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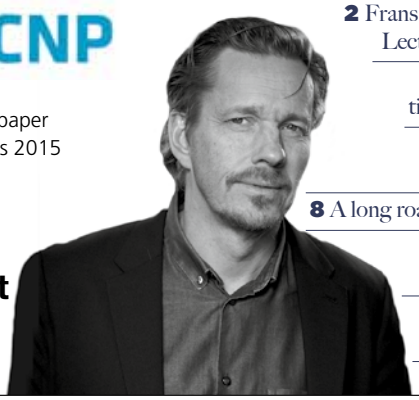

ECNP DAILY NEWS

Welcome to Amsterdam

It's difficult to make an organisation that already does things well do them even better. As a foundation directed to the understanding and translation of research for the benefit of patients, especially those patients with a psychiatric disorder, ECNP has had an exceptional year, which is set to culminate in an exceptional congress.

The EU's Innovative Medicines Initiative has provided a great model for funding the translational research that is the core activity of ECNP. It is therefore very exciting that the ECNP Experimental Medicines Network has recently won the opportunity to bid for a major grant under the IMI2 programme (PRISM). If successful, the ECNP office would participate directly in one of the work packages, which is a major first. ECNP has been a key participant in re-structuring the European Brain Council so that we get the message across in Brussels that research into mental illness is undervalued.

In Nice last March our Consultation Meeting looked at the exciting potential role of diagnostics in psychiatry; we are actively seeking ways to interest diagnostics and biotech companies in using ECNP as a vehicle for developing their applied neuroscience.

We are seeing the fruits of our new information strategy, which I hope will help to get balance into the public debate on treatment in psychiatry. It means being proactive in commenting on news stories, which takes time, but is clearly successful.

In a similar vein, the Neuroscience-based Nomenclature (NbN) project is progressing as planned. The challenge now is behavioural change, which occurs at very unpredictable speed and in very unpredictable measure.

These initiatives have and will continue to nourish our approach to the content of the congress.

ECNP aims to offer you the best in applied and translational neuroscience over these four days. There would be no congress, however, without the participants who literally create the atmosphere that inspires the science.

Guy Goodwin
ECNP President

Highlights this year

Symposia on Saturday

We start the scientific sessions today, Saturday, to make a tighter four-day meeting that's maximally time-efficient for participants. The first five sessions will be held at 16:50–18:30, just before the Keynote Session.

Keynote session

The Keynote Session (today at 18:45–20:00) is our official welcome to all congress participants. The Keynote Lecture will be given by renowned primatologist Frans de Waal on 'Prosocial primates: co-operation and empathy'.

Plenary lectures

Six plenary lectures will anchor the programme, two a day on Sunday–Tuesday, at 11:15 and 14:00. Our lecturers this year are Tallie Z. Baram, USA; Andreas Heinz, Germany; ECNP Neuropsychopharmacology Award winner Francesc Artigas, Spain; Brain Prize Award winner Trevor W. Robbins, United Kingdom; Anna Monika Prize Award winner Ned H. Kalin, USA; and Marion Leboyer, France.

Awards

The ECNP Neuropsychopharmacology Award will be conferred this year on Francesc Artigas, Spain, and the ECNP Media Award on Mary G. Baker, MBE, United Kingdom. Also, for the first time, the Anna Monika Prize will be presented at the ECNP Congress, jointly to Ned H. Kalin, USA, and Carmine M. Pariante, United Kingdom.

EUFAMI session

For the first time this year, we will have a dedicated session for issues specifically concerned with the emerging role of the carer. It will be held this afternoon at 14:00–14:45.

Biomarkers session

In the Clinical Research track this evening (16:50–18:30), the outputs of ECNP's special meeting on biomarkers in the clinic, held earlier this year, will be presented and new directions marked out.

Regulatory update session

This year also sees the second of our highly successful dialogue sessions with the European Medicines Agency (EMA). This will take place on Monday evening (accompanied by a light dinner).

Career development sessions

As part of our commitment to junior scientists, we continue career development sessions, with a career veteran discussing practical, day-to-day career challenges, such as 'how to give an effective talk' and 'how to make a winning poster' in an open, interactive format.

THE 28TH ECNP CONGRESS

KL.01: **Keynote Session** Auditorium **Saturday** 18:45–20:15

Prosocial primates

What we can learn about cooperation and empathy

This year's Keynote Lecture will be delivered by the eminent primatologist Frans de Waal – the Charles Howard Candler Professor at Emory University in Atlanta, Georgia, USA, and director of the Living Links Center at the Yerkes National Primate Research Center. His illustrious career has inspired the field of primate cognition, and his work continues to prosper around themes of empathy, cooperation and fairness.

Professor de Waal's lecture – taking place this evening in the Auditorium – will focus on the level of cooperation observed between primate societies, and how this cooperation is based on empathy. *ECNP Daily News* had the pleasure of talking with Professor de Waal to further explore what he will be sharing with the audience: "Empathy is a big topic in the neurosciences, and not just in primates: empathy has been shown in many studies of rats and mice, and I believe that it is found in all mammals," he said.

He delved deeper: "Many believe the origin of empathy is maternal care, because females – from human to elephant – need to take care of their young. They need to pay attention to when they are distressed, hungry or in danger; they need to be sensitive to the emotions of their young, and that's where the sensitivity to someone else is learned from."

Professor de Waal noted that this would explain the sex differences observed in the expression of empathy, which tends to be a more female characteristic, and is demonstrated in adult humans reacting more empathetically when given oxytocin, which is considered to be a maternal hormone.[1]

"Cooperation is quite a different beast, as it can be done for entirely selfish reasons, for example where two individuals will get something that they could never get alone,[2]" said Professor de Waal. "And that's found widespread in the animal kingdom, not just in mammals."

While Professor de Waal has robust evidence demonstrating cooperation across many species, his interest lies not in whether they cooperate, but instead with their comprehension of cooperation – whether they understand that they need a partner, and what that partner needs to do.[3]

With regards to translating this information, Professor de Waal gave some perspective: "I'm not sure how I would use this in a medical or clinical setting, but I do believe that this research will create a different mind-set." Indeed, he challenges the notion that humans, being so sophisticated, have recently created these unique social constructs as a cultural invention, or that these "rules" are determined by education. "My work shows that empathy and cooperation are very ancient tendencies that we have inherited from primates; and that they're not just part of human nature, but part of animal nature," he said.

"This work shows that the 'good' side of humanity has an evolutionary background, and questions the belief that humans are inherently nasty and selfish."

> "We are biased towards individuals who are similar to us, so the flip side to empathy is that we have trouble empathising with strangers."
>
> Frans de Waal

Professor de Waal noted that in some ways, working with animals – where emotions can be measured – is easier than working with humans, who can hide or deny their feelings: "In a way I am happy to work with animals who cannot fill out questionnaires because I am not sure I trust what people tell themselves or others."

He continued: "Animals elicit emotions, which are external manifestations that I can measure and study. We study fear in rats,[4] and love in voles,[5] but the feelings of an animal are basically inaccessible to me, as are those of a human."

Professor de Waal then discussed how research supporting intrinsic cooperation and empathy could help to influence society as a whole: "There has been a shift in opinion, after the crises of 2008, when people lost confidence in economists. At that time, the use of the words 'empathy' and 'solidarity' in newspaper articles and internet blogs increased dramatically. A society based purely on money and market forces is really not tenable, and my work contributes to this idea. Many animals live in societies, and both cooperation and solidarity are very common characteristics."

Professor de Waal also considered an interesting challenge: how can we maintain empathy when our 'tribe' is expanding, living in large cities under globalisation? "Empathy is extremely biased in humans, in chimps, and we also have seen it in rodent studies," he said.

Describing a study of yawn contagion in chimpanzees, which is related to empathy, and stems from the primitive motor memory mimicry system,[6] Professor de Waal noted that chimps will yawn when they see chimps that they know also yawning, but are unaffected by chimps they do not know.

"We live in large-scale societies where there are lots of people who are not like us, and we have to deal with strangers," said Professor de Waal. "We are biased towards individuals who are similar to us, so the flip side to empathy is that we have trouble empathising with strangers. But we are meeting that challenge by exposing ourselves to the perspectives of others with television and the internet – we see videos of people who are affected by various issues or disasters, and we start to empathise, even though they are very far away, and they may be very different to us."

> "Empathy and cooperation are very ancient tendencies that we have inherited from primates... they're not just part of human nature, but part of animal nature."
>
> Frans de Waal

Professor de Waal will deliver his lecture 'Prosocial primates: cooperation and empathy' during this evening's Keynote Session, taking place at 18:45–20:00 in the Auditorium. The lecture will be followed by a Welcome Reception in the Auditorium Lounge.

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PLENARY LECTURES

PL.01: **Neural correlates of chronic early-life stress** Auditorium **Sunday** 11:15–12:00

Early-life stress:
A ticking time bomb for adult emotional health?

The first plenary lecture of this year's ECNP Congress will take place tomorrow morning, with Tallie Z. Baram (University of California-Irvine, CA, USA) taking the audience through neural correlates of chronic early-life stress, with the core message being that early-life adversity is incredibly influential on emotional health and emotional disease later in life.

"Unlike the effect of stress during adulthood, the consequences can be permanent, by way of reprogramming in the brain," she told *ECNP Daily News*. "The other unique aspect of early-life stress is that whatever causes stress later in life doesn't seem to do so earlier in life."

Professor Baram expanded on this concept, first noting that there are some very special factors that perturb the brain early in life, which then can cause emotional stress. From her own work, and that of others, it has been shown that the consistency and predictability of signals is an important – if not the most important – parameter. "If you have fragmented and unpredictable environmental experiential signals that make their way into the developmental brain, that creates terrible stress, and also seems to be involved in how early-life stress 'reprograms' the brain," she said.

"But we don't really know if it is the stress itself, or the signals that provoke the stress, that cause changes in brain function that then translates into later-life resilience or vulnerability."

Other questions that persist include how 'stress' – however it is defined – actually causes vulnerability or resilience. To that end, Professor Baram has focused on rodent models that have examined the connectivity of neuronal populations, and how they contribute to vulnerability and resilience. "What part of the brain does early-life experience, including stress, change? Are all neurons changed? Is it a particular part of the brain?" she questioned.

"The answer is not fully known, but we do know that some parts of the brain are indeed changed very early on – a classical one being the hypothalamus, where stress-sensitive neurons reside. And we have shown, as others have as well, that the number of excitatory synapses to stress-sensitive neurons is governed by early-life experience. This may be stress – which increases the number of synapses – or the opposite of stress, i.e. optimal, wonderful, maternal care, which reduces excitatory synapses to stress-sensitive neurons in the hypothalamus."

In addition to altering the communication between brain cells, this change in excitatory synapse number also changes what happens inside stress-sensitive neurons. As excitatory synapses govern a variety of intracellular mechanisms – including those mediated by calcium – this in turn modulates the expression of stress-sensitive genes to epigenetic mechanisms. "So you completely reprogramme these neurons," noted Professor Baram. "These are likely not the only neurons that are reprogrammed, but they are the ones that are programmed very early in life. Clearly, there are epigenetic changes later in life within neurons in the hippocampus, the prefrontal cortex and other important brain regions."

Taken as a whole, one can see that a chain of events takes place from aberrant early-life experience (e.g. fragmented care), to stress, to altered connectivity in stress-sensitive brain regions (or changes in synapse number), which ultimately translate to heightened or diminished sensitivity to future stress in later life. "Most emotional disorders are stress sensitive, particularly depression, anxiety and post-traumatic stress disorder – so this really provides, for the first time, description of a complete mechanism from early-life experiences (such as stress) to emotional outcome."

Crucially, if this mechanistic pathway is taken into consideration, then it opens up potential avenues for early intervention. But how long is the window to treat those at risk, i.e. before influences initiate the proposed 'reprogramming' process in the brain? In the extensive Romanian orphan study by Nelson, Fox and Zeanah,[1] among other works, it has been proposed that up until the age of two, children will be able to recover much better from early-life environmental stressors.

"I would like to consider that two years may not necessarily be the case, or at least that it depends on the degree of the deprivation – which those particular children suffered terribly," said Professor Baram. "In rodent models we are able to very effectively intervene early on in life, and beyond the early-life stress period, but are less successful when we try to intervene during adulthood."

Staying on the topic of animal work, Professor Baram stressed that rodent analogues are very fitting in this kind of work, with principles being very similar to that of humans. "For example the CRH [Corticotropin releasing factor] peptide, one of our focuses, is identical in humans and rodents," she noted. "It is different in pigs, cows and sheep, for example, but both the actual molecule, the actual regulation – everything – is similar in rodents and humans."

Professor Baram continued, describing her recent collaborative work with humans.

> "Most emotional disorders are stress sensitive ... so this really provides, for the first time, description of a complete mechanism from early-life experiences (such as stress) to emotional outcome."
>
> Tallie Z. Baram

Funded by the NIMH, the notion of fragmentation and unpredictability of maternal signals to the developing brain as an important predictor of emotional outcome of children is being studied. Specifically, fragmentation and consistency of maternal mood and heartrate patterns – both parameters that might be sensed by the foetus – have been assessed all the way from 15-weeks of foetal growth.

"Children exposed to varied patterns of maternal signal during foetal life, and to different patterns of maternal care postnatally, were followed-up in terms of their emotional outcomes and developmental intelligence outcomes," described Professor Baram. "Early results at the age of one and two years, and now at 9, 10 and 11, suggest that these patterns and their consistency and fragmentation are important."

The human work is being achieved via sophisticated imaging such as diffusion tracer imaging, and functional MRI – which reveals the connectivity, functional integrity and communication pathways between important brain structures. "We are doing this work parallel to rodents, where we can do the same type of imaging using really high-powered MRIs," said Professor Baram.

In closing, Professor Baram emphasised that, before we can really begin to think about tangible interventions, the first question left to answer would be to what degree a rodent's principles and mechanisms reflect the situation in children? She delved deeper: "For that purpose, these types of analyses allow you to make some hopefully fairly strong inferences. These are things that are ongoing, and I think if we establish indeed what principles are common then the question is can we use intervention studies from rodents in children?"

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Further reading

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3. Gunn et al, J Neurosci 2013.

EDUCATIONAL

E.04: **Anxiety disorders: from new targets to new treatments** Elicium 1 **Monday** 09:00–10:40

Anxiety disorders: A rethink of approaches and targets

"If people are very ill, they may initially opt for one particular therapy ... [but] maintaining treatment can become an issue, especially with side effects."

Nic van der Wee

Anxiety disorders are amongst those with the greatest prevalence, most striking socio-economic burden and tend to have a chronic or recurrent course. Meta-analyses demonstrate only moderate numbers with full remission, many of whom will relapse and experience side effects, often leading to poor medication compliance or discontinuation. While guidelines for treating anxiety disorders with pharmacotherapy and psychotherapy are formulated on the basis of evidence from clinical trials,[1] the limited efficacy, effectiveness and tolerability of current pharmacotherapies means there is an unmet need for new treatment targets and approaches.[2]

The future perspectives for anxiety disorder treatment will be critically assessed in an educational session held on Monday morning, in which the need for new targets will be of particular focus. "The session is about where we are in the pharmacotherapy of anxiety at the moment, and what could be the way forward," session speaker Nic van der Wee (Leiden University Medical Center, the Netherlands) told *ECNP Daily News*. "It definitely involves psychotherapy and pharmacotherapy coming together, and also looking into cognitive enhancement."

Discussing why there may be differences between what clinicians and patients consider to be essential properties for an 'ideal' drug for the treatment of anxiety disorders, Professor van der Wee commented: "If people are very ill, they may initially opt for one particular therapy to reduce their anxiety, but when it becomes manageable, the side effects may become more of an issue. In this case maintaining treatment can become an issue, especially with side effects like sexual dysfunction.

"If observer-rated scales alone are used for drug effectiveness assessments, without consideration of the patient-reported outcomes, there may be huge discrepancies between the verdict of physician and that of the patient." He added that this also holds true whether the non-response of a drug treatment is actually valid, as in some cases incorrect dosing and treatment duration, or poor patient compliance are to blame: "We need to look into real-world efficacy of treatment."

With regards to maintenance treatment, it need not take the same form as initial treatment, and currently a multidisciplinary approach is recommended for treatment of anxiety disorders: data has shown that combination therapy (pharmacotherapy and psychotherapy) is most effective.[3] If the patient has more symptoms, they can be shifted to pharmacotherapy from CBT. The current multidisciplinary guidelines in the Netherlands recommends that the first course of treatment, in non-complex cases, should be psychotherapy. Whilst CBT can be highly effective, it brings its own potential complications as Professor van der Wee pointed out: "There may be issues with CBT in terms of availability and if someone is in remission from pharmacotherapy there is not much left to do CBT on."

He added: "It's about balancing the pharmacological and psychological effects – they are both very important with regards to initial treatment and maintenance, but sustainability is important too."

Continuing with this patient-centric tactic, Professor van der Wee went on: "As for personalised medicine, it's a matter of debate: is there one drug for one patient, and a different drug for another? Whilst that might be too simplistic an approach, because we see involvement at different levels – biologically as well as psychologically – I do believe that by better stratifying our patients, we can narrow down the therapeutics to those that will be effective on/in particular individuals."

Expanding on this, he touched upon today's 'holy grail', the biomarker – a concept of huge interest thanks to the potential for stratifying patient subpopulations, as well as both tracking drug responses and predicting drug efficacy. But Professor van der Wee offered a cautiously optimistic outlook on this approach to psychiatric disease in the real world: "The issue with biomarkers is that we have many studies showing biomarkers in samples that are not replicated in cohorts of patients."

He continued: "We most certainly need to investigate biomarkers to improve our understanding of the underlying psychopharmacology of diseases, especially if they are combined with clinical markers, like trauma or abuse." However, he added that in a field of high expectations where outcomes can differ hugely from one disorder to another, there is a pragmatic clinical perspective – i.e. the need to balance biomarkers' predictive capabilities with other factors, for instance how much they cost, and how invasive are they.

"I do believe that by better stratifying our patients, we can narrow down the therapeutics to those that will be effective on/in particular individuals."

Nic van der Wee

"I think that genetic biomarkers would be the most relevant in pharmacogenetics – just figuring out whether someone was a rapid or poor metaboliser of a drug would have a massive effect on how you would arrange the pharmacotherapy," said Professor van der Wee. "Epigenetic biomarkers may be more informative than classic genome-wide testing for patients, thus this concept is very interesting for research, but we are not sure yet how it can be applied treatment-wise."

In his closing remarks, Professor van der Wee turned to drug repurposing as a particularly promising solution in anxiety disorders, noting that by re-evaluating and re-characterising potential, hitherto-undiscovered properties of clinically-used agents, there may be great scope for potential anxiolytic use.

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CLINICAL TREATMENT

S.01: **TNM symposium – Adult separation anxiety disorder** Elicium 2 **Saturday** 16:50–18:30

Unravelling the genetic nature of anxiety disorders:

Towards individualised diagnosis and therapies

Katharina Domschke is a professor of Psychiatry at the University of Würzburg, Germany, with a clinical focus on depression, anxiety disorders, stress-related disorders, obsessive-compulsive disorders and eating disorders. Professor Domschke will be sharing her experience this afternoon, with a stimulating talk on the genetic dissection of anxiety disorders, posing the question of whether 'separation anxiety disorder' can be distinguished. Speaking to *ECNP Daily News*, she began by illustrating the necessity for research in biological psychiatry, saying: "Clinical genetic studies propose a genetic influence of 30-60% for the pathogenesis of anxiety disorders, and there is a complex genetic aetiology."

Determining genetic and environmental risk factors is at the core of diagnosis and treatment of psychiatric disorders. Describing the techniques utilised leading up to their group's more recent findings, Professor Domschke said: "In order to work out which chromosomal loci and which genes are involved, we need to study the molecular genetics. This involves performing linkage, association and genome-wide association studies to measure the effects of risk genes."

Since 2000, Professor Domschke has been actively involved in the field of biological psychiatric research with a strong focus on the epigenetics, imaging genetics and pharmacogenetics of anxiety, and her research group has been pivotal in revealing associations of different genetic variants with anxiety disorders, for example G protein-coupled receptor RSG2,[1,2]; different polymorphisms in genes encoding catecholamine catabolism enzymes catechol-O-methyltransferase,[3] and monoamine oxidase A[4]; various polymorphisms of the serotonin receptor 1A gene[5]; as well as modulation of the gene for neuropeptide, oxytocin[6], to mention but a few.

However, it was the discovery of an association between genetic variations in the neuropeptide S receptor gene (which Professor Domschke affectionately refers to as her "baby") with panic disorder that captured attention of those studying the pathogenesis of anxiety disorders. A huge focus in Professor Domschke's research group is finding a functional role for this neuropeptide. A functional polymorphism in the NPSR1 gene has been linked to aberrant cortico-limbic interactions[7]; and NPSR1 A/T polymorphism is associated with anxiety-, depression- and activity-related traits, various disorders and suicidal behaviour.[8]

Professor Domschke described one of the most fashionable research developments in this area: epigenetics. Epigenetics encompasses mechanisms that regulate gene expression without actually altering the genotype – instead comprising gene modulation such as methylation and demethylation. She explained: "The waxing and waning of DNA methylation may be the link between genes and the environment; and these could even be transmitted transgenerationally."

Professor Domschke continued: "Our group was the first to show GAD1 methylation's association with panic disorder; we showed that hypomethylation is associated with both panic disorder and a high number of negative life events.[9] New data is now showing psychotherapy as having an effect on DNA methylation, demonstrating its biological effect."

> "The waxing and waning of DNA methylation may be the link between genes and the environment."
>
> Katharina Domschke

The measurement of genetic and environmental biomarkers of mental disorders and treatment response is in its infancy, and large genetic studies in concert with translational research are essential to improve the understanding and predictability of mental disorders. Professor Domschke gave an example of how genetic and environmental risk factors may interact to influence the propensity for development of anxiety disorders: "There is a close aetiological and epidemiological connection between separation anxiety disorder and panic disorder. They are both highly heritable … and it has been suggested that this link may be conferred via CO_2 sensitivity – an endophenotype common to both disorders."[10]

Looking to the future, Professor Domschke went on to describe her three main research goals: "First is the detection of early genetic risk factors and epidemiology using biomarkers as preventative measures," she said, adding: "At the moment, these biomarkers are largely universal selective measures such as neuropsychiatric tests and anxiety measures, but ideally we would like to see more specific biomarkers so those at high risk can be targeted early.

"Second is to develop an individually-tailored therapeutic approach to therapy – for example using a panel of about 10 risk factors as biomarkers in concert with functional brain imaging, to measure and compare responses to drug therapy.

"Finally would be the development of new and innovative approaches to patient treatment, for example, an intranasal neuropeptide S treatment for humans. This has been shown to decrease anxiety in mice and rats by researchers at the University of Regensburg [Germany] and the Max Planck Institute."[11, 12]

These studies on (epi)gene-environment interactions will help to elucidate maladaptation to separation life events with the ultimate goal of developing novel, individualised approaches to diagnosis and therapies.

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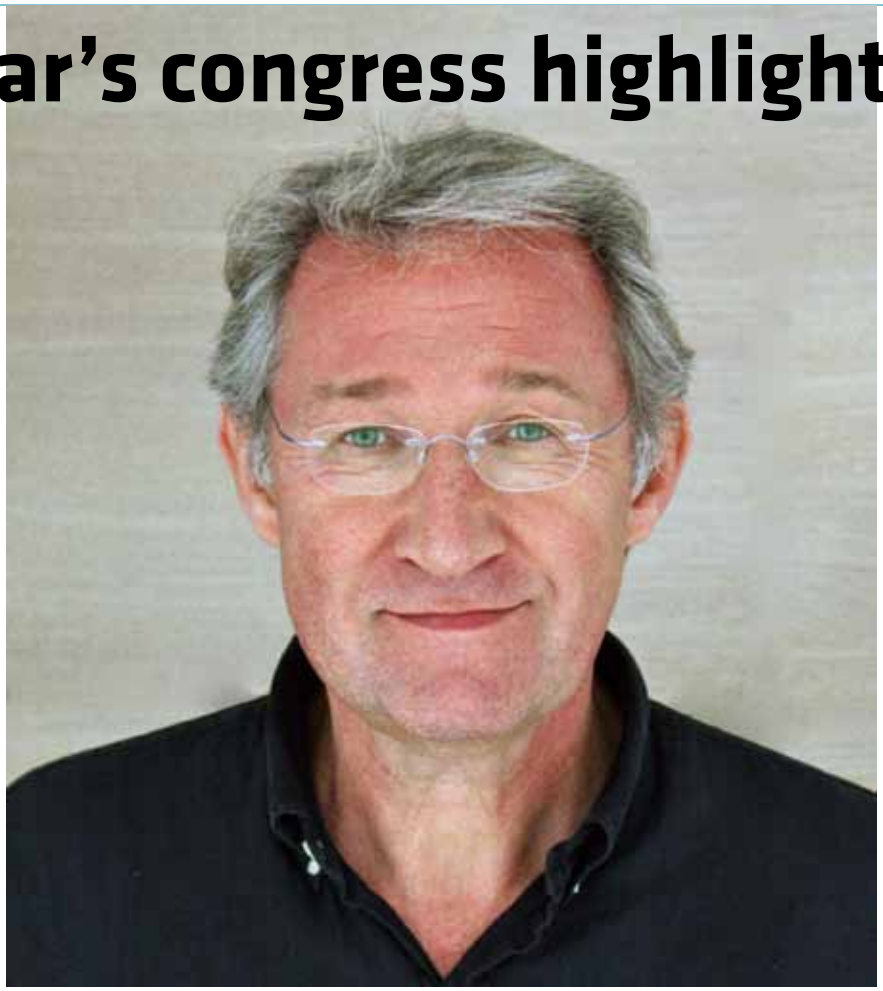
THE 28TH ECNP CONGRESS

Highlights in Amsterdam

This year's congress highlights



Plumbing the depths of many key research topics, the scientific programme of the 28th ECNP Congress boasts a Keynote Lecture by internationally-acclaimed primatologist Frans de Waal this evening, and thereafter is punctuated by six plenary lectures by well-known names at the leading edge of neuropsychopharmacology. To share his perspectives on the congress highlights, Wim van den Brink (Academic Medical Centre Amsterdam, the Netherlands), chair of the 28th ECNP Congress Scientific Programme Committee, spoke to *ECNP Daily News* about the topics that feature most prominently this year.

Professor de Waal's Keynote Lecture 'Prosocial primates: co-operation and empathy' (page 2) provides the centrepiece to the Keynote Session that takes place this evening (18:45–20:00, Auditorium). Publishing prominently both in scientific journals and in popular work, Professor de Waal's first book, *Chimpanzee Politics*, compares the power relationships within chimpanzee social groups with those of human politicians.

"Frans de Waal will talk on the issue of cooperation and empathy," said Professor van den Brink. "He will explain how this works among apes and what we can learn from them about human behaviour. He has worked for many years with chimpanzees, and he really has very interesting things to say. It will be a fantastic lecture."

Sunday morning follows with the first plenary lecture on the neural correlates of chronic early life stress, presented by Tallie Z Baram (11:15–12:00, Auditorium). "Everybody knows that early-life stress is very important in almost all psychiatric disorders," said Professor van den Brink. "And this translational point of view will be interesting. I think there is a lot of speculation about what is happening in the brain in early-life stress, and we don't know enough about it."

Going on to highlight Francesc Artigas's Sunday afternoon plenary lecture focused on the development of more potent and effective antidepressants (14:00–14:45, Auditorium), Professor van den Brink stressed the importance of the issue, demonstrated by the fact that classic antidepressants can take between two and eight weeks to bring about any noticeable effect.

Then, drawing attention to the plenary lecture of Brain Prize winner Trevor Robbins, who will talk on the topic of impulsivity and compulsivity (Tuesday, 11:15–12:00, Auditorium), Professor van den Brink continued: "These were concepts that, for many years, were used as opposing poles of a dimension. Now we understand them as being more continuations of the same thing. In a lot of patients we see that impulsivity often co-occurs with or develops into compulsivity – we see this in OCD as well as addiction. This is a really an important new insight."

The role of early life stress and childhood disorders that persist into adult psychiatric disorders is certainly a prominent theme at this year's congress. "Unlike most other disorders and diseases in humans, psychiatric disorders start earlier in life," explained Professor van den Brink. "This is partly why they create such a burden to society."

"We have sessions on disruptive behavioural disorders and ADHD, with the latter being a much debated issue among professionals, the lay public and even politicians; although there is no doubt that many children that start off with a serious form of ADHD will develop all kinds of other mental disorders later on.

"This is also interesting because there was an announcement that scientologists will be protesting outside the conference this year. They are against all forms of psychopharmacology, but they particularly focus on the pharmacological treatment of children with ADHD, despite this year's *Lancet* report that untreated children with ADHD have a much higher probability of injuries and emergency room visits than treated children with ADHD.[1] We think, therefore, it needs a lot of attention."

> "Frans de Waal will talk on the issue of cooperation and empathy. He will explain how this works among apes and what we can learn from them about human behaviour."
>
> Wim van den Brink

> "In a lot of patients we see that impulsivity often co-occurs with or develops into compulsivity...This is a really an important new insight."
>
> Wim van den Brink

Professor van den Brink also drew special attention to the plenary lecture of Ned Kalin on anxious temperament (Tuesday, 14:00–14:45, Auditorium), which seems closely connected to what is now called adult separation disorder; an issue that is discussed during the TNM session on Saturday afternoon (16:50–18:30, Elicium 2). The emergence of the disorder, previously held to occur only in children, has prompted work looking at intervention and prevention.

"In terms of medication, there is a lot of interest in oxytocin," explained Professor van den Brink. "This is the bonding hormone that is also being used now in schizophrenia and autism – these are disorders where bonding and interaction is important. We will have the first findings in the use of oxytocin presented too ['Oxytocin in schizophrenia: new research findings'; Monday 09:00–10:40, Auditorium]."

Encouraging delegates to pay a visit to all of the plenary lectures, Professor van den Brink spoke of the remaining two, 'The role of motivation and reward in mental disorders' by Andreas Heinz (Monday, 11:15–12:00, Auditorium) and 'Is it time for immunopsychiatry?' by Marion Leboyer (Monday, 14:00–14:45, Auditorium): "Together with many other sessions on many different topics and covering almost all psychiatric disorders, these plenary lectures will be an exciting experience," he concluded.

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28TH ECNP CONGRESS AT A GLANCE

TIME	ROOM	SATURDAY 29 AUGUST	SUNDAY 30 AUGUST	MONDAY 31 AUGUST	TUESDAY 1 SEPTEMBER
07.45-08.45	D201 D202 D203		**Brainstorming sessions** BS.1 Inflammation in psychosis BS.2 Signal detection in RCTs BS.3 Transmitters in cognition	**Brainstorming sessions** BS.4 Medicines Chest: 1st examples BS.5 More antidepressant side effects BS.6 Antipsychotic switching	**Brainstorming sessions** BS.7 Variable mice drug responding BS.8 Personalised Tx depression BS.9 Biology of disruptive behaviours
09.00-17.00	Exhibition area		**Exhibition**	**Exhibition**	**Exhibition**
09.00-10.40	Auditorium Elicium 2 Forum Emerald Elicium 1		**Symposia** CT S.05 Electroconvulsive therapy CR S.06 22q11.2DS and schizophrenia risk TR S.07 New insights in compulsivity PR S.08 MicroRNAs and treatment ET E.02 ADHD and life course	**Symposia** CT S.13 Oxytocin in schizophrenia CR S.14 From impulsivity to habit TR S.15 Neural networks in disorders* PR S.16 Sleep and depression ET E.04 New treatments for anxiety	**Symposia** CT S.21 CNS drug repurposing CR S.22 Familial imaging in psychosis TR S.23 Stress as a risk factor PR S.24 mTOR in mental disorders ET E.06 CNS medication in pregnancy
10.40-11.15	Poster podium Poster & Exhibition areas Poster area		**Travel award ceremony** **Coffee break** **Poster viewing**	**Travel award ceremony** **Coffee break** **Poster viewing**	**Travel award ceremony** **Coffee break** **Poster viewing**
11.15-12.00	Auditorium		**Plenary lecture PL.01** Neural correlates of chronic early-life stress	**Plenary lecture PL.03** The role of motivation and reward in mental disorders	**Plenary award lecture PL.05** Impulsivity and compulsivity: neural substrates and neuropsychiatric implications
12.00-14.00	Poster & Exhibition areas		**Lunch**	**Lunch**	**Lunch**
12.15-13.45	Poster area		**Poster session**	**Poster session**	**Poster session**
12.15-12.45	Poster podium		**Rapid-fire poster session**	**Rapid-fire poster session**	**Rapid-fire poster session**
12.15-13.00	Emerald				NS.01 How the Neuroscience Based Nomenclature can change my practice
12.15-13.15	Emerald			**General assembly of ECNP members**	
12.15-14.00	Elicium 2 Elicium 1	**Satellite symposia** C.01 Mania with depressive symptoms C.02 Optimising the treatment of MDD			
13.00-13.15	Poster podium		**Poster award ceremony**	**Poster award ceremony**	**Poster award ceremony**
13.15-13.45	Poster podium		**Career development session** CD.01 Making award winning posters	**Career development session** CD.02 How to give an effective talk	**Career development session** CD.03 A job beyond research
14.00-14.45	Emerald	ES.01: Emerging role of the carer			
14.00-14.45	Auditorium		**Plenary award lecture PL.02** Can we improve speed and efficacy of antidepressant treatments?	**Plenary lecture PL.04** Is it time for immuno-psychiatry?	**Plenary award lecture PL.06** Anxious temperament: results from a translational neuroscience approach
14.45-15.00	Poster & Exhibition areas		**Coffee break**	**Coffee break**	**Coffee break**
14.45-16.30	Elicium 2 Elicium 1	**Satellite symposia** C.03 Defining remission in depression C.05 Functioning and schizophrenia			
15.00-16.40	Auditorium Elicium 2 Forum Emerald Elicium 1		**Symposia** CT S.09 Medications for FT dementia CR S.10 Pharmacological fMRI TR S.11 Interactions in psychosis PR S.12 New targets for treatment* ET E.03 Child mood disorders	**Symposia** CT S.17 Medications for autism CR S.18 Use of imaging in schizophrenia TR S.19 CNV in schizophrenia PR S.20 The gut microbiome ET E.05 Future of neuropsychopharmacology	**Symposia** CT S.25 Medication and fear extinction CR S.26 Biomarkers of suicidality TR S.27 Neuroimaging markers PR S.28 Inflammation and depression ET E.07 Atypical antipsychotic drugs
16.50-18.30	Elicium 2 Forum E104-107 Emerald Elicium 1	**Symposia** CT S.01 Adult separation disorder CR S.02 Biomarkers for clinical use? TR S.03 Brain circuits in addiction PR S.04 PolySia-NCAM schizophrenia ET E.01 Conversions			
17.15-19.00	Auditorium Elicium 2 Forum E104-107 Emerald Elicium 1		**Satellite symposia** C.06 Partial agonists in treatment of schizophrenia C.07 Cognitive dysfunction in depression C.08 Personalised treatment of schizophrenia C.09 Interest in and enthusiasm for meta-analyses C.10 Managing psychiatric emergencies	**Satellite symposia** C.11 Treatment of alcohol dependence C.12 Debating adult ADHD management in 2015 C.13 Cognitive dysfunction in depression C.14 Schizophrenia: investigating antipsychotics	
18.45-20.00	Auditorium	**Keynote session** incl. Keynote lecture KL.01 Prosocial primates: cooperation and empathy			
19.00-21.15	Emerald			**Regulatory update session** RU.01 Depression: inadequate treatment response	
20.00-21.30	Auditorium lounge	**Welcome reception**			

TRACKS

- CT CLINICAL TREATMENT TRACK
- CR CLINICAL RESEARCH TRACK
- TR TRANSLATIONAL RESEARCH TRACK
- PR PRECLINICAL RESEARCH TRACK
- ET EDUCATIONAL TRACK

*Junior Scientist symposium

CLINICAL RESEARCH

S.02: **Biomarkers in the clinic – are we there yet?** Forum **Saturday** 16:50-18:30

Still a long road for clinical biomarkers?

A session that will dissect contemporary perspectives on clinical biomarkers for ADHD, psychosis, depression and other disorders will take place this afternoon, with the underlying question being 'Are we there yet?'.

Tackling the topic of potential biomarkers for psychosis prediction during the session will be Paolo Fusar-Poli (Department of Psychosis Studies, King's College London, UK), who will focus on the clinical relevance of stratifying people at risk for psychosis, in order to prevent the onset of this severe and disabling psychiatric condition.

"First of all I must stress that there are no such biomarkers validated in clinical psychiatry," Dr Fusar-Poli told *ECNP Daily News*. "There are some suggestions, but findings are somewhat conflicting, despite meta-analyses."

Despite the lack of validated psychosis biomarkers, Dr Fusar-Poli noted that the field is alive and well in its search for candidates: "The field is extending from neurobiology, and by that I am thinking of structural grey matter alterations, white matter alterations and functional alterations, and also neurochemical alterations, mostly including dopamine and glutamate. Neurocognition is the second area that has attempted to identify biomarkers to predict the onset of psychosis, and then there is the clinical field – basically trying to identify clinical predictors of longitudinal transition to psychosis.

"Then obviously we have environmental markers such as trauma or exposure to previous life events. They may not qualify as standard biomarkers, so if we want to speak of neurobiological markers, I think there the evidence is still only preliminary."

As Dr Fusar-Poli described, the field is now moving towards integrating different ideas, becoming almost 'agnostic' as to what kind of marker is better suited to predict the onset of psychosis. "We are trying to combine these different measures – not just neurobiology, but also environmental and personal markers, as well as clinical markers and neurocognitive markers to build a predictive model for the outcome, using sophisticated methods."

Comparison between studies is a particular challenge when analysing the potential of a candidate biomarker, in part due to differences in patient demographics, imaging modalities, evaluation methods and other factors.[1] As such, consistency across different countries, samples and high-risk services is still highly questionable, as Dr Fusar-Poli detailed: "If you think of the best approaches identified with, for example, machine-learning methods – grey matter alterations predicting the onset of psychosis – they have been mostly investigated in one or two sites.

"While those methods will employ validation techniques … no external validation of the suggested classifier has been properly done. So we don't know whether a neuroimaging classifier developed in, say, Munich or Bern is valid in London, for example. Hence there is an urgent need for external validation, and this is why the field is now trying to create international databases and international projects to try and promote replication and validation of biomarkers across different consortiums."

> "There is an urgent need for external validation [of biomarkers], and this is why the field is now trying to create international databases and international projects to try and promote replication and validation."
>
> Paolo Fusar-Poli

Dr Fusar-Poli also noted that standardisation of clinical assessment would help minimise differences in the definition of patients at risk of psychosis. "This is something we are trying to address, collaborating with the National Institutes of Health [NIH] in the US, moving towards specific projects to merge data, and standardise a tool to assess people at risk for psychosis."

On that topic, Dr Fusar-Poli highlighted that there are three, large, international studies underway dedicated to stratifying psychosis risk, and prediction of onset. These trials are split between the UK, Germany and the US, with Dr Fusar-Poli being involved in the London-based PSYSCAN trial.[2]

Commenting on a core future goal, he concluded: "It is trying to merge these databases in order to achieve harmonisation of clinical assessment, and replication and validation of biomarkers. Most of them will be based on machine-learning codes, combining the different elements: so not just neuroimaging, but also neurocognition, clinical symptoms, and environmental predictors as well."

Hans Boström

'Digital health biomarkers' for ADHD

Also speaking during the session will be Hans Boström (Qbtech AB, Stockholm, Sweden) who will discuss the clinical implementation of neurobiological measures in the management of ADHD.

Since 2010, Dr Boström has been Medical Director at Qbtech – a company that started on the back of an innovative update to traditional continuous performance tests (CPTs) for ADHD, whereby a camera was incorporated to measure activity of those undertaking the test. This added functionality was able to focus on the hyperactivity component of ADHD, which so many other CPTs under-examine. "Most of todays' CPTs do not include a dedicated hyperactivity component," he told *ECNP Daily News*. "Instead they basically calculate it from an algorithm."

Once this new, improved 'QbTest' was realised, the company began to focus on what could be done to develop the technology further, with hopes to implement a useful testing modality in the clinic.

Inevitably, questions also arose from peers as to the validity and clinical applicability of the test, particularly in terms of how useful it would be when compared to DSM-V criteria for diagnosis of ADHD. "What we are trying to do now is to challenge that," said Dr Boström.

"What we initially focused on was documenting how the test could differentiate between normative people, and those with ADHD. By doing that you first have to sample the normative data, which we have on approximately 1,300 subjects, ages 6 to 60, and then when you measure someone in whom you suspect ADHD, you will get a score – we call it a Q-score – which is the difference in standard deviation, more or less, to what is normative. When you have 1-2 standard deviations from norm, there is a higher likelihood that you

have problems that are associated with ADHD."

This evaluative phase showed that the QbTest had approximately 90% sensitivity and specificity – a result which earned it an informal classification as a biomarker. "I think in a way it we could call it a 'digital health biomarker'," noted Dr Boström.

Despite this result, he noted that in a clinical setting, 'normative' patients rarely come through the door. "Rather you have people with a lot of comorbidities, which could be depression, bipolar disease – anything like that. So what we are struggling with right now, and what I will talk about, is differential diagnosis.

"How can a test like this differentiate typical ADHD from typical borderline or bipolar disorder or depression? We are developing specific algorithms that look at several parameters together. It is not as advanced as an artificial neuronal network, rather you measure different types of response profiles, and then the test compares the test profile from specific patient groups, and then you can post the likelihood of whether you belong to the ADHD group or not."

Dr Boström will also touch upon endophenotypes – specifically recounting a study looking at healthy siblings of ADHD sufferers. "What we could see there interestingly was that hyperactivity, for example, was increased in the healthy siblings, although they did not have the disease," he said

"That shows that hyperactivity, as we measure it, could be an endophenotype of ADHD. That you have the vulnerability for the disease, but for whatever reason, you haven't got it."

Another area sparking interest for Dr Boström is the ability to test the efficacy of a medicine. With present-day methods being largely based on asking patients how they feel after taking medications, Dr Boström argued that this 'arbitrary' evaluation could really benefit from QbTest's more objective assessment. "What we can do is measure the profile before treatment, at the first dose, and then after three and six months," he said. "And then we can see quite early if there is a response to the medicine.

"This is more important today, because we have a lot of new drugs coming in to the field. Before it was mostly methylphenidate, but now you also have dexamphetamine, and others such as atomoxetine. QbTest is very objective way to show if a medicine works or not, and we have witnessed both over- and under-prescription of drugs, so the tool can be quite effective in pitching the level of adequate treatment."

Looking to the future, Dr Boström noted that collaboration was key in order to better implement this kind of objective testing in the clinic. By furthering data collection, and by merging that brain data with clinical assessment, the combination could bestow more diagnostic power. "The interesting aspect of CPTs, compared to MRI and other very advanced technology, is that it is quite easy to do in the clinic," he said.

"But ultimately, we want to know what the test adds in terms of clinical value. If you install test equipment, do you improve the time to diagnosis in that clinic? Do you improve the way you use medicine? We also have a lot of studies in that arena."

In his closing remarks, Dr Boström framed the importance of this digital health corner of the broader biomarker arena, first underlining that, due to its simplicity, use of the test in the home could be an attainable goal in the near future. "I think it will be a new era for CPT," he said. "It has been looked at over the shoulder somewhat, at least by a lot of psychologists who rely on long interviews for diagnosis."

He concluded: "It is also very important as a take-home message that it is not a standalone test. You have to use this objective test in combination with a clinical impression, and the rating scale. If you have those three in place, you have a much better view of ADHD."

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2. PSYSCAN – Translating neuroimaging findings from research into clinical practice. http://ec.europa.eu/ [Accessed August 2015]

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ECNP

ECNP Journal: *European Neuropsychopharmacology*

Behind the scenes at *European Neuropsychopharmacology*

Jaanus Harro (University of Tartu, and Psychiatry Clinic of the North Estonia Regional Hospital, Tallinn, Estonia) is Field Editor of *European Neuropsychopharmacology*, the official journal of ECNP, which encompasses clinical and basic research in the field. He also oversees congress abstract publication, as well as being a member of the ECNP Communication Committee, and of the Workshop Committee that oversees the annual Nice Workshop, next taking place 17-20 March, 2016.

As the final reviewer of all submitted abstracts – which have amounted to over 1,000 over the past few years – Professor Harro gave a little insight into his position, and the process of abstract selection, in an interview with *ECNP Daily News*: "ECNP has a well-established peer review system for the abstracts," he said. "Most often, each has been rated and commented on by three reviewers, but this can range from two to six. I do read all abstracts to note technical issues.

"When the Scientific Programme Committee or the Workshop Committee respectively set up priorities or require other input, such as a proposal for an award committee, then I help to incorporate these suggestions into the decision-making process and provide draft proposals. All this is based mostly on the reviewer's suggestions – which are the oxygen for the process – but it may now and then be necessary to balance these across panels."

Speaking of the challenges of the role in terms of balancing content, taking into account shifting themes whilst maintaining the breadth that the journal's name spans, he explained that the eventual balance of topics of publication necessarily reflect the scope and coverage of submitted work: "We place emphasis on quality," he stressed, adding: "A challenge is always there if the reviewers have wildly different opinions of an abstract."

> "ECNP has a well-established peer review system for the abstracts. Most often, each has been rated and commented on by three reviewers, but this can range from two to six."
>
> Jaanus Harro

Speaking of Jan van Ree, the founding Editor and former Editor-in-Chief of *European Neuropsychopharmacology*, Professor Harro said: "He stands out in particular as the person who established the robust and efficient system that we have. He personally instructed me on how to begin and taught me the tricks of the trade. I hope the standard he achieved has been kept, and that he is satisfied with the journal."

Read the latest from *European Neuropsychopharmacology* at www.europeanneuropsychopharmacology.com

PRECLINICAL RESEARCH

S.04: **Merging mouse and human data on the role of PolySia-NCAM** Emerald **Saturday** 16:50–18:30

Cortical plasticity mediators in schizophrenia

Juan Nacher (University of Valencia, Spain) has worked extensively on the role of adhesion molecule NCAM and its polysialylated form, PolySia-NCAM, in the structural plasticity of interneurons in health and psychiatric illness. This afternoon, he opens a preclinical research symposium dedicated to the molecule and the part it plays during neurodevelopment and schizophrenia.

Structural remodelling, or plasticity, is a critical facet of cognitive processes and the dynamic response of brain structures to stimuli. The mediators of plasticity in both excitatory and inhibitory neurons are of particular interest to illuminating the mechanisms underlying psychiatric disorders, and indeed inhibitory neuron remodelling has been demonstrated after chronic stress.[1]

PolySia-NCAM has been implicated as a plasticity mediator by its association with a subpopulation of cortical interneurons, as Dr Nacher explained in conversation with *ECNP Daily News*: "NCAM has the ability to incorporate long chains of sugars that make NCAM anti-adhesive. So when NCAM is polysialylated, it cannot bind to another NCAM molecule of another cell.

"When this occurs, it is easier for the neuron to change its structure, or to even allow some processes such as migration or synaptogenesis to happen. This is very important during the development of the CNS, but we have found that this also occurs during adulthood in certain regions. When the PolySia sugar is present the neurons are apparently more able to change their structure or even to become isolated from the neighbourhood."

In the cerebral cortex, most PolySia is found on certain interneurons, which sets these apart from other interneurons in terms of structure and connectivity. More specifically, they demonstrate reduced arborisation and fewer synaptic connections.

Going back to the beginnings of his research in PolySia-NCAM, Dr Nacher recalled: "Because this is a molecule that is related to plasticity, we started to ask whether it could be modulated by some molecules that are very important to psychiatric diseases, like dopamine and serotonin. In fact, the expression of this molecule is modulated by these monoamines.

"So we then looked at the brains of schizophrenic patients, and we found that the expression of this molecule was altered in some regions of the prefrontal cortex, which is a critical region in schizophrenia. These changes in this molecule, from NCAM to PolySia-NCAM, occur in parallel to changes in the expression of molecules related to inhibitory neurons in the prefrontal cortex."

Interestingly, both NCAM and the enzymes that bond the PolySia sugar to NCAM have been identified as candidate genes in schizophrenia in certain genetic studies. Recent work by Gianfranco Spalletta, who will also be speaking during the symposium, has evidenced the correlation of clinical and brain structures with serum NCAM and PolySia levels in schizophrenia.[2]

Dr Nacher's group, along with others, have also shown in mouse that altering genes involved in NCAM and its polysialylation during development results in dramatic changes in cortical inhibitory networks. Moreover, they have demonstrated alterations in these cortical inhibitory neurons and in the expression of PolySia-NCAM in animal models of schizophrenia.

> "We have worked with antipsychotics and anti-depressants; both of these have a strong impact on PolySia-NCAM, and at the same time reorganise the inhibitory neurons in the prefrontal cortex."
>
> Juan Nacher

> "We looked at the brains of schizophrenic patients, and we found that the expression of [PolySia-NCAM] was altered in some regions of the prefrontal cortex."
>
> Juan Nacher

Current schizophrenia medications have been shown to significantly influence NCAM and PolySia-NCAM, noted Dr Nacher: "We have worked with antipsychotics and anti-depressants; both of these have a strong impact on PolySia-NCAM, and at the same time reorganise the inhibitory neurons in the prefrontal cortex."

But a growing body of knowledge regarding the mechanisms of plasticity involved in schizophrenia is argument enough for the identification of therapeutic molecules that could reverse developmental aberrations in NCAM. Indeed, this forms one of the directives of the ERA-NET NEURON consortium, out of which this symposium arose.[3]

"We don't have definitive results on that yet," explained Dr Nacher. "But this is the direction we are working in. There are several peptides that can mimic PolySia and some that mimic NCAM, so we can play around with these to try to reverse the alterations that these molecules have during development."

Dr Nacher joins other speakers in a symposium on both mouse and human data on the role of PolySia-NCAM in neurodevelopment and schizophrenia, this afternoon between 16:50 and 18:30 in the Emerald room.

References

1 Nacher J et al. Structural plasticity of interneurons in the adult brain: role of PSA-NCAM and implications for psychiatric disorders. Neurochem Res. 2013 Jun;38(6):1122-33.

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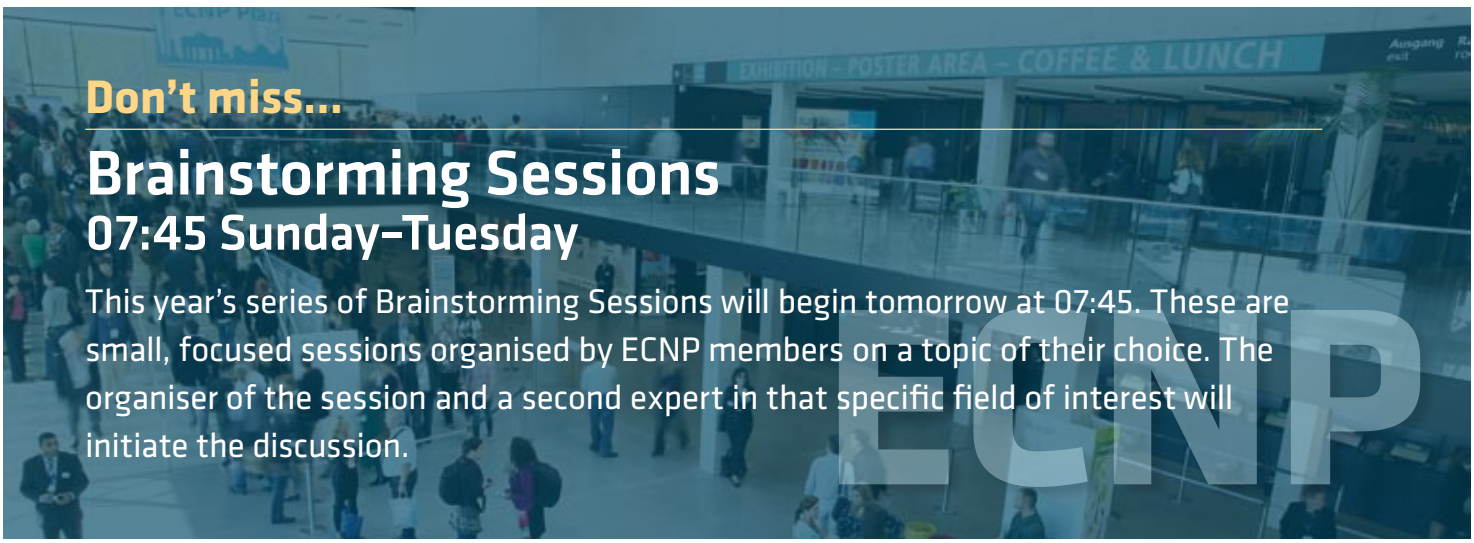
3 ERA-NET NEURON consortium. www.neuron-eranet.eu/index.php



Don't miss...

Brainstorming Sessions
07:45 Sunday–Tuesday

This year's series of Brainstorming Sessions will begin tomorrow at 07:45. These are small, focused sessions organised by ECNP members on a topic of their choice. The organiser of the session and a second expert in that specific field of interest will initiate the discussion.

Available for Apple and Android

Questions? Please go to the ECNP Plaza

ECNP *neuroscience applied*

PRECLINICAL RESEARCH

S.08: **MicroRNAs: leading actors in the scenario of mood disorders** Emeraldv **Sunday** 09:00–10:40

miRNA profiling for prediction of antidepressant response

Major depressive disorder (MDD) is a devastating illness that significantly affects family and personal relationships, sleeping and eating habits, and work and school life. Its impact on functioning and wellbeing has been compared to that of chronic medical conditions like diabetes mellitus.[1] The most common drugs used to treat MDD are selective serotonin reuptake inhibitors (SSRIs), but the exact mechanism of SSRIs in relieving depression is not fully elucidated: remission from depression takes several weeks, despite rapid onset of serotonin reuptake inhibition, pointing to neuronal rewiring and synaptogenesis or neurogenesis.

ECNP Daily News spoke with Noam Shomron (Tel Aviv University, Israel) prior to his talk 'Gene and microRNA expression in the mode of action of treatments for major depression', where he will show his pioneering study into SSRI responsivity. "More than 30% of patients with MDD do not respond well to first-line treatment with SSRIs," he began. "We want to assist in the trial and error approach to selecting the right drug and the right dose. We used a surrogate cell – LCL (lymphoblastoid cell lines), which are immortal lymphocytes lines, transformed with Epstein-Barr virus,[2] and we exposed them for a short duration (three days) to SSRI paroxetine.

"Previous studies have looked at polymorphisms and their associations with drug responses and have focused on the serotonin transporter, but none of the studies were reproducible. Our results suggest that there are other measures that can be used to evaluate drug dose. We noted a marked correlation between cell growth and differential responses to SSRI. We then took the extreme cases – the cells that had either grown very slowly (or been damaged by the SSRIs), and those that had proliferated really well and we compared their miRNA."

Using genome-wide miRNA expression to profile the LCL upon exposure to SSRIs, Dr Shomron's approach was to look at these cells with a very wide scope. The results showed 61 differentially-expressed genes, none of which were related to serotonin, the serotonin transporter or transcription of serotonin. Instead, at the top of the list (and six-fold lower in paroxetine sensitive cells) was CHL1, a cell-adhesion protein and close homologue of L1. On the basis of these findings CHL1 was identified as a tentative SSRI sensitivity biomarker.

Photo by Kfir Ziv 026

"We want to assist in the trial and error approach to selecting the right drug and the right dose."

Noam Shomron

Dr Shomron continued: "More encouraging still was the discovery that CHL1 was expressed in the brain,[3] that it was implicated in both schizophrenia and autism,[4,5] and it also was involved in neuronal guidance.[6] In animal studies it has been shown that CHL1 is co-expressed with L1 in the dorsal thalamus and this neuronal pathway is implicated in mood control in wild-type mice.[7] Furthermore, the CHL1 knockout mouse showed a shift in the axon from thalamus to the visual cortex and altered connectivity in the prefrontal cortex."[8]

These data, collected from Dr Shomron's small study (10 cells, studying gene expression, costing $10,000) was corroborated two years later by a large and costly study carried out by the STAR*D consortium that looked at 1149 DNA samples, and clinical data for 998 MDD patients. The authors also ranked the different polymorphisms, showing five genes possibly involved in mood disorders and to Dr Shomron's delight, CHL1 was amongst them.[9]

Galvanised by this data, Dr Shomron repeated these gene expression studies with a longer, 21-day exposure to SSRI paroxetine. Once again the serotonergic transporter was not involved, but this time neither was CHL1. Instead the protein ITGB3 – coding for integrin beta-3 – was differentially expressed between the responders and non-responders.[10] This gene is found expressed in the hippocampus and frontal cortex and is essential for serotonergic activity,[11] and is implicated in autism,[12] and early-onset schizophrenia.[13]

It is known that ITGB3 binds to serotonin transporter,[14] but it is unknown is how CHL1 is involved. Dr Shomron postulated that excess CHL1 attracts ITGB3 (thereby competing with the serotonin transporter), which then makes the transporter less active.

The final question is whether ITGB3 or CHL1 expression can be used as biomarkers for SSRI response biomarkers. The potential value of these miRNAs as tentative SSRI response biomarkers has proven in mice,[15] and these findings implicate ITGB3 in the mode of action of SSRI antidepressants providing a novel link between CHL1 and the serotonin transporter. Dr Shomron is currently extending this study in humans, testing whether these miRNAs have predictive responsivity to SSRIs in humans using simple blood test by comparing 100 patients and after treatment. For now, it is clear that human LCLs are a powerful and cost-effective tool showing great potential as response biomarkers for individualised treatment.

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TRANSLATIONAL RESEARCH

S.07: **Translational insights into compulsivity** Forum **Sunday** 09:00–10:40

Getting to the roots of compulsivity

Compulsivity forms the focal point of a translational research session taking place tomorrow morning, chaired by Jeffrey Glennon (Radboud University Nijmegen Medical Centre, the Netherlands) and Joseph Zohar (Tel Aviv University, Israel). The session will explore a number of current investigations that are succeeding in tying together compulsivity's heterogeneous origins, with cross-diagnostic comparisons reinforcing the notion that a dimensional approach to psychiatry lays a fruitful stepping stone towards novel therapeutic targets.

Among the work under discussion is TACTICS (Translational Adolescent and Childhood Therapeutic Interventions in Compulsive Syndromes[1]), an EU FP7 consortium which aims to identify the neural, genetic, and molecular factors involved in the pathogenesis of compulsivity, which Dr Glennon coordinates alongside Jan Buitelaar (Radboud University Nijmegen Medical Centre, the Netherlands). The multidisciplinary venture, which combines 11 partners from seven different countries, combines methods such as structural neuroimaging, neurochemistry, behavioural study, genetics, proteomics and Bayesian machine-learning, in both humans and animals, in order to better understand the underlying mechanisms behind the trait that plays a role in psychiatric disorders such as autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD), as well as in the drug-seeking behaviours that often emerge in attention deficit-hyperactivity disorder (ADHD).

Dr Glennon will be presenting recently-uncovered genetic networks underlying compulsivity as part of the TACTICS study. In an interview with *ECNP Daily News*, he detailed the dynamic nature of the trait that – if properly understood – could be harnessed for a more patient-specific approach to therapy: "We are interested in the switch, in the case of ADHD drug-seeking, from impulsivity to compulsivity – whether it is part of the same trajectory. We are also interested in the common mechanisms across those with different disorder diagnoses that have this compulsive trait. Although there are different kinds of compulsivity, we are interested in whether they have the same pleiotropic mechanisms underlying it."

TACTICS is now three years into its five-year research cycle. Its overarching proposal, explained Dr Glennon, is that the top-down control of fronto-striatal circuits, underpinned by glutamate-dopamine-serotonin interactions, are altered to give rise to compulsive traits, and that controlling this could be anti-compulsive.

"We have had some interesting results coming out in terms of the genetics and epigenetic mechanisms," he continued. "In particular, we started to focus on what are named microRNAs – small, non-coding RNA molecules that could basically alter the outcome of whether you see a gene translated into a protein by altering messenger RNA expression.

"We think of these microRNAs as essentially conductors of an orchestra of several genes and that these microRNAs might give us some epigenetic understanding of these compulsive traits. Barbara Franke [Radboud University Nijmegen Medical Centre, the Netherlands], Jan Buitelaar and I started analysing large genome-wide association studies in OCD. From that analysis by Ilse van de Vondervoort and Geert Poelmans, we found that insulin signalling genes played very prominent roles. This association between insulin signalling, their microRNA regulators and compulsivity is confirmed in animal models showing compulsive behaviour. Conversely, type II diabetes animal models exhibit compulsive behaviour."

During his talk, Dr Glennon will touch upon the connection between insulin signalling and fronto-striatal networks, linking this together with the epigenetic regulators of insulin genes, where differences have also been found in both humans and animal models of compulsive-like behaviour. Indeed, one of the aims of the TACTICS proposal was to see if elevated glutamate transmission and compulsivity could be substantially linked.

Tied in with this aim is the explicit demonstration of the correlation between overactivity within fronto-striatal circuits and compulsive behaviour. "This is a key goal of our cross-disorder fMRI studies within TACTICS; that we can substantiate that link," said Dr Glennon. "We had a review paper published in 2015 which showed that glutamate transmission changes in these compulsive disorders across the lifespan.[2] So it is really important, then, to understand compulsivity with regards to a particular time point. As a child, an adolescent, or an adult, glutamate tone is very different. Therefore, how you treat that glutamate tone may actually require tailor-made strategies suitable for that age group.

"They should also be suitable in terms of gender effects. We did not know whether these changes in glutamate transmission could hold equally for girls as it does for boys. There was not a lot of literature on this topic when we started the project, so we became particularly interested in exploring this. But particularly with age-related changes in glutamate transmission, as measured by the Glx signal [the combination of glutamate and glutamine that is quantified in proton magnetic resonance spectroscopy (MRS)], you see a very robust change across time."[2]

To move beyond this review, which looked at 59 individual studies in order to reach the hypothesis of age-related changes in fronto-striatal glutamatergic circuits, Dr Glennon and colleagues are now acquiring their own MRS data across different diagnostic categories: ASD, OCD and ADHD. Currently, explained Dr Glennon, they are substantiating the level of interaction that lies between the genetic mechanisms related to glutamatergic genes and fronto-striatal changes. Furthermore, to address novel treatment strategies in juvenile compulsivity, the TACTICS researchers (notably Ralf Dittmann of the Central Institute for Mental Health, Mannheim, Germany) are embarking on Phase IIb studies to determine whether the NMDA receptor antagonist memantine is anti-compulsive in clinical cohorts.

"TACTICS is really a story related to glutamate- and insulin-related signalling," concluded Dr Glennon. "And that is something that we are very excited about because this connection between insulin, glucose metabolism and compulsivity is not something that was really very prominent in the literature. We think this is an exciting way to think about compulsivity."

> "We are interested in the switch, in the case of ADHD drug-seeking, from impulsivity to compulsivity – whether it is part of the same trajectory."
>
> Jeffrey Glennon

> "It is really important to understand compulsivity with regards to a particular time point. As a child, an adolescent, or an adult, glutamate tone is very different."
>
> Jeffrey Glennon

More details on the TACTICS consortium can be found at tactics-project.eu

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TRANSLATIONAL RESEARCH

S.07: **Translational insights into compulsivity** Forum **Sunday** 09:00–10:40

Neuroimmunological regulators of compulsivity

Tomorrow morning's symposium, 'Translational insights into compulsivity,' concludes with Giovanni Laviola (Istituto Superiore di Sanità, Rome, Italy) discussing his recent work on identifying the neuroimmunological regulators of compulsivity. Dr Laviola and colleagues have published a series of works over the past decade exploring the consequences of immune disruption in animal models, and he related these findings to compulsive behaviours during an interview with *ECNP Daily News*.

Dr Laviola began by describing the emergence of his present ideas: "Everything started almost 10 years ago, with the input of a Russian colleague, Dr Oleg Granstrem [Pavlov's State Medical University, St. Petersburg, Russia], who was working at Emory University [Atlanta, USA] with Professor Svetlana Dambinova. They were interested in the detection of autoantibodies (aAbs) against various glutamate receptors as a diagnostic tool for ischemic stroke consequences and prevention."

While doing so, Dr Granstrem also designed small fragments corresponding to the sequence of the dopamine transporter (DAT) protein, based on the most likely extracellular location of an epitope supposedly bound by aAbs.

With these DAT-derived fragments in their hands, Dr Laviola (along with colleague Walter Adriani of Rome's Istituto Superiore di Sanità) conducted a repeated immunisation study in mice.[1] "As expected, the immunised animals were found to actively generate DAT-directed aAbs," recalled Dr Laviola. "Notably, their immune activation was accompanied by profound changes in behaviour – the flexibility to shift a choice in operant paradigm settings, as well as slight hyperactivity and altered dopaminergic parameters in the striatum.

"It was then easy to speculate that the presence in plasma of DAT-directed aAbs could in some way be associated with their targeting the brain and thus affecting changes in procedural memory, if not even in the formation and expression of behavioural habits, in human subjects as well."

Just how far these mechanisms can be ascribed to the precipitation of analogous behaviours in human psychiatric illness, relative to other factors, remains a knotty question; but the field is young, with clues abundant in the literature: "Some psychiatric conditions linked to some autoimmune forms of encephalitis have been ascribed to, for example, NMDA-aAbs and/or AMPA-aAbs. But nothing is known yet for DAT-aAbs.

"For ADHD-related symptoms, the only study available so far is our own, in which we investigated affected children with or without methylphenidate administration therapy. It should also be noted that we reported the behavioural landmarks and plasma levels of DAT-aAbs interacting with the presence of polymorphisms in the DAT protein (the variable number tandem repeat (VNTR) alleles). This means that autoimmune mechanisms in this case are not likely to act alone – rather, they interact with genetic factors."[2]

The basis of behaviours characteristic of ADHD – alongside compulsive behaviours in substance abuse, gambling disorder, hypersexuality, OCD, Tourette's syndrome, and others – is a leading research theme. Moreover, explained Dr Laviola, the possibility that aAbs might tap directly into neural striatal circuits is intriguing.

Drs Laviola and Adriani's 2012 paper outlines some of the mechanisms by which immune insults on the brain might be mediated[1]. Considering the notion that the immune system is continuously involved in the formation of autoantibodies, Dr Laviola described how this might in some select circumstances lead to psychopathology: "Normally, the cell clone producing an aAb will be terminated, because the target epitope is recognised as 'self'. But – as is the case in multiple sclerosis, wherein a cell clone starts to produce aAbs against myelin – is it not possible that another cell clone could produce aAbs fighting against dopamine terminals in the striatum?

"In the case of the DAT 10/10 polymorphism, it is likely that there is a genetically-driven overproduction of DAT. The elevation in DAT-aAbs may well be considered as an adaptive process aimed to counteract the excessive DAT levels. If this is true, autoimmunity should be regarded not as a pathology, but instead as a 'normal' homeostatic process. The pathology may stem from a disruption of this immune control over genetic expression of a protein."

Dr Laviola believes that aAbs could be harnessed as biomarkers of immune processes regulating neurotransmission proteins such as DAT, and perhaps even dopamine receptors, with non-invasive peripheral measures providing a window on goings on within the brain. He also noted that brain DAT function is highly relevant with respect to vulnerability to compulsive syndromes, as well as to some addictive behaviours, to ADHD, and to risk-taking and sensation-seeking vulnerabilities.

"We may predict that elevation in DAT-aAbs titres could be useful to screen for people with a given behavioural profile, likely to engage in 'risky business,' for instance. Imagine what avenues could be opened if the screening for DAT-aAbs would allow us to distinguish those whose immune issues go on to precipitate psychiatric illness from those who do not!"

> "As is the case in multiple sclerosis, wherein a cell clone starts to produce aAbs against myelin, is it not possible that another cell clone could produce aAbs fighting against dopamine terminals in the striatum?"
>
> Giovanni Laviola

> "Some psychiatric conditions linked to some autoimmune forms of encephalitis have been ascribed to, for example, NMDA-aAbs and/or AMPA-aAbs. But nothing is known yet for DAT-aAbs."
>
> Giovanni Laviola

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ECNP

The ECNP Office

Behind the scenes at the ECNP Congress

Each year, a wealth of individuals work closely together to ensure that the annual ECNP Congress runs smoothly in its temporary home. Every detail, from venue choice to scientific programme, from budget to room layout, and even what food to serve at the Welcome reception must be worked out in advance, and there are a myriad of links in the chain that need to be in place – often with little time to spare. "We've had some tight planning this year, as the congress has been moved earlier, to August," recalled Godelieve Escartín, Project Manager Congresses and Meetings at the ECNP Office.

"But our very committed and experienced team at the ECNP Office – and the dedicated individuals at Colloquium Brussels (who handle many aspects such as registration, hotel reservations and onsite management) – have made it possible to arrange everything on time!"

Ms Escartín, alongside another dozen members of the core ECNP Office, collectively oversee all scientific, communicative, educational and operational aspects of the college, its meetings and initiatives. With emphasis on rotational, structured experience, it means each year may see a different person taking the lead on projects such as the ECNP Congress.

And the 28th ECNP Congress in Amsterdam will mark a landmark 10th year for Ms Escartín, giving her a special perspective on how the ECNP Office has developed in the last decade. "During those 10 years I have witnessed many changes and improvements at ECNP," she said. "Every year new projects and initiatives are born, and it is always a challenging yet rewarding process to be able to realise them in the best possible way.

"I have always worked in the logistics team, and when I started we organised three to four meetings besides the annual congress, with many tasks done by our contracted congress organisers. Now a decade later, we organise around 15 meetings besides the congress, and almost all of the tasks are handled by the ECNP Office."

Of course, the ECNP Office also relies on a vast and varied collection of other people to make each meeting – particularly the Congress – a success: "Without all of the volunteers from each of the different committees, we would not be able to organise a congress with such a high level of scientific excellence," said Ms Escartín.

"The Scientific Programme Committee, and especially its chair Wim van den Brink, are in very close contact with my colleagues at the office to make sure there is a scientific programme filled with nothing but the best speakers. Thanks to them we have a very well-balanced programme, and a very high level of science at our congress.

"A project manager cannot realise a successful project without a good team, and once again my colleagues at the Office, at Colloquium Brussels, and also our main suppliers (which we use every year) make it so much easier to realise such a large and complex project."

As each year beckons, the organisational team are also tasked with implementing any new initiatives that are introduced at the Congress, and in 2015 there are several new updates: "Every year we try to improve the programme of our congress, and we try to implement new topics, sessions or other ideas," said Ms Escartín. "This year we introduce the EUFAMI session, held at 14:00 on Saturday, as we also would like to focus on the other side of brain disorders: the role of the family carer.

"Furthermore, we also wanted to give more emphasis to the Career development sessions, thus we moved them to a lunch-time slot, and relocated them to the thriving poster area. In these sessions, advice will be given by senior members on aspects such as how to make a good poster, a stand-out presentation, or how to forge a career outside of research – topics which are especially interesting and useful for junior scientists.

"In addition, every year we try to improve not only the scientific parts of the congress, but also all other parts, like the app. To that end, this year we introduce the ECNP App, which incorporates the congress as always, but also encompasses other meetings, meaning the app can be used all year round. Furthermore, we've improved our e-posters, making sure all physical posters are also shown in e-poster format, and keeping the award area exclusively as an e-poster-only area."

> "Without all of the volunteers from each of the different committees, we would not be able to organise a congress with such a high level of scientific excellence."
>
> Godelieve Escartín

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CLINICAL TREATMENT

S.21: Drug repurposing in CNS: how to maximise the benefits **Auditorium** Tuesday **09:00–10:40**

Drug repurposing: The US experience

During Tuesday's drug repurposing symposium, co-chaired by Michael Davidson and Jan van Ree, Carla Canuso (Janssen Research & Development, NJ, USA) will be providing an industry perspective on the challenges and successes encountered in drug repurposing initiatives based on experience with the US programme, New Therapeutic Uses, run by the National Center for Advancing Translational Sciences (NCATS).

The New Therapeutic Uses programme[1] is a collaborative venture, as Dr Canuso described in conversation with *ECNP Daily News*: "The programme is designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutics development," she said. "The initiative began with a pilot programme in 2012, as part of the NIH's newly established NCATS. This programme matches researchers with a selection of pharmaceutical industry assets to test ideas for new therapeutic uses, with the ultimate goal of identifying promising new treatments for patients."

> "[NCATS] matches researchers with a selection of pharmaceutical industry assets to test ideas for new therapeutic uses."
>
> Carla Canuso

In its pilot programme and a subsequent request for proposals, NCATS posted information on over 75 compounds from eight pharmaceutical companies.[2] Academic investigators submitted brief proposals, and the best were selected for review by the pharmaceutical companies. Companies then determined which projects they wished to pursue, and Collaborative Research Agreements were established and full grant proposals were submitted.

Across the pond, the UK's MRC-Industry Asset-Sharing Initiative[3] and ECNP's Medicines Chest[4] follow in a similar vein. And indeed, the willingness of pharmaceutical companies to give investigators access to so-called 'deprioritised compounds' has led to collaborations funded by private foundations as well.

"There are many benefits of this approach for companies, including shorter drug development times and leveraging prior investments to ultimately bring new treatments to patients. There are in fact pharmaceutical companies that focus specifically on drug repositioning by in-licensing assets that are Phase II ready.

"However, larger pharmaceutical companies often must make strategic business decisions around which assets to take forward into full development. Therefore if a compound is not successful in the first indication in which it is tested, it may be 'deprioritised' or 'shelved'. Additionally, while a given company may have expertise in the original indication, it may not possess the same capabilities in another therapeutic area or disease state."

One key challenge in negotiating with private companies, explained Dr Canuso, is that the enduring value of such compounds must be clearly demonstrated to management and internal partners, in order for them to justifiably renege on previous decisions that led to the discontinued development of these compounds in the first place. "It is important to identify internal allies and champions for each specific proposal," she added. "These are often individuals who have a history with the compound and are eager to see it tested further."

Although studies from the New Therapeutic Uses programme are still underway, the programme is already seeing evidence of success, as Dr Canuso: noted "For example, a group of investigators at Yale University School of Medicine demonstrated that a drug originally developed for various cancers can reverse memory deficits and synapse loss found in Alzheimer's disease mouse models.[5]

"A subsequent clinical trial of patients with mild-to-moderate Alzheimer's showed the compound to be reasonably safe and well tolerated, and able to achieve substantial CNS penetration with oral dosing.[6] As a result of this translational line of research, the investigators have recently launched a larger Phase IIa clinical trial of a promising new therapy with a novel mechanism of action."

> "It is important to identify internal allies and champions for each specific proposal. These are often individuals who have a history with the compound and are eager to see it tested further."
>
> Carla Canuso

This is a welcome tale, and one that sharply contrasts the on-average 14-year journey required from discovery of a therapeutic target to approval of a new drug – a process that is estimated to fail in 95% of cases.

Following its 2012 birthdate, New Therapeutic Uses made its first nine funding agreements in 2013. Encouragingly, five of these pertained to CNS disorders. Another round of funding was released in 2014, and while NCATS funding announcements are currently closed, the high level of investigator response to this grant mechanism will lead to future funding announcements.

Dr Canuso will be presenting 'The snags and the hitches of starting a trial with a proprietary compound: experience from the NCATS,' as part of the symposium on CNS drug repurposing taking place on Tuesday morning between 9:00 and 10:40.

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Rapid-fire posters offer snapshots of exemplary research

After first being implemented at last year's ECNP Congress in Berlin, the Rapid-fire (RF) poster sessions will return this year, giving 18 of the highest-scoring poster presenters the chance to exhibit an e-poster of their work in front of an audience.

Each RF poster presenter is selected based on the quality of their abstract, and receives this added exposure in addition to their participation in the usual poster sessions. Held on Sunday, Monday and Tuesday between 12:15–12:45, each RF poster session will feature six speakers, for five minutes each.

ECNP Daily News caught up with one presenter from each of the three sessions to find out more about the kinds of studies these exemplary posters will be showcasing.

Mireia Rabella Figueras

L'Institut de Recerca del Hospital de Sant Pau, Barcelona, Spain

In the first RF Poster session, held on Sunday, Ms Rabella Figueras will describe her work centred on the neurophysiological evidence of impaired self-monitoring in schizotypal personality disorder, and its pharmacological reversal.

As she details in her poster abstract, schizotypal personality disorder (SPD) is a schizophrenia-spectrum disorder characterised by odd or bizarre behaviour, strange speech, magical thinking, unusual perceptual experiences, and social anhedonia. Schizophrenia itself has been associated with anomalies in dopaminergic neurotransmission, as well as deficits in neurophysiological markers of executive function, such as error-related negativity (ERN), a component of an event-related potential (ERP).

ERN manifests after performance errors, therefore it is considered a correlate of behavioural monitoring. It relies on adequate fronto-striatal function, is dopamine sensitive, and thus SPD and schizophrenia have been proposed to share a common neural basis.

With this in mind, Ms Rabella Figueras implemented a study to investigate whether SPD patients show deficits in behavioural monitoring when compared to healthy controls (as measured by ERN). Crucially, risperidone – an antipsychotic – was also employed to see whether this deficit could be reversed.

> "... deficits on behavioural monitoring in schizotypal personality disorder patients, measured with ERN, were reversed with risperidone."
>
> Mireia Rabella Figueras

"The study was carried out according to a double-blind randomised, cross-over, placebo-controlled design," she told *ECNP Daily News*. "SPD and controls participated in two different experimental sessions in which they were tested after receiving a placebo (lactose capsule) or an oral dose of 1mg of risperidone."

She added: "A behavioural task and electroencephalography recording (EEG) were conducted two hours after drug administration, when the peak risperidone plasma levels were expected. A choice reaction time task, the Eriksen flanker task, was then used. Participants were required to respond to the centre letter of a five-letter array, designated as the 'target', with either a left-hand or right-hand response; the goal of this procedure being to aim for a reaction time that would yield approximately 10-15 % of errors. Subjects were encouraged to respond to the stimuli as fast as possible and to correct their errors as fast as possible whenever they detected them."

As Ms Rabella Figueras described, in the absence of risperidone, the analysis of behaviour from both groups showed that, under placebo, performance was worse in the SPD group, with significantly slower reaction times, and increased time taken to correct errors. After risperidone administration, SPD patients showed reduced correction time, but interestingly, correction time increased in the control group. "Thus, risperidone normalised patients' behavioural performance," she said.

"The same effect was observed in ERN amplitude: While risperidone reduced ERN amplitude in controls, it was increased and restored in patients. As such, deficits in behavioural monitoring in SPD patients, measured with ERN, were reversed with risperidone."

Describing the clinical implications of the findings, Ms Rabella Figueras stressed that the study gave credence to the use of ERN as a measure of predicting response to risperidone in psychotic spectrum disorders. "This biological marker of predisposition to psychosis should be included as a predicting response variable to the pharmacological treatment with risperidone," she said, adding: "This would be useful in naïve first-episodes of psychosis, in which adequate pharmacological treatment only could be found through trial and error.

"In this case, risperidone could be an indicated treatment for patients with deficits in ERN. Similarly, It would be useful to include ERN measures in Ultra-High-Risk patient follow-ups to control and study further this variable along the illness process."

> "... if neurofeedback training effectively enhances dopaminergic sensitivity for non-drug related rewards in cocaine users, this could be a novel treatment strategy to reduce drug-using behaviour in cocaine addiction."
>
> Matthias Kirschner

Matthias Kirschner

Department of Psychiatry, Psychotherapy and Psychosomatics, University of Zürich, Switzerland

On Monday, Dr Kirschner will join his fellow RF poster presenters to discuss his work evaluating self-regulation of the dopaminergic reward system, and its implication for cocaine addiction. "Cocaine addiction is a severe chronic disorder influencing neuroplasticity in the dopaminergic reward circuits[1]," began Dr Kirschner. "These maladaptive neuronal changes contribute to compulsive drug use and reduced sensitivity to previously rewarding life situations or natural reinforcers.[2] In contrast to this, sensitivity to drug cues is enhanced. However, until now, treatment of cocaine addiction is limited and often ineffective.

"Recent research in the field of real-time fMRI (rtfMRI) revealed a novel method to self-regulate key structures in the dopaminergic reward system, i.e. neural activity in the substantia nigra and ventral tegmental area (SN/VTA), with positive mental imagery.[3] This self-regulation of SN/VTA can be trained and improved via rtfMRI mediated neurofeedback.[4]

"For the first time, we tested this innovative method in a clinical population of cocaine users (CUs) to evaluate its potential capability as a novel treatment strategy. We tested i) whether CUs are able to self-regulate SN/VTA activity by imagination of non-drug-related cues, and ii) if CUs can improve this self-regulation ability with rtfMRI neurofeedback training. If feasibility of this approach is demonstrated in CUs, it might have the potential to improve therapeutic options in cocaine addiction, and patients may be able to increase their sensitivity to natural and non-drug related reinforcers in SN/VTA, i.e. in brain regions usually activated by drug cues."

Using a cross-sectional design comprising CUs, and matched healthy controls, participants were advised to voluntarily upregulate neural

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THE 28TH ECNP CONGRESS

Rapid-fire poster sessions

Rapid-fire posters offer snapshots of exemplary research

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activity in the SN/VTA via positive mental imagery. During an rtfMRI task, visual feedback of neural activity was provided. The main outcome measure from the study was the increase in blood oxygenation-level dependent (BOLD) activity induced by positive mental imagery in the SN/VTA and related regions.

Each participant underwent four functional runs (a baseline run without feedback, two runs with feedback, and a transfer run without feedback), with each run subdivided into nine blocks of alternating 'Rest' (20 s) and positive imagery (or 'Happy Time'; 20 s), totalling approximately six minutes.

As Dr Kirschner described, so far 12 participants with cocaine use higher than 1g/week (for at least 6 months) and 14 healthy controls were included in the ongoing study. "We successfully implemented the novel rtfMRI method previously developed by Sulzer et al.[4] for healthy controls in a clinical population of CUs, and all participants completed the full session and were able to perform the rtfMRI mediated neurofeedback task."

Briefly touching upon the main findings, he continued: "One, we replicated findings from Sulzer et al.[4], showing that healthy participants are readily able to self-regulate activity within in their brains' reward systems. Two, we extended the work of Sulzer et al. by showing for the first time that cocaine users are also able to self-regulate and activate their reward system by positive imagery of non-drug related cues. This constitutes the first step towards the use of rtfMRI self-regulation as novel non-invasive treatment strategy in cocaine addiction.

"Three, preliminary results suggest that both groups, healthy controls and cocaine users, are able to improve self-regulation of neural activity in the dopaminergic midbrain based on rtfMRI mediated neurofeedback. So far, we did not observe any group difference between healthy controls and cocaine users in our preliminary analysis including only 12 and 14 participants per group."

"Why is it that some people can use cannabis heavily for 20 years and still function properly, and others can't take cannabis once without having paranoid symptoms, or develop psychosis?"

Erika van Hell

Ms Rabella Figueras, Dr Kirschner and Dr van Hell will join a total of 18 speakers in this year's three Rapid-fire poster sessions, taking place on Sunday-Tuesday between 12:15 and 12:45 at the Poster Podium.

References

1. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology. 2008;33:166–80.

2. Volkow ND, Baler RD, Goldstein RZ. Addiction: pulling at the neural threads of social behaviors. Neuron. 2011;69:599–602.

3. Sulzer J, et al. Real-time fMRI neurofeedback: progress and challenges. Neuroimage. 2013a;76:386–99.

4. Sulzer J, et al. Neurofeedback-mediated self-regulation of the dopaminergic midbrain. Neuroimage. 2013b.83C, 817–825.

With this in mind, Dr Kirschner went on to comment on the implications for cocaine addiction, first highlighting that dysfunction of the dopaminergic reward system, especially an imbalance between high drug and drug cue sensitivity, and reduced response to non-drug related rewards, have been suggested to be core deficits in cocaine addiction. "In patients with cocaine addiction this dopaminergic imbalance may contribute to the tendency to favour drug taking behaviour instead of non-drug related life situation (e.g. social activities with family)," he said.

"Therefore, if neurofeedback training effectively enhances dopaminergic sensitivity for non-drug related rewards in CUs, this could be a novel treatment strategy to reduce drug-using behaviour in cocaine addiction."

In his closing remarks, Dr Kirschner emphasised that future research and clinical studies would be needed to establish the effectiveness of this approach and its potential clinical use. He described some of this potential future work: "We aim to evaluate the association between self-regulation of neural activity within SN/VTA and the sensitivity of this region to drug-related cues as assessed in a drug-cue reactivity task within the same participants.

"Finally, we are aiming to test if neurofeedback-assisted training of self-regulation of the reward system can reduce cocaine use in a future clinical study."

Erika van Hell

Oldebroek, the Netherlands

In the final RF poster session, held on Tuesday, Dr van Hell will be presenting work that has been investigating how two important constituents of cannabis, Δ9-Tetrahydrocannabinol (THC) and cannabidiol (CBD), affect brain activity during rest. "THC is associated with cognitive deficits particularly in the areas of memory and attention," she told *ECNP Daily News*. "Generally, reaction times increase, more mistakes are made, and complex tasks in terms of dividing attention between several things is more difficult.

"In addition, THC is psychoactive, which means that acutely, perception changes (sounds can change, colours can change, people can hear voices or things that other people can't hear), or people can become paranoid or anxious. These effects are not associated with the administration of CBD."

Dr van Hell went on to frame the genesis of her study, noting: "CBD has gained interest in recent years as it seems to be counteracting some of the effects that are caused by THC. One interesting finding is that CBD works as an anti-psychotic, and as such, might be a helpful addition to the medication that is currently available for schizophrenia patients."

The overall aim of the large study which Dr van Hell has been involved in is the exploration of the link between cannabis and psychosis, and the development of schizophrenia. "Why is it that some people can use cannabis heavily for 20 years and still function properly, and others can't take cannabis once without having paranoid symptoms, or develop psychosis?" she said.

"One question we had was how it works with the combination of THC and CBD – we know quite a bit about THC, and there is more and more about CBD, but the actual combination of the two has never really been under systematic investigation … so that's what we have tried to do."

She added: "We were interested in the combination, because there are indications that there are less psychotic symptoms, and less anxiety in people who generally use cannabis with higher levels of CBD."

Dr van Hell performed a double-blind, cross-over, placebo-controlled study with 15 frequent cannabis users, 15 infrequent users/non-user controls, tested with five randomised drug sessions with a one week washout. Subjects received: a) placebo; b) THC alone; c) CBD alone; d) Low-dose THC and CBD in combination; and e) High-dose THC and CBD in combination. EEG was used to measure 32 channels across the scalp during five minutes of rest, before and after drug administration.

Results showed that administration of acute THC, and to a lesser extent CBD, increased resting-state brain activity, but CBD in combination with THC could normalise brain function. There was reduced alpha power in the EEG at rest for the frequent users when compared to infrequent, thus indicating chronic cannabis use is linked to altered brain function, and is also likely to change cannaboid sensitivity.

Dr van Hell noted a take-home message from these data: "As CBD in combination with THC can normalise brain function, this is important to keep in mind when using CBD as medication."

Issue 2

Filled with highlights, interviews and live coverage of the Congress so far

ECNP DAILY NEWS

Available Sunday morning!

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Can you identify 10 neurotransmitters in the wordsearch below?

Words could appear horizontally (forwards or backwards), diagonally or vertically.

E	I	N	T	H	I	L	N	S	U	T	T	O
A	S	E	R	O	T	O	N	I	N	N	X	N
U	N	N	D	N	T	O	O	N	X	Y	I	E
E	N	I	L	O	H	C	L	Y	T	E	C	A
E	T	M	N	N	P	N	S	O	N	P	R	X
S	S	A	A	O	A	A	C	I	I	H	T	O
P	Y	T	M	O	T	I	M	G	Y	H	T	E
C	E	P	H	A	N	A	P	I	T	O	M	T
A	N	Y	U	T	T	G	L	A	N	I	E	C
L	E	R	P	S	R	U	U	E	M	E	X	Y
I	R	T	I	I	Y	P	L	O	M	I	O	H
E	N	H	E	M	A	B	A	G	I	M	E	C
N	L	I	S	P	S	O	Y	O	S	N	I	A

Answers will be revealed in Issue 2 of *ECNP Daily News*

TODAY'S PROGRAMME SATURDAY

TIME ROOM	SESSION	
12.15 - 14.00		**Satellite symposia**
	Elicium 2	C.01 The burden of mania with depressive symptoms and the consequences of suicidality
	Elicium 1	C.02 Optimising treatment strategies for patients with MDD who do not respond adequately to antidepressants
14.00 - 14.45	Emerald	ES.01 **EUFAMI family carer focused session** – Emerging role of the carer – how healthcare systems need to change (including ECNP Media Award ceremony)
14.45 - 16.30		**Satellite symposia**
	Elicium 2	C.03 Defining remission in depression: is MADRS enough?
	Elicium 1	C.05 Functioning and quality of life as a long-term treatment goal in schizophrenia
16.50 - 18.30		**Symposia**
	Elicium 2	CT S.01 TNM symposium – Adult separation anxiety disorder: boundaries, causes and potential treatments
	Forum	CR S.02 Biomarkers in the clinic – are we there yet?
	E104-E107	TR S.03 Functional changes in limbic and sensorimotor brain circuits underlying the development of drug addiction
	Emerald	PR S.04 Merging mouse and human data on the role of PolySia-NCAM in neurodevelopment and schizophrenia
	Elicium 1	ET E.01 Psychogenic movement disorders and psychogenic seizures
18.45 - 20.00	Auditorium	**KL.01 Keynote session incl. Keynote lecture:** Prosocial primates: cooperation and empathy
20.00 - 21.30	Auditorium lounge	**Welcome reception**

CT CLINICAL TREATMENT TRACK CR CLINICAL RESEARCH TRACK TR TRANSLATIONAL RESEARCH TRACK PR PRECLINICAL RESEARCH TRACK ET EDUCATIONAL TRACK