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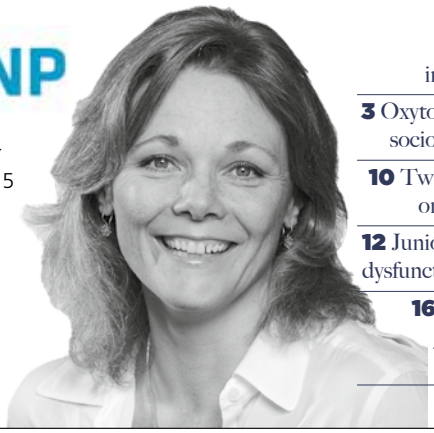

ECNP DAILY NEWS

Keynote Session marks official opening of 28th ECNP Congress

Frans de Waal delivers his Keynote Lecture

ECNP President Guy Goodwin delivered a warm and informative welcome address for the 28th ECNP Congress in Amsterdam on Saturday evening, commenting: "The objective of ECNP is to advance the science of the brain, and most crucially to apply that science for promotion of better treatment and enhanced brain health.

"We can achieve this by bringing people together: scientists, clinicians and industry, to apply neuroscience and ultimately improve the lives of the patients with psychiatric disorders."

Speaking of ECNP's journal, *European Neuropsychopharmacology* (ENP), Professor Goodwin continued: "We have a number of advances to the journal that are very exciting, including a mobile version that aids in our efforts to increase submissions."

A key facet of ECNP's efforts in furthering research is in its funding opportunities: "Although we can't afford to actually support research, we have supported research networks," explained Professor Goodwin, highlighting the EU's Innovative Medicines Initiative (IMI) in particular. "This is a fantastic way to get industry and the European Union to jointly fund applied neuroscience for psychiatric disorders," he said. "We are a part of a recent call which will form part of the dissemination work package if successful.

"Also we are involved in helping to obtain funding for Horizon 2020, a scheme which is challenging because of the breath of the calls. But we will continue to help people who want to do it."

Professor Goodwin also outlined other initiatives by the ECNP, including high level pharmacotherapy training workshops, which the College hosts in Venice and Oxford, and future clinical research methods workshops running in Barcelona next year. Touching upon the power of new collaborative relationships, Professor Goodwin emphasised the importance of dialogues with biotech companies, in order to further innovation in psychiatry, and improve clinical trials.

ECNP has an aspiration to galvanise public excitement in applied neuroscience, something which has already been put into practice via the hugely successful 'Brain Day', held in Amsterdam immediately prior to the Congress, and attended by over 500 members of the public. This meeting will also emphasise involving patients in their understanding of their conditions and choices of treatment.

> "The objective of the ECNP is to advance the science of the brain, and most crucially to apply that science promoting better treatment and enhancing brain health."
>
> Guy Goodwin

In his closing remarks, Professor Goodwin introduced the prestigious keynote speaker, the primatologist and leading behavioural neuroscientist Frans de Waal – an expert in social and cooperative behaviour in primates. Professor Goodwin spoke of Professor de Waal, saying: "He is an extremely honoured guest, and one of the leading behavioural neuroscientists."

PLENARY LECTURES

PL.04.01: **Is it time for immuno-psychiatry?** Auditorium **Monday** 14:00–14:45

A swelling focus in 'immuno-psychiatry'

Immuno-psychiatry offers great promise in unearthing our understanding of how infections, stress, genetics and other risk factors predispose to psychiatric illness, delegates will hear this afternoon during the next instalment of this year's distinguished programme of plenary lectures.

"The hope is that we will be able to offer prevention, not only in terms of giving people drugs, but in terms of changing modifiable risk factors that would otherwise add to the burden, such as diet, sleep, physical exercise, drug avoidance; all sorts of factors that we could persuade people at an early age to pay more attention to," Marion Leboyer (Mondor University hospital, Hôpitaux de Paris, Créteil, France) told *ECNP Daily News*.

Immuno-psychiatry as a concept appears to have gathered interest in recent times, driven by observations that the progression of major mood disorders, suicidal behaviour, but also psychotic disorders are associated with factors including inflammatory responses, cell-mediated immunity, oxidative stress, autoimmune responses and epigenetics.[1] The immuno-inflammatory cascade in mood disorders is believed to be rooted in the interactions between the immune-genetic background and environmental factors such as infections or early stress.[2]

"What we can dream of is that one day we will be able to identify at-risk subjects, and follow them up with particular recommendations."

Marion Leboyer

Interest has also sparked due to observations that the abnormal immune-inflammatory cascade likely plays a significant part in the burden of medical comorbidities (seen in more than 50% of bipolar patients alone[3]) such as obesity, auto-immune diseases, type-II diabetes and cardiovascular disease.

"I think the main interest of immuno-psychiatry, as we call it, is firstly that it provides different ways of explaining and finding mechanisms behind these disorders," continued Professor Leboyer. "The second aspect is that it probably allows for the identification of diagnosis and prognosis biomarkers, which we didn't have before. Third, it will likely aid in innovative treatments and prevention."

In terms of candidate biomarkers, Professor Leboyer listed several key interests, including pro-inflammatory cytokines, C-reactive protein, autoantibodies and immunogenetic variants, to name a few. "What we are probably going to end up with is a collection of different types of biomarkers that we can use in combination," she said.

"What we can dream of is that one day we will be able to identify at-risk subjects, and follow them up with particular recommendations, but we are still at the stage where we are doing research."

She continued, touching upon the 'physical comorbidities' (if they can so be defined) that come part and parcel with psychiatric disorders: "For now, I think the main message is that psychiatric disorders are really a disorder of the body and the brain, not only the brain.

"Immuno-psychiatry, as we call it ... provides different ways of explaining and finding mechanisms behind these disorders."

Marion Leboyer

While speaking about 'comorbidities' is still very modern, I think we should look for new terms to describe the process at play here: for example, starting with an early infection, interacting with a given immune-genetic background to develop abnormal immune-inflammatory cascade and then developing medical and psychiatric disorder afterwards."

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CLINICAL TREATMENT

S.13: **Oxytocin in schizophrenia: new research findings** Auditorium **Monday** 09:00–10:40

Oxytocin tips the scale in socio-emotional balance

The brain oxytocin (OXT) system – particularly its role in the regulation of a socio-emotional balance in health and disease – will be brought to the fore this morning when Inga Neumann (University of Regensburg, Germany) shares her work in the Auditorium.

As Professor Neumann will underline, OXT has received a great deal of interest in recent times due to its anxiolytic and pro-social properties, revealed in animal studies, opening up the possibility of its therapeutic application in social anxiety disorder, autism or other conditions with emotional and social deficits.

However, detailed mechanisms of action are still largely unknown, thus in her work, Professor Neumann has been exploring OXT use in animal models of social and non-social anxiety[1] and chronic psychosocial stress[2] in selectively-bred rodents (with either high or low anxiety levels), or in a novel model of "social fear conditioning"[3], which she will also introduce during today's session. "The endogenous brain oxytocin system is altered, when animals are socially fear conditioned, and in a very specific way," she told *ECNP Daily News*. "Oxytocin receptors change, as does oxytocin release within specific brain regions in response to normally-occurring social interactions."

She continued: "Studying the endogenous OXT system, for example in response to social fear or under conditions of chronic stress is one important aspect, but then another one is, of course, ascertaining what synthetic oxytocin is doing. First of all, we need to test various doses, and second we need to test what happens after long-term treatment with OXT. Moreover, we are also interested to see what specific molecular cascades synthetic oxytocin starts, when applied to the brain, so we are studying intraneuronal signalling cascades, which are coupled to the OXT receptors. And then we look which target genes are altered by OXT."

In her broader work, Professor Neumann has shown that OXT reverses social fear within the dorso-lateral septum, but, in contrast, attenuates cued fear extinction. As such, there appears to be differential, even opposing effects on social versus cued fear extinction. Furthermore, chronic OXT infusion during exposure to chronic psychosocial-stress prevented the increase in general anxiety in mice; however, chronic OXT at higher doses even increased anxiety and central OXT receptor binding.

In her closing remarks, Professor Neumann will link her animal work with the broader human work that will also be focused on during today's session. "What I want to demonstrate is that human research is limited due to methodological constraints, therefore we need a lot of basic research to figure out any aspects of OXT actions and functions, before OXT can be safely used as a therapeutic option in humans," she said.[4]

"Also, human studies need to be essentially extended with respect to different doses or gender- and age-dependent effects. Moreover, human research has to channel more effort to test how intranasal OXT affects the endogenous system. Another point that is also particularly pertinent in human research is distinguishing between patient cohorts (e.g. people with social anxiety, schizophrenia or autism) with and without a dysfunctional OXT system, as successful treatment with OXT may only achieved in the former.[4]

"You can treat people who have a perfectly acting OXT system with synthetic OXT, but they will not have a better outcome. But people with a dysfunctional system – for example a reduced level of OXT synthesis and, consequently, reduced OXT level in plasma in response to an OXT challenge – they may profit from treatment. So what I might also touch upon is the use of OXT in saliva as an easy OXT biomarker to see if we can reveal inter-individual differences."

"... human research is limited due to methodological constraints, therefore we need a lot of basic research to figure out any aspects of OXT actions and functions."

Inga Neumann

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CLINICAL RESEARCH

S.22: **Neuroimaging characteristics of child and adolescent offspring of SZ and BD** Elicium 2 **Tuesday** 09:00–10:40

Dutch bipolar and schizophrenia study confirms need for early intervention

While the evidence increasingly points to areas of commonality in the biological underpinnings of schizophrenia and bipolar disorder, areas of divergence remain, particularly in the early stages of the disorders, delegates will hear in Tuesday morning's session dedicated to the neuroimaging characteristics of child and adolescent bipolar and schizophrenia offspring.

"With a prevalence of 1-2% in the general population, bipolar disorder (BD) and schizophrenia (SZ) are not very common," Manon Hillegers (University Medical Center Utrecht, the Netherlands), who will be speaking first in the session, told *ECNP Daily News*. "With this low prevalence rate, large population cohorts would be necessary to study the early developmental stages of BD and SZ.

"BD and SZ have a strong genetic basis and run in families – that is why the most robust risk factor for developing bipolar disorder and schizophrenia is a confirmed family history. First-degree relatives of affected individuals have approximately a 10-fold increased risk of the disorder. Therefore longitudinal, familial high-risk studies (offspring studies) have made major contributions to our understanding of the early natural course of these disorders in youth."

With this in mind, Dr Hillegers will discuss the Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) – a longitudinal offspring study with follow-up measurements every three years at the University Medical Centre Utrecht.[1] "The DBSOS is a dynamic cohort with ongoing inclusions of children (aged 8-18 years) of a parent with bipolar disorder or schizophrenia and healthy controls," described Dr Hillegers. "The aim is to prospectively study the children's' development on different levels; brain, behaviour and cognition, in order to understand the specific and overlapping early trajectories of severe mental illness."

She went on to note that both disorders typically onset in adolescence and early adulthood, with a broad range of non-specific antecedents of the illness dominating the early course. What's more, familial risk for SZ and BD is only partially diagnosis specific: "Approximately 50%-60% of the SZ- and BD-offspring develop psychopathology other than a psychotic or bipolar disorder, such as mild mood disorders, anxiety disorders and behavioural disorders," said Dr Hillegers.

> "Longitudinal, familial high-risk studies (offspring studies) have made major contributions to our understanding of the early natural course of [schizophrenia and bipolar disorder] in youth."
>
> Manon Hillegers

"By longitudinally mapping illness trajectories and brain development we will be able to identify at which point these differ from each other and from transient normative (pubertal) behavior in youth. Furthermore, important predictive factors such as family history load, environmental stress and parental illness characteristics on the developmental trajectory can be studied."

As Dr Hillegers detailed, in the DBSOS, 37 SZ-offspring, 90 BD-offspring and 47 controls – all aged between 8 and 18 years (mean age 15.4) – were assessed for psychopathology (K-SADS-PL), (CBCL/6–18) and cognitive functioning (WISC/WAIS). A subsample of medication naïve offspring underwent structural and functional magnetic resonance imaging (sMRI/fMRI).[2]

Discussing the results, Dr Hillegers continued: "At all three levels studied, namely psychopathology, sMRI and fMRI brain measures, SZ-offspring compared to BD offspring and controls show the highest impairment, with high levels of psychopathology, smaller global and local cortical volumes and an impaired frontal-subcortical network.

"Although so far none of the offspring developed BD or SZ, the lifetime prevalence of a psychiatric diagnosis according to DSM-IV was high. Furthermore, compared to controls, the psychiatrically-affected offspring showed the smallest volumes. However, we also found a high risk offspring effect for unaffected subjects compared to controls."

Turning to the future directions for her work, Dr Hillegers commented that the next steps would be to develop a prediction model for BD and SZ offspring based on the high risk profiles using longitudinal data within staging models, as well as developing and studying the effect of an online intervention game on these types of patients.

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ECNP

The Scientific Programme Committee

Ringing in the changes
Reflections on three years as SPC Chair

Reprising his role as Scientific Programme Committee (SPC) Chair for the last year of his term, Wim van den Brink (Academic Medical Center Amsterdam, the Netherlands) has served as the cornerstone of a process which sees leading experts choosing the year's very best work in neuropsychopharmacology and applied neuroscience. Taking time out from preparations for both this and next year's congress, he spoke to *ECNP Daily News* to give some insights into the machinery at work behind the scientific programme's development.

The role of SPC Chair, he explained, is a labour of love not lightly undertaken: "To find someone for the role is not easy because it is quite a lot of work. It needs about half a day a week throughout the whole year, and there are some times when you are busier than others. We were very happy that Astrid Linthorst wanted to do the job, and I am happy to be a member of her committee during this transitional phase."

With his research planted for the most part in clinical ground, Professor van den Brink pointed out that this contrasts sharply with Professor Linthorst's basic science background: "She definitely has a slightly different sense of what the congress should be, and this is of course balanced by the others on the committee.

"We want people to participate from many countries in order to stimulate a high quality of research. That is the goal of ECNP."

Wim van den Brink

"But we might see a little bit more basic research, which we think is very important at ECNP Congress. We tend to have a stronger mix of basic science and clinical science than, for example, the European Psychiatric Association meeting (not that we are any better or worse), whereas they tend to have a stronger emphasis on clinical and applied research.

"Of course, we at ECNP try to make sure that the basic science is clinically relevant, because 70% of our participants are psychiatrists. It is easy to think that we would serve them best by giving them only clinical and applied research, but perhaps we should be giving them a little more – if you want to be ready for the next ten years of progress, you have to know about the basic sciences as well. The basic science sessions are well attended, and they are essential to what the ECNP stands for."

The process of selecting around 25 to 30 symposia out of a total of 120 proposals is no mean feat, and once the committee agrees on the shortlist, the process of redressing imbalances in geographical and gender representation begins.

"If we just invited the people mentioned in the symposia, we would end up with congress speakers being 90% male – and 98% from Europe, America and Australia," explained Professor van den Brink. "There are still not a lot of symposia that come from Central and Eastern European countries or other parts of the world, so we really encourage those people to submit symposia. There are plenty of places, such as Poland, Russia and Turkey, where great research is being conducted."

On the topic of gender, he went on to note a curious phenomenon, not exclusive to the scientific community, that hints at the complexity of the gender gap: "It is not a tough process to find female speakers even from other regions," noted Professor van den Brink, "But we find that there is a very high rate of declined invitations on their part. We still don't understand that completely. We really want more female speakers – so when we invite them, let them say yes!"

In fact, the gender gap is not at all an issue at ECNP's Junior Scientist symposia, which are one of Professor van den Brink's highlights of the congress. The Rapid-Fire poster sessions, introduced during his tenure as SPC Chair, provide another great opportunity for rising stars to appear under the spotlight to present their work to interested delegates. Another of the congress' segments particularly useful for junior scientists are the Career Development sessions, also established during Professor van den Brink's chairmanship.

The overarching aim of such methods of encouragement is straightforward: to find the best and brightest, the most exciting research and techniques – but this is at the very least: "As ECNP, we are educators," concluded Professor van den Brink. "We want people to participate from many countries in order to stimulate a high quality of research. That is the goal of ECNP."

Pick up a copy of *ECNP Daily News*, Issue 4 (Tuesday) for an interview with incoming SPC Chair Astrid Linthorst.

CLINICAL RESEARCH

S.18: **TNM Symposium – Neuroimaging as a clinically useful tool: the time has arrived** Elicium 2 **Monday** 15:00–16:40

Neuroimaging for patient stratification
From the bench to the clinic

This afternoon at the ECNP Congress will see Philip McGuire (Institute of Psychiatry, London, UK) take to the stage to present an absorbing discussion on the application of neuroimaging in the early detection of psychosis in high-risk patients.

As a professor of psychiatry & cognitive neuroscience, head of department in psychosis studies, as well the academic lead of the Psychosis Clinical Academic Group, which integrates psychosis research with clinical services, Professor McGuire is dedicated to harnessing neuroimaging in clinical applications.

Speaking with *ECNP Daily News*, Professor McGuire outlined the limitations in clinical assessment, saying: "Predicting risk factors in mental illness is problematic on the basis of interview-centred clinical assessments, and this is important with psychosis, where there are many unpredictable clinical outcomes. Patients can have a variety of different symptoms, but are united by a high risk of developing schizophrenia, which makes the clinical picture confusing and this underscores the need to have objective measures."

Patients with psychotic disorders normally have prodromal symptoms up to five years prior to the first episode,[1] and long-term prognosis of first-episode psychosis is heavily dependant on successful treatment. Furthermore, from a group of clinically-identical, high-risk individuals it can be difficult to predict which individuals will develop psychotic symptoms (although estimates suggest 30%), and which patients will fully recover.[2]

Additionally, antipsychotic medication – the mainstay of psychosis treatment – is ineffective in around one-third of psychotic patients. A trial and error process is used to determine patient responses and there is no way to predict which patients will respond to which treatment. Professor McGuire commented: "It would be more efficient and ethical to selectively target the ultra-high-risk people rather than indiscriminately giving a preventative treatment to people who are going to get better anyway. These high-risk patients are usually medically naïve, so are a clean population to study."

Describing the first of his main research goals, Professor McGuire explained that he wanted to use imaging as a tool to detect those at high risk of developing psychosis. Structural abnormalities such as regional frontal and temporal grey matter volume reductions,[3] and enlargement of the ventricles,[4] have been associated with outcomes in schizophrenia for some time. Recent investigations carried out by Professor McGuire and co-workers have focused attention on functional brain interactions, revealing a wide spectrum of connectivity abnormalities including the connections integrating the frontal cortex.[5] Other work in his group demonstrated an association of cortical and subcortical activation as well as thalamic glutamate levels with functional outcome.[6] Recent data from Professor McGuire's group have also showed that increased vulnerability to psychosis is associated with deactivation failure in the medial prefrontal cortex and precuneus[7] and also with aberrant functioning in emotional brain systems,[8] and these may represent an a opportunity for detecting the pathophysiology of early psychosis.

The increased availability and reduced costs of MRI scans have made this an achievable goal, particularly compared to the potential costs – economical or otherwise – of the treatment of schizophrenic patients. However, there are technical and logistical requirements, which of course increase with more complex scanning procedures such as serial scanning. Although PET scanning is not routinely carried out in many imaging units and is still very costly (£8,000 compared with £100 for an MRI scan), Professor McGuire's research group is currently investigating different proxy markers for PET that could be obtained with a simple blood test.

> "Predicting risk factors in mental illness is problematic on the basis of interview-centred clinical assessments, and this is important with psychosis, where there are many unpredictable clinical outcomes."
>
> Philip McGuire

Professor McGuire's second goal is to develop a predictive tool that can be used in the clinical setting, in the same way that that a commercial device could be used by a clinician without special expertise (such as a GP using a blood pressure cuff). "In psychiatry there are no objective tests in routine practice, normally we rely on interviews and questionnaires, yet the rest of medicine uses blood test or scans," said Professor McGuire.

Echoing the sentiment of many imaging researchers wishing to shift neuroimaging from its research domain, and into the clinic, he continued: "In the imaging field there is so much amazing schizophrenia research, but no one has been able to take that knowledge and make it into something useful for a mainstream clinician. High-risk psychosis is one of the most promising areas for translational neuroimaging research. We want to try and

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translate research findings into something that will make a difference."

Although imaging is his principal research modality, Professor McGuire and his team have been focusing on multimodal integration with cognitive and (in particular) genetic testing in concert with imaging. He explained: "The magnitude of the effect of a single gene on the risk of an individual developing schizophrenia is quite small. A more powerful approach is the use of polygenic scoring where hundreds of risk genes for schizophrenia are examined. Using this approach, 1000 genes linked to schizophrenia could be examined and a score of +600 would be considered high risk, and this could be used to confer susceptibility for someone who has not yet had an episode."

Clearly there is an enormous interest in biomarkers to help clinicians stratify clinical populations into subgroups to differentially treat people according to what's going to happen to them. These findings are also critical for early treatment because their subsequent level of functioning may depend on the extent neurophysiological and neurochemical dysregulation when first presenting to clinical services.

> "In the imaging field there is so much amazing schizophrenia research, but no one has been able to take that knowledge and make it into something useful for a mainstream clinician."
>
> Philip McGuire

Professor McGuire presents 'Using neuroimaging to predict outcomes in psychosis' as part of the Targeted Network Meeting session 'Neuroimaging as a clinically useful tool: the time has arrived', held this afternoon at 15:00–16:40 in Elicium 2.

PRECLINICAL RESEARCH

S.20: **The gut microbiome: a new frontier in brain research** Emerald **Monday** 15:00–16:40

Gut feeling: changes in gut microbiota influence the wiring of the brain

Recently, growing evidence suggests that not only can the brain affect gastrointestinal activity, but that changes in the gastrointestinal activity can also affect brain function. Exploring this link – the gut-brain axis, Jane Foster (McMaster University, Hamilton, Ontario, Canada) spoke to *ECNP Daily News* to describe how microbes within the gut influence anxiety-like behaviour.

Her initial work investigating behaviour using the elevated plus maze with germ-free mice (mice exposed to antibiotics) showed reduced anxiety compared to normal mice and this has been robustly replicated. These mice also express long-term changes in plasticity-related genes in the hippocampus and amygdala.[1]

"So the big question is – how do the microbiota change the brain's wiring to affect behaviour?" began Professor Foster. "We've shown that if you give back the bacteria as an adult, the behaviour remains the same. It's hard-wired during early life and adolescence and we want to map out the brain systems involved in that."

She added: "One of the things we have looked at in the germ-free mice is whether their stress system is altered in early life, so we looked at stress hormones in mice at four weeks (pre-puberty) and compared it to that of adult mice [germ free vs normal]."

The hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine system that is subjected to programming by early life events. Previous work by Sudo et al. in investigating the HPA response to stress demonstrated that germ-free adult mice had heightened plasma adreno-corticosteroid levels.[2] Professor Foster's group repeated this in Swiss Webster germ-free mice and examined how microbiota may modulate the gut-brain axis to influence behaviour including immune signalling, neural pathways, altering neurotransmitter levels and gene expression in the CNS, and changes in intestinal permeability. They found higher resting hormone levels (compared to normal mice) but only an exaggerated response to stress in the females. Critically they found that the four-week-old germ-free mice, regardless of the presence of stressors, had heightened levels of stress hormones, postulating that alterations in gut microbiota during early development can influence the wiring of the stress axis.[3]

> "We think that the bridge between mood and food is affected in early life, and then it is completely rewired during adolescence."
>
> Jane Foster

Professor Foster said of these results: "Something is happening in adolescence in the absence of microbiota. At four weeks old it's like they are stressed all the time, but somehow by 10 weeks they've recovered." Clinically this is interesting because psychological problems are common in adolescents, and these could be linked to their diet and microbiota early in life. Furthermore the germ-free mouse suggests that there is a reparative process. She added, "We don't know what it is yet, we're working on it and think it might be serotonergic-based."

"The conundrum is that while adult mice have higher levels of corticosterone, they display less anxiety-type behaviour, like a lion trainer. In fact in some of the mouse strains we see the opposite effects: some with higher corticosterone levels have less-anxious behaviour."

Professor Foster continued, "We think that the bridge between mood and food is affected in early life, and then it is completely rewired during adolescence."

One possible link between mood and food that Professor Foster's group is investigating is Neuropeptide Y: a stress hormone produced in the arcuate nucleus, which is also a feeding hormone. She expanded: "Neuropeptide Y is a potent stimulator of the stress response so it is possible that the link between feeding and stress system is out of balance. This ties in with eating disorders which are highly prevalent during adolescence too."

The high co-morbidity between gastrointestinal diseases, such as irritable bowel syndrome, and psychological symptoms such as anxiety and depression has lead many researches to focus on the pathogenic role of stress. With regards to utilising these findings in a clinical setting, Professor Foster believes that the next step is to use neuroimaging as a tool to link mood and food, and while this has been investigated by gastroenterologists, the influence of the gut micobiota is yet to be elucidated.[4]

Professor Foster is involved in a network that is studying OCD, ADHD and autism in children, in which they perform brain imaging, behavioural testing and also study the microbiome. She is also part of a depression network, searching for biomarkers for depression. Both networks are focussed on better stratification of patient populations to give them the right treatment. "Based how the brain is wired, we want to stratify the patients for the best treatment, and a lot of that lands with the immune system." she commented.

Discussing potential biomarkers and how to stratify at-risk patients, Professor Foster said: "Inflammation is a part of depression, and there's no debate that cytokines are increased but they may not be causative. We are interested in adaptive immune cells too, T-cells and how the peripheral system modulates the microgila in the brain. The level of cytokines may not be as important as how the immune cells the brain or periphery communicate on a daily basis."

In her immune-neurodevelopment studies, Professor Foster's group has begun to immunophenotype the children's leucocytes in order to measure the balance of macrophages to T-cells. Commenting on this approach, she said: "On a grander level, measuring lipopolysaccharide and bacterial products in the blood might also serve as a good clinical marker."

Professor Foster concluded by saying: "Our work is focused on anxiety, with a research interest in neurodevelopment and risk to mental health. In studying these changes in brain wiring we can attempt to identify pathways that increase the risk of developing anxiety disorders. Understanding such links could help transform treatment, especially in terms of diet."

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BRAINSTORMING SESSIONS

BS.3: **Neurotransmitter interactions and cognitive function: can this optimally be studied in humans?** Room D203 **Sunday**

How far can we understand neurotransmitter

Brainstorming sessions offer a platform for group discussion of a key issue within a field of expertise. Yesterday morning, Mitul Mehta (Institute of Psychiatry, King's College London, UK) and Anke Sambeth (Maastricht University, the Netherlands) were joined by session chair Arjan Blokland (Maastricht University) and a great number of early-rising delegates to ask whether and how neurotransmitter interaction and cognitive function can be reliably studied in humans.

Setting out the issues surrounding this question at the outset of the session, Dr Mehta began by acknowledging that neurotransmitter interactions are evident throughout research in both humans and animals: "We are not questioning the existence of interactions," he said. "There are many different mechanisms that have been described in molecular terms that lead us to understand the specific potential for interaction between neurotransmitter 'systems'."

Moving towards a broader perspective of pharmacodynamics and kinetics – away from the 'mono-neurotransmitter' frame – is a shift closer to understanding the complexities that gives rise to the vastly different behavioural responses to drugs that are evidenced in clinical trials, despite evidence of their consistent action within the brain from PET and MR data.

Human studies, Dr Mehta pointed out, are limited in their scope relative to animals, but there are nevertheless different ways of uncovering where and how a drug interacts: "There are different options here. We can give one drug and test another drug system. Or, if you are doing PET imaging for dopamine release, you can test different compounds, opioids for example, and assume that interactions are behind any link. You can also give one drug and try to block the effect of this drug with a drug for another system; and of course, if you have animal and anatomical data to back up the theory behind this then you have an interpretation framework. You can give two drugs independently and then together to study their interactions. If you can measure the status of one system – whether that is through metabolites, PET imaging or MRS – you can regress that against the effects of your interaction drug as well."

Animal studies offer the opportunity to investigate these interactions with fewer limitations, pointed out Dr Sambeth: "In animals we can use many more drugs – those that are still in development or those that never made it to the market, for instance…In an animal, you can also inject the drug straight into, for example, the hippocampus. But if we give, for instance, citalopram to humans, it goes all over the brain to all of the serotonergic receptors – some of which will improve memory, some will impair memory and some will affect attention while others affect vigilance.

"That is simply because we can't inject into the hippocampus in humans. This relates to timescales as well, because where we see effects immediately following injection in animals, we have to wait a few hours after giving subjects their pill, hoping that enough of the substance gets to the brain."

Audience members pointed out that drug dosage is another variable that is related to inconsistencies both between animal and human studies, and between human subjects. Higher doses of a drug can increase its binding promiscuity, which can have a prominent bearing upon behavioural and other outcome measures. Dr Blokland pointed out that metabolic rates in animals such as rats and mice are much higher than those of humans. Citing the work of Harriet de Wit (who has published extensively on the challenges of translational research[1]), he explained that higher doses tend to bring about peak levels sooner, whereas lower doses bring about the same peak with a slower onset: "Dr de Wit found very different effects of dose on behaviour. Comparing animals, which have a rapid onset in the brain, to humans that experience a slow onset, we might see different effects because of this."

(From left) Anke Sambeth, Arjan Blokland and Mitul Mehta

> "In animals we can use many more drugs – those that are still in development or those that never made it to the market, for instance."
>
> Anke Sambeth

On the incongruity between findings in animals and humans, an audience member ventured that chronic effects of drugs should not be ignored: "A lot of the studies we are talking about here are acute studies in both humans and animals. But I am stricken by the fact that, say, the cholinesterase inhibitors in humans take three up to six months to have the maximal effect. We really don't see any clinical benefit immediately."

Stressing that the focus of all such investigations is to bring about demonstrable changes in cognitive parameters in humans, Dr Mehta noted that a complete and thorough understanding of interactions is not necessary; however, developing a better understanding of what influences cognition (and hence its surrogate markers such as EEG or MRI) is important: "This fits in well with moving from acute to chronic studies as well. What matters in humans is the outcome – what is happening to the system. This is where we can link with animals better because we can make system measurements."

07:45–08:45

interaction in humans?

Just how analogous surrogate markers of cognition are to behavioural outcomes was also discussed. Noting the incongruity between fMRI and behavioural testing outcomes, Dr Mehta cited his own work in humans using low-dose ketamine, which identified very consistent fMRI results but highly variable behavioural results.

Findings such as these suggest that greater attention could be paid to back-translation, which can steer the translational process with respect to specific goals and questions. Dr Blokland posited that there were general doubts as to the similarity of neuropharmocological effects of drugs in animals and humans (depending on the study being conducted), with factors such as the life experiences and present states of mind of study participants muddying the water. Pertinent to this, he continued, animal studies are marred in their validity to humans, because animals are raised in stimulation-poor environments.

Citing his own work, he explained: "What I have done, after weaning, is to put these animals in a big cage with a rich environment. I then tested the effect of drugs, and the results looked very different [to conventionally-raised experimental animals]. So, in animal models, it is not only the task and the pharmacodynamics – it is also the animal itself that might be very different. The brain is wired completely differently if you raise animals in a rich environment."

> "Comparing animals, which have a rapid onset in the brain, to humans that experience a slow onset, we might see different effects because of this."
>
> Arjan Blokland

Dr Sambeth added: "We also don't know enough about neurobiological differences between species. Until we know that, we should not really be looking at interactions because it is too difficult to try to explain."

As a translational researcher, Dr Sambeth highlighted that great care must be taken in selecting behavioural tasks in animals that can be translated into human work. Notably, she said, verbal tasks are consistently used in humans as analogous to object recognition tasks in animals as a measure of episodic memory: "Those tasks are truly, really different," she said. "So can I translate my findings here? If you look at brain activity between the rats and the humans while they are doing these tasks, they differ quite a lot."

Translatability relies on identifying analogous tests that test similar faculties in animals and humans, possibly avoiding verbalisation, as one audience member suggested. Tests such as the set-shifting and stop-signal tasks have a greater capacity for translation, as noted by Dr Mehta.

Individual neurotransmitter systems tend to react predictably to the drugs that target them with specificity, despite much greater variations in behavioural outcomes. Asking to what extent it is feasible to explain behavioural variation by the interactions between neurotransmitter systems, Dr Mehta received a number of suggestions of additional explanatory variables, such as genetic background, age and gender.

With regards to translational models, the consensus was that such factors are important to consider in animal studies too – different models emphasise certain traits and behavioural tendencies, which could be useful in investigating the particular effects of a drug in, for example, anxious individuals. Indeed, convergence in behavioural outcomes between animals and humans has been achieved by honing in on such traits in this way.

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TRANSLATIONAL RESEARCH

S.19: **From bench to bedside and back with precision...** Forum **Monday** 15:00–16:40

Two heads are better than one in NEWMEDS success story

The Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) project was funded by the European Union (7th Research Framework Programme) under the Innovative Medicines Initiative (IMI). The broad aim of the NEWMEDS project is to find new methods for the development of drugs for schizophrenia and depression. Later today, Tine Bryan Stensbøl (H. Lundbeck A/S, Copenhagen-Valby, Denmark), the coordinator of the NEWMEDs project, will provide an overview of the programme as the final report is submitted to the EU.

In an interview with *ECNP Daily News*, Dr Stensbøl spoke about the origins of the project and its impact on drug development: "The NEWMEDS programme was put together with 23 partners on board: 10 academics, 10 industry partners, and three SMEs (small and medium-sized enterprises) under the Innovative Medicines Initiative. The IMI ties academic expertise in animal models, genetics, functional MRI [fMRI] and PET imaging, clinical settings and analysis methods together with expertise and incentive in drug discovery and development. When NEWMEDs was conceived IMI was very new, so getting industry to work together on precompetitive projects was difficult."

However Dr Stensbøl's very candid approach to members sharing their data paid dividends: "If you were in NEWMEDS, you were there to share data," she said. "The IMI proved to be a good platform, and the partners involved were courageous and willing to share. This was demonstrated as relationships grew, and as project leader this was a very nice thing to see."

She added: "Organisationally this was a new way of doing public-private partnerships, i.e. with industry partners paired with academic institutions. The project was split into 10 different work packages, each with an industry lead and an academic lead. Although the academics actually received the funding from the EU, we thought it important to have the industry leads coordinate the work packages to ensure full commitment. This meant that the joint leads shared responsibility, and when myself and my co-leader at King's College London, Shitij Kapur, collaborated on a work package, we would have regular meetings to ensure appropriate progression of milestones and to discuss scientific matters and issues arising between industry and academia."

With this new mind-set, Dr Stensbøl fought for Lundbeck to put three mouse lines into the consortium, which everyone was then able to work on. "Academics compete on scientific publications, so this was a brave move, but worthwhile: industry partners and preclinical academics generated vast amount of data using these models, in particular regarding their translational capacity to humans. We know that these don't exactly model schizophrenia, rather each one models an aspect of schizophrenia.[1]

"Our experience at NEWMEDS shows that industry is willing the share data."

Tine Bryan Stensbøl

As the project moved along, Dr Stensbøl's group became very focused on associations between the alleles of copy-number variants (CNVs) and disease pathogenesis. "It began just prior to initiating the NEWMWEDS programme, and we had some CNV work packages that expanded and became more scientifically interesting."

She continued: "I really believe that academics and industry need to work together, particularly in the use of novel drugs and novel targets in the CNV field. The study on cognitive training showed results we were not expecting.[2] We found that studying cognition in schizophrenia is extremely difficult."

Dr Stensbøl went on to describe a work package lead by Jonathan Rabinowitz that involved creating a database of clinical trial data from more than 30,000 schizophrenia patients, pooled from many studies. "This lead to interesting findings about the way we do clinical trials," she said. "Clinical Trials of depression and schizophrenia treatment can be compromised by high placebo response. Data from this work package showed that women had a diminished placebo response in schizophrenia treatment, suggesting that if the number of women in a clinical trial was increased, the trial could be more efficient. A similar trend was observed for depression treatment.[3]

She added: "The industry partners are very interested in optimising the way that clinical trials are carried out, and from an ethical standpoint, a conclusion must be reached as quickly as possible. Our experience with NEWMEDS shows that industry is willing the share data."

A critical aspect of the programme was the commitment to resources. Specifically, whatever EU/IMI gave was matched in either time or resources by industry partners. Describing some of the challenges faced, Dr Stensbøl said: "As there was no guarantee about how the distribution would work between partners, everyone had to rely on the project lead to manage milestones, and some were willing to commit more resources than others: and that was the tricky part. How can we justify that one company provides double of what another provides? As Lundbeck was taking the lead, I was willing to commit a substantial amount of resources regardless of what we got back – If you want to get value, you have to get your hands dirty."

Transparency was also key, as it became clear that yearly face-to-face meeting for all the partners, where each openly shared what they had delivered, made it clear to everyone just how much resource had been committed from each source.

Dr Stensbøl concluded: "This progression would not have been possible without public-private partnerships. Despite the initial criticism of IMI, it has been an absolute success, and this is because of a great team – a lucky constellation of the right people who were committed, and saw this as a unique opportunity to work with the best peers, who are all focused on the same thing."

"I really believe that academics and industry need to work together, particularly in the use of novel drugs and novel targets in the CNV field."

Tine Bryan Stensbøl

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CAREER DEVELOPMENT

Career development sessions at the 28th ECNP Congress

Career development sessions kick off with poster workshop

The Career development (CD) sessions are specifically designed to offer training and advice for junior scientists, but are open to all levels and ages. Held at the Poster podium at 13:15–13:45 daily, each of the sessions will tackle a particular overarching topic.

Sunday hosted the first of this year's CD sessions, with Martien Kas (the Netherlands) sharing tips and tricks on how to make an award-winning poster.

Head to the Poster podium on Monday and Tuesday at 13:15 for the remaining CD sessions, 'How to give an effective talk' and 'A job beyond research', respectively.

The General Assembly

The General Assembly, the annual general meeting of ECNP members, is ECNP's highest deliberative body. It is held every year during the ECNP Congress and is chaired by the ECNP president or vice-president. Additional ('extraordinary') general assemblies may also be convened by the General Assembly or the Executive Committee. Forty ordinary members constitute a quorum (fifty in the case of extraordinary general assemblies).

The functions of the General Assembly include:

- The election of the president and Executive Committee
- Final oversight of the organisation's financial affairs
- The annual subscriptions to be paid by members
- Amendments of the constitution
- Final determination of the organisation's dissolution or merger
- For further information on the remit of the General Assembly, head to http://www.ecnp.eu/about-ecnp/constitution.aspx

The 2015 General Assembly will be held today at 12:15–13:15 in the Emerald room

TRANSLATIONAL RESEARCH

S.15: **Junior Scientists symposium – Dysfunctional brain circuits in psychiatric disorders...** Forum **Monday** 09:00–10:40

Going viral: designer receptors reveal neurobiology underlying behaviours

This morning's Junior Scientists symposium opens with Linde Boekhoudt (Brain Center Rudolf Magnus, the Netherlands) talking about her application of chemogenetics in dopamine neurons to model psychiatric endophenotypes and disrupted neural circuits.

Chemogenetics, also known as DREADD (Designer Receptors Exclusively Activated by Designer Drugs), is a technology developed by the lab of Bryan Roth (UNC School of Medicine, NC, USA)[1]. Viral vectors can be used to induce expression of 'designer' receptors in a targeted cell population; such G-protein coupled receptors are activated exclusively by designer ligands.

"In my experiments, I used hM3Dq, which is a Gq-coupled designer receptor that increases neuronal activity when activated by its ligand Clozapine-N-Oxide (CNO)," explained Ms Boekhoudt to *ECNP Daily News*. "By using a cre-dependent designer receptor in TH::Cre transgenic rats, we could specifically activate dopaminergic neurons in the rat midbrain."

In this way, Ms Boekhoudt's group were able to specifically activated two subpopulations of dopamine neurons in the rat midbrain – the ventral tegmental area (VTA) and substantia nigra pars compacta (SN) – providing a crystal clear window into the roles these neurons play: "It is known that the dopaminergic circuit is crucially involved in the control of locomotor activity. However, much remains unclear about how neuronal activity is related to behavioural outcomes, and if different neuronal subpopulations have different functions.

"Our results show that enhanced activity of either VTA or SN dopamine neurons increased home cage locomotor activity. However, only VTA activation resulted in a very pronounced hyperactive phenotype. This shows that indeed different subpopulations of midbrain dopamine neurons are differentially involved in the regulation of locomotor activity."

In order to remotely control the signalling of neuronal subpopulations, DREADD relies on the ability to both single out a target population of cells with a viral vector, which then go on to respond to activation as intended. Commenting on the validity of the designer receptor method, Ms Boekhoudt was positive: "I think conceptually the DREADD technique is very elegant, since it is both simple and effective. One of the great advantages of this technique is that you are not disturbing neuronal activity with the designer receptor itself. Only when you give CNO, you will induce a transient effect. This way, you can repeatedly test behavioural effects within the same animal, and for example test multiple doses of CNO. This increases the reliability of the observed effects.

"One conceptual issue in this type of research would always be specificity. We use the cre-lox system to specify the neuronal population of interest. We chose to use TH::Cre rats, to specifically target dopaminergic neurons. However, in this case we cannot discriminate between different projection targets, e.g., VTA dopamine neurons may project to the nucleus accumbens, or prefrontal cortex. Other approaches can be used to specify populations based on projection sites, for example the combination of CAV2Cre and DREADD[2]."

> "Conceptually the DREADD technique is very elegant, since it is both simple and effective."
>
> Linde Boekhoudt

In behavioural neuroscience, the technique is blooming, with an increasing body of literature focussing on tracing out the web of distinct behaviours, such as locomotor activity, back to its origins. "In particular, it will give insights on the role of GPCR signalling in these mechanisms and neuronal circuits," explained Ms Boekhoudt. "This is especially important since GPCRs are a widely used target for pharmacological therapies, and thus are interesting candidates for novel therapeutic targets."[3,4]

Exploiting the fine targeting of techniques such as DREADD could have many uses, continued Ms Boekhoudt, such as gene therapy. By way of minimal promotors, it could be possible to boost drug therapy efficacy and minimise side effects, whilst allowing effect size and timing to be controlled.

Weighing up the designer receptor technique against its allies, Ms Boekhoudt went on: "Chemogenetics is closely correlated to optogenetics. Both techniques have their own advantages and disadvantages. Optogenetics is particularly interesting when you want to manipulate neuronal activity on a millisecond scale. On the other hand, DREADD is usually less prone to complications, since you do not have to deal with delicate additional equipment such as lasers and cables.

"Another difference is the use of ion channels in optogenetics versus GPCRs in DREADD. As mentioned above, GPCRs are in general more relevant for pharmacological therapies. It is worth noting that recently the Roth lab has recently developed a new inhibitory DREADD, namely KORD[5,6]. Since this receptor is activated by a different ligand than hM3Dq, it is possible to use the two receptors in the same animal, and study neuronal activation and inhibition at the same time. This is definitely something that I am interested in."

Returning to her work, Ms Boekhoudt emphasised the complicated nature of her investigations into the neural basis of emergent behaviour in psychiatric disorders.

> "[We showed] that indeed different subpopulations of midbrain dopamine neurons are differentially involved in the regulation of locomotor activity."
>
> Linde Boekhoudt

Indeed, such disorders are better understood intrinsically only when teased apart into behavioural dimensions, whose relationship to specific neurotransmitter systems can then be quantified. "We can look at specific behavioural outcomes that are related to psychiatric symptoms, such as impaired attention and impulsive actions.

"By combining these paradigms with DREADD, we can investigate to what extent (in this case dopamine) neuronal activity affects these outcomes, and whether or not there are different contributions of, e.g., dopamine neurons in the VTA and SN. Eventually, this would increase our understanding of the neurobiology underlying psychiatric disorders, and hopefully improve therapeutic strategies."

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TRANSLATIONAL RESEARCH

S.15: **Junior Scientists symposium – Dysfunctional brain circuits in psychiatric disorders...** Forum **Monday** 09:00–10:40

It's about time: from IEGs to behaviour

Also speaking during this morning's Junior Scientists symposia will be Diptendu Mukherjee (Alexander Silbermann Institute of Life Science, Hebrew University, Israel), who will be presenting on the process of uncovering the transcriptional profiles that encode observable behavioural experiences. In particular, he focuses on immediate early genes (IEGs), expression profiles of which are observed following neuronal activity and are thought to be the seeds of adaptive brain changes. Studying as part of a group on experience-dependent plasticity, Mr Mukherjee's ongoing PhD work explores transcriptional programmes that underlie plasticity related to cocaine addiction.

IEGs are expressed as part of the first wave of transcriptional response to a stimulus, occurring classically around 15 minutes to one hour following it. This sets off a cascade, by which the proteins encoded by these IEGs compute the outcome of the stimulus; downstream effector genes then bring about changes in synaptic efficacy. By studying IEGs in greater depth, explained Mr Mukherjee to *ECNP Daily News*, it will be possible to clarify the role they play in long term plasticity.

"Most of what people have done up to now is to look at single genes and implicate their roles in drug abuse," he said. "Or they have looked at epigenetic markers or chromatin modifications. But studies pertaining to global changes in the transcriptome are rather rare. Though there are some reports of the importance of IEGs (such as Arc, c-Fos, and others) in determining computational outcomes of a stimulus in-vitro, their role in-vivo – how they induce long term plasticity – is not ascertained."

Crucial to this study of IEGs, he explained, is the demonstration that they are directly relevant to the behaviour in question. In order to do this, the group looked at different kinds of rewarding and aversive experiences: "We had a panel of five different types of behaviours, starting from experiences with cocaine, sucrose drinking, feeding, footshock, and lithium chloride (an aversive pharmacological experience much like foot-shock)," he said. "We then studied the transcription profile of the immediate response. What we have seen is that the IEG expression is different in each of these experiences, both in terms of identity and level of expression."

The group found that a change in IEG profile accompanied first exposure to cocaine. With repeated doses, another unique IEG profile emerged, and yet another if cocaine was given after a period of abstinence.

"That is what led us to the hypothesis that these IEG profiles have a role in encoding specific experiences. So we extended the study to different kinds of behaviours, and we are now looking at 15 different kinds of experience that define the five different behaviours. We see that every time we have a different transcriptional profile, which can be used to differentiate that particular experience, both aversive and rewarding."

"Studying plasticity induced in these cocaine responsive ensembles, we will be able to determine a definite mechanism that underlies drug-induced maladaptive behaviour."

Diptendu Mukherjee

The group have profiled 200 IEGs – a long list which they have narrowed down for the purposes their studies to 100 of the most relevant for the 15 experiences under study. RNA sequencing analyses are carried out of the entire transcriptome in seven brain structures: the accumbens, dorsal striatum, prefrontal cortex, amygdala, hippocampus, hypothalamus, and ventral tegmental area. Each of these regions is mapped according to the expression of these 100 genes, under each of the 15 experiences.

Out of this emerges a rich body of data that could give clues as to where and when to intervene to prevent sensitisation to cocaine. The group is currently using different tools to investigate one such clue: a candidate gene of the Early Growth Response family – although Mr Mukherjee was cautious given the preliminary nature of the results they have acquired to date.

"This candidate gene is induced robustly in response to acute exposures of cocaine. We are utilising different tools for manipulating the expression of this gene and for studying its role in cocaine-elicited behaviour. Using this approach, we will not only identify the role of this gene in behaviour, but also have an insight into the mechanisms by which IEGs function, and how they regulate plasticity. In other words, by manipulating one point in this initial response, we are changing the entire transcriptional network and adaptive behavioural response.

"Moreover, making use of the activity-specific expression of this gene, we are motivated to identify specific neuronal ensembles that are responsive to cocaine. Then, studying plasticity induced in these cocaine responsive ensembles, we will be able to determine a definite mechanism that underlies drug-induced maladaptive behaviour."

These investigations are ongoing, and there are plenty of very practical issues that must be surmounted to achieve reliable results. A great deal of analysis comes out of extracted brain regions whose physical sizes are minute in small rodents such as mice, and hence extraction can be challenging. On top of this, loss of RNA and transcriptome information can arise from variation in the way tissues are processed. Hence, great care needs to be taken regarding animal preparation and tissue processing.

Despite these obvious challenges, the technique's success has turned the group's attention towards clinical applications. Human brain biopsies are an undesirable prospect to say the least, and the group is studying the viability of measuring transcriptional profiles of the circulating blood. Blood shares around 50% to 80% of its transcriptome with the brain, and previous studies in the field have already uncovered tissue-specific markers.

"Blood-omics has been shown to be quite useful for analysis in neuropsychiatric disorders such as autism, schizophrenia, and others," said Mr Mukherjee. "We have very preliminary evidence indicating that we might be able to use IEG profiles in the blood as markers that could be used to differentiate experiences; hopefully, we will be able to extend our findings into the clinical arena."

"[The role of IEGs] *in-vivo* – how they induce long-term plasticity – is not ascertained."

Diptendu Mukherjee

A closer look at inflammation in schizophrenia

Concluding this morning's Junior Scientists symposium on the role of dysfunctional brain circuits in psychiatric disorders, Sophie Holmes (University of Manchester, United Kingdom) will discuss her recent investigations into the role of neuroinflammation in schizophrenia. Taking time out from her thesis writing to speak to *ECNP Daily News*, she described the basis of her work.

As Ms Holmes detailed, immunology and schizophrenia were first linked a century ago, when it was observed that patients with microbial disease occasionally presented with psychosis during its course. Now a leading research topic, understanding of the role of inflammation in schizophrenia has converged via a number of angles.

Ms Holmes noted: "Studies have suggested an association between infection in utero and an increased risk for schizophrenia later in life[1]; an increased risk for schizophrenia in those with autoimmune disease[2]; and increased concentrations of inflammatory markers in the blood in patients with schizophrenia[3]. There is also evidence of an association between the Major Histocompatibility Complex (MHC) region, which encodes hundreds of genes that control immune function, and schizophrenia[4].

"There is a link between stress and schizophrenia, which could be mediated by the HPA axis and inflammatory factors[5]; and RCTs show promising effects of anti-inflammatory drugs, such as minocycline, in reducing particularly the negative symptoms of schizophrenia[6,7]. But there are still many unanswered questions regarding causality, heterogeneity across subjects, the effects of medication on inflammation and the role of peripheral inflammation versus neuroinflammation."

Neuroinflammation can be measured in vivo using positron emission tomography (PET) and radiotracers that bind to the Translocator Protein (TSPO), which is upregulated on activated microglia. Noting particular PET studies that evidence increased TPSO in schizophrenia[8,9], Ms Holmes cited more recent work that found no such association. Investigating why this is so has been the subject of her thesis: "Most of the patients in these studies were on antipsychotic medication, which has been found to have immunomodulatory properties. Therefore, further clarification of the role of neuroinflammation in schizophrenia, and the effects of antipsychotic medication, is needed."

> "There are still a lot of unanswered questions regarding the role of inflammation in schizophrenia."
>
> Sophie Holmes

> "Low mood is seen in so many psychiatric and neurological disorders and inflammation may be the driving force."
>
> Sophie Holmes

Describing her study design, she continued: "Our study assessed the presence of microglial activation in antipsychotic free patients (n=8), those on the antipsychotic risperidone (n=8) and healthy controls (n=16), using PET. Overall, TSPO expression was higher in all patients with respect to controls; but interestingly, this increase is largely driven by those patients on antipsychotics. TSPO expression was significantly higher in medicated versus un-medicated patients. Although this is a small sample, it suggests the antipsychotic risperidone may be associated with increased TSPO expression, indicative of microglial activation. Clearly this needs to be investigated further in a larger sample, but if confirmed this would have important implications for treatment."

Her group also found a correlation between TSPO expression in the anterior cingulate and the negative symptoms of schizophrenia. The involvement of the anterior cingulate in emotional regulation suggested to the group that inflammation in this region might be related to the lack of affect and anhedonia seen in people with schizophrenia. "This is also consistent with the minocycline trials, which showed significant improvements in the negative symptoms of schizophrenia specifically," noted Ms Holmes.

Inflammation doesn't seem to be specific to schizophrenia, which, Ms Holmes argued, only lends credence to the cross-diagnosis similarities in psychiatric disorders. "Inflammation seems to be present across numerous other psychiatric, neurodevelopmental and neurological disorders, such as bipolar disorder, autism spectrum disorders, Alzheimer's disease, Parkinson's disease and multiple sclerosis." she said. "We have also conducted the same study in a cohort of medication-free patients with moderate-to-severe depression and have found a similar overall increase in TSPO expression.

"Again, the anterior cingulate showed the greatest increase between patients and controls. It could be that inflammation in the anterior cingulate is a shared mechanism representing the mood change seen in both depression and schizophrenia. There is often a strong overlap between the two disorders: symptoms of depression are common in those with schizophrenia. Indeed there is significant overlap in symptomatology across numerous diagnostic categories. So it doesn't seem as if inflammation is going to be specific to one disorder, however it could be reflective of a certain symptomatology. Low mood is seen in so many psychiatric and neurological disorders and inflammation may be the driving force."

A fundamental question remains as to the origin of inflammation found in the brain. Despite evidence in the literature of circumstance wherein peripheral inflammatory markers access the brain to cause various physiological and behavioural changes (for example, 'sickness' behaviours), Ms Holmes and colleague have not found any correlations between peripheral and central inflammation – and this is consistent with previous PET studies. "It could be that the neuroinflammation we are seeing is independent of any inflammation in the periphery, i.e. it starts in the brain," she postulated. "But a lack of correlation could also be due to the high levels of variability we get when measuring markers of inflammation in the blood.

"There are still a lot of unanswered questions regarding the role of inflammation in schizophrenia. But with so many researchers now looking into this area, its role will become clearer, hopefully leading to more effective treatments for those suffering from this debilitating disorder.

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REGULATORY UPDATE SESSION

RU.01: **Strategies for treatment resistant depression and partial response** Emerald **Monday** 19:00–21:15

Regulatory updates on treatment-resistant depression

Following on from last year's pioneering success, the 28th ECNP Congress in Amsterdam will see the return of a dedicated Regulatory update session – a highly-successful joint venture with the European Medicines Agency (EMA), which this year will feature an open dialogue on the strategies for treatment-resistant depression.

The session, held this evening at 19:00–21:15 in the Emerald room, will be chaired by Celso Arango (Spain), and Manuel Haas – who is Head of Central Nervous System and Ophthalmology, Scientific and Regulatory Management Department at the EMA in London, UK. Alongside the two chairs, the session will feature three speakers who will share their regulatory, industry and academic perspectives.

Speaking to *ECNP Daily News*, Mr Haas underlined the symposium's genesis, structure and goals: "The session was conceived as an open platform for engagement between EMA and its stakeholders," he said. "A strong work relationship with academia is important to us; this is why I am very pleased that this session is jointly organised and co-chaired with ECNP.

"The intention is to promote transparency of regulators' work, and to facilitate the uptake of the most up-to-date scientific developments in regulatory science activities. Providing science-based and feasible guidelines to facilitate the development of helpful anti-depressants and their access by patients in need is a big responsibility of the EMA. Capturing healthcare professionals and industry perspectives is key in trying to achieve that."

> "Providing science-based and feasible guidelines to facilitate the development of helpful anti-depressants and their access by patients in need is a big responsibility of the EMA."
>
> Manuel Haas

Looking to the EMA guideline document, which covers many facets of the topic, Mr Haas commented on what exactly constitutes 'treatment-resistant' depression, and whether there are some uncertainties in both definition and treatment: "It is a grey area, and the lack of operational definition for treatment resistance is acknowledged in the guideline," he said. "But the guideline currently makes a distinction between treatment resistant depression [TRD] and partial response [PR].

"In both populations the anti-depressant therapy fails to elicit a sufficient response despite adequate dosage and treatment duration. The distinction lies in the level of response obtained. TRD patients must have shown inadequate response after at least two consecutive treatments. In this population, the guideline recommends that new drugs are studied in monotherapy, essentially to limit unnecessary polypharmacy. In partial responders a clinically meaningful – yet insufficient –response is observed and the guideline recommends augmentation and add-on strategies in this situation.

"These are general recommendations, and each programme must be considered individually. Whether this distinction between TRD and PR is relevant and both populations can be operationally defined will be an important topic for discussion during the Regulatory update session."

Moving on to the discuss the treatment options available in the present day, Mr Haas noted that while depression is a common and serious mental illness, up to a third of patients do not respond satisfactorily to currently-available therapies, thus he passionately supports the search for new treatments, including novel pharmacotherapies.

In this search for new therapies, an issue that warrants discussion is how long to undertake trials, as Mr Haas described: "The length of trials may differ depending on the mechanism of action of the drugs. While trials should not be unnecessarily long, the study duration must be sufficient to detect an effect. The duration of short-term trials is usually of 6-8 weeks.

"In Europe, the effect observed in short-term trials must be demonstrated at least in one double blind long-term trial, as the duration of a depressive index episode usually stretches over months. There is no recommended duration for long-term, relapse prevention trials since the duration of the episode itself varies considerably; however six month randomised withdrawal trials are common. Recurrence prevention trials differ from relapse prevention trial as their objective is to show the drug ability to prevent new episodes."

As indicated in the EMA guideline, the pooling of different patient cohorts – especially in terms of age ranges – must also be considered carefully. "Older people tend to not respond the same way as younger adults to anti-depressants", said Mr Haas. "It is therefore difficult to pool older and younger adults in confirmatory trials. Separate trials are preferred but not mandatory, as long as a sufficient number of old and very old people are included in the clinical trials and the safe and efficacious use of the medicine can be established for them.

"As indicated in the guideline, safety and efficacy results obtained in adults cannot be extrapolated to children and adolescents. They must be studied separately, using adequate dosages and appropriate rating scales."

As he concluded his conversation with *ECNP Daily News*, Mr Haas took the chance to sum up the hopes of the Regulatory update session, saying: "It will be an open, interactive session with the potential to inform future regulatory guideline updates and scientific advice, with the overall goal of patients having better access to helpful medicines."

The Regulatory update session will be held at 19:00–21:15 this evening, in the Emerald room. During the session, drinks and a light buffet dinner will be served for participants with a valid meal voucher. Pick yours up at the ECNP Plaza during the congress.

ECNP

ECNP Fellowship Award

ECNP Fellowship Award handed to six exemplary recipients

At yesterday evening's ECNP Dinner – held in the inspiring surrounds of the Cobra Museum in Amstelveen – the six recipients of this year's ECNP Fellowship Award were given their esteemed prizes. Following on from interviews of the first three recipients in Issue 2, *ECNP Daily News* caught up with the remaining Award winners to find out about their work, and what the ECNP Fellowship Award means to them.

Eldar Hochman

Israel Sackler Faculty of Medicine, Petah Tikva, Israel

Dr Hochman is presenting a study exploring seasonal patterns of manic episode admissions among bipolar I disorder patients – particularly how they are associated with both the male gender, and higher rates of psychotic features.

"People who suffer from bipolar disorders are more vulnerable to develop mood variations in response to seasonal change," he told *ECNP Daily News*. "However, data regarding the significance of manic

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ECNP Fellowship Award

episode seasonality for the course of bipolar I disorder are lacking. In the present study we attempted to identify clinical and demographic features that discriminate between bipolar I disorder patients with and without seasonal pattern of manic admissions.

"We conducted a retrospective cohort study, with a review of electronic medical records, collecting data on 148 bipolar disorder patients with at least two admissions of the same mood polarity to a mental health centre, between 2005 and 2013. Demographic and clinical characteristics were compared between bipolar I disorder patients with or without seasonal patterns of manic admissions. Univariate and multivariate analyses, using logistic regression models, were performed, in which clinical characteristics were predicted by seasonal pattern, and controlling for covariates.

"The results of this study suggest that male bipolar I disorder patients are at increased risk of developing manic states (increased energy, elevated mood, impassivity and more) in specific seasons of the year, with the presence of psychotic symptoms (impaired reality test). As suh, these patients should visit their psychiatrist more frequently around their vulnerable season, and may benefit from increased doses of their medications."

Dina Popovic

Hospital Clinic De Barcelona, Spain

"My poster describes the results of the BRIDGE-II-MIX study, a large multicentric crossectional study aiming to estimate the frequency of mixed states in patients with major depressive episodes (MDE), according to different definitions, and to compare their clinical validity by looking into specific features, such as suicidality," described Dr Popovic.

Dr Popovic's analysis compared characteristics of MDE patients with and without a history of suicide attempt (SA). In order to do this, psychiatric symptoms, socio-demographic and clinical variables of 2811 subjects with MDE were collected, with history of SAs being was registered in 628/2811 patients.

"Among patients who attempted suicide, female sex, familiarity for bipolar disorder, psychotic and atypical features were significantly more frequent," she said. "Past response to treatment with antidepressants of patients who attempted suicide included more (hypo)manic switches, treatment resistance, mood lability and irritability. Multivariate analysis evidenced that risky behaviour, psychomotor agitation and impulsivity, borderline personality disorder and substance abuse disorders were the variables most frequently associated with past suicide attempts."

Dr Popovic added that among subjects who attempted suicide, 75 patients (11.9%) fulfilled DSM-5 criteria for MDE, with mixed features, and 250 patients (39.8%) fulfilled the research-based diagnostic criteria for a mixed depressive episode.

"In conclusion, important differences between MDE patients with and without previous history of SA have emerged," continued Dr Popovic. "Early identification of symptoms such as risky behaviour, psychomotor agitation and impulsivity in MDE patients and treatment of mixed depressive states could represent a major step forward in suicide prevention."

Błażej Misiak

Medical University, Wroclaw, Poland

In his work, Mr Misiak has been focused on baseline cardiometabolic risk in a cohort of first-episode schizophrenia patients. Framing the purpose of his study, Mr Misiak commented: "It is now well established that schizophrenia patients have shorter life expectancy mostly due to increased cardiovascular risk. However, less is known about cardiometabolic disorders in first-episode patients since there is a scarcity of studies comparing patients at the early course of psychosis with healthy controls.

"This research gap has inspired me and my colleagues to investigate cardiometabolic disturbances in first-episode schizophrenia patients. We found that this group of patients is characterised not only by subthreshold metabolic dysregulation, but also by significantly higher prevalence of comorbid metabolic disorders in comparison with healthy controls. Although the majority of our patients were not drug-naïve on the day of recruitment, we found no correlation between treatment parameters and metabolic disturbances.

"These findings suggest that cardiovascular risk in schizophrenia patients is also related to the underlying illness, apart from the known influence of environmental factors. I think that the most important future direction in this field is to investigate whether there are common genetic underpinnings for schizophrenia and metabolic disorders."

"I am honoured to receive the ECNP Fellowship Award 2015 as a recognition for my contribution to the field of mood disorders. Receiving this award gives me an opportunity to present my work in front of a worldwide professional audience, and helps in establishing academic communication and networking. I hope this award will help in a transition to becoming an independent research faculty member."

Eldar Hochman

"Winning this award is particularly significant for me, considering that ECNP is the organisation that has played an important role – probably the most important – in the development of my career so far ... Receiving such important recognition from an organisation that truly is dedicated to promoting junior scientists is an particular honour!"

Dina Popovic

Posters from each of the six ECNP Fellowship Award winners is on permanent display in the Award area of this year's poster exhibition. For details on how you can apply for the ECNP Fellowship Award, head to http://www.ecnp.eu/awards/ECNP-fellowship-award/

"In my opinion, this award is a great honour for every laureate. I have recently decided to engage in full-time in research, although I am also undertaking residency training in psychiatry, and the ECNP Fellowship Award has convinced me that the research path I now follow is a good choice."

Błażej Misiak

THE 28TH ECNP CONGRESS

Travel & Poster Awards

Poster Awards at the 28th ECNP Congress

Congratulations to Sunday's recipients of the ECNP Travel Awards, and ECNP Poster Awards! There will be more award ceremonies held on Monday and Tuesday in the Award area of the poster exhibition.
A list of all the winners will be available on the ECNP website very soon…

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Puzzles and Games

Guess who?

1. Theorised that physiological abnormalities may be the root of mental disorders.

2. Acknowledged 'physiological psychology' in the treatment of illnesses involving emotions

3. Founded hospital in Paris for prostitutes and 'mentally defective'

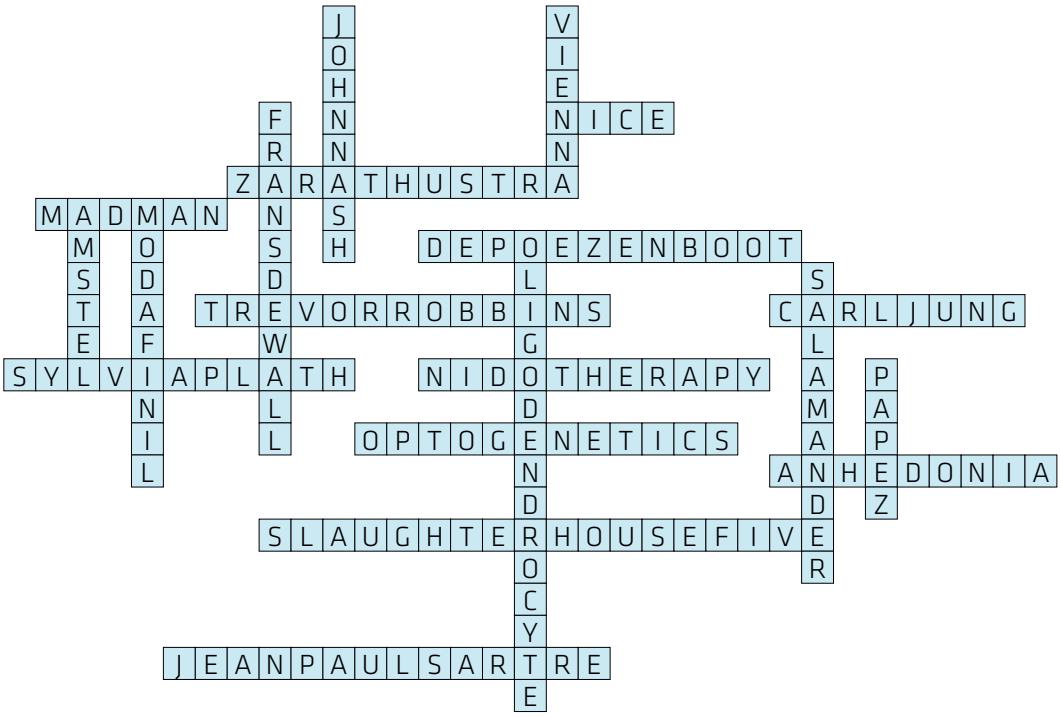
4. US Founding Father and one of the earliest modern advocates of the humane treatment of the mentally ill

5. Best known for noting the role of the hippocampus in memory

6. Physiologist famed for his work in classical conditioning

Answers will be revealed in Issue 4 of *ECNP Daily News*

Crossword solution from Issue 2



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TODAY'S PROGRAMME MONDAY

TIME	ROOM	SESSION
07.45 - 08.45		**Brainstorming sessions**
	D201	BS.4 The Medicines Chest; an initiative to revitalise CNS clinical pharmacology studies
	D202	BS.5 Unconventional side effects of long-term antidepressant treatments
	D203	BS.6 When antipsychotic drugs should be switched in partial responders or non-responders in the acute treatment of schizophrenia
09.00 - 17.00	Exhibition area	**Exhibition**
09.00 - 10.40		**Symposia**
	Auditorium	CT S.13 Oxytocin in schizophrenia: new research findings
	Elicium 2	CR S.14 From impulsivity to habit? Neuropsychopharmacological mechanisms underlying addiction
	Forum	TR S.15 Junior Scientist symposium - Dysfunctional brain circuits in psychiatric disorders: new clinical and preclinical insights
	Emerald	PR S.16 Translational research on sleep and depression
	Elicium 1	ET E.04 Anxiety disorders: from new targets to new treatments
10.40 - 11.15	Poster podium Poster & exhibition areas Poster area	**Travel award ceremony** **Coffee break** **Poster viewing**
11.15 - 12.00	Auditorium	**PL.03 Plenary lecture** – The role of motivation and reward in mental disorders
12.00 - 14.00	Poster & exhibition areas	**Lunch**
12.15 - 13.45	Poster area	**Poster session**
12.15 - 12.45	Poster podium	**RF.02 Rapid-fire poster session**
12.15 - 13.15	Emerald	**General Assembly of ECNP Members**
13.00 - 13.15	Poster podium	**Poster award ceremony**
13.15 - 13.45	Poster podium	**CD.02 Career development session** – How to give an effective talk
14.00 - 14.45	Auditorium	**PL.04 Plenary lecture** – Is it time for immuno-psychiatry?
14.45 - 15.00	Poster & exhibition areas	**Coffee break**
15.00 - 16.40		**Symposia**
	Auditorium	CT S.17 Psychopharmacological treatments in autism spectrum disorder
	Elicium 2	CR S.18 TNM Symposium – Neuroimaging as a clinically useful tool: the time has arrived
	Forum	TR S.19 From bench to bedside and back with precision – the case of CNV research in schizophrenia: outcome of the IMI-NEWMEDS Consortium
	Emerald	PR S.20 The gut microbiome: a new frontier in brain research
	Elicium 1	ET E.05 EPA educational session - The future of neuropsychopharmacology in Europe: the EPA perspective
17.15 - 19.00		**Satellite symposia**
	Elicium 2	C.11 The natural history of alcohol dependence - importance of early and continuous intervention
	Forum	C.12 Adult ADHD management in 2015: are we doing enough for our patients?
	Emerald	C.13 It's all about the patient: clinical cases of cognitive dysfunction in major depressive disorder
	Elicium 1	C.14 Antipsychotics in schizophrenia: investigating the evidence
19.00 - 21.15	Emerald	RU.01 **Regulatory update session** – Strategies for treatment resistant depression and partial response

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