained what he anticipated the new system would include, stressing the importance for patients, who quite often carry out their own research into the medications prescribed to them. He said: "I think we expect it to reflect the current scientific knowledge. We expect it to give useful pharmacological information for the clinician, and we expect it to reflect the rationality of using a particular compound. This in turn increases compliance, because the patient understands what we are doing; it makes sense to them. Unfortunately, none of this is true for our current nomenclature in neuropsychopharmacology.

"Current nomenclature is confusing: we talk about antidepressants, but we often prescribe them for anxiety; we talk about antipsychotics, but many times we prescribe them for depression and anxiety. We can take an example from hypertension, where nomenclature is based on mechanisms. Somehow the nomenclature in psychopharmacology is stuck back in the 1960s, as if nothing has happened since then. So we are really looking at all of this. The nomenclature initiative was proposed by the ECNP and composed of the four major colleges on neuropsychopharmacology: ECNP, ACNP in the USA, AsCNP in Asia, and CINP (the International College of Neuropsychopharmacology). All these colleges decided to look at this to see if we could come up with a better system."

Joseph Zohar

David Nutt then spoke of some of the issues regarding the present system, highlighting the notion that some of its consequences are not at all trivial: "One of the problems is with acronyms, which sometimes make sense and sometimes don't. Some of the acronyms have mechanistic value, but others do not. We have this huge class of drugs that are simply referred to as 'others', and we really want to work towards having a classification system where every drug has a classification that gives useful information about the drug.

"Bundling them together is of no use whatsoever; in fact it may be dangerous, because you might think that all 'others' are the same, but they are not. Another problem with the current nomenclature is that some drugs are referred to by their structural name, such as the tricyclics. This conveys no pharmacological knowledge whatsoever, because many other drugs, like antihystamines, are also tricyclics."

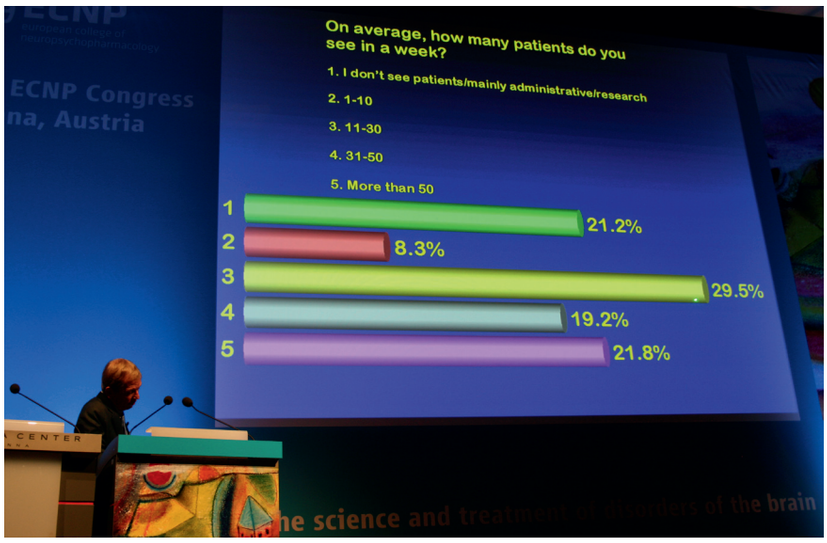
While Professor Nutt focussed on antidepressants, Professor Stahl illustrated the pharmacological complexity of antipsychotics, showing that different drugs actually bind to an array of receptor sites in the brain to different degrees. Addressing the underlying mechanisms that could explain the different uses of drugs as either antidepressant or antipsychotic, he said: "The short answer is that we don't know why they are antidepressant. Possibly 5HT1A actions are good candidates; these often raise dopamine and have other potentiating effects on serotonin. 5HT2C are involved, and blocking 5HT7 receptors is linked to anti-depressant action."

Speaking about how categorisation of these different neurobiological actions could help to classify drugs, Professor Stahl distinguished the terminologies that would help to achieve that: "We've heard three 'multi's' today: multimodal, multiaxial, and multifunctional. What we think multifunctional might mean is if you have the same kind of biological pharmacology many times". An example of this would be a drug that binds to different receptor sites of the same binding site structure (such as a G-protein coupled receptor).

He continued: "But all of pharmacology could perhaps be divided into four modes: an enzyme is a mode; a G-protein receptor is another mode; and ion channels, both ligand and voltage linked. And so what we want to do is to talk about 5HT1A, 2C and 7 as possibly those linked to why these drugs are linked to antidepressants, and not the 5HT2A and D2 actions. There are some overlaps and there are some differences; for example 5HT1A is a property of some but it's not a property of all."

Professor Nutt described what the new system might look like, saying: "The first axis is an overarching perspective on what the drug is and what it does. The second axis is the name of the drug that we will use as scientists and clinicians, and as journal editors. We are working very hard to keep editors involved in the discussion process, so that any changes we do make as a group will be translated into editorial policy, which will translate the way in which people think about these drugs internationally. Axis three looks at neurobiological activity, which will involve both animal and human work."

An additional two axes, describing clinical observations and indications, will make up the five axes upon which clinicians will be able to make more informed decisions about what they prescribe. Professor Nutt concluded: "We will endeavour to reframe all the 150 drugs that are currently in common clinical practice in psychiatry throughout the world in terms of these five axes."



Are there relevant biomarkers of bipolar disorder?

From philosophy to pragmatism in bipolar disorder

The aetiologies of complex disorders remain largely elusive, and overcoming these hurdles may require a radical rethink of our existing conceptions of discrete psychiatric conditions, Sabine Bahn (Director of the Cambridge Centre for Neuropsychiatric Research CCNR, University of Cambridge, UK and Chair in Translational Neuropsychiatry at the Erasmus Medical Centre in Rotterdam, The Netherlands) told delegates in a session that examined the role of biomarkers in bipolar disorder.

Professor Bahn is on the leading edge of multi-omics research, with the aim of identifying new diagnostic measures of complex psychiatric conditions such as bipolar disorder. Speaking to *ECNP Daily News*, she described how this practical approach can yield much needed tangible improvements in patient diagnosis and treatment, explaining: "We currently diagnose patients by asking questions which are neither sensitive nor specific, and we know that current symptomatologies do not really define diseases specifically."

Professor Bahn believes that multi-omics can help to identify hypotheses regarding causative disease mechanisms, which in turn could identify useful novel targets for intervention as well as diagnosis. Describing this process, she said: "When you don't know the causes of a complex disease, it is best to have an open mind in the initial stage. We use technologies that cover a wide range of analytes, looking at proteins, metabolites, and expressed genes so that they are explored at the systems level in the biological sense."

Much of our recent understanding of mental disorders has arisen from studies in drug efficacy, but these have often focussed attention on effects rather than causes of disease, as Professor Bahn illustrated: "We now know that changes in neurotransmitter receptors in bipolar disorder may not be the root cause of the disease. We are trying to pinpoint the origin of these disturbances with the assumption that bipolar disorder is not a single disease entity. We are doing that by looking at post-mortem brains, as well as peripheral tissues, such as blood, to allow the investigation of large patient cohorts at diverse disease and treatment stages."

The identification of changes that can be measured in blood samples is a clear aim of Professor Bahn's current research, and her team have already had some successes: "We have been most successful in developing a blood test to aid in the diagnosis of schizophrenia," she said. "It measures 51 proteins in the blood, helping to identify patients with a high chance of a schizophrenia diagnosis."

The understanding of complex psychiatric disorders is rapidly changing to include metabolic and immune abnormalities as well as more classic neuropharmacological phenomena, and this inclusive approach can only serve to strengthen diagnostic certainty and personalised treatments. An interesting consequence of this may be a new diagnosis mindset based on a spectrum of individual symptomal factors, as Professor Bahn described: "We have always considered schizophrenia and bipolar disorder as single disease entities, but they are almost certainly not; they are composed of multiple etiological entities and patient sub-groups.

Sabine Bahn

"This would certainly explain why our treatments are failing, because we are lumping patients together based on their symptomatic presentation. The aim of our research is to appreciate the complexity that cannot be gleaned from externally observed behavioural symptoms alone."

Citing an instructive analogy, Professor Bahn continued: "It would be the same as treating a fever irrespective of the cause of the fever. This is futile – it could be viral, or bacterial, or something else. So we need to find out what is driving the pathology and identify the different disease entities."

Distinguishing bipolar and unipolar depression is perhaps a particularly pressing clinical need, given that selective serotonin reuptake inhibitors prescribed to a bipolar patient whose index presentation is of depression can in fact precipitate a manic episode. Professor Bahn traced out the unknowns that are currently being addressed in research, saying: "As well as distinguishing bipolar from unipolar depression on first presentation, there is the question as to whether there is a signature of bipolar disorder which is stable over the different mood phases – through manic and depressive – and maybe even before symptoms present.

"So we are collaborating with Professor Brenda Penninx, the PI of the Netherlands Study of Depression and Anxiety (NESDA); a longitudinal study of 3,000 patients with initial presentations of anxiety and depression. Within this cohort, there are patients that initially had a unipolar disorder but over the course of six years developed a bipolar disorder; can we predict these at baseline, at the index presentation?"

Multi-omics is a 'forensic' discovery approach serving to improve holistic understanding of disorder processes, and Professor Bahn is hopeful that producing practical diagnostic tools will bring about a shift in the perception of her field: "For me, this is a practical problem. It may be difficult, but the aim is to bring about new insights and technological advances to help patients. This is likely to be an incremental process."

TEM session: Is depression a disorder of reward?

Being blunt: The role of reward in depression

Understanding the mechanisms of depression is the approach leading us to improved therapies, both psychological and pharmacological, Catherine Harmer (Professor in Cognitive Neuroscience at the University of Oxford Department of Psychiatry, UK) communicated to delegates in a Targeted Expert Meeting (TEM) during the congress.

Professor Harmer stressed that the developments in depression research, and how its relation to the dopamine 'reward circuit' is being unravelled, give us a more complete understanding of the relationship between different psychological symptoms and specific neuronal circuits of the brain.

Offering a summary of her talk to *ECNP Daily News*, she first described the focus and aims of the TEM symposium entitled 'Is depression a disorder of reward?': "It reflects the TEM held last year, where we brought together different preclinical and clinical experts on depression and focussed on the question of the role of reward abnormalities in depression." This union of both researchers into animal models and clinicians ensures continuing dialogue by which new theoretical understanding can be shared, and new therapies postulated.

Professor Harmer went on to describe the relationship between dopamine and depression: "We've known that problems of reward and potentially therefore of dopamine, which is very much linked to reward, are involved in depression; this is largely because of the symptom of anhedonia, where patients report an absence of pleasure in normally pleasurable activities. This is one of the core symptoms of depression."

Building on the work from animal studies over previous decades, research in humans has only really taken off in the past five years. Professor Harmer noted that this human research has solidified the link between depression, dopamine and the specific brain structures affected: "These problems in processing reward are linked to the symptoms of lack of pleasure and anhedonia in depression, and this also seems to be reflective of decreased dopamine in the striatum."

These developments exemplify a more translational approach to pharmacological as well as psychological treatments in mental illness, not only to develop novel therapies, but to tailor existing ones to specific symptoms of such complex disorders. This understanding of the reward circuit in depression also explains some side effects described by many patients: "Dr Ciara McCabe talked about how current antidepressants affect reward processing, and that actually they seem to be having paradoxical effects: where you might have thought that SSRIs selective serotonin reuptake inhibitors would boost reward processing, it was actually found that they seem to suppress it," said Professor Harmer.

"If you look in the literature, this seems to make a lot of sense: SSRIs aren't particularly good at treating these symptoms, and patients will often describe feeling 'blunted' or emotionally flat. This shows that although the negative aspects of depression are taken away, some of the rewarding and pleasurable mechanisms are too."

This lack of specificity provides a goal for future drug development, as Professor Harmer notes: "It may be that some antidepressants aren't very good at targeting this particular problem of anhedonia in depression, although they are very good at targeting other aspects of the illness. There is a lot of work being carried out to find out how current drugs work – what they do right and what they do wrong – and how we could formulate new drugs and new psychological treatments that could address these problems."

Speaking of the future of this field, Professor Harmer optimistically drew together the benefits of improving understanding with improving varied and combined treatment approaches, in order to address the varied range of symptoms that may be presented in depression: "I think there is huge potential for research in this area, and we have only really just begun. There are advances in brain imaging that make it possible to make real advances to look at processes in humans.

Catherine Harmer

"One of the speakers, Dr Martin Soelch, spoke about looking directly at patients' dopamine levels, not just blood oxygen activation. These sorts of technologies are very expensive and difficult at the moment, but you can imagine when it will be the routine – it will really help us to understand the role of dopamine in reward problems in depression. Also in the pharmaceutical industry, new drug treatment compound development in depression will focus on how to avoid these symptoms of emotional blunting. So I think the field is open to moving forward, both regarding what goes wrong in depression as well as targeting different aspects of it for treatment."

Pathological gambling and addiction: neurobiological mechanisms and treatment possibilities

The neural mechanisms of pathological gambling

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'."

These criteria include a pre-occupation with

gambling, loss of control, the inability to stop gambling and gambling with increasing amounts to achieve the desired excitement (similar to tolerance). As such, Dr Goudriaan 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

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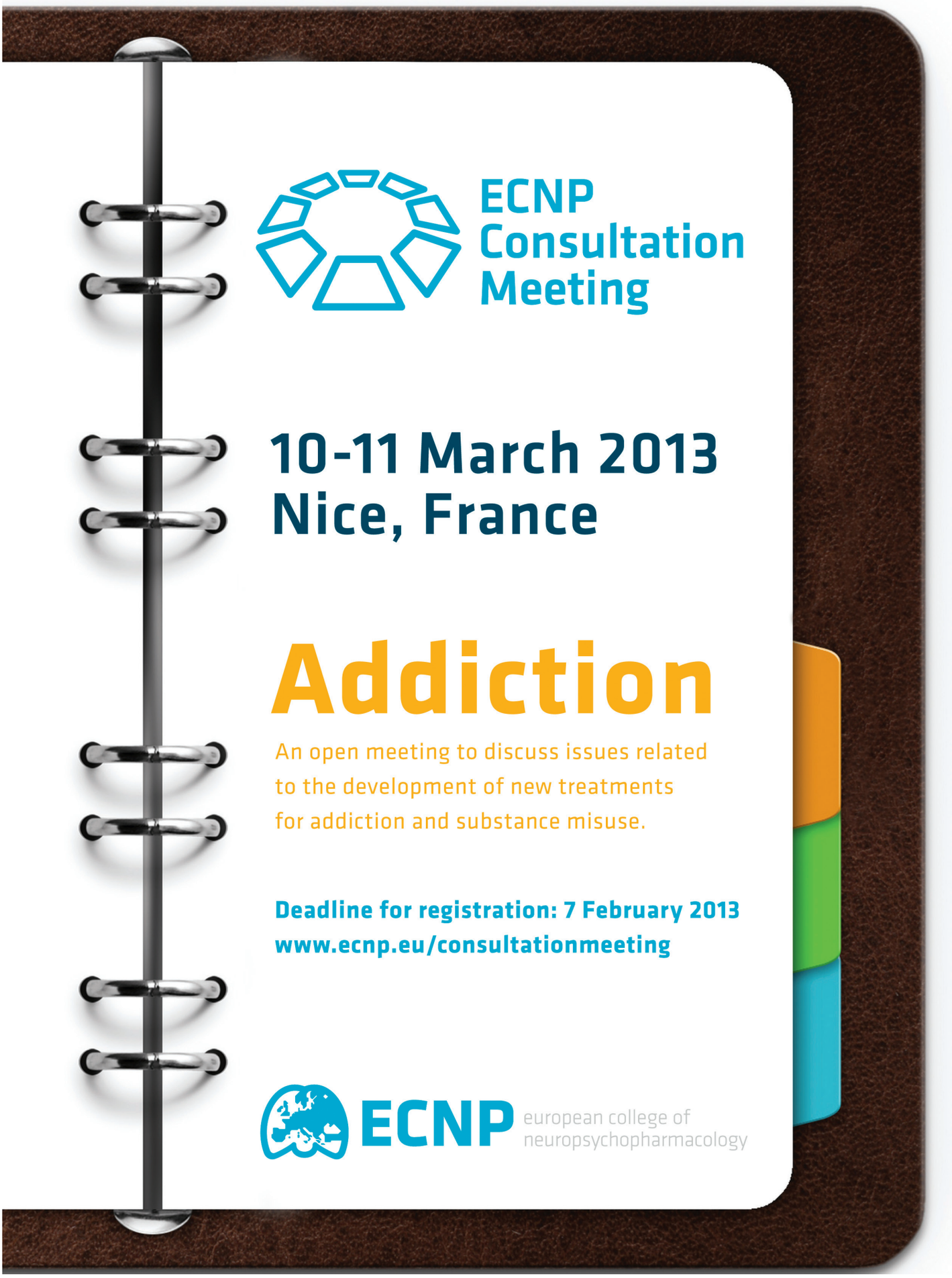

The ECNP Office

Organising a congress with thousands of delegates from the world over is no easy feat, but the ECNP Office does it each and every year. And that is but part of the puzzle, alongside the ECNP Schools, Workshops, Seminars, other meetings and of course the continual logistical, financial and scientific aspects. "I think it is very important that ECNP is not just about the congress, but a lot of other possibilities beyond that," ECNP Project Manager Ms Spitzer told *ECNP Daily News*.

Ms Spitzer has been working for the ECNP Office for four years, but this year she took on the role as project manager for the Vienna congress. As she well knows, the work that goes into each congress begins years before the actual event itself. "We already started publishing the congresses up until 2019," said Ms Spitzer. "We start three years before the actual congress really in detail."

Within this time, the team organises all the details at the venue, arranges the scientific programme and manages many other logistical criteria to ensure a smooth congress. Of course, the office works very closely with the ECNP committees: "For us it is really great that we can have such a good relationship with the ECNP committees. They are very open and that helps a lot because we can act quickly," said Ms Spitzer.

She added: "Of course we have got together with a couple of suppliers. One of our main suppliers is Colloquium Brussels. They do hotels, registration and onsite management for us."

> *"I think it is very important that ECNP is not just about the congress, but a lot of other possibilities beyond that."*
>
> *Melinda Spitzer (ECNP Project Manager)*

For the 25th year, the ECNP Office arranged several new initiatives to further enhance the congress experience as a whole. Ms Spitzer explained: "In the last year, the office has really been trying to get in touch with the participants more and more. That was a main goal. We've improved a lot in promotion (including *ECNP Daily News*), social media we do more and more, and we prepared the ECNP Plaza because we really thought it was important for delegates to get together, exchange experiences and keep in contact afterwards."

This was clearly a successful venture, as the ECNP Plaza was packed with participants looking for a central place to meet up and network. Similarly, the breakfast meetings established themselves as a great boon to the experience of young scientists, offering as they do the chance to learn from more senior, experienced participants.

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Young Scientists symposium – New insights into major and bipolar depression: mood, cognition and pain

Breaking new ground in co-morbidity models of pain and depression

Chronic pain and depression have a complex and intricate relationship, with the presence of one factor increasing the likelihood of the other, delegates heard on Sunday afternoon in the second of two young scientist symposia at the congress. Despite this observation, there have been relatively few studies that have focussed on the neurobiological mechanisms underlying the co-morbidity of depression and pain. "Up to 70% of patients suffer from both, but there is a huge lack of understanding of why there is such an overlap," Nikita Burke (Physiology and Centre for Pain Research and NCBES Neuroscience Cluster, National University of Ireland, Galway) told *ECNP Daily News*.

Ms Burke has been investigating the links between pain and depression, focussing on nociceptive responding and chemokine expression in rat models. Beginning by explaining the impetus for her research, she stressed that while studies have demonstrated a role for chemokines in depression or in pain, i.e. independently, no one has probed them within the confounds of co-morbidity. "My whole thesis was to examine, specifically, the role of the immune system and inflammatory mediators," she said, adding: "What I wanted to do was develop a model of depression and pain co-morbidity that would allow us to look at the role of inflammatory mediators in discrete regions within the central nervous system."

In her model, male Sprague Dawley rats (180–220g, n = 12–13) underwent either sham surgery or olfactory bulbectomy (OB): "The OB model is a well-validated model of depression. We have previously demonstrated that it exhibits mechanical allodynia, and hyperalgesia to an inflammatory stimulus."

She continued: "We wanted to combine this with a model of chronic persistent pain, in order to more accurately mimic the clinical situation. In this case we used spinal nerve ligation, which is a model of neuropathic pain." This model involves

> *"Many chronic pain patients suffer from depression, thus the presence of depression in these patients, and vice versa, may alter their response to amitriptyline."*
>
> *Nikita Burke (Physiology, National University of Ireland, Galway, Ireland)*

Plenary lecture: Opioid systems: probing molecular processes of brain function

Shedding light on opioid systems in the brain

Marking the final plenary lecture in the special 25th anniversary programme calendar, Brigitte L Kieffer (Institut de Génétique et de Biologie Moléculaire et Cellulaire Parc d'innovation, Illkirch, France) took to the stage on the penultimate afternoon to discuss her seminal work in the field of opioid receptors. Her work in isolating the first gene encoding an opioid receptor has led to a new and exciting era in research, and *ECNP Daily News* was on hand to find out more about the short-term and long-term research goals that have emanated from this discovery.

"There are two main research areas," said Professor Kieffer. "First – the possibility to express high levels of recombinant receptors, and mutant versions of these, has led to the study of their structure and to understand how opioid drugs bind to receptors. This culminated very recently with Brian Kobilka receiving the Nobel Prize for having solved the atomic structure of several G protein-coupled receptors. The mu-opioid receptor (the receptor for morphine, published in *Nature* April 2012) was one of them.

"Second is the possibility to modify the gene in vivo in order to understand the role of each receptor in brain function and disease. There are many outcomes for both basic and clinical research." Professor Kieffer's lecture at the congress focussed on pre-clinical work with targeted mutagenesis in mice – something that has paved the way in understanding more about the way each receptor is linked to behavioural responses. Discussing the main messages to be communicated about this topic in her plenary lecture, she said: "Targeted mutagenesis in mice has allowed us to establish the role of mu – but not kappa and delta – in both analgesic and addictive effects of clinically used opiates.

Brigitte Kieffer

> *"We can establish the role for delta and kappa receptors in enhancing and lowering mood, respectively, and the potential of delta agonists and kappa antagonists as antidepressants in mood disorders."*
>
> *Brigitte L Kieffer (Institut de Génétique et de Biologie Moléculaire et Cellulaire Parc d'innovation, Illkirch, France)*

"We can establish the role for delta and kappa receptors in enhancing and lowering mood, respectively, and the potential of delta agonists and kappa antagonists as antidepressants in mood disorders. We can establish the role of receptor trafficking and internalisation in the development of tolerance. Finally, we can discover new roles for old receptors, and new mechanisms or their functions using more sophisticated engineering approaches, and discover new targets for psychiatric research."

With this in mind, what are the next steps for Professor Kieffer's research?: "The next steps will be one, medicinal chemistry for new drugs based on preclinically established targets; two, parallel brain imaging and genetic analyses in genetically modified animals and human patients for translational research."

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the tying of the L5-L6 spinal nerves in the rodents to cause symptoms of neuropathy including allodynia and hyperalgesia. Combining these two models, Ms Burke administered amitriptyline – an antidepressant used commonly as a first line treatment for neuropathic pain – in order to test whether, firstly, nociceptive response to mechanical, heat and cold stimuli would be altered.

"We found in the control animals, amitriptyline has little effect on nerve injury induced mechanical allodynia, but it did reverse thermal hyperalgesia and cold allodynia, which has been shown before with this drug. But when we looked at the model of depression – the OB rat – we found that amitriptyline had no effect on the heat and cold allodynia, but it did reverse mechanical allodynia. So we concluded that the antidepressant amitriptyline has a differential effect on nociceptive responding following nerve injury, depending on whether or not it is in the presence or absence of this depressivelike phenotype."

Nikita Burke

In terms of the clinical repercussions of this research, Ms Burke emphasised that while amitriptyline is a widely used drug, these observations may ring alarm bells as to the likely efficacy of the treatment: "So many chronic pain patients suffer from depression, thus the presence of depression in these patients, and vice versa, may alter their response to amitriptyline," she said.

Moving on to discuss the second part of the investigation – the amitriptylinic alteration of chemokines in the prefrontal cortex, Ms Burke explained its implication: "The prefrontal cortex is a key region in the regulation of both emotion and pain. We saw in animals that had both depressive-like behaviour and chronic pain that there was a massive increase in chemokine expression in the prefrontal cortex. We looked at CCL2, CXCL10 and CCL5, and amitriptyline had no effect on CCL2 or CXCL10, but it completely blocked the OB-associated increase in CCL5. Also, we found that this was positively correlated with the antidepressant effect that we've seen in the animals."

With these promising pre-clinical results established, Ms Burke underlined that her future research will pursue further avenues building on these discoveries by blocking the activation of microglia in order to delve deeper into specific isolation of the immune system. Ideally, the next step in the timeline of the research would be to move into clinical studies, to examine if inflammatory mediators are indeed altered in patients with depression-pain co-morbidity. "Clinically, it would be great to make doctors aware, I suppose, that neurobiology of those suffering from both depression and pain may not as be as you would expect," Ms Burke said in closing.

Glutamate co-transmission in brain: where, when, how and what for?

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 heard in pre-clinical track symposium on Monday. "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," he said. 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," Professor Trudeau 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 spoke about this concept of co-transmission in the dopamine system, and there was Dr El Mestikawy who talked 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 attended this meeting because it alerted 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 was delivered by Gudrun Ahnert- Hilger who discussed the co-existence of GABA (gamma-aminobutyric acid) and glutamate in defined

Louis-Eric Trudeau

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". He said: "It may be a question of, eventually, gene therapy rather than drugs," 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 a 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 more as a gene therapy approach rather than a pharmacological approach."

The neural mechanisms of pathological gambling

Continued from page 18

said. "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.

The test utilised visual cues of people drinking beer, for example, which in turn increased 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 cingulate 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," she said.

Probing another aspect, her team then investi-

Next year's scientific highlights

The 26th ECNP Congress

5-9 October 2013, Barcelona, Spain

With the special 25th anniversary ECNP Congress now complete, the ECNP organisers, committees and offices are already focussed on making sure the 26th congress will be even more informative, insightful and comprehensive.

As newly appointed chair of the Scientific Programme Committee, Wim van den Brink (Amsterdam Institute for Addiction Research, University of Amsterdam, the Netherlands) is at the forefront of shaping next year's programme. To that end, Professor van den Brink spoke to *ECNP Daily News* to give a glimpse to how the congress will expand next year, and what hot topics will take centre stage.

"At least one of the things that we haven't dealt with before so often is the whole issue of anti-social behaviour, which is getting more and more attention both in youngsters and in adult patients," he began. "This is really a new thing that's coming up: looking at the neurobiology and the possible treatment of youngsters with conduct disorders and also the anti-social behaviour. Previously we did not have a lot of issues focussed on that."

He continued: "Of course another very important focus in the upcoming ECNP meeting will be the whole issue of Alzheimer's disease and the developments that are being made in that area. We'll have a basic research symposium there on Alzheimer's and the role of mitochondrial dysfunction."

Wim van den Brink

As such, these issues cover a range of patients from the very young to the very old, with gender differences receiving a similar amount of emphasis: "Another important issue is the role of sex hormones in the vulnerability for different neuropsychiatric disorders – a new approach to the general issue of gender differences," said Professor van den Brink.

Another crucial issue will be the role of epigenetics, as he explained: "Under the influence of the environment, our genes, and especially the expression of our genes, change. And they may change in such a way that we actually transmit them to the next generation. So there are both risks involved but also future developments for treating not only the patients themselves but also the next generation. Epigenetics will be an important issue in the Barcelona meeting."

For the 25th congress that has just passed, a number of key innovations were implemented that proved to be a resounding success. Firstly, the ECNP Plaza – a place for networking, social interaction and of course the exchange of ideas – was more popular than could have ever been anticipated, thus it will now take pride and place in all future meetings.

Similar praise was witnessed for the range of young scientist symposia, leading to plans to expand these further next year: "We are actually thinking about having special sessions at the end of the evening which could go on a little bit longer, and people can stay after the meeting and maybe sit together with some refreshments and continue discussion among other young scientists," said Professor van den Brink.

Of course, no future congress would be complete without the hotly-anticipated keynote and plenary lectures, the latter of which were expanded this year to a total of six, with plans to emulate this again next year.

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gated 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."

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