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ECNP DAILY NEWS

Thank you...

to everyone for making the 26th ECNP Congress a resounding success! Over the last few days we've all shared in the insights, perspectives, challenges and triumphs that are at the core of our international gathering of neuropsychopharmacology and its related fields.

We hope you enjoy the remaining two days of the comprehensive programme, and we wish you a safe journey home.

See you in October 2014 in Berlin.



PLENARY LECTURES / BRAIN PRIZE 2012

PL.06 The Brain Prize Plenary Lecture

Karen Steel and Christine Petit to deliver the 2013 Brain Prize Plenary Lecture

Identifying the molecular basis of deafness puts us on a road to developing novel therapies for both early and late onset cases of hearing loss. Karen Steel (King's College London, UK) and Christine Petit (College de France, and Institut Pasteur, Paris, France), joint winners of the 2012 Brain Prize, spoke to *ECNP Daily News* ahead of their Plenary Lectures at to discuss their exemplary work in elucidating many of the ways in which deafness comes about.

Deafness has many causes, including genetic factors that influence the deterioration of certain structures in the auditory system. Understanding the underlying molecular mechanisms of deafness has formed the foundation of therapeutic development and

continues to do so. "For deafness in particular, because the number of sensory cells in the ear is very small, genetics is the best way of finding molecular mechanisms rather than any biochemical approach, because there is so little material in each ear to study," said Professor Steel. "So, genetics has been extremely effective in identifying the essential molecules involved in normal hearing processes, which, when you have a mutation in that particular gene, lead to deafness. It is a way of getting access to the critical molecules involved."

Karen Steel (King's College London, UK)

molecules involved."

Advancements in molecular tools to study genetics, coupled with the sequencing of the mouse genome, have greatly invigorated genetics over recent years. Mouse models, generated by targeted mutation, are used extensively to bridge the gap between phenotypic expression and genes involved in deafness, as Professor Petit explained: "To understand the various forms of human deafness, in the absence of possible direct observation of the cochlea, the auditory sensory organ, and the most frequent target of the gene de-



Karen Steel

Photo courtesy of Wellcome Trust

"Genetics has been extremely effective in identifying the essential molecules involved in normal hearing processes, which, when you have a mutation in that particular gene, lead to deafness. It is a way of getting access to the critical molecules involved."

Karen Steel (King's College London, UK)

logical, biochemical, electrophysiological and biophysical studies, of the engineered corresponding mutant mice. Together, we have thus been able to decipher some molecular networks underlying known cochlear functions,

Continued on page 2

fect, we extensively rely on multidisciplinary analyses, including morpho-

underlying known cochlear functions,

PL.06 The Brain Prize Plenary Lecture

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Continued from page 1

to clarify how some cochlear structures operate, and even to discover cochlear structures and to decipher their roles in sound processing."

Generating these mouse models has involved large coordinated efforts that began over a decade ago, using ENU (N-ethyl-N-nitrosourea) to create random point mutations throughout the genome; these mice were then bred with wild-type mice and the offspring were screened for hearing and balance function. "I have initiated two separate programmes aimed at finding new mouse mutants affecting hearing," said Professor Steel. "The first one was an EC-funded programme and that ran from 1997 to 2000, although the mouse mutants that we got we are still studying today. It really laid the foundations for a lot of further work. That programme involved two large mutagenesis programmes that were just getting started: one in Munich and the other in Harwell (near Oxford in the UK). This was an EC-funded programme that covered five different groups in four European countries: Germany,

UK, France and Israel.

"Once we got the abnormal animals and could breed from them, we were able to characterise the phenotype – to find out exactly what was wrong with the ear – and then go through this process of positional cloning, which means identifying the mutation, based on finding its location on a particular part of a chromosome. From that, we identified the mutations involved in 24 different mutants that had hearing or balance problems. We identified altogether 13 different genes. Of those 13 genes, nine of them were completely novel. They were all of course good candidate genes for involvement in human deafness, and some of those have now gone on to be associated with human deafness as well."

Professor Steel also initiated the Mouse Genetics Program, funded by the Sanger Institute and Wellcome Trust. "We took advantage of a different large scale mutagenesis project that Bill Skarnes [Sanger Institute, UK] started. He was targeting genes in ES [embryonic stem] cells that you can use to make mouse mutants from. Over the years, he had been building up a library of ES cells, each with a different gene targeted. He now has over 13,000 of the mouse genes – two thirds of mouse genes targeted in ES cells. When we started, he was only just beginning this project. We took those ES cells and we generated mouse mutants from them, and because they were targeted we knew which genes were affected. Then we put in place a screening programme that tested for signs of many different diseases.

"We've now screened about 600 of these mouse lines (we've made 900 at the Sanger Institute). Although I've recently moved to King's College London, the project is going ahead at the Sanger Institute and I am still involved with it, particularly the auditory screening. This project has directly led to the establishment of a large international consortium called the International Mouse Phenotyping Consortium (IMPC), which involves labs around the world following this same procedure." Using this screen, Professor Steel has identified twelve new genes involved in normal hearing processes, all candidates for human hearing loss.

Professor Petit's work has addressed mainly the genetic basis of human deafness. As a pioneer of

this field, she has brought up over 20 novel causative genes. She said: "What we have contributed most, so far, is the deciphering of the normal molecular physiology of hearing and molecular pathophysiological pathways of hereditary early onset forms of deafness in humans. Considering the possible continuity between the early and the late onset forms of deafness, in terms of underlying pathogenic processes, we are now in a position to use what we have learned about early onset forms to address the pathogenesis of the late-onset forms. Improving our understanding of the molecular physiology of normal hearing and deafness can lead to knowledge that can be of direct benefit to patients, both in terms of clinical assessment and treatment.

"Having deciphered the pathogenic processes of the various deafness forms, we are now in a position to conclude whether or not the auditory prostheses (hearing aids and cochlear implants, which are presently the only way to improve or restore hearing) could be beneficial, or will have no effect – or even, for some forms of deafness, could be detrimental to residual hearing. This last scenario calls for the development of alternative approaches to prevent or alleviate hearing impairment. Rooting my genetic approach on human deafness, it naturally follows that one of my objectives is to prevent, alleviate or to cure deafness. Having clarified a network of molecular interactions, you can intervene on some proteins of the pathways that are more favourable targets for therapeutic approaches than others."

Pharmacological agents and gene therapy are, according to Professor Petit, two of the most promising lines of investigation when it comes to helping patients in the short to middle term. Together with José-Alain Sahel (Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Paris, France), she is moving towards gene therapy in retinitis pigmentosa in Usher-1 syndrome, a hereditary condition that affects both hearing and sight. "When I was conducting my research, I always had in mind whether or not our results could be useful for patients," she said. "During my ECNP talk, I will discuss one deafness form for which we have recently found a way to prevent the worsening of hearing impairment, in the corresponding mouse model. We now plan to move to clinical trial. In terms of therapy, we are very much focused on the possibility of



Christine Petit

using existing drugs to alleviate or prevent hearing impairment; there is evidence that some can be efficient. We are also developing gene therapy approaches."

The study of mouse models can also lead to the uncovering of unsuspected particular features in some human deafness forms. "In humans, hearing is the sense of the communication. It is a necessary condition to oral language acquisition, conversational exchanges and to enjoy music," explained Professor Petit. "From an in-depth analysis of the processing of some sound physical parameters in the mouse models of human deafness, we can anticipate that although hearing threshold is only moderately elevated in some patients, speech intelligibility and music perception are likely to be very seriously affected in patients. This leads us to proceed with a more detailed analysis of auditory perception in these patients."

Emphasising the impact of basic discoveries on improving clinical diagnosis and action, Professor Petit noted: "It is a real contentment to consider the medical impact of our basic research, regarding the elucidation of deafness causes, the reevaluation of the meaning of some auditory tests, the changes in the way of exploring hearing impairment in humans, and the therapeutic perspectives. My lab is deeply involved in the transfer of newly gathered basic knowledge to clinicians."

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Karen Steel and Christine Petit will deliver their Brain Prize Plenary Lecture 'Deafness: on the road from genes to therapy,' at 13.30-14.15 this afternoon in the Auditorium.

INTERFACE RESEARCH

S.11 Epigenetics: challenging new findings in psychiatry Room F Monday 7 October 09:00-10:40

A pathway to novel therapies in PTSD

Epigenetic differences have been found in post-mortem brains of people with a major depressive disorder, and studying the transcriptional responses to environmental stressors can help determine new treatment paths in psychiatry. In a symposium aimed at fostering advancements in behavioural epigenetics, held yesterday, Johannes Reul (University of Bristol, UK) presented data on the role of glucocorticoids in this epigenetic and transcriptional response, outlining their role in the molecular mechanisms that influence the consolidation of memories. These findings could be relevant to conditions such as post-traumatic stress disorder (PTSD), not only in learning more about its aetiology, but also in formulating novel therapies for memory dysfunction in this condition.

"Glucocorticoids work everywhere in the body to support metabolic processes, but they also act in the brain," said Professor Reul. "These stress-induced hormones play a very important role in creating memories of this stressful event. Although glucocorticoids have been investigated for more than 60 years, we still do not really know how they act on the brain. We think that they do so by interacting with signalling mechanisms, epigenetic and transcriptional mechanisms."

"The hippocampus is very important for mediating glucocorticoids in the brain, and certainly in learning and memory. When you want to look at glucocorticoid sensi-

tive, hippocampus-dependent behaviours, you can look at different behavioural models, like the fear conditioning paradigm: the Morris water maze and also the forced swim test.

"The forced swim test is mainly used to test antidepressant drugs, but you can also look at it from a purely behavioural point of view. If

a glucocorticoid receptor antagonist just before the forced swim test, you will find an impaired behaviour the following day during the retest. So glucocorticoids are important during the consolidation phase after the initial test."

The underlying mechanisms by which glucocorticoids are involved in memory

consolidation were, until recently, not known. Through a series of animal experiments, Professor Reul first demonstrated the importance of glucocorticoid receptors in the dentate gyrus for mediating the learning effect, both in short and long term adaptive behavioural responses. By studying the signalling and epigenetic mechanisms, such as

"If you block the glucocorticoid receptor by injecting a glucocorticoid receptor antagonist just before the forced swim test, you will find an impaired behaviour the following day during the retest. So glucocorticoids are important during the consolidation phase after the initial test."

Johannes Reul (University of Bristol, UK)

you force an animal, a rat or a mouse, to swim in a bucket of water from which he cannot escape, you will see the next day that the animal displays a lot of immobility behaviour. The animal just floats in the water for the majority of the time and does not try to escape. We think that this is a kind of adaptive response, based on the experience of the previous day, because the animal cannot escape and so he is conserving his energy.

"The typical thing about the forced swim test is that it is very much dependent on glucocorticoid hormones. If you block the glucocorticoid receptor by injecting

histone modification and DNA methylation changes, that underlie the immobility response, his group were able to define the signalling pathway that resulted in the gene transcriptional changes in the dentate gyrus. These findings were achieved by a series of

"We think that the molecular mechanisms underlying memory formation of traumatic and stressful events may help to resolve conditions like PTSD and other affective disorders in the future."

Johannes Reul (University of Bristol, UK)



pharmacological and gene deletion analyses, immunofluorescence, co-immunoprecipitation, and chromatin immunoprecipitation.

"Glucocorticoids enhance the consolidation of stress-associated behavioural responses, like the immobility response [in the forced swim test], by facilitating the NMDA/ERK MAPK signalling pathway to the chromatin, resulting in the distinct epigenetic and gene transcriptional changes in the dentate gyrus granule neurons," said Professor Reul. "Furthermore,

we have found evidence that DNA-demethylation of promotor regions of immediate early genes (and possibly other genes) are a prerequisite for expression of these genes to occur and also the expression of the behaviour. We think that the molecular mechanisms underlying memory formation of traumatic and stressful events may help to resolve conditions like PTSD and other affective disorders in the future. We think that the c-Fos and Egr-1 promoters are in a condensed state, and require demethylation, and this is independent of histone modifications to occur. This is very important for immediate early gene induction and the behavioural responses."

PRECLINICAL RESEARCH

S.20 The role of glutamate for the treatment of neuropsychiatric disorders Room J Tuesday 8 October 09:00-10:40

A novel strategy to combat mood disorders

Despite significant advances in the treatment of mood disorders, there are still considerable limitations to existing strategies, thus novel therapeutics based on a more complete understanding of the pathophysiological processes underpinning the disorders would be a particular boon for better patient health. Such is the message of Gerard Sanacora (Yale University, Psychiatry, New Haven, USA), who will be speaking this morning at ECNP Congress during a session dedicated to new and revolutionary treatments for neuropsychiatric disorders.

While the serotonin, noradrenalin and dopamine systems – collectively under the ‘monoaminergic’ umbrella – are high profile targets in the therapeutic mood disorder armamentarium, recent evidence from open-label studies (such as the Sequenced Treatment Alternatives to Relieve Depression study, or STAR*D) determined that remission rates in patients were disappointing.¹ Despite this observation, development of novel drugs is hindered by a lack of pathophysiological understanding.

To that end, during the session, Dr Sanacora will describe preclinical and clinical

[Glutamatergic neurotransmitter targeting] truly is a novel mechanism... the large majority of our current treatments very much grew up out of monoaminergic hypotheses, so I think that's the first thing that makes people excited: that we might have a truly novel target."

Gerard Sanacora (Yale University, Psychiatry, New Haven, USA)

studies that have now identified profound anti-depressant effects stemming from drugs that target the glutamatergic neurotransmitter system, even persisting in patients who were unresponsive to standard monoaminergic antidepressant medications.¹

"I will talk about what we've been learning about the pathophysiology of these disorders themselves, and why the glutamatergic system appears to be a very promising target for development," Dr Sanacora told *ECNP Daily News*. "And then I'll spend

quite a bit of time discussing the novel approaches to targeting these systems, and talk about some of the preclinical rodent models suggesting that this is a potentially viable approach."

In addition, Dr Sanacora plans to outline a number

BRAINSTORMING @ ECNP

BS.3 Can psychiatrists predict violent and homicidal behaviour? Room Y3 Sunday 6 October 07:45–08:45

Can we predict suicide?

A brainstorming session that focussed on whether psychiatrists can predict suicidal, homicidal and violent behaviour took place on Sunday morning, with experts gathering to share their views back and forth with the audience.

First to speak in the session was Michael Davidson (Sheba Medical Center, Ramat-Gan, Israel) who began by answering the question concisely that no, it is not possible to predict suicide. Expanding on this, he said: "Suicide is a high impact, low probability event, and the prediction power of the demographic and phenomenological variables is very low (and no biological markers exist). No data exists to support preventive intervention at the individual level, therefore it is essential to carefully weigh the benefit/risk ration before intervening."

With tales of legislative action and public outcry reported in the media, Professor Davidson described the perception of suicide prediction in the public eye as a "thorny" issue. While some people may argue that a psychiatrist's skills and expertise surely bestow them with the ability to predict suicide, rushing to correct these



"Should professional organizations say louder and clearer we cannot predict, we cannot prevent, we cannot assume responsibility? What would that mean for us?"

Michael Davidson
(Sheba Medical Center, Ramat-Gan, Israel)

assumptions could simply disempower professionals even further. "Should professional organizations say louder and clearer we cannot predict, we cannot prevent, we cannot assume responsibility?" said Professor Davidson. "What would that mean for us?"

He went on to say that, put simply, it is likely to remain a complicated issue, and in the end people who claim psychiatrists should be able to predict

suicide are often misled by statistics. Offering an example, Professor Davidson noted that even though a person who has a previous unsuccessful suicide attempt will be at about 20 times higher risk, when you speak of multiplying a very rare event by this factor, it still remains very rare. "It's a little bit like saying if I buy 1 or 20 lottery tickets," he said. "If I buy 20 lottery tickets, my chance of winning the

big prize is still 20 times more than with one ticket, but I still have next to no chance of winning the lottery."

Also speaking during the session was Mark Weiser (Sheba Medical Center, Ramat-Gan, Israel) who presented data to support the joint notion by him and Professor Davidson that suicide is unpredictable. To begin, he showed data from a military study looking at the suicide rates of 91,000 soldiers, aged 18-21. Of course, it is to be expected that living and working conditions in this setting would perhaps lead to higher risk, but to better examine the actual rates of self-harm and suicide the soldiers were investigated comprehensively.

Results from the study showed that roughly 7.9 in 100,000 subjects would commit suicide per year, thus Dr Weiser stressed that it should still

of ongoing clinical trials, highlighting both ketamine and other potentially therapeutic agents that target N-methyl-D-aspartate (NMDA) receptors, for instance AZD6765 and GLYX-13.

"I think the consensus is pretty unanimous that this is probably the most promising area within the field for research," commented Dr Sanacora, moving on to discuss a number of points he considered particularly exciting: "One is that it truly is a novel mechanism. It's not based on monoaminergic targets in any way. And really the large majority of our current treatments very much grew up out of monoaminergic hypotheses, so I think that's the first thing that makes people excited: that we might

have a truly novel target.

"I think the second thing that makes people very excited is it seems to be effective in patients where the classic medicines haven't worked... so it seems to be effect in a treatment-resistant population, which is very interesting. And the third point which I think makes it very appealing is that these drugs, and especially ketamine, seem to have a rapid onset of effect, with clinical benefits occurring within the first hours of treatment. So unlike the classic antidepressants, of which people typically need to wait several weeks to see a clinically significant improvement, trials with these drugs (and the largest amount of data comes from ketamine) suggest than within four hours

there is a very noticeable and clinically significant improvement in the patients." With this in mind, it follows that faster onset drugs will offer particular benefits in emergency room settings, where the critical hours of intervention are all the more sensitive.

Dr Sanacora will describe the development of novel therapeutics for mood and anxiety disorders in more detail during this morning's session 'The role of glutamate and metabotropic glutamate receptors for the treatment of neuropsychiatric disorders' at 09:00-10:40 in Room J.

Reference

- 1) Sanacora G et al. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov.* (2008); 7: 426-437.



be categorised as an extremely rare event. "That's the real problem of predicting suicide, because it's very rarely happens," he said.

In an attempt to delve deeper into possible trends and indications that might assist in predicting suicide risk, results from the study were further subdivided to only include those that had reported self-harming or suicidal thoughts to their mental health professional. The data showed 9.8% confessed to having thought about harming themselves, while 5.8% said they had already done so in the past.

"If you think about hurting yourself, it increases your risk by about 1.5, so something that is very rare is just a little bit 'less rare', but still useless for prediction," said Professor Weiser. In a similar vein, those previously diagnosed with mild anxiety or depressive disorders, personality disorders and other low-risk disorders had a moderately increased baseline



Mark Weiser and session Chairman Gil Zalsman

risk of suicide, but this became much more significant (7.59 risk multiplier) in those who reported suicidal ideation as well.

"That seems huge, but what

does this actually mean?" continued Dr Weiser. "It means that 1 in 2000 people are going to kill themselves, so again what can you do about this? Even in this high-risk group it is basically impossible to predict."

Every suicide in the study was followed by the military, thus incorporating data from family members that could be used to gauge whether victims had a history of depressive periods, drug abuse, undiagnosed disorders or other risk factors that were not apparent prior to their death.

"Basically what stands out is absolutely nothing," said Dr Weiser. He added that despite reports stating that approximately 25% of the suicide victims had instances of "depressed mood", given that this was a military study, the harsh living and working conditions would make it unreasonable to expect family members not to gauge some discomfort or depression-like symptoms in their loved ones. "225 people completed suicide, but again there is nothing that stands out," he said.

Dr Weiser moved on to discuss another study began approximately 25 years ago in which 5,000 people from the civilian population (aged 25-34) were randomly assessed by a visiting care worker for their suicide risk. Suicidal ideation was reported in 8.2% of people, while 2.2% had previously attempted suicide. Revisiting the subjects in the present day, eight of the 5,000 cohort committed suicide, representing a six in 100,000/year rate. Examining these data more closely, it was determined that of those suicides, only one person had reported suicidal ideation or had previous attempt at baseline.

Offering his conclusions, Professor Weiser reiterated the take-home message that these data help reinforce the notion that it is simply not possible to predict suicide.

"If you think about hurting yourself, it increases your [suicide] risk by about 1.5, so something that is very rare is just a little bit 'less rare', but still useless for prediction."

Mark Weiser (Sheba Medical Center, Ramat-Gan, Israel)

INTERFACE RESEARCH

S.27 Alzheimer's dementia and mitochondria dysfunction Room F Wednesday 9 October 09:00-10:40

Old drugs, new therapies in Alzheimer's

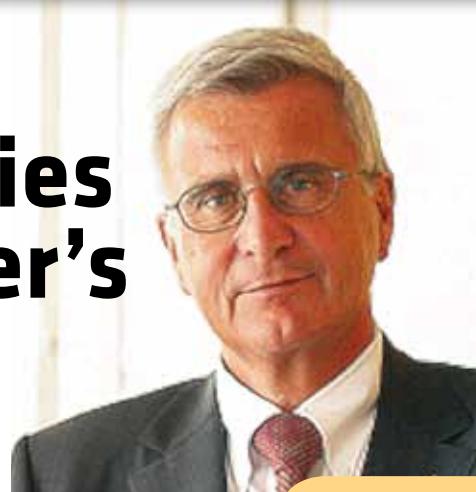
Mitochondrial dysfunction is increasingly making itself known as a prominent piece in the aging puzzle in Alzheimer's disease (AD), and the latest understanding of pathophysiology and emerging therapies surrounding this phenomenon will be discussed tomorrow morning at ECNP Congress. *ECNP Daily News* spoke to Walter E Müller (University of Frankfurt, Germany) to discuss how mitochondria are involved in the vicious cycle of AD, as well as the promising therapies he is testing at the moment.

Mitochondria are crucial for cell metabolism, yet significantly they contribute to the production of reactive oxygen species, which in turn can damage the mitochondria themselves, promoting cell degeneration and apoptosis. "They are crucial for brain aging but they are also crucial for neurodegenerative disease," began Professor Müller. "This is long known in Parkinson's disease and for even longer in AD."

Describing the factors particular to AD that influence the vicious cycle that can be established by propagating levels of oxidative stress, he continued: "In AD, at some point the beta amyloid starts to aggregate very early. Beta amyloid has an additional effect on mitochondrial function, so on its own it impairs mitochondrial function, it elevates free radicals, it alters the cell function, it might lead on to induce apoptosis, and very importantly the cell produces more free radicals. It also stimulates beta amyloid production. So actually, you have two vicious cycles: the aging cycle and the beta amyloid cycle. Each by itself is sufficient, but when both come together you have this major effect."

The causal relationship between oxidative stress and the beta amyloid cascade is not yet understood. Professor Müller cited evidence supporting either case, from familial patients suggesting that beta amyloid comes first, and genetic studies of the ApoE4 polymorphism that suggest oxidative stress to be the triggering event.

"And why, then, doesn't everyone get AD? Well, this is more or less a philosophical question. If everyone gets old enough, they probably would get it. But obviously the coping mechanisms would be different. Some of us are able to cope with it: some patients have a lot of beta amyloid and are able to cope with it very well; others are severely disturbed mentally and cognitively and have very little, so it



is not correlated. I think it is now accepted that the plaques are not critical. This is the reason why the whole strategy failed so far, because they were mainly plaque-related, and plaques are only the trash. They do do some damage without question, but only around the area of the plaque."

Moving on to describe the three compounds,

gingko biloba, piracetam and dimebolin, that he will be presenting tomorrow morning, Professor Müller said: "The one with the best clinical data so far is gingko biloba extract. We have many positive studies; we also have negative studies but in the majority there is some effect which improves mitochondrial function. The mechanism is very interesting because it might be a starting point. It is not yet the final solution, because the therapeutic benefit is present but it is not very impressive."

Piracetam, first synthesised in 1964, has also shown promise in improving mitochondrial dysfunction and, unlike gingko biloba, its mechanism of action is partially understood. Professor Müller said: "We do not have new studies in AD patients; we only have older ones, which suggest that it is beneficial in cognitively impaired patients. For

"You have two vicious cycles: the aging cycle and the beta amyloid cycle. Each by itself is sufficient, but when both come together you have this major effect."

Walter E Müller (University of Frankfurt, Germany)

gingko we do not know the molecular mechanism, but piracetam probably interferes with the membrane structure and membrane fluidity that is a critical factor in regulating mitochondrial function. Piracetam also improves cognitive function in elderly animals and reduces

"Two larger mitochondria can be divided to make smaller ones. This mechanism is not yet completely understood, but it seems to be important in regenerating and repairing mitochondria."

Walter E Müller (University of Frankfurt, Germany)

oxidative stress. Very interestingly, it also reduces, according to our theory, amyloid beta production – a 25% reduction of amyloid beta. This is definitely not relevant to the symptomatology of the patient however, because secretase inhibitor reduces amyloid beta by 80%, and this does nothing for

patients' symptoms. But it is proving that the theory and preclinical data are correct.

"The last compound is a new one called dimebolin, which is very difficult to judge as to whether it is of clinical benefit, because we have only two positive studies and several others suggest it is of no clinical benefit (at least in AD). This compound also seems to have mitochondrial mechanisms, probably by interfering with the permeable transition pore, which is crucial for regulating mitochondrial function.

"So we have three different compounds, but none are the final solution for the therapeutic problem. We are now at the point where we have very little. First, we should rethink whether we should

use old compounds, which are very cheap and well tolerated. They are a starting point; if you develop a mechanism in more detail, you can then look for compounds that target and improve mitochondrial function much better and that show a better therapeutic response in patients. This is the basic idea."

Starting out with cell and animal models of aging and AD as well as using human blood cells of

AD patients, Professor Müller's group were able to characterise the deficit and demonstrate therapeutic interventions (using oxygen consumption as a tool) at the levels of mitochondrial membrane potential, ATP production, and of different complexes and their functions. Explaining the dynamic regulation of mitochondria that occurs in response to intra- and extracellular cues, Professor Müller continued: "Two larger mitochondria can be divided to make smaller ones. This mechanism is not yet completely understood, but it seems to be important in regenerating and repairing mitochondria. They produce free radicals and they are a target of free radicals, so they need a very active repair mechanism.

"Fission and fusion probably occur because only the small mitochondria can be axonally transported. Piracetam especially has a very impressive effect on fission and fusion, but mainly when it is impaired. In healthy cells, we see very little or nothing. But if the balance between fission and fusion is impaired, for example by over expression of beta amyloid or by the generation of free radicals, then the balance is switched to a large number of small mitochondria (to the fission side). So this is probably an important target, because fission and fusion are regulated by a specific protein whose expression is different between healthy cells and cells which show mitochondrial dysfunction. We are also looking for this protein and the expression rate, because this could be a target for future compounds."

Professor Müller will present 'Therapeutic intervention at the mitochondrial level' as part of the symposium entitled Alzheimer's dementia and mitochondria dysfunction: from pathophysiology to therapeutic intervention, taking place tomorrow morning at 09:00 in room F.

INTERFACE RESEARCH

S.19 Reward as an underlying mechanism of psychiatric disorders Room F Tuesday 8 October 09:00-10:40

A fresh look at disorder classification

A symposium making the case that psychiatric disorders can be composed of various degrees of impairment along basic behavioural dimensions, such as reward, aversion, and memory formation, will take place this morning at ECNP Congress. In an interview ahead of the session, Andreas Heinz (Charité - Universitätsmedizin Berlin, Germany) reasoned for this new framework of understanding, outlining his latest comparative research in reward anticipation across different disorders.

Professor Heinz first defined the problem of current psychiatric assessment as being based on phenomenology, rather than on the mechanisms that underlie them. "In learning from reward, you can distinguish between the anticipation of reward and the feedback," he said. "There is a strong new biological indication from animal models that particularly the response to conditioned cues is reflecting in phasic dopamine signal, and this motivates the subject to go for the reward. There have been studies that have tried to assess this in different disorders.

"What we have done now is to take all the studies we have done in our department together, which is about 120 subjects and 60 controls in different disease entities, to try to see if we can cut across these disease entities to find common correlates and whether there is an alteration in all of them or some of them. As you might assume, it is in some of them. In schizophrenia and alcoholism it is quite plausible, because the underlying neurobiological systems – particularly the dopaminergic reward part – can be altered [in these disorders]. So across these disorders, when you fail to anticipate reward you seem to have an affective correlate, in terms of a negative affect, which is quite plausible because if you don't encode, or react to, reward that is anticipatory then probably you are less motivated and effectively less positive towards things that are going on in your environment."

This back-to-basics approach is reflected in the NIMH's Research Domain Criteria project (RDoC),



"Probably these different disorders can be dissected into different impairments; there can be an impairment in the anticipation and joy of reward and in other disorders this may be complemented by alterations in working memory or reaction to punishment."

Andreas Heinz (Charité - Universitätsmedizin Berlin, Germany)

where disease categories in biological research be based instead upon dimensions of observable behaviour and neurobiological measures. Professor Heinz's research group carried out their proof-of-concept with respect to reward-related behaviour, demonstrating the phenomenological correlate in negative mood states that accompany an impairment of reward anticipation across different diagnostic groups. "We had patients with alcohol dependence and patients with schizophrenia, where the reward

cut across the diagnostic boundaries, such that we use our neuroleptics, our dopaminergic medication across boundaries also. It is a long time ago now that we would say that they are specific for schizophrenia, or that antidepressants only work in major depression."

Professor Heinz was keen to emphasise that, while this is a reductionist approach, it nevertheless is an approach that seems to be propagating great leaps in our understanding of healthy and disordered brain states. "I think we are close to a situation we had about 100 years ago when behavioural analysis and behaviourism got dissatisfied with psychoanalysis," he said. "We had very complex theories of why humans behave in certain ways.

"Then came along the Watsons and Skinners of the 1920s and 1930s, and Pavlov from Russia, bringing simple mechanisms like Pavlovian conditioning and operant conditioning (which is nothing but learning from reward and punishment). With these mechanisms we tried to explain not the whole of human behaviour but a substantial part.

"The idea now in neurobiological research is to carry that over into neurobiological models. We know how people react to Pavlovian and operant conditioning, and we can understand the biological correlates. We can model behaviour in a mathematical way and see to what degree people are driven by this kind of learning. For these basic behaviours we can more easily find a biological correlate than when you try to correlate a very complex behaviour (like somebody feeling persecuted and hearing voices in schizophrenia). But there is probably something

that we can learn from reward and punishment: how does [an individual] attribute importance to environmental cues and does that have something to do with reinforcement learning? Can we mathematically understand that and how would such basic altera-

"It is a long time ago now that we would say that they are specific for schizophrenia, or that antidepressants only work in major depression."

Andreas Heinz (Charité - Universitätsmedizin Berlin, Germany)

Continued on page 8

INTERFACE RESEARCH

S.19 Reward as an underlying mechanism of psychiatric disorders Room F Tuesday 8 October 09:00-10:40

A fresh look at disorder classification

Continued from page 7

tions interact with all of the complex biographical history that this person has?"

Professor Heinz concluded by speaking about his current work, in which he is applying the same approach as his work in reward processing to aversion. "Everybody

assumes that aversion plays a large role in major depression, because they think that people are very sensitive to negative feedback, but it actually looks like it plays an underestimated role in other mental disorders," he said.

"We have recently reported that in schizophrenia, we have found

increased activation in the amygdala in response to aversive cues, which might have a lot to do with social withdrawal. We are looking to do the same approach for learning from aversive experience, again across these diagnostic groups that we have easy access to, to ask is this also a dimension that you can find? This fits

with the idea that there is a lot of treatment of negative affect also across diagnostic borders."

Professor Heinz presents 'Dysfunction of reward anticipation in psychoses, affective disorders, addiction and ADHD - a transnosological correlate of negative mood' as part of the session entitled 'Reward as an underlying mechanism of psychiatric disorders', taking place this morning at 09:00 in room F.

EDUCATION

E.07 Pharmacotherapy and the developing brain: benefits and potential risks Room M2 Wednesday 7 October 09:00-10:40

Thinking a head: Pharmacotherapy and the developing brain

Tomorrow morning will play host to a session that will examine the benefits, and pitfalls, of pharmacotherapy on the immature brain, with particular focus on how compounds may alter the long-term trajectory of an individual's personality traits, social abilities and cognitive performance.

"Nowadays a lot of children are being prescribed medication, and we don't really know what the long-term effects are on the brain development," Liesbeth Reneman (Academic Medical Center, Amsterdam, the Netherlands) told ECNP Daily News ahead of her presentation during the session. "This has never been tested in clinical trials; the latter evidently being for ethical and medical reasons as we did not have the techniques available before..."

As Dr Reneman described, it is now estimated that ADHD affects between 5% and 10% of schoolchildren in the EU. However, use of ADHD drugs, such as methylphenidate increased by more than 50% in last six years in the UK, from 158,000 in 1999 to 661,463 in 2010. This is despite a paucity of data, and in many cases a lack of dedicated licenses

for the use of the drugs in children. "Most medications are registered based on adult data, or preclinical data, and while that has been considered the 'gold' standard, there may be unknown effects when the brain is still in development," she said.

Responding to this need for further study, Dr Rene-



"ePOD further emphasises the importance of ensuring a proper diagnosis when prescribing methylphenidate and fluoxetine to the paediatric population."

Liesbeth Reneman (Academic Medical Center, Amsterdam, the Netherlands)

man and her colleagues have developed the ePOD project, tasked with in-depth investigation of the neurobiological effects of methylphenidate and fluoxetine. "A large part is focussed on preclinical work, on animal work, and then we have clinical trials," said Dr Reneman.

She added: "In the animal work we focus on the brain and on development, and for the methylphenidate work we focus on the dopaminergic

system, because that is where the drug has its primary action. For fluoxetine we focus on the serotonin system."

Using non-invasive MRI assessment – as well as *ex vivo* assessments looking at serotonin transporter density, neurotransmitter levels and other invasive events – the ePOD investigators are particularly interested to see whether the effects of the drugs in adult rats differ from those seen in young rats. This

will then in turn be transposed to human studies.

The methylphenidate study itself is roughly halfway, with a total of 50 children and 50 adults with ADHD planned to participate in the 16-week assignment of either methylphenidate or placebo, thus tomorrow's session will serve as a chance for Dr Reneman to present preliminary results of the pre-clinical studies. "In the methylphenidate trials in animals, we expected to see a stimulating effect on the white matter and cortical grey matter in the brain, [but] we could only partially replicate those findings," she said.

"However these were non-ADHD rats, and the

clinical reports were all in ADHD patients. But we did see some other effects or opposite effects on the grey matter and the volume of the striatum, the brain region on which methylphenidate has its primary action. So there were some small structural changes also."

She continued: "We saw transient effects on the memory task – the object recognition task – and neurogenesis in these young animals. They are very subtle changes, but they are frequently opposite from adults, so we really need the human trial data in which we use the same MRI assessment to correctly interpret these findings.

"The results of our study will provide new insights into the modulating effect of age on methylphenidate and fluoxetine treatment, and increase our understanding of the working mechanism and long-term safety of methylphenidate and fluoxetine in children and adolescents. In the meantime, ePOD further emphasises the importance of ensuring a proper diagnosis when prescribing methylphenidate and fluoxetine to the paediatric population."

'Effects of psychotropic drugs (psychostimulants, antidepressants) on the immature brain – what are consequences for the adult life?', during the session 'Pharmacotherapy and the developing brain: benefits and potential risks', 09:00-10:40, Wednesday 7 October, Room M2.

GPCRs and the pathways to better treatment response

The genomic revolution has given us insight into the byzantine complexity of cellular development and communication processes, and, more recently, multiple risk loci have been identified to be common to various psychiatric conditions. While these findings inform us about cellular and molecular processes, delivering significant advances in medical treatment by selectively targeting these particular loci will represent a challenge that may seem overwhelming. Marc Caron (Duke University Medical Center, Durham, NC, USA) spoke to *ECNP Daily News* about his approach of characterising molecular pathways downstream of receptor activation in order to tease apart the ways in which neurotransmitter activity is mediated, a tried and true approach for drug development, but with a new twist.

The days when we might have considered simple therapeutic targets emerging directly from genome-wide analysis of psychiatric disorders – discovering, say, ‘the gene for schizophrenia’ – are well and truly over. “My reading of this, and I think any cell biologist would agree with this, is that these are diseases of homeostatic control of cell function – the life of the cell,” said Professor Caron. “I call this, to use a crude expression, ‘cell biology gone amok’, because essential cellular processes have been disrupted. Whether you have a mutation in this or that particular gene, [the outcome] also depends on what other genetic makeup you have. That will be the thing to dictate whether you will develop schizophrenia, or major depression, or autism – it is not potentially that particular gene, but how

that particular gene might contribute along with the rest of your genetic make-up.”

While the genetic commonalities between different psychiatric disorders could help us to more finely categorise them, Professor Caron and his colleagues have taken a different approach. “I am not a clinician, so I talk from the position of a basic scientist. The way that these disorders have been treated is basically by treating the systems (serotonin, dopamine, glutamate) where the manifestations are,” he said. “Where do the symptoms emerge? From the contribution of the hundreds or thousands of mutations, and the weakest system flares up, giving defects in serotonin, in glutamate, in dopamine systems. That is what we have been treating, albeit with limited success for many years. Many of these compounds target what we work on, so admittedly it’s a biased view. But many of these drugs target, directly or indirectly, GPCRs [G-protein coupled receptors].”

When a GPCR is activated, it activates heterotrimeric G-proteins and generates secondary messengers or modulates ion channels. Cataloguing the evolution in our

engaging signalling proteins other than G-proteins, Professor Caron continued: “As the receptor remains in an activated form, it gets desensitised – phosphorylated. Then, the phosphorylated receptor binds to arrestin molecules, and eventually the signal, which occurred through the G-protein, is turned off. What we have realised, since initial observations we made in 1996 and later on in around 2000, is that this agonist-ligated receptor complex that is phosphorylated, associated with an arrestin, is capable on its own to activate other signalling pathways. These signalling pathways had not previously commonly been associated with GPCR activation. They are more of the kind that tyrosine kinase growth factor receptors activate, like the MAP-kinase pathway.

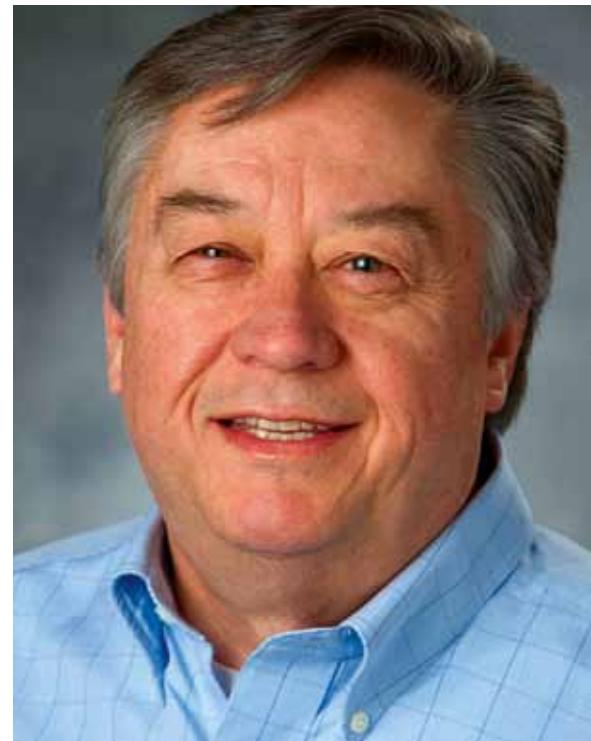
“The interesting thing is that over the years it has been shown that these two signalling pathways have two main properties that distinguish them. G-protein signalling is usually rapid, but it turns off rapidly. Arrestin mediated pathways are slightly slower (although they happen quite fast too) but they are more protracted, lasting for minutes

“Whether you have a mutation in this particular gene or that particular gene, [the outcome] also depends on what other genetic make-up you have. That will be the thing to dictate whether you will develop schizophrenia, or major depression, or autism.”

Marc Caron (Duke University Medical Center, Durham, NC, USA)

understanding of GPCRs over the past two decades, which has led to the discovery that GPCRs may communicate by

and sometimes for hours (when we do this in the lab in cells). Invariably, when it’s been looked at in a handful of



Marc Caron

Photo courtesy of Indiana University, USA

receptors, they appear to serve functional selectivity.”

This is a long departure from the notion that GPCRs simply signal through G-proteins. More importantly, it presents an untapped opportunity to the research community, given that 30 to 50 percent of drugs target GPCRs. “There are a few examples where it has been shown that G-protein activation by a given receptor mediates the beneficial effect of a drug, whereas the arrestin mediates the side effect of a drug, and vice versa,” said Professor Caron. “There are many, many ways to promote functional signalling, the G-protein versus arrestin biased signalling of these receptors is the best characterized. This is now a very well-studied concept.

You can vary the intracellular complements of proteins that interact with these receptors, and they will change the readout from a ligand.”

Continued on page 10

PLENARY LECTURES

PL.05 The future of molecular pharmacology and drug discovery 11:00–11:45 Tuesday 8 October Auditorium

GPCRs and the pathways to better treatment response

Continued from page 9

Creating a genetic mouse model allowed Professor Caron and his colleagues to study the function of arrestins. "These animals did not respond as usual to amphetamine," he said. The response of rodents to amphetamine has been used for decades as a pharmacological model to assess the efficacy of antipsychotics. "All clinically effective antipsychotics to date interact with the D2 dopamine receptor; they interact with lots of other receptors too, but they all must interact with D2 receptors. When we gave amphetamine to the mice that had no arrestin, we saw little to no response to amphetamine. So we started looking to see if there were other potential signalling pathways down-

stream of the D2 receptor.

"We found out that the D2 receptor was capable of engaging a pathway that was not canonical for GPCRs. The arrestin downstream of D2 receptors is capable of interacting with a protein kinase called Akt, which is upstream of another kinase called GSK-3. Some of the antipsychotics appear to inhibit that pathway preferentially, and we have subsequently done genetic manipulations to eliminate various components of the pathway, which mimic the action of antipsychotics."

Professor Caron is currently exploring several ways in which these pathways can be modulated. Using synthesised compounds selective for D2 receptors (in col-

laboration with Jian Jin and Brian Roth of the University of North Carolina at Chapel Hill, United States), Professor Caron's team are studying those that are capable of acting through either the G-proteins or the arrestin pathway. Compounds selective for D2 receptor/arrestin interactions act as antipsychotics in animal models but seem to have lower side effects. "Another approach is that we are eliminating some of the components, like arrestin, in every dopamine D2 receptor-expressing neurons, to try to map which neuronal pathway is really responsive to antipsychotics.

"The last approach is that we have generated mutants of the D2 receptors which are only capable of functioning through the

G-protein or through the arrestin pathway. We are reconstituting these mutated receptors along with the wild-type receptors into genetically modified mice that have had their endogenous D2 receptors knocked out selectively in various neurons. We will be able to tell, both biochemically and behaviourally, what behaviour you get if you have a receptor that can only signal through the G-protein or through the arrestin pathway."

With a cautious reminder that this work is still at the proof-of-concept stage, Professor Caron described how he is coupling it with the expression of a biochemical tool – a component of the ribosomal machinery – that will be expressed along with the receptor in a cell-specific pattern. This will allow the isolation of messenger RNAs transcribed *in vivo* (in mice) in response to the selective activation of one pathway or the other. Hence, this

work will circle back to its beginnings in the hope of identifying novel targets that will be selective for the D2 receptor in the neurons that are mediating the effects of antipsychotics.

Professor Caron concluded: "Thus, our combined approaches should allow us, first, on the basis of the new concept of GPCR functional selectivity, to identify leads to develop more selective and efficacious antipsychotics; second, to identify previously unappreciated cell specific targets for therapy. Is it going to work? I don't know, but we are very hopeful! It seems like an interesting approach worth exploring since all currently available drugs were developed without these new concepts in mind."

Marc Caron will deliver his plenary lecture 'The future of molecular pharmacology and drug discovery in psychiatry,' this morning at 11:00–11:45 in the Auditorium.

Scientific cafés

The scientific cafés at the ECNP Congress in Barcelona provided the perfect networking platform. This year's new and improved concept saw the afternoon symposia flow seamlessly into a scientific café of a matching topic. The session



chair and speakers were also in attendance, allowing colleagues to interact more directly with members of the faculty. The cafés were rich with 'mixing and mingling' from many different sessions, marking an ideal time to exchange thoughts, ideas and conversation in a relaxed setting.

CLINICAL RESEARCH

S.18 Sex-hormone fluctuations in neuropsychiatric disorders Room H Tuesday 8 October 09:00–10:40

Stressing the importance of sex hormones

Gender differences in vulnerability to certain psychiatric disorders at different stages of life is something that is not yet harnessed in preventative strategies. Liisa Galea (University of British Columbia, Canada) spoke about the effects of hormone fluctuations in both women and men in an interview with *ECNP Daily News*, underlining the possibility of improved risk profiles and adjunct therapies that could emerge from improving our knowledge in this area.

What is the broad role of sex hormones in stress?

Most people can understand that the stress axis plays a role in a number of mental disorders. Most people are probably also familiar with the fact that women are more likely to be diagnosed with a lot of stress-related mental health disorders. What people might not be as familiar with is that both the stress and the sex hormone axes (the hypothalamic-pituitary-adrenal axis (HPA) and hypothalamic-pituitary-thyroid (HPT) axes) interact very intimately. In fact while the sex hormone axis will stimulate the stress axis in females, it actually does the opposite in males – so testosterone inhibits the stress axis.

It is complicated, but it might be a reason as to why we see some of these prevalent sex differences in mental health disorders. It is certainly not just a sex hormone axis, there is interplay between the two, and probably a lot of other factors are involved as well. But there are only so many dimensions we can work on at a time. I think that is true that you have to be a reductionist, while we have to be aware that there are so many other factors that play a part. Even if you are looking at cells in a dish, it is probably important whether the cells came from a male or a female, or from a stressed animal or non-stressed animal.

What particular disorders are you addressing at ECNP Congress?

I will talk largely about depression and about a couple of animal models of depression based on the unique profile of females. Men obviously get depressed too, and I will be talking a little about how testosterone can influence the vulnerability to depression in males, but also how it could be used as a possible adjunct treatment. I have a little work in post-mortem tissues as well, looking at depressed males and females across the lifespan and looking at neuroplastic markers in relation to antidepressants and antipsychotics.

You talked about testosterone being a possible adjunct therapy. Does this mean testosterone is protective in depression?



Can you describe the differences in hormone profiles in females and men within different disorders?

Any time you see a sex difference in anything – a behaviour, a trait, a neuropsychiatric disorder – it should suggest that sex hormones are involved either early or late in life, or both. Schizophrenia doesn't actually have a difference in sex profile in terms of incidence, while there are differences in terms of vulnerability in different ages. Men are more likely to get it early and women later. But when you look at women across their menstrual cycle they do report more admission to hospital and they do endure more psychotic symptoms when they have lower levels of oestrogen.

In terms of female depressed patients, I don't know of that many studies that have shown differences across the menstrual cycle. You will see more of a tie to female hormones with more dramatic [hormonal changes], like the post-partum or perimenopausal periods. Post-partum is the period of greatest risk of developing depression in a woman's lifetime. Although there is very little research in this (and this is something I would like to address), it seems as though it is the first pregnancy that is the most vulnerable; the second is a little less vulnerable. Also, the perimenopausal phase (the ten years prior to menopause) is also a time of great risk of developing depression.

In Canada, we recently had a high profile case of a woman that killed her two children and then herself, and she had just been trying to seek treatment for post-partum depression. We are doing a disservice to women, because we are not recognising that it is a very normal reaction; up to 80% of women experience post-partum blues. There are many emotions (and this is not only the case for women) that emerge after childbirth, and there are biological reasons for the greater vulnerability to developing these feelings.

It is important to consider sex as a factor, not just as a confounding factor to covary out. We shouldn't be afraid to look at the differences between men and women, because clearly we are built differently and our brains are different. As it turns out, treatments likely need to be tailored differently to men and women.

Liisa Galea will present 'Stress and sex hormones: effects on mental health', which is part of the session, 'Sex-hormone fluctuations as a vulnerability model for neuropsychiatric disorders', taking place today at 09:00–10:40 in room H.

"If you give male rats a chronic unpredictable stress, you see that male rats that have lower levels of testosterone are more likely to show these kinds of stress-related endophenotypes, both in terms of hippocampal neuroplastic markers in the brain and behavioural outcome."

Liisa Galea (University of British Columbia, Canada)

CLINICAL RESEARCH

S.22 The neurobiology of persistence in antisocial behaviour Room H Tuesday 8 October 14:30-16:10

Benefits in-kind for oppositional defiant disorder

Reducing the likelihood of persistence of antisocial behaviour into adulthood is a clear goal in children diagnosed with disruptive behaviour disorders. Understanding the way in which different individuals process reward can not only help us to gain a fuller understanding of such disorders, but it can also help in the development of personalised therapies. Speaking to *ECNP Daily News* ahead of the congress, Moran Cohn (VU University Medical Center Amsterdam/De Bascule, the Netherlands) described his recent work in this field.

The monetary incentive delay task is designed to reward or

punish subjects responding to a positive, negative or neutral cue, depending on whether they respond within a short time window. In this way, it separates gain anticipation from gain outcome, and loss anticipation from loss outcome. Dr Cohn's investigation involved participants in their late teens (with a mean age of 17.6) who had been arrested before the age of 12 and were then diagnosed with oppositional defiant disorder (ODD) or conduct disorder (CD), who were categorised as either persisting or desisting in this disruptive behaviour.

"What we found was that, when the persistent group was compared to the healthy control group as well as the desisting group (the group who had the problem previously but not anymore), they showed different outcome processing," said Dr Cohn. "Both gain and loss outcome processing were different. The persisters showed higher differential reactivity to the loss outcome and lower to the gain outcome. So it was not a general hypo- or hyper-reactivity, but rather that the direction of the effect was dependent on the condition.

The second analysis dealt with relating these measures to psychopathic traits. "If you look at studies on antisocial behaviour, psychopathy is often used [in adults]. In children we wouldn't say that there are actually psychopaths, because they are still developing. But still, we can see that there is variation in these traits across the population, and that some children are more callous and show less emotional response and are sometimes less empathic. That is one of the dimensions; the other two are the narcissistic or grandiose side of psychopathy, and the impulsive and irresponsible lifestyle. We used the YPI [Youth Psychopathic

"We found that only callous unemotional traits (the pattern of lower emotional responses) was correlated with lower amygdala responses to gaining money."

Moran Cohn (VU University Medical Center Amsterdam/De Bascule, the Netherlands)

Traits Inventory], which is a self report measure used for such personality traits. We found that only callous unemotional traits (the pattern of lower emotional responses) was correlated with lower amygdala responses to gaining money."

In a post-hoc analysis, callous-unemotional traits tended to be associated with persistent antisocial behaviour. Persisters demonstrated higher callous-unemotional traits than both other groups. Using a mediation model with the extracted parameter estimates for responses in the amygdala during gain outcome processing, Dr Cohn's group determined that this mediated the relation between callous-unemotional traits and persistence.

It is possible that individualised therapy needs to take gender differences into account, as well as differences in behavioural traits. Dr Cohn noted that about 10% of the study cohort were female, a figure that is typical in epidemiological studies. He continued: "Our department is involved in a larger European project where they are going

to focus on girls' delinquency and disruptive behaviour, because there is not so much data about it. We do think that it is a serious problem and there seem to be some different correlates there. Abuse is quite common in boys [as well as girls]; within the cohort there was a large proportion of those who had experienced abuse and other kinds of childhood adversity.

"What I think is a really interesting development is that previously most studies have focussed on what these children cannot do or how are they dysfunctional, and I think it would be really interesting to look at what kind of incentives these kids are more sensitive to. It grabs my attention that money, for example, seems to be quite relevant to them. We do have to be sensitive and not impose our view of what should be relevant to them in trying to change their behaviour. I hope that these types of studies can help to inform us of other types of reinforcers that are relevant to them. Of course, there are other options, such as neuro-feedback intervention, but I wouldn't say that this will be the solution to all of these problems."

"What I think is a really interesting development is that previously most studies have focussed on what these children cannot do or how are they dysfunctional, and I think it would be really interesting to look at what kind of incentives these kids are more sensitive to."

Moran Cohn (VU University Medical Center Amsterdam/De Bascule, the Netherlands)

Moran Cohn will present 'Neuroimaging of fear conditioning and reward/punishment anticipation in the persistence of anti-social behaviour' as part of 'The neurobiology of persistence in antisocial behaviour', which takes place today at 14:30 in room H.





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Maiden voyage for new junior scientist networking venture



"Believe your own results. Do experiments to ask questions. Don't do experiments to find support for theories, because almost all of the theories we have will end up being wrong."

David Nutt (Imperial College London, UK)

The Hard Rock Café in downtown Barcelona was filled with junior scientists on Sunday night for the first ever ECNP 'Science on the Rocks' evening organised by the newly-appointed Junior Members Advisory Panel (J-MAP).

This first outing for Science on the Rocks was met with a packed-out attendance of junior scientists eager to meet and greet their fellow colleagues, and also gather some insight from guest speaker David Nutt, the Edmond J Safra Chair of Neuropsychopharmacology and Director of the Neuropsychopharmacology Unit in the Division of Brain Sciences at Imperial College London, UK.

With an informal and close-knit atmosphere, Professor Nutt and his audience grabbed a drink from the bar before gathering around the tables to discuss some of the challenges and revelations he has learned from his own journey thus far.

"Science is an enormously complex and difficult career trajectory," he began, before

underlining the importance of events like Science on the Rocks for sharing highs and lows with fellow early-career scientists, and building a basis for more collaboration at future ECNP Congresses. "We're hoping that an exercise such as this will help you get to know each other, in the context of ECNP, and encourage you to come in the future years."

From the outset, Professor Nutt kept an open exchange flowing with the audience, gauging personal opinions and quizzing the attendees as to their favourite or most self-

influential scientist, which, following one suggestion of Sigmund Freud and his work with cocaine, sparked a recount of Professor Nutt's first working experience in the late 70s.

"Freud's first experiments were trying to understand the mechanisms of cocaine, and apply it," he said. "And the first experiments of my scientific career back in 1979 were to give rats cocaine... and the reason for this is if you keep giving rats cocaine, you desensitise them, and eventually have seizures. I was using these cocaine-sensitised

seizures as a model for electroconvulsive therapy (ECT)."

He continued, stressing that while cocaine-induced seizures did cause some biological changes, some of which mimic ECT, unfortunately the other damaging effects of cocaine precluded its use. But speaking of similar work with benzodiazepine for seizure, in which it worked exactly opposite of how it was expected to, Professor Nutt underlined the importance of continuing

to iterate our knowledge, no matter if that is by actually getting your theory wrong. "In a way... you are right," he joked.

Another message he was keen to hammer home was to be perseverant with research. Roadblocks faced may come in many formats, be they simple errors in hypotheses, or even more unfortunate realities such as commercial rivalry or the wrongful accreditation of discoveries. But great lessons learned from the past can be a guiding light in a wider scientific journey that could be actually remarkably simple: we must always strive to know more.

With this in mind, Professor Nutt underlined the importance of confidence and exploration in research goals, saying: "Believe your own results. Do experiments to ask questions. Don't do experiments to find support for theories, because almost all of the theories we have will end up being wrong."



ECNP INITIATIVES

ECNP Travel and Poster Awards

Congratulations!

ECNP Travel Award and ECNP Poster Award winners: MONDAY

Travel Award winners

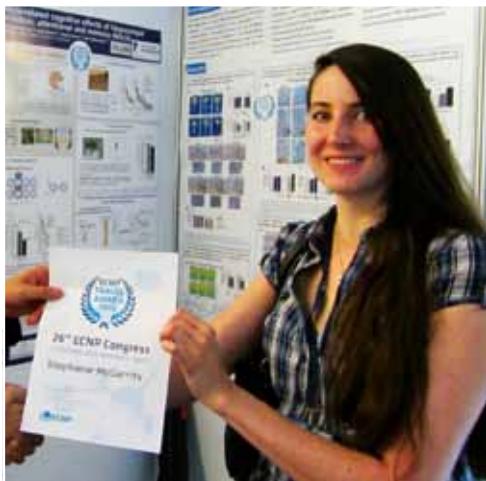
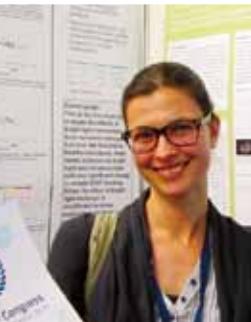
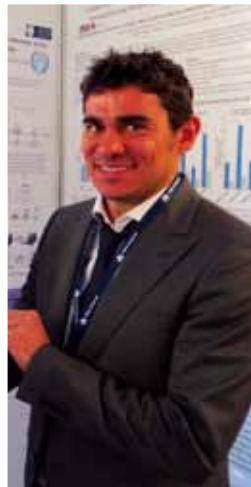
Elzbieta Kostrzewska
Andrea Di Francesco
Emily Saunderson
Beata Horvath
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Valentina Licheri
Marta Rysz
Anton Lievkh
Brenda Elvira Munk Mc Mahon
Anne Uhlmann
Julius Burkauskas
Rotem Saar-Ashkenazy
Stephanie McGarry

P.1.a.004
P.1.a.008
P.1.a.017
P.1.b.008
P.1.f.003
P.1.g.040
P.1.g.058
P.1.g.082
P.1.i.007
P.1.i.026
P.1.j.004
P.1.j.020
P.1.j.026

Poster Award winners

Floor van Heesch
Sylvie Bourgoin
Ana Ricobaraza

P.1.f.003
P.1.g.017
P.1.g.041



INTERVIEWS

Incoming President

Interview: Guy Goodwin



On Monday afternoon, Guy Goodwin (University of Oxford, UK) stepped into the role of ECNP President, placing him at the helm of the college's future visions and ventures. To that end, *ECNP Daily News* caught up with Professor Goodwin to ask him what highlights he feels make the yearly ECNP programme so special, and what perspectives and plans will shape the next chapter of the ever-evolving ECNP story.

What do you think makes ECNP, its yearly congress and the other calendar of events so attractive to members and attendees? Are there particular highlights you think stand out?

The annual conference is quite simply the best of its kind. It brings together scientists, clinicians and industry to focus on treatment innovation in brain diseases and particularly psychiatric diseases. It breaks down barriers and it will never be tribal. Furthermore we have focused a lot of our recent effort on the involvement of younger people in research through the Nice workshop and clinical practice through the ECNP schools.

In a similar vein, how do you think the college, and the congress, has evolved in the past few years?

The last three years has seen a lot of changes. We have been galvanized by the leadership of Yossi Zohar and the management of Alex Schubert. We have also had a highly active and supportive executive council and really outstanding scientific leadership of the Scientific Programme Committee by Sven Ove Ögren, Michel Hamon and now, Wim van den Brink.

Now that you are stepping into the role of ECNP President, what is your vision for the future? Are there specific topics and initiatives that you are particularly keen to see evolve?

My vision is a shared vision that the Council of ECNP have evolved themselves in recent years. We know where we want to position ourselves. We are moving on from a narrow focus on pharmacology because

"The future of ECNP depends largely, if not entirely, on the people who join it. We want an involved membership, and to achieve that we will not just listen to what people want, we want to take advantage of your talents too."

Guy Goodwin
(University of Oxford Department of Psychiatry, UK)

neuroscience applied to neurology and psychiatry will inform other physical modalities of treatment and psychological interventions. Psychological interventions in particular have relied too much on folk psychology and the conventions of traditional psychodynamic psychotherapy. There is tremendous potential to unleash new ways of training the brain, if we understand better the underlying biases that contribute to functional disorders. Moreover, if we can harness the power to connect through the internet, psychological interventions could be made available widely and cheaply.

Thinking about the structure of ECNP, it was started to create a rela-

tively small annual meeting, but the objectives are now more ambitious. The annual congress remains the heart of what we do but we believe we have a responsibility to create new pillars that support our objectives for research and clinical training. ECNP Workshop for Junior Scientists in Nice has been an extraordinary success for junior scientists, and the work we see presented there feeds the annual congress. The ECNP Schools in psychiatry demonstrate and promote good practice across Europe. Again our focus is on the brightest and the best young people in the different countries who will be the leaders of their discipline in the future.

Finally, the ECNP Networks are key to facilitating European funding of research in applied brain science. They are in a nascent phase. Some, like the Child and Adolescent Network have been very successful. Others have had difficulties because the FP-7 calls have not been right for them, but we are learning how to manage this. It is the legacy policy of the late Yves Lecrubier, and a critical initiative which addresses the central need to promote investment in brain science at the European level. While this can only be justified by exceptional scientific ideas, it must also receive a higher strategic importance from politicians and policy makers. Hans-Ulrich Wittchen's work on the cost and burden of brain diseases for the European Brain Council is seminal in underpinning the argument that research spending should more nearly reflect the magnitude of the clinical and societal problem

of mental and neurological disease. How we communicate that message is a challenge that takes many of us out of our comfort zone. However, achieving such communication is critically important.

In closing, is there anything you would like to communicate directly to this year's ECNP Congress audience?

The future of ECNP depends largely, if not entirely, on the people who join it. We want an involved membership, and to achieve that we will not just listen to what people want, we want to take advantage of your talents too. So become active members of ECNP: we promise a great ride!

Early triggers for mental disorders can be prevented

Many mental disorders are triggered in utero or in early life and are largely preventable in terms of incidence and severity if there is due attention to care in pregnancy, birth and early years. This is the key message of Celso Arango, Associate Professor of Psychiatry at Marañón General University Hospital, CIBERSAM, Madrid, Spain, who will be speaking this morning in a press briefing session that will explore the psychiatric classification and diagnosis of child and adolescent disorders.

Noting that approximately 70% of mental disorders start in utero, early childhood and early adolescence, even if diagnosis does not occur until adulthood, Dr Arango commented: "The first psychotic symptoms might appear at age 25, but these are developmental disorders and the aetiology occurs at a very young age. For example, anxiety disorders might arise due to inadequate attachment to parents from birth."

He added that supporting studies have shown that pregnant mothers who are under stress or experience infections

have offspring that are three times as likely to develop schizophrenia 30 years later.

But for the most part, many mental disorders, for example, ADHD, schizophrenia, bipolar and unipolar disorders, and Obsessive Compulsive Disorder, which are caused by early life events, are preventable in terms of incidence and severity, Dr Arango underlined. "Good healthcare during pregnancy will contribute

to the prevention of mental disorders," he said.

"Women who avoid smoking, drinking, aim to avoid stress, minimise infections and have good care in labour, in particular minimising risk of hypoxia, will definitely show a reduction in prevalence of mental disorders. This is something we can prevent in many cases and if they do occur then they could be less severe."

Dr Arango went on to note that unlike many fields of medicine,

prevention is very effective in psychiatry, and if intervention is given early on then it is not only efficacious but cost effective too. Indeed, studies presented by London School of Economics show that early intervention units for children and adolescents with psychotic symptoms eventually have fewer psychotic symptoms and lower transition to psychosis later on.

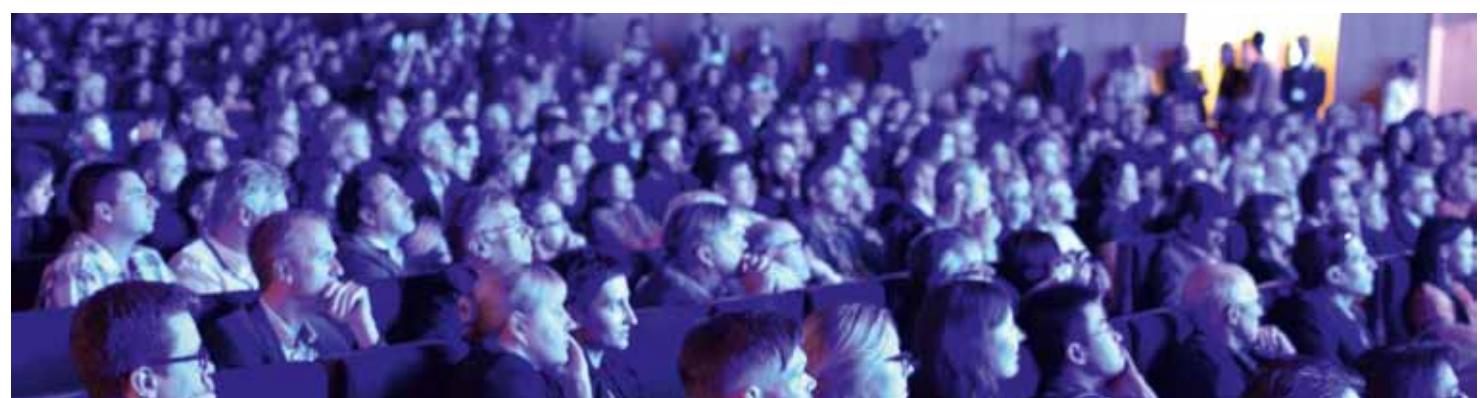
Regarding pharmacological interventions for paediatric mental disorders, Dr Arango stressed that drugs for ADHD are some of the most effec-

tive drugs in psychiatry. For instance, the effect size of ADHD drugs is three times the effect size of anti-depressants, or twice the effect size of drugs to treat schizophrenia or bipolar disorder. "The drugs we use to treat ADHD are far more efficacious than drugs in oncology and cardiovascular disease," he said.

Information contained in press releases are provided by the abstract's author, and reflect the content of the studies. They does not necessarily express ECNP's point of view.

"Women who avoid smoking, drinking, aim to avoid stress, minimise infections and have good care in labour, in particular minimising risk of hypoxia, will definitely show a reduction in prevalence of mental disorders. This is something we can prevent in many cases and if they do occur then they could be less severe."

Celso Arango (Marañón General University Hospital, CIBERSAM, Madrid, Spain)



ECNP Wordsearch**ECNP Wordsearch**

This year's new and improved concept will see the afternoon symposia flow seamlessly into a scientific café of a matching topic. The session chair and speakers will be asked to attend, and you will also

have the chance to mix and mingle with other participants who just attended the same session.

See if you can find the names of the fifteen scientific cafés taking place at ECNP Congress 2013. Words may run backward, forward, up, down, or diagonally and always in a straight line.

O	D	N	C	U	D	U	E	M	N	S	N	S	N	R	N	I	Y	I
O	I	E	O	N	O	M	E	N	C	L	A	T	U	R	E	R	T	B
Y	T	R	D	A	L	I	H	T	C	M	O	S	I	L	O	J	I	R
H	E	S	A	T	A	R	L	C	Z	A	N	I	N	E	Y	R	V	A
N	Y	C	S	L	N	A	M	O	I	B	U	T	N	S	I	R	I	I
D	T	H	T	C	O	R	I	B	I	H	A	N	M	U	M	L	T	N
P	C	I	A	I	I	P	I	N	D	N	D	E	B	I	P	O	C	I
N	P	Z	A	E	T	T	I	N	O	A	D	I	N	O	D	G	E	M
R	U	O	I	V	A	H	E	B	L	A	I	C	O	S	I	T	N	A
N	S	P	T	E	T	B	Y	N	C	O	C	S	L	N	I	I	N	G
P	I	H	T	Y	U	S	A	S	E	E	T	R	A	D	Y	I	O	I
E	E	R	C	D	P	D	T	M	I	G	I	O	I	T	S	L	C	N
N	N	E	V	E	M	N	A	N	N	A	O	I	C	N	Y	H	N	G
O	O	N	L	N	O	E	A	C	T	I	N	N	O	O	O	M	I	L
A	N	I	A	S	C	L	N	I	I	N	C	U	U	R	O	A	A	J
I	P	A	O	A	B	M	C	I	M	S	A	J	D	M	O	E	R	L
E	Y	M	O	O	D	O	W	N	S	Y	N	D	R	O	M	E	B	C
T	B	U	S	S	Z	C	B	T	P	S	Y	C	H	O	S	I	S	P
O	O	H	U	E	C	G	P	C	S	H	A	I	D	D	C	C	O	N

Answers for yesterday's word jumble

Main component of amyloid plaques A B E T A

Frontal lobe region linked to speech production B R O C A

Inner ear structure important for hearing C O C H L E A

Discoverer of classical conditioning P A V L O V

"One cannot step twice into the same river" H E R A C L I T U S

Almond shaped nuclei, part of the limbic system A M Y G D A L A

A large division or section of the brain L O B E

Partial or complete loss of memory A M N E S I A

Star-shaped glial cell A S T R O C Y T E

ECNP CALENDAR OF EVENTS

2014

6-9 March	ECNP Workshop for Junior Scientists on Europe, <i>Nice, France</i>
4-6 April	ECNP Seminar, <i>Veles, Macedonia</i>
6-11 April	ECNP School of Child and Adolescent Neuropsychopharmacology, <i>Venice, Italy</i>
8-10 May	ECNP Seminar, <i>Croatia</i>
18-21 October	27 th ECNP Congress, <i>Berlin, Germany</i>
14-16 November	ECNP Seminar, <i>Serbia</i>

2015

29 Aug-1 Sept	28 th ECNP Congress, <i>Amsterdam, The Netherlands</i>
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2016

17-20 September	29 th ECNP Congress, <i>Vienna, Austria</i>
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2017

2-5 September	30 th ECNP Congress, <i>Paris, France</i>
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2018

6-9 October	31 st ECNP Congress, <i>Barcelona, Spain</i>
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2019

7-10 September	32 nd ECNP Congress, <i>Copenhagen, Denmark</i>
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For regular updates on ECNP initiatives please visit:

www.ecnp.eu and www.ecnp-congress.eu



Stay informed, stay connected

In addition to this newsletter, ECNP offers a variety of other news and media channels designed to keep you at the forefront of our latest activities, initiatives and developments:

Websites (www.ecnp.eu | www.ecnp-congress.eu)

The ECNP websites provide a myriad of information on matters related to our organisation. Follow links to sign up for e-bulletins and news updates.

Message from the President

A monthly personal e-message from the President.

President's Blog: http://www.ecnp.eu/publications/presidents_blog

E-news

Monthly overview of latest news within ECNP.

Talk of the Month

Short video talks by distinguished scientists, aimed at making ECNP science more accessible to the general public.



Facebook (www.facebook.com/myECNP)

Find ECNP on Facebook to subscribe to the news feed and join meeting 'events' throughout the year.



Twitter (twitter.com/ECNPsweets)

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