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ECNP
DAILY NEWS

Thank you all for your enthusiasm and continuing support

The 25th anniversary ECNP Congress has seen the meeting of over 5,000 scientific minds in what has so far been an outstanding few days. Delegates came from across the globe to share knowledge and expertise, to forge and build relationships, and to enjoy the fun in the city of Vienna as well.
Official figures indicate that 72% of delegates have come from Europe, 12% from Asia, 7% from South America, 5% from North America, 3% from Africa, and 1% from Australia and New Zealand (statistics are rounded off and based on the number of registered participants until Tuesday 15 October).

Deep brain stimulation (DBS) in psychiatry: a decade of experience Tuesday 16 October 14:40 **Hall D**

A stimulating future for DBS

This afternoon's programme will feature a session dedicated to the use of deep brain stimulation in psychiatric applications, offering delegates a chance to look at how this technology has been incorporated into the field over the last 10 years.

Damiaan Denys

"We implant electrodes in the human brain, and these electrodes end up in a specific brain area, a brain target, that is associated with the particular disorder," session presenter Damiaan Denys (Academic Medical Center, Amsterdam, The Netherlands) explained *ECNP Daily News*.

"And with these electrical currents we can modulate brain targets and the circuitry that are related to these particular targets. It is a technique that is pretty old – it has been used for twenty to thirty years in Parkinson's disorder neurology, in general for movement disorders. Worldwide, in neurology, approximately 85,000 patients have been implanted in the last 25 maybe 30 years."

Owing to observations that some Parkinson's patients undergoing DBS in the 1990s exhibited improvement in their co-existing obsessive compulsive disorder (OCD) symptoms, the use of DBS for OCD began to pick up momentum. "It all started in 1999 with one paper in the Lancet where three patients with obsessive compulsive disorder were implanted."

During the last decade, people have started to implant electrodes in patient with unresponsive treatment-refractory OCD. "You have to imagine that these patients are very, very ill," said Professor Denys. "They are doing this for 10-20 years, and for approximately 16 hours a day they are involved in all of these compulsions, and completely unable to live. They do not respond to any treatment. Not to drugs or behavioural therapy whatsoever."

Despite the increase in DBS use for

Continued on page 4

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.

Professor Freund will be one of the distinguished plenary lecturers featured at this special 25th anniversary congress, thus *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 would like to emphasise 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 synchronizing 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 septal-hippocampal 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[3]. 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.[2] 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.

Tamás Freund

Professor Freund will give his plenary lecture 'Operational principles of inhibitory circuits in the cerebral cortex' at 11:00 on Tuesday 16 October in Hall D

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Immunotherapeutics for Alzheimer's disease approaching late stage clinical development Wednesday 17

Amyloid reconsidered: The promise of i

This morning's programme plays host to a session that will take a closer look at the latest immunotherapies for Alzheimer's disease. As presenter and co-chair of the session, Norman Relkin (Associate Professor of Clinical Neurology and Neuroscience at Weill Cornell Medical College) spoke to *ECNP Daily News* about recent advances in Alzheimer's disease (AD) research. Some of the most exciting developments in this field have been in immunotherapy, which is showing great potential in addressing what he refers to as "the single most important problem facing us in the coming century."

AD research has provided and continues to provide invaluable information in predicting, diagnosing and treating the disease. For Professor Relkin, a key catalyst was the first successful use of immunologic therapies on amyloid plaques in animals. He explained: "For the past 30 years, the field has struggled to figure out a way to either remove or prevent the accumulation of amyloid. Until the early 1980s, no one had even been able to dissolve amyloid in a test tube; it was such as insoluble protein. And yet in 1999, Dale Schenk showed that immunising mice with amyloid-beta produced antibodies that were able to remove plaques from the brain very rapidly. This was a startling finding – the first time that anyone had shown that an element of AD pathology could be altered by a man made intervention. That really jump-started the field."

The journey from animal to human treatments has seen inevitable failures that have nevertheless been constructive in developing a real understanding for Alzheimer's disease mechanisms, which in turn has provided promising targets for further research. New trials using humanised mouse monoclonals, which fail to prevent disease progression whilst succeeding to clear amyloid plaques, indicate that this might not be the right target, as Professor Relkin reasoned: "The message that we are getting from the completing phase of monoclonal immunotherapy trials is that removing plaques from the brain is not therapeutically effective, and there are three theories as to why that is. The first is the somewhat pessimistic view that the amyloid hypothesis was wrong, and that the accumulation of amyloid in the brain is more or less a meta-phenomenon and that other pathology is responsible; people that believe this are turning away from the amyloid hypothesis and focusing on other therapy – also immunotherapy – that focuses on a much earlier stage of development, targeting the tau protein instead."

Returning to amyloid, Professor Relkin continued: "The second view is that the medicine was correct, but it was applied at the incorrect stage of the disease. These investigators are

Plenary lecture: 'Opioid systems: probing molecular processes of brain function 16 October 13:30 **Hall D**

Shedding light on opioid systems in the brain

Marking the final plenary lecture in this special 25th anniversary calendar, Brigitte L Kieffer (Institut de Génétique et de Biologie Moléculaire et Cellulaire Parc d'innovation, Illkirch Cedex, France) will take to the stage this afternoon to discuss her seminal work in the field of opioid receptors.

Professor Kieffer's 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 level 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 this Congress will focus 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.

"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 antidepressant 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 pre-clinically established targets; two, parallel brain imaging and genetic analyses in genetically modified animals and human patients for translational research."

Professor Kieffer will give her plenary lecture 'Opioid systems: probing molecular processes of brain function' today at 13:30 in Hall D.

"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 antidepressant mood disorders."

Brigitte L Kieffer (Institut de Génétique et de Biologie Moléculaire et Cellulaire Parc d'innovation, Illkirch Cedex, France)

October 9:00 **Hall GH**

mmunotherapy in Alzheimer's disease

taking the same antibodies and will use them in a new generation of prevention trials. The government has just announced a 100 million dollar initiative to do such a trial, and I will talk about that briefly."

Perhaps the predominant innovation in recent years is the notion is that soluble oligomers, not plaques, form the toxic species in the disease and are responsible for brain dysfunction, as Professor Relkin explained: "The third view as to why removing plaques is ineffective is that the concept of removing plaques is in itself inherently wrong. I use the analogy of the battle of Gettysburg, where there were a huge number of people killed; to this day, people still find bullets on the battlefield: if you dig them up now, it doesn't change the outcome of the war. And plaques are like that – they are a sign of pathology that involved amyloid many, many years ago. Indeed, when you try and remove plaques, you actually stir up more of these toxic species." This interesting proposal has garnered much support in the research community, and certainly offers a plausible explanation for the lack of correlation between amyloid accumulation and dementia, as well as the continuing progression of the disease following amyloid removal.

"This is the year of immunotherapy."

Norman Relkin (Associate Professor of Clinical Neurology and Neuroscience, Weill Cornell Medical College, New York, USA)

Professor Relkin will be speaking about the present state of immunotherapy research in the TEM symposium. He summarized its main theme, saying: "This is really the year of immunotherapy. There are two trials using humanised monoclonals, and a third one – the trial that I lead – is an intravenous immunoglobulin (IVIG)." Speaking of the results of the first two trials, which were completed just prior to ECNP congress, Professor Relkin said: "The IVIG trial will be completed in December, with results coming out in the spring of 2013. The other two immunotherapy trials using monoclonal antibodies have already announced their results and both were negative in terms of failing to achieve their primary efficacy objectives. But the data is not all negative, particularly for solanezumab. There are some interesting nuances that I will discuss in my presentation."

Professor Relkin expressed his understanding of the distinct effects of IVIG and monoclonal antibodies treatments, saying: "I believe that the distinction between the human IVIG immuntherapies and the humanised mouse monoclonals is that the human version actually targets the oligomers, and it does not actually prevent fibrils from forming; indeed, it might actually promote fibrils as a protective measure in the disease." Referring to the new therapeutic approaches that echo the brain's method of compensation for an excess of soluble amyloid, he said: "The human body actually seems to react to the disease in the opposite manner to what the first generation of immunotherapies tried to achieve, and we are hopeful that these new therapies are going to make a difference in terms of efficacy."

Professor Relkin will give his presentation 'IVIG treatment for patients with Alzheimer's disease' as part of the session which he will co-chair: 'Immunotherapeutics for Alzheimer's disease approaching late stage clinical development'; Wednesday 17 October, 09:00, Hall GH.

EPA session: Unmet needs Tuesday 16 October 09:00 **Hall F2**

Meeting the requirements of mental health disorder

The unmet needs in the treatment of schizophrenia, unipolar depression and alcohol dependence will be evaluated this morning in a special session by the European Psychiatric Association (EPA). Tackling this issue in schizophrenia will be István Bitter (Chair of the Department of Psychiatry and Psychotherapy at Semmelweis University, Budapest, Hungary), who spoke to *ECNP Daily News* to describe which unmet needs he feels are most pertinent.

He said: "The first should maybe be unmet needs in the treatment of symptoms of schizophrenia. In spite of all of the developments, we still have a lot of patients who do not respond to available medication.

"They still have positive symptoms such as hallucinations and delusion, and even more patients have negative symptoms such as affective flattening, lack of initiative and social isolation, social problems in life and cognitive decline."

Furthermore, he added that suicidal behaviour is in fact part of the symptomatology of schizophrenia, with very few medications that can combat this suicidal ideation. This in turn means that suicide contributes to the very high death rate (often early in life) associated with schizophrenia. These high mortality rates – stemming partly from suicide and partly from the high level of co-morbidities in patients – clearly represent another unmet need.

"Another major group of unmet needs in patients with schizophrenia is related to social adjustment and social disability which develops in association with schizophrenia," said Professor Bitter. "Here we are talking about major needs such as a lack of proper accommodation or food, and some of them are in need of care, especially in daytime activities that they cannot spend their time doing as they used to.

"Many times they have a very high level of psychosocial distress within the family or outside of the family, and a big issue is the usage of drugs. There is a need to prevent the usage of drugs and alcohol in these patients."

Professor Bitter added that since schizophrenia is a disorder that starts at an early age, unfortunately patients will often drop out of high school or university education. Similarly, many are unemployed, and without government benefits to help this only exacerbates the issue.

"So one can have a very long list actually," he said. "Those who are bit older might have children, and they need help with childcare because sometimes they are unable to cope with these problems. All of these issues, either with symptomatology or social problems, are complicated with the relapsing course of the disorder, and one of the unmet needs is that the medication which we can prescribe nowadays are not taken, but even if taken the chance of a relapse and hospitalisation is still very high."

Offering his thoughts on the most prevalent unmet need, Professor Bitter said: "The largest need is psychosocial support and intervention systems, which is in place in some countries – some richer and more developed countries – but still with very major differences in access to those services

> *"Even recently in the European Union (EU) there are countries where those psychosocial services are extremely under developed, and access to them is really the privilege of very few patients suffering from schizophrenia."*
>
> *István Bitter (Semmelweis University, Budapest, Hungary)*

He added: "Even recently in the European Union (EU) there are countries where those psychosocial services are extremely under developed, and access to them is really the privilege of very few patients suffering from schizophrenia."

Given this limitation in psychosocial support, what does Professor Bitter feel is the main hindrance in improving this facility throughout the EU?: "I think it is twofold," he said. "One, the money is a major issue: This is a very costly service but certainly once there is a well developed and well functioning system it is not that costly anymore, because you then may reduce some other services such as hospital beds or prisons, for example (which happens in many countries where psychiatric patients with schizophrenia end up in prisons instead of ending up in health care). "

For countries that have more financial constraints, it follows that a different approach needs to be undertaken when setting up psychosocial support, as it simply isn't feasible to model this system on other countries with much higher financial status: "To transfer this knowledge and this system is hopeless, for financial reasons, but developing others systems would promote initiative and the acceptance that maybe a country with a lower gross domestic product or financial resources will need a different type of service," said Professor Bitter.

He added: "It's not the same as importing a new anticancer or anti-schizophrenia medication which is the same worldwide."

Remaining on the topic of medications, Professor Bitter gave his thoughts on the current use of second generation antipsychotic drugs for schizophrenia: "The second generation drugs are now available in most countries within the European Union, so the situation is much better than a couple of years ago since most of them are now off patent, i.e. they are generally much cheaper than they used to be.

"What we face now are a couple of issues. One is that, unfortunately, we hoped they would be much more efficacious against negative symptoms and cognitive symptoms than they in fact are. Another issue is that still we have a major problem with the compliance, or as we say it today the 'adherence' of patients. They stop taking their medications sometimes after a few days after they are discharged from hospital, or after they get a prescription, and certainly it seems that second generation of drugs are much better in this regard; patients are taking these drugs longer in real life than the first generation drugs. "

He continued: "But the length of treatment is usually not longer than the average of a few months. We are talking basically about lifelong disorders for many patients, so unfortunately while there is a problem that the new delivery methods of these second generation medications – which are not new, but newly developed – might help, certainly they are much more costly than the tablets or liquids that are off patents already."

Professor Bitter will give his presentation on the unmet needs in the treatment of schizophrenia during the EPA session 'the true unmet needs in the therapeutic armamentarium seen from a clinical perspective'; Tuesday 16 October, 09:00, Hall F2.

Deep brain stimulation (DBS) in psychiatry: a decade of experience Tuesday 16 October 14:40 **Hall D**

A stimulating future for DBS

Continued from page 1

OCD patients during the last 10 years, Professor Denys believes a lot more evolution could have been done in this time. He said: "If you just look at the progression that we made in psychiatry with deep brain stimulation, it is a bit disappointing. I think, on average, no more than 120 patients have been implanted worldwide. So the progression is very slow, which is not a bad thing, because of course it is ethically sensible to start a new treatment with a lot of reflection and so on, but on the other hand the cases that we have done are very limited."

He added that while these patient numbers are low, the interest in performing DBS in psychiatric disorders has mounted, with a wide-ranging number of applications that are beginning to emerge. In fact, in the last decade people have rapidly transferred the technique from OCD to major depressive disorder.

Professor Denys continued: "Then came addictive disorders, like heroin addiction and alcohol addiction, eating disorders like anorexia nervosa and probably obesity. And every six months or each year there is a new indication for brain stimulation in psychiatry. The number of indications – the number of disorders – has exponentially grown. It grows all the time, grows very fast, but it is still limited to a few cases. Five, six cases, 10 cases, and in the best circumstances 50, 60 or 100 cases."

He added that this observation was from a clinical perspective, but from a research perspective something very interesting has been occurring. He explained: "This may even, in my opinion, change the whole paradigm, the whole scientific perspective that we have in psychiatry. In the 80s and 90s, psychiatry, particularly neurobiology, was dominated by pharmacology. It was all about the serotonin system, dopamine system, interaction between noradrenalin and dopamine and serotonin, and impact of drugs on receptors and so on.

> *"With these new deep brain stimulation techniques, we suddenly see (and although we still talk about a limited number of patients, the research side is different) that we can change complex symptoms within milliseconds."*
>
> *Damiaan Denys (Academic Medical Center, Amsterdam, The Netherlands)*

"The whole research and treatment of pharmacology, as well the imaging, was centred around the main hypothesis that neurotransmitters were disturbed in psychiatric disorders. With these new deep brain stimulation techniques, we suddenly see (and although we still talk about a limited number of patients, the research side is different) that we can change complex symptoms within milliseconds. For

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 Melinda Spitzer told *ECNP Daily News*.

> *"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)*

Melinda has been working for the ECNP office for four years, but this year she has taken 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 Melinda.

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."

In this 25th year, the ECNP Office has 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's a main goal. We've improved a lot in marketing (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."

The ECNP Plaza has been packed with participants looking for a central place to meet up and network. Similarly, the breakfast meetings have been 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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example I am able to reduce anxiety in these patients on the condition that I have good parameters with my electrode I can see reduction within one or two seconds – a huge reduction in anxiety of over 80/90 percent. And in a wide range of different symptoms you can see these effects. Changes in mood, changes in anxiety, changes in obsessions."

Professor Denys continued, outlining that these extremely rapid changes were found to not be limited to one symptom. Intriguingly, OCD patients treated with DBS exhibited changes in mood, which has been a very critical observation: "It questions, actually, the validity of our psychiatric diagnosis," he said. "Similarly, when we treat patients with major depressive disorder, they have less obsessions, and they are not really interested in ruminating these thoughts."

As such, Professor Denys believes that these findings may change our perspective in psychiatry, particularly from a neurobiological viewpoint in which a shift to more rapid oscillation of brain areas can be achieved. He added: "So is it global dynamic brain activity that has to become much more important? Is the connectivity between brain areas? Is the phase activity between oscillations of neuronal cell groups? So it's more global, it's more dynamic and it's faster. And this is the new perspective. In my opinion this will lead to new techniques that we need to develop."

Looking to the future for the field, Professor Denys referred to a shift in direction that we may need to undertake. He said: "A few hundred cases with a wide range of indications? This research aspect shows that we should maybe change our focus. Instead of going to neurotransmitters, focus more on global brain activity. It is much more relevant for psychiatric disorders than neurotransmitters."

Harking back to the huge difference in numbers between DBS use in neurology and in psychiatry, would it be fair to suggest that there is still a great deal of reluctance in believing DBS will confer a benefit for psychiatric disorders?

"I think you are right – there is a reluctance within the psychiatric field," he replied. "The idea of putting electrodes in the brain is completely new. I know psychiatry has become much more neurobiological in the last 20-30 years, but still there is a group of people and they are really afraid that we put way too much emphasis on the brain side.

"Of course in neurology there was no discussion at all. It is quite clear that it might help. It's much more on the somatic side, on the real medicine side. This means that there is no reluctance at all to put an electrode in the brain."

He continued: "But psychiatrists, I think, doubt much more whether it is really important based upon the discussion between the brain and the mind. They are much more on the mind side, and they are afraid of making it too neurobiological. And the second thing is that, in general in psychiatry, people are more reluctant to use invasive techniques."

However, overall it seems that deep brain stimulation has a promising future in psychiatry, and there is great hope that in the next decade we will be able to extrapolate this technology out for the benefit of even more patients.

'The mechanism of action of deep brain stimulation: preclinical and clinical evidence', as part of the session 'Deep brain stimulation (DBS) in psychiatry: a decade of experience'; Tuesday 16 October, 14:40, Hall D. The session will be immediately followed by a DBS café at 16:10 in foyer GH.

Is depression a disorder of reward? Tuesday October 16 14.30 **Hall E**

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, delegates will hear this afternoon. Catherine Harmer (Professor in Cognitive Neuroscience at the University of Oxford Department of Psychiatry, UK) spoke to *ECNP Daily News* about new developments in depression research, and how its relation to the dopamine 'reward circuit' is being unravelled, giving us a more complete understanding of the relationship between different psychological symptoms and specific neuronal circuits of the brain.

She spoke first about the focus and aims of the TEM (Targeted Expert Meeting) 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 notes 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 will talk 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.

Catherine Harmer

> *"Current SSRI drug treatments for depression seem to be having paradoxical effects: where you might have thought that antidepressants boost reward processing, it was actually found that they seem to suppress it."*
>
> *Catherine Harmer (Professor in Cognitive Neuroscience at the University of Oxford Department of Psychiatry, UK)*

"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

Live from the 25th ECNP Congress

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) described the need to identify these problems, and he explained 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, they could be 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.

Joseph Zohar demonstrating the voting system in the session

"The nomenclature initiative was proposed by the ECNP and composed of the four major colleges on neuropsychopharmacology: ECNP, ACNP in the USA,

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.

"One of the speakers, Dr Martin-Soelch, is going to be speaking 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."

Professor Harmer will co-chair the TEM symposium 'Is depression a disorder of reward?' at 14.30 this afternoon in Hall E. The session will be immediately followed by a scientific café on depression at 16.10 in foyer E.

ECNP'S CONGRESS PARTNERS

Working towards a common goal

A critical part of every ECNP Congress are the contributions of ECNP's partners and supporters – the allied organisations, companies and other collaborators who offer insight, expertise and depth, and who together make the congress such a success. "These partnerships are very important to us," says ECNP President Joseph Zohar, "because they enrich the programme and by providing access to another dimension of information and insights, significantly expand the overall congress experience."

This year those partnerships have added 14 outstanding satellite symposia and a world-class exhibition, providing a wide variety of information and additional opportunities for reciprocal exchange. "ECNP has been extremely lucky in the quality of partnerships we've been able to build up over the years," says Professor Zohar, "and we're very thankful to all of the satellite symposia organisers and exhibitors. I'd encourage all delegates to take advantage of this resource at the 25th ECNP Congress."

With strong partnership comes the ability to sweeten every advance, and weather every storm.

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WPA - XVI World Congress of Psychiatry

David Nutt

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."

David Nutt 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 problems 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 focused 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."

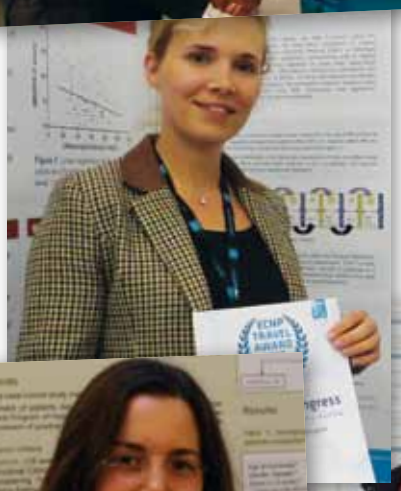
Speaking about how categorizing these different neurobiological actions could help to classify drugs, Professor Stahl distinguished the terminologies that would help to achieve that: "We've heard three 'multi's today: multimodal, multiaxial, and multifunctional. What we think multifunctional might mean is if you have the same kind of biological pharmacology many times". An example of this would be a drug that binds to different 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," he said. 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."

> *"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."*
>
> *Joseph Zohar (ECNP President, Chaim Sheba Medical Center, Department of Psychiatry, Tel Hashomer, Israel)*

Poster and travel awards @ ECNP congress



Congratulations to all of the recipients of an ECNP Poster Award and ECNP Travel Award on Monday.

Poster Award winners:

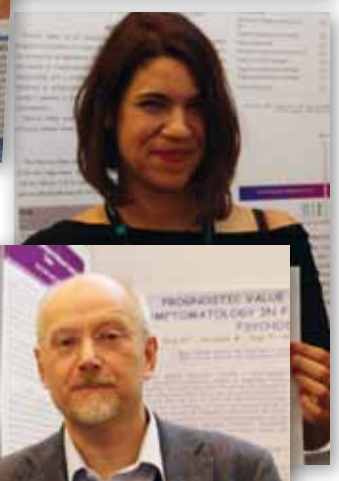
Gerard R. Dawson, United Kingdom
Poster number: P.2.c.024

Henricus G. Ruhe, The Netherlands
Poster number: P.2.c.030

Kylli Jaako, Estonia
Poster number: P.2.h.001

Travel Award winners:

P.2.a.008 Charlotte Hellgren, Sweden
P.2.a.012 Jessica de Wild-Hartmann, The Netherlands
P.2.a.027 Maria Serra, Spain
P.2.b.011 Katarzyna Mlyniec, Poland
P.2.b.012 Lidia Bravo, Spain
P.2.b.013 Laura Perez Caballero, Spain
P.2.b.016 Daniela Felice, Ireland
P.2.c.002 Georg Kranz, Austria
P.2.c.017 Christoph Spindelegger, Austria
P.2.c.028 Annamaria Cattaneo, Italy
P.2.d.007 Maria Giese, Switzerland
P.2.d.015 Richard O' Connor, Ireland
P.2.d.016 Carl Björkholm, Sweden
P.2.e.014 Marc Valentí Ribas, Spain
P.2.e.015 Dina Popovic, Spain
P.2.e.020 Nuria Cruz Culebra, Spain
P.2.e.027 Iria Grande, Spain



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ECNP

The ECNP-NI Child and Adolescent Network: recent advances Tuesday 16 October 09:00 **Hall D**

A bright future for children and adolescents

Alessandro Zuddas (University of Cagliari Center for Pharmacological Therapies in Child & Adolescent NeuroPsychiatry, Italy) is co-chairing today's update on the work of the ECNP-NI Child and Adolescent Network. 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.

Alessandro Zuddas

Using the example of depression, Professor Zuddas began by describing 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 said: "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 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)*

The safety concerns are growing for children and adolescents using medication that have only been studied in adults. 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 ECNP-NI Child and Adolescent Network: recent advances' session; Tuesday 16 October, 09:00, Hall D

How relevant are animal models to understand and treat psychiatric disorders? Wednesday October 17 9.00 **Hall F2**

'Invaluable' animal models in psychiatry

Bill Deakin (Professor of Psychiatry and Director of the Neuroscience and Psychiatry Unit, University of Manchester, UK) will be moderating today'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 are 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 views psychosis and schizophrenia as perhaps the greatest challenges in animal modelling, given the need to address 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 at 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 is 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."

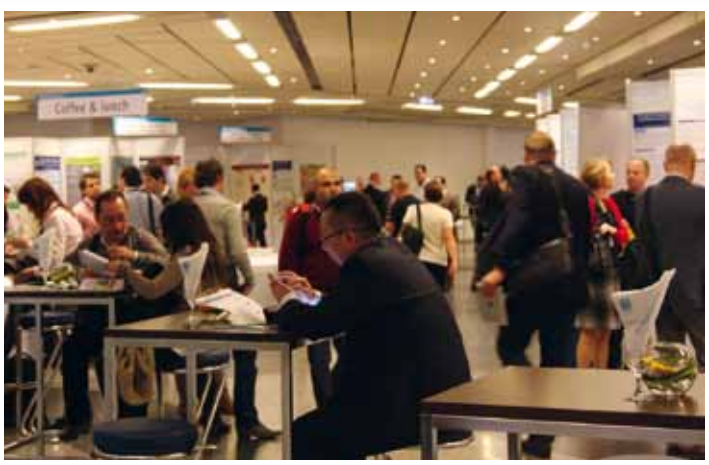
Modelling behavioural traits is, Professor Deakin said, the most complete way of addressing a drug's function. He explained: "We need studies in humans, mainly in drugs that mimic psychosis, so that then we can give those drugs to animals to induce psychosis and figure out how they work. The trouble 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."

Going 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."

Anxiety and depression are 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."

'How relevant are animal models to understand and treat psychiatric disorders?'; Wednesday 17 October, 09:00, Hall F2



The ECNP-NI Child and Adolescent Network Tuesday 16 October 09:00 **Hall D**

Antipsychotics in the young

We should lean towards an evidence-based approach when prescribing antipsychotics, delegates will hear this morning during an ECNP Networks Initiative (ECNP-NI) session dedicated to children and adolescents.

The collection of ECNP-NI networks – to which 'children and adolescents' belongs – promote essential clinical, psychological, biological and therapeutic variables to be analysed in clinical studies and pharmacological trials. Furthermore, the Initiative aims to foster exchange and collaboration.

"My idea was just to give an overview regarding the developments both in the evidence-based use of antipsychotics and in the adverse effects," Carmen Moreno (Hospital General Universitario Gregorio Marañón, Child and Adolescent Psychiatry Department, Madrid, Spain) told ENCP Daily News ahead of her presentation in the session.

Dr Moreno emphasised that while popularity for the use of antipsychotics in ADHD and conduct disorder has increased, she would very much like to convey the message to those in attendance that antipsychotics should be used only when there is a strong indication to do so: "Unfortunately they are overused in some cases," she said.

In the case of children and adolescents, Dr Moreno stressed that some psychiatrists do not take into account the adverse effects associated with antipsychotics, nor do they perform routine weight measurements for example. "That needs to be done so that these children and adolescents won't develop any adverse events that are more common than we think."

She continued: "The insurance on the one hand is just to make sure we are giving the right diagnosis, so I think this is one thing. Depending on the diagnosis the therapeutic approach is going to change and definitely the alternative is just to promote evidence-based treatments. Many times people need to use antipsychotics because with other treatments are not approved or are not supported by insurance companies."

When treating conduct disorder, Dr Moreno said that her approach would be to begin with behaviour therapy, and if that is not enough then she would utilise medication. That is, unless there is pressure to hurry: "Sometimes people are in a rush and expecting to get better right away, or without some symptoms, and so sometimes we do not follow the evidence-based guidelines," she said.

Treatment of patients using evidence from well-defined randomised trials is a particular path that Dr Moreno feels is important, thus whenever possible this is her approach.

"Of course if we decide that antipsychotics is something we need to do, we definitely need to balance risk and benefits, and be very careful in choosing," she said, adding: "it's a matter of knowing what can happen and be ready to have an answer in case something happens."

"Depending on the diagnosis the therapeutic approach is going to change and definitely the alternative is just to promote evidence-based treatments. Many times people need to use antipsychotics because with other treatments are not approved or are not supported by insurance companies."

Carmen Moreno (Hospital General Universitario Gregorio Marañón, Child and Adolescent Psychiatry Department, Madrid, Spain)

Carmen Moreno

'Antipsychotics in children and adolescents: what have we learned in the past decade?', as part of 'The ECNP-NI Child and Adolescent Network: recent advances' session; Tuesday 16 October, 09:00, Hall D

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


Nikita Burke

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* ahead of her presentation during the session.

To that end, 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 the tying of the L5-L6 spinal nerves in the rodents to cause symptoms of neuropathy including allodynia and hyperalgesia.

> *"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)*

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 depressive-like phenotype."

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, she explained its implication: "The prefrontal cortex is a key region in the regulation of both emotion and pain."

She continued: "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.

EPA session: Unmet needs Tuesday 16 October 09:00 **Hall F2**

Depression medications in need of a boost

Unfortunately, depression is still stigmatised and not recognised enough as it should be, delegates will hear this morning in a European Psychiatric Association (EPA) session that will examine the unmet needs in a variety diseases.

"I would say that we are better off than in the days 20 or 50 years before, but still there is a problem: Psychiatric diseases like depression are underfunded and under researched," Siegfried Kasper (Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria) told *ECNP Daily News*.

"So given this overall impression about psychiatric disorders and specifically depression, when we look to depression itself we have to say that in the future unfortunately we will not have many new mediations."He added that one of the problems is that antidepressants still take too long to work (~10-14 days for suitable efficacy)

> *"I would say that we are better off than in the days 20 or 50 years before, but still there is a problem: Psychiatric diseases like depression are underfunded and under researched."*
>
> *Siegfried Kasper (Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria)*

Another crucial issue, as Professor Kasper stressed, is that the available medication still has too many side effects. Using selective serotonin reuptake inhibitors (SSRI) as an example, side effects include sexual dysfunction, which in turn causes many patients to stop taking their medication. Headaches and gastrointestinal symptoms are also associated with SSRI medications.

"When it comes to other classes, like the SNRI (Serotonin–norepinephrine reuptake inhibitor), some of them have the problem of hypertension; some of them have problems with increased sweating which needs to be substantiated," said Professor Kasper.

There are, however, some agents which show promise to reduce these side effects, as he described: "An example of a new mechanism of action is agomelatine which does not go to all these monoanergic receptors and transporters. It has a more favourable side effect profile."

Overall, Professor Kasper was keen to underline that looking to the future, there are not enough studies yet for treatment-resistance depression, thus there is a need in daily clinical practice to differentiate between different presentations of the disease: inadequate response, treatment resistant, treatment refractory and chronic depression. "For treatment resistant depression we need further study as to how to combine or add on another medication in order to have a patient in a better symptomatological field," said Professor Kasper.

Siegfried Kasper

Professor Kasper will give his presentation on the unmet needs in the treatment of unipolar depression during the EPA session 'the true unmet needs in the therapeutic armamentarium seen from a clinical perspective'; Tuesday 16 October, 09:00, Hall F2.

Cross-species insights on the neurobiology of cognitive flexibility Tuesday 16 October 09:00 **Hall IK**

A flexible take on genetic susceptibility

Cognitive flexibility, its role in a number of nerve disorders and cutting-edge research to study its intricacies using animal models will be the focus of a session this morning at the congress. "We're interested in cognitive flexibility because we're interested in the neurobiology of psychiatric disorders," Leonie de Visser (Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands) told *ECNP Daily News*.

"We're not trying to model specific disorders like autism or schizophrenia for instance, but we tried to look at endophenotypes. So specific symptoms of the disease that can be more easily modelled in rodents, because as you can imagine it is almost impossible to find a schizophrenic mouse."

"But cognitive flexibility is a core symptom of many nerve developmental disorders such as autism, mental retardation or schizophrenia. So we were thinking that if we zoom in on the cognitive flexibility that we can measure in animals, we can find neuro markers and a genetic makeup of this specific type of behaviour."

In essence, as Dr de Visser commented, it is better to look at specific endophenotypes or specific dimensions of behaviour that you can model across a species instead of trying to model the full complex disorder.

Moving on to discuss the cognitive rigidity that is known to be present in autistic and schizophrenic patients, Dr de Visser added that they also show this behaviour in daily life. "They have this really rigid behaviour, and rigid behaviour is something you can see in mice also," she said. "You can define repetitive behaviour to be things like self grooming which is done quite a lot, and also what we did was a specific set shifting task in which we measure both set shifting models – so reversal learning (and attenuation) and those two are very valid measures of cognitive flexibility."

Leonie de Visser

When posed the question of how this work may lead to clinical studies, Dr de Visser began by saying that of course it is difficult for a pre-clinical scientist to be confident that anything will lead to a treatment, and there certainly is a large gap between the work they are doing and eventual clinical cures. However, she did discuss her work with contactin 4 – a gene that has been found in genome-wide association studies to be linked to autism and anorexia nervosa, which is also characterised by very rigid behaviour.

> *"Cognitive flexibility is a core symptom of many nerve developmental disorders such as autism, mental retardation or schizophrenia. So we were thinking that if we zoom in on the cognitive flexibility that we can measure in animals, we can find neuro markers and a genetic makeup of this specific type of behaviour."*
>
> *Leonie de Visser (Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands)*

Dr de Visser explained: "We knocked this gene out in a mouse to see whether this cognitive rigidity is affected. And that is precisely what we do see in this mouse, so it seems that contactin 4 is a really relevant gene in terms of its relation to affecting cognitive flexibility... so we can see that and also if you look at different inbred strains of mice – strains that are genetically homogenous – you can compare strains of different genetic backgrounds to see whether a genetic background is indeed relating to your phenotype, in our case cognitive flexibility. With this approach we see very interesting difference between genetic background and cognitive flexibility.

Dr de Visser will give her presentation 'Genetic susceptibility underlying cognitive flexibility' during the session 'Cross-species insights on the neurobiology of cognitive flexibility' today at 09:00, Hall IK

Questions? Please go to the ECNP Plaza

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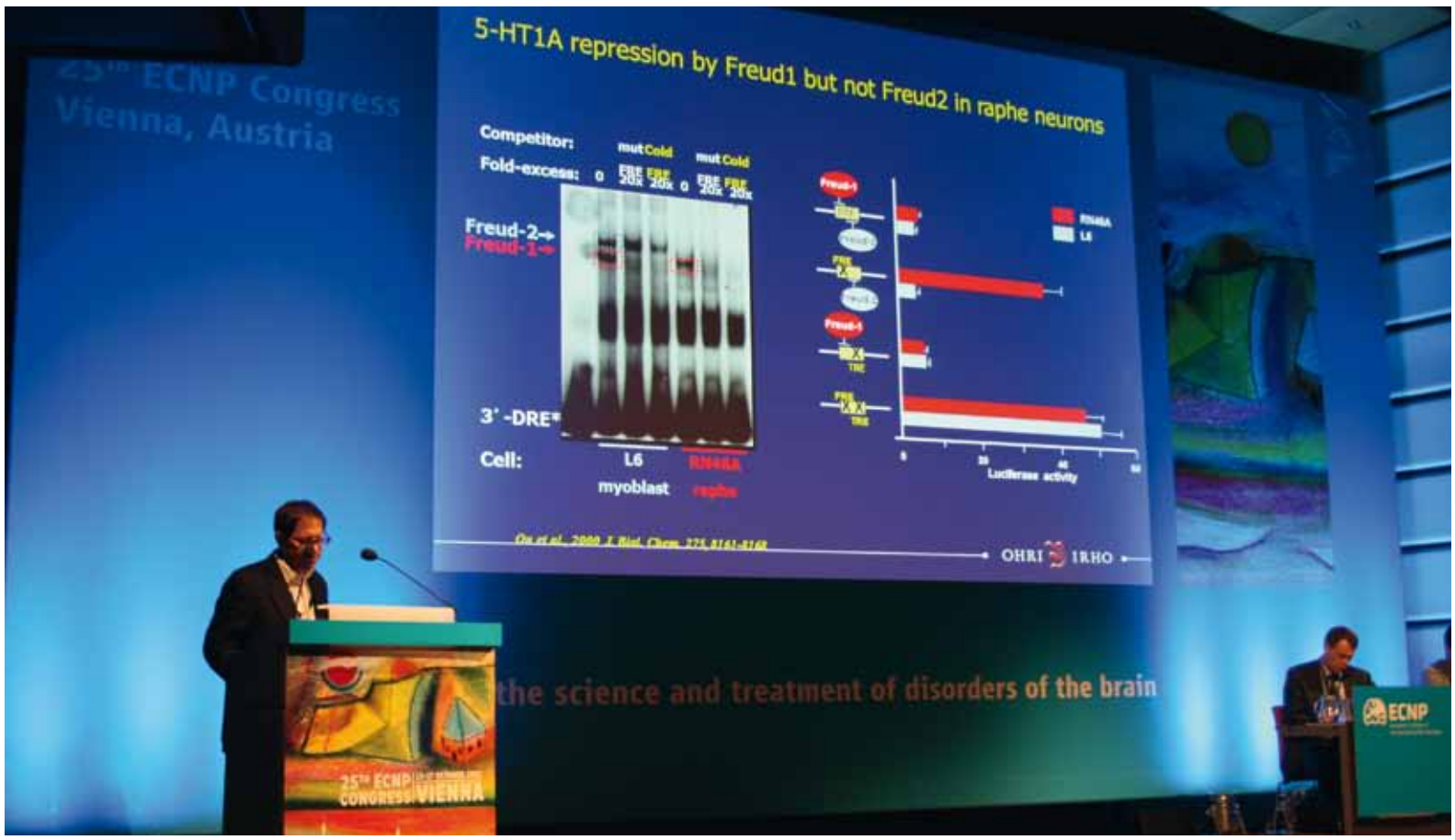
Live from the 25th ECNP Congress

New mechanisms and novel therapeutics



Depression is one of the major illnesses of the brain, and serotonin is widely studied for its involvement in this and a number of other mental disorders. Paul R Albert (Neuroscience Research Institute, University of Ottawa, Canada) touch upon this issue in his presentation yesterday at the congress, detailing his recent findings in the role of transcriptional regulators – the promoters and repressors – of the 5-HT1A autoreceptor, proposing that these could provide valuable targets to restore the normal regulation of the serotonin system.

Dr Albert began by describing the role of 5-HT1A receptors in the brain, saying: "The effect of all 5-HT1A autoreceptor binding is to decrease the excitability of the neurons, and one of the things that attracted us to the 5-HT1A receptor is that it has a number of distinct roles: first, as an autoreceptor, where it is expressed on the cell body and dendrites of the neuron and it regulates the firing activity; and second, it's expressed in the heteroreceptors in cell bodies and dendrites of the target cells in the CNS. 5-HT1A plays an important role in regulating the activity of the entire serotonin system through this inhibitory autoreceptor function, and it also plays an important role in mediating serotonin at target tissues."

Clinicians are familiar with the three week delayed effect of SSRIs, and although such drugs rapidly inhibit serotonin reuptake to increase serotonin in the synapse, this phenomenon also occurs in the neuronal cell bodies, as Dr Albert explained: "This increase in the cell body and dendrites activates the 5-HT1A receptors. The net effect is that you don't get much change in serotonin initially. However, after three weeks of treatment when you start to see clinical responses, at that time you will also see a desensitisation of the receptor and in some cases actually a down-regulation of the receptor, an increase in firing of the neurons to their normal level and now, because you've blocked the reuptake, you get this increase in serotonin that correlates with the time course for clinical improvement."

An increased incidence of autoreceptors on presynaptic receptors in the Raphe nuclei could theoretically reduce neuronal firing. However, the picture from animal studies is less clear, as Dr Albert explained: "In knockouts where you get rid of the autoreceptors, we see a very dramatic increase in the firing of serotonin neurons and an increase in serotonin, particularly in response to SSRIs."

Dr Albert went on to suggest: "The three week delay suggests that processes such as transcriptional downregulation is taking place to actually prevent the production of new receptors to replace the new ones that are being desensitised." The promoter region of a gene serves to initiate transcription, and contains binding sites for transcription factors that activate or repress gene expression.

Dr Albert continued: "There are very strong enhancer elements that are non-selective and activate a gene in almost any tissue. Then upstream you have a series of repressors that turn off the gene in cells that do not normally express the receptor. But even in neurons, these repressors have some activity, regulating the basal expression of the receptor. We found a group of transcription factors that are particularly important in determining this basal expression. In particular, Freud-1 is important pre- and post-synaptically, whereas Freud-2 is not effective pre-synaptically, but regulates post-synaptically. That brings me to the concept that different transcription factors can have different actions depending on the tissue, specifically whether it is pre-synaptic or post-synaptic."

> *"This polymorphism became interesting when we collaborated with psychiatrists, and we found that the G/G genotype of the G(-1019) allele was enriched in depressed patients as well as in suicides."*
>
> *Paul R Albert (Neuroscience Research Institute, University of Ottawa, Canada)*

Freud-1 is localised in the prefrontal cortex, in the pyramidal neurons, and Dr Albert identified colocalisation with 5-HT1 receptors, which implicates it in serotonin regulation, as well as finding it to be involved in repression of dopamine D2 receptors. Dr Albert said: "So this single transcription factor can coordinate the activity of the serotonin system as well as the dopamine system. In addition, Freud-1 was linked to non-syndromal mental retardation, so it is also involved in regulating cortical development and may regulate other genes involved in this. So by targeting this one transcription factor, you can regulate a number of key genes involved in neurotransmission, the regulation and activity of different neurotransmitter systems."

Studying the 5-HT1A promoter in humans, Dr Albert identified a polymorphism, C(-1019)G, located within the repressor/enhancer region that was experimentally linked to not only depression in patients but also to treatment resistance. He said: "This polymorphism became interesting when we collaborated with psychiatrists, and we found that the G/G genotype of the G(-1019) allele was enriched in depressed patients as well as in suicides. Since our initial studies, several other groups have found similar sorts of findings in major depression, treatment-resistant depression, and in different personality traits.

"In addition, it seems to be associated with panic disorder and different anxiety disorders. So this fits somewhat with the alterations in post-synaptic 5-HT1A receptors. It was also found that the G/G genotype of the G(-1019) allele conferred resistance to treatment and antipsychotics and SSRIs. So the genotype is regulating the predisposition to depression as well as the response to antidepressants. Whatever mechanism was disrupted at the G(-1019) allele was important to desensitise the receptors."

It is thought that the disruption of the 5-HT1A promoter via the C(-1019)G polymorphism is involved in the disruption of receptor regulation that is also evident from some studies, perhaps due to Freud-1 being unable to bind to the G(-1019) allele. Dr Albert said: "You would then have an increase in 5-HT1A autoreceptors, reducing the firing rate of serotonin neurons and predispose to major depression." While it is certain that Freud-1 is not alone in regulating 5-HT1A receptor expression, it certainly suggests that transcription factors are a key research area in the future of personalised medicine.


ECNP
Issue 1
Sunday
14 October
2012
ECNP DAILY NEWS
Welcome to the
ECNP
Issue 2
Monday
15 October
2012
ECNP DAILY NEWS
Keynote lecture starts congress with a bang
The Keynote Session on Saturday evening was filled with awards, speeches and live entertainment that served as a befitting tribute to the opening of the landmark 25th ECNP Congress. Of course, a crowning moment of the session was the keynote lecture, 'The plastic brain', delivered by prestigious and renowned expert Colin Blakemore (Department of Physiology, Anatomy and Genetics, University of Oxford, UK).

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ECNP Daily News would like to thank all the interviewees and contributors for your help in making the newspaper. We would also like to express our warmest thanks to everyone involved in making this a great congress.

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