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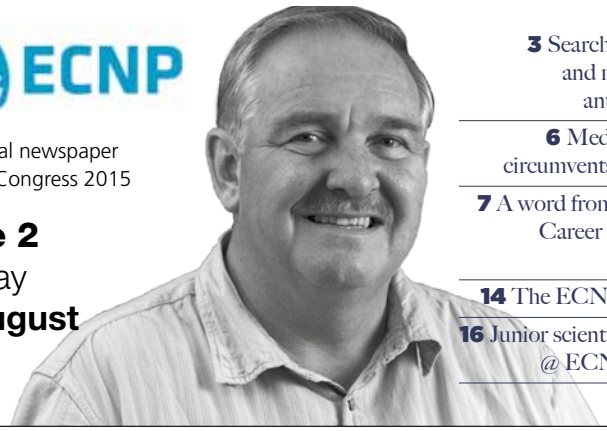
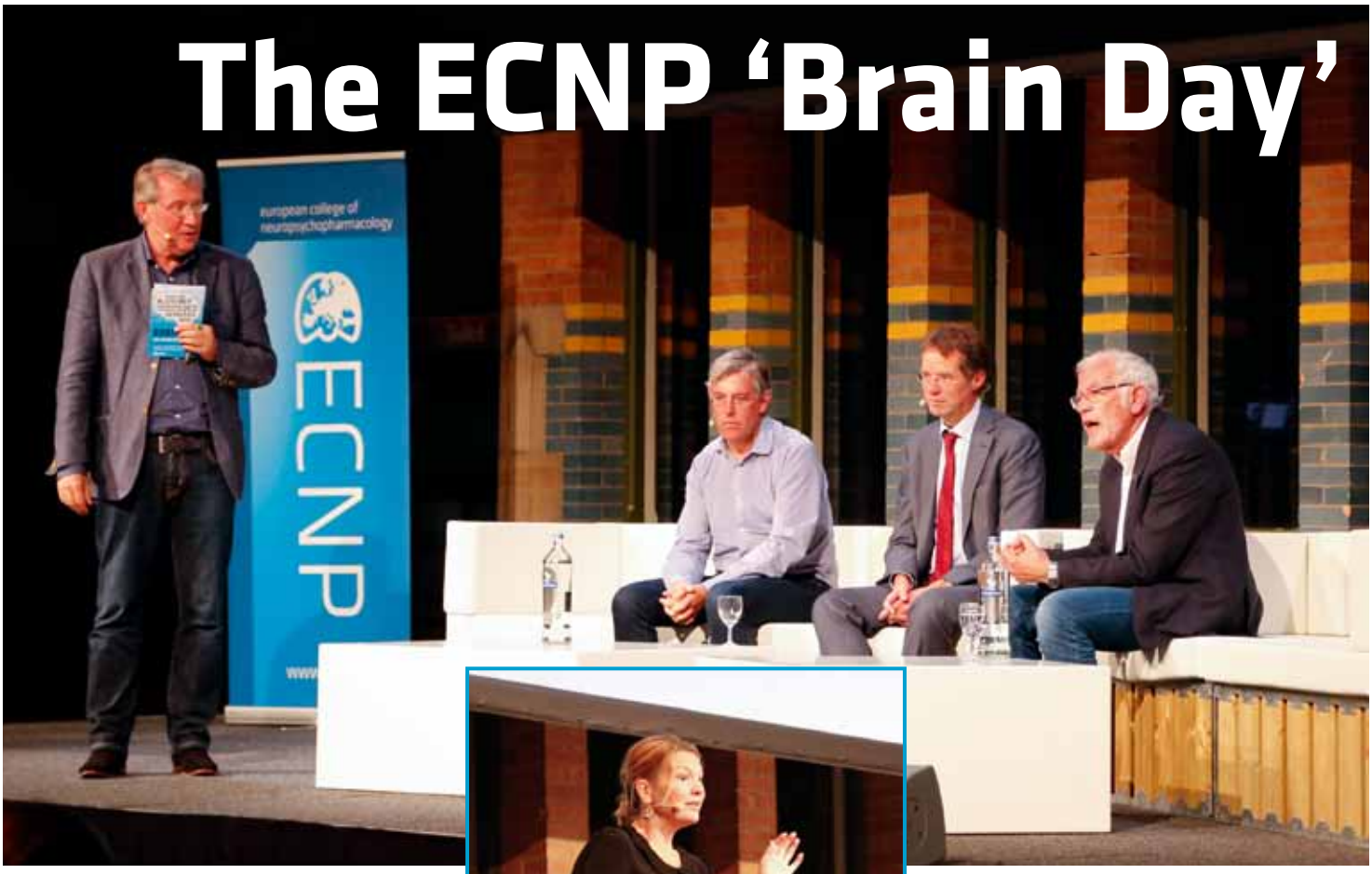


ECNP
DAILY NEWS

The ECNP 'Brain Day'



On Friday ECNP presented its second public information day in conjunction with the ECNP Congress, the 'Brain Day', held in the historic Beurs van Berlage in central Amsterdam. Over 500 people turned out from across the country – including patients, their family members, students, health workers and members of the general public. A public-good initiative of the College's to bring the science of the ECNP Congress to a wider audience, the Brain Day brought together seven of the Netherlands' top neuroscientists to explain the latest developments in brain research and how they are being translated into new and better treatments for those suffering from neuropsychiatric disorders.

28th ECNP Congress Scientific Programme Committee chair Wim van den Brink (University of Amsterdam) chaired the day, opening proceedings by introducing the brain and how the discoveries being made by researchers are unravelling its mysteries and changing the lives of those struggling with its various disorders.

To emphasise the linkage to 'real-life' challenges, the programme was designed to follow the changes in the brain – and the stresses and problems these can generate – across the human lifecycle. Eveline Crone (University of Leiden) began by discussing the adolescent brain, the special ways it functions, and how we connect this to brain structure and development. Jan Buitelaar (Radboud University Nijmegen) picked up the theme by looking at ADHD and its implications for the children and adolescents suffering from it. Leading on from this, Wim van den Brink looked at 'the hungry brain' and the processes of addiction, where these originate and how they can be contained and treated. Iris Sommer (University of Utrecht) then explored hallucinations, why these occur, what they mean and their relationship to cognitive function.

After a break for coffee and interaction, Aartjan Beekman (Free University Amsterdam) tackled depression, why it is so prevalent, how it relates to brain structures, and what this means for possible treatments. Damiaan Denys (University of Amsterdam) followed by looking at OCD and how deep brain stimulation – the 'pacemaker for brain' – works for those suffering from the disorder, and the ethical considerations DBS presents. Rounding the

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ECNP

The ECNP Brain Day

The ECNP 'Brain Day'

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programme off, Dick Swaab (University of Amsterdam and 2014 ECNP Media Award Winner) discussed the aged brain, and what we are learning about Alzheimer's, and how to postpone its onset and appalling effects.

Feedback from attendees was extremely enthusiastic. "There's clearly a huge appetite amongst the general public to learn about the brain and how it works," said Wim van den Brink. "I'm very happy that we were able to serve that demand with the Brain Day, and that it was such a huge success." "We're extremely grateful for Wim for putting this together," said ECNP President Guy Goodwin. "The Netherlands continues to produce some of the best neuroscience in the world, and it was great to see an all-star line-up of some of its very best neuroscientists here today."

THE 28TH ECNP CONGRESS

ECNP Media Award

First-rate communicator Mary Baker receives the ECNP Media Award

The ECNP Media Award celebrates the work of those who promote improved understanding of the complexity and impact of disorders of the brain, stimulate discussion, and challenge stigma and stereotypes.

This year's award, presented during yesterday's patient session on the 'Emerging role of the carer – how healthcare systems need to change', was given to immediate past-President of the European Brain Council (EBC), Mary Baker, MBE - an outstanding communicator and advocate.

Renowned for her stimulating and productive discussion, Dr Baker has an unparalleled record of success in achieving results that effect change. She is driven in her campaigning and communication of brain diseases, and in particular, she carries a message of pressing need for everyone in society to take responsibility for their health – both mental and physical.

Guy Goodwin presents the ECNP Media Award to Mary Baker

> "We cannot go on conducting research just because the science dictates it so. Society needs to be engaged with it."
>
> Mary Baker

Throughout her work Dr Baker has striven to emphasise the importance of communication across all strata of society, and the healthcare community. "We cannot go on conducting research just because the science dictates it so," she said. "Society needs to be engaged with it, and it is in this respect that I've tried really hard to make this my major contribution to all the work [the brain disease community] does."

"If people don't understand the importance of the scientific work then it will be blocked – remember what happened to Galileo," she added.

Dr Baker commented that she was staggered to be the recipient, noting: "Frankly, I was very surprised and I feel honoured, because until I worked at the EBC I did not have a fully comprehensive understanding of neuropsychopharmacology."

She highlighted that she was incredibly impressed at the efforts that the ECNP, particularly David Nutt and Guy Goodwin, were making to engage with regulatory authorities in particular. "That's a significant challenge."

Dr Baker recalled that, once Professor Nutt had visited the EMA and met with senior people, both parties were able to begin working together productively. "You need to go to the top. Once they had met the senior people at the EMA and a mutual respect was established, then they found a way forward," she said.

"It's all about working together, stopping tribalism and improving communication with society," she concluded.

In support of Dr Baker's award, ECNP President Professor Goodwin commented: "She is one of the field's great communicators, with a unique ability to bring alive the link between research in the lab, and the experience of patients struggling with disorders of the brain. She's an excellent recipient of this award."

PLENARY LECTURES

PL.02: **ECNP Neuropsychopharmacology Award Lecture** Auditorium **Sunday** 14:00–14:45

Antidepressants: can we improve their speed and efficacy?

The hypothesis that antidepressant effects only emerge after weeks of therapy has largely been overturned with the advent of rapid-acting treatments such as ketamine and deep brain stimulation (DBS). The process of uncovering the neurobiological bases of these clearly distinct mechanisms continues to busy research minds, and the current state of progress will be discussed by this year's ECNP Neuropsychopharmacology Award winner Francesc Artigas (CIBERSAM-IIBB(CSIC)-IDIBAPS, Instituto de Investigaciones Biomédicas de Barcelona, Spain), during his lecture this afternoon at the congress.

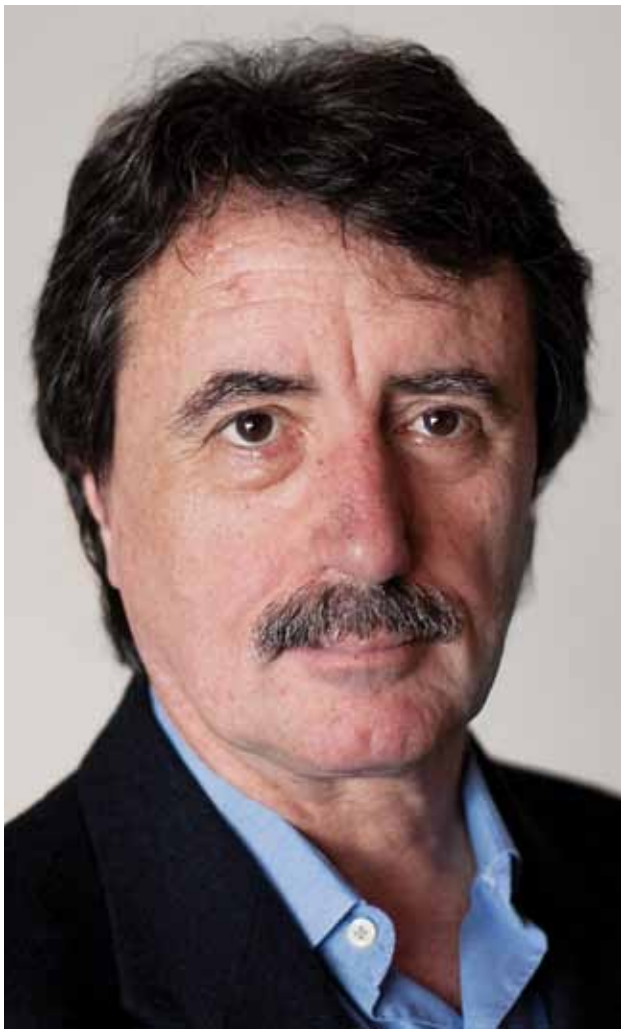
Progress in the understanding of the neurotransmitter systems involved in both rapid-acting and classical antidepressant treatments has been instructive in the ongoing search for novel targets in the brain, explained Professor Artigas to *ECNP Daily News*. Moreover, it has opened the doors to new possibilities for treatment: "Before, many people were dubious that the human brain can react rapidly to treatment," he said. "There was the thinking that antidepressants had limited efficacy due to the inability of the brain to improve more rapidly. These new strategies have shown that this rapid antidepressant action is really possible."

The mechanisms of ketamine and DBS differ from those of the classic antidepressant drugs (which act on the monoamines) in that they act by modulating the function of glutamatergic neurons. Glutamatergic neurons make up about 80% of the neurons populating the human cortex, explained Professor Artigas, which may go some way to explain its potency: "Many people are trying to investigate how ketamine and DBS work. We of course are working on ketamine too – we have worked a lot not only with ketamine but with a similar agent, phencyclidine (PCP).

> "We can knock down the expression of serotonin genes in serotonin neurons, and obtain a very rapid and effective antidepressant mechanism."
>
> Francesc Artigas

We have published a series of papers since 2007 showing that PCP enhances the activity of thalamic and cortical neurons[1,2,3], and we are now trying to understand if ketamine does the same. We have some very, very preliminary data suggesting that both drugs share some mechanisms, inhibiting GABAergic neurons in the thalamus."

Amid investigations into the role of the glutamatergic system, the need to clarify the role of the monoamines remains; ketamine is certainly no replacement for classic antidepressant treatment, bringing about only short-lived antidepressant effects. This has led Professor Artigas and colleagues to focus their efforts on bringing about increased serotonergic activity with ketamine's rapidity and potency, by changing the expression of a crucial puzzle piece in major depression – the serotonin transporter (SERT).



SERT is the most common target of antidepressants, with chronic administration eliciting its downregulation, resulting in increases in serotonin transmission and hippocampal plasticity. Professor Artigas' recent investigations have involved the use of small interfering (si) RNAs to knock down SERT expression in mice, eliciting a rapid antidepressant effect[4]: "We link the siRNA to sertraline (one of the selective 5HT reuptake blockers, SSRI) in order to direct the siRNA to these serotonin neurons.

"We can knock down the expression of serotonin genes in serotonin neurons, and obtain a very rapid and effective antidepressant mechanism. Of course, this is still in the preclinical stage and we have a long way to go, but this is a new strategy to increase the function of serotonin neurons which is much more effective than the classical uptake blockers."

Up to now, the stumbling block in translating this approach into a viable therapy has been its method of administration; the integrity of the blood-brain barrier, together with the complexities of the human brain, would certainly hamper the process of getting interfering RNAs into the brain at all, let alone to the right region. By conjugating siRNAs to the sertraline ligand and administering the drug intranasally, the group were able to specifically target serotonin neurons of the dorsal raphe non-surgically.

Relying on the relatively permeable nature of the nasal epithelium (through which molecules can then enter the CNS via the olfactory or trigeminal pathways), intranasal administration effectively bypasses the blood-brain barrier and has proven safe and highly effective in a number of clinical applications. "This is a route used for those drugs that do not cross the blood-brain barrier well," said Professor Artigas. "This administration route is increasingly used and there are many recent clinical studies using the intranasal route to deliver drugs or peptides into the CNS, particularly in neurological disorders."

> "New strategies have shown that this rapid antidepressant action is really possible."
>
> Francesc Artigas

The proven safety and efficacy of sertraline-conjugated siRNA is keenly awaited in a climate in which only 30% of patients treated with classic antidepressants experience a remission of symptoms following first treatment. By administering effective treatments sooner, explained Professor Artigas, it is possible that the transition to chronic depression could be prevented: "The classical antidepressant drugs produce a very limited effect. Many patients show only very small improvements, and that results in recurrences. Our view is that, if the improvement is more effective with the first treatment, those recurrences and chronic depression will be reduced."

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CLINICAL RESEARCH

S.09: **Psychopharmacology of frontotemporal dementias – towards new therapies** Auditorium **Sunday** 15:00–16:40

Repurposed SSRI offers hope in fronto-temporal dementia

This afternoon's symposium dedicated to fronto-temporal dementia (FTD) will see experts characterise the disorder with regards to its behavioural characteristics, pathology, genetic aetiology and the great potential for new and repurposed pharmacological interventions. They will also describe the need for new approaches to drug trials for this disease and the role that presymptomatic (genetic) testing may play, not just for diagnosis but for early interventions.

In an interview ahead of the session, James Rowe (University of Cambridge, UK) reasoned a new framework of understanding of FTD, and outlined his latest pharmacological neuroimaging research into the role of serotonin in impulsivity in FTD.

Firstly, Dr Rowe spoke of the FTD definition: "FTDs are very distinct and separate types of dementias in their symptoms, genetics and pathology. They are relatively common, comprising about 5% of all dementias, and no treatment exists to either cure or even impact symptoms."

"The behavioural variant of FTD (bvFTD) is very challenging because it causes changes in personality and behaviour that manifest in impulsivity. This can put the individuals' lives at risk and increase the burden on their carers; another behavioural manifestation is the loss of warmth, social contact and empathy."

As disinhibition is a central feature of bvFTD, Dr Rowe and co-workers were interested in impulse control and its potential for modification. He explained: "We've been looking at impulsivity not just in terms of neuropsychiatric behaviours, but also how brain networks are involved in impulse control using neuroimaging."

Serotonergic function is closely associated with inhibitory control,[1] and has been shown to be deficient in bvFTD,[2] so increasing serotonin levels was a potential therapeutic strategy for Dr Rowe and co-workers. "We used citalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant, for patients who have bvFTD to investigate whether the drug restores behaviour, and also whether it boosts the brain areas normally involved in controlling our behaviour," he said.

"The behavioural variant of FTD (bvFTD) is very challenging because it causes changes in personality and behaviour that manifest in impulsivity."

James Rowe

Measuring responses to the Go-NoGo paradigm with magnetoencephalography and electroencephalography, they investigated aberrant inhibitory control in bvFTD patients and the extent to which this could be modified by citalopram.[3] The previously-attenuated inhibition response in bvFTD patients was enhanced by citalopram, relative to placebo treatment, and responses were also increased in the right inferior frontal gyrus. Dr Rowe elaborated: "We have been able to show that these drugs can really work, and the abnormalities you get on everyday tests correlate with everyday difficulties. We also saw that these drugs boost frontal lobe regions that are involved with controlling impulsive behaviour. These areas have not just shrunk a bit – they have run dry of serotonin."

With a network approach in mind he explained how serotonergic drugs re-establish behaviour though restoration of frontal systems and inhibitory control networks: "We've managed to show this using the patient's brain imaging and pharmacology, creating a very joined-up story that both looks forward to treatment and also connects back to the basic science research. This is not just about treatment, it also validates a whole method of drug research: repurposing drugs and using brain imaging to ascertain that they are working in the right place to improve function."

There is a strong genetic aetiology in FTD, with 30–50% of patients having a family history of the disorder.[4] This offers an opportunity to treat people before symptoms are apparent, with the ultimate goal of prevention. However, treating presymptomatic individuals poses a big challenge:

"These areas have not just shrunk a bit –they have run dry of serotonin."

James Rowe

how is it possible to detect treatment effectiveness in essentially healthy individuals? Utilisation of non-invasive imaging modalities such as neuroimaging offers the potential to detect functional and structural changes both spatially and temporally, allowing for longitudinal monitoring of disease progression.

"I think that imaging is the most powerful, safe and convenient way of detecting change, because it can help with diagnosis and also determine the illness trajectory. Other biomarkers are also important: PET and CSF analysis are possible but more challenging tests; blood tests could also be future biomarkers but we're a long way of doing this; magnetoencephalography is a simple, quiet and relaxing procedure too so it's our leading biomarker for FTD currently."

With regards to the loss of empathy and social perception of FTD patients, Dr Rowe's group have begun a trial of oxytocin administration in genetic carriers of FTD using imaging to elucidate drug action. He believes that this will be a turning point in the outlook towards treatment: "This is a strong positive message about the prospect of treatment," he said. "Historically the public have been very negative about this, but we're seeing a change in the attitudes and prospects for treatments."

These studies demonstrate a translational approach to neurological disease, and offer great hope for both future cures and symptomatic relief. Concluding, Dr Rowe commented that a great feature of the ECNP Congress is the potential for repurposing established medication: "Drugs that are proven in one context can teach us about their use in another."

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CLINICAL RESEARCH

S.06: **22q11.2DS deletion (velo-cardio-facial) syndrome: a multi-modal approach...** Elicium 2 **Sunday** 09:00–10:40

Findings in 22q11.2DS hold 'important clinical implications for child and adolescent psychiatry'

A recent report from the International Consortium on Brain and Behaviour in 22q11.2 Deletion Syndrome (22q11.2DS, or velo-cardio-facial syndrome) found psychotic disorders occurring in 41% of such adults over the age of 25, making the condition one of the strongest risk factors for psychosis. One of the largest studies into psychiatric morbidity of the syndrome, the report concludes with a call for better monitoring and management of 22q11.2DS.[1]

The paper's first author, Maude Schneider (Office Médico-Pédagogique Research Unit, University of Geneva, Switzerland), will join others at the ECNP Congress today in a symposium bringing to light the risk factors for schizophrenia in 22q11.2DS. In an interview with *ECNP Daily News*, she described what could be achieved with a greater focus on identifying and treating such symptoms, not just for those with 22q11.2DS, but for those with idiopathic schizophrenia too.

"Previous findings have shown that the clinical expression of schizophrenia in patients with 22q11.2DS is not fundamentally different from what is typically observed in idiopathic schizophrenia," she said. "When they develop schizophrenia, patients with 22q11.2DS experience positive symptoms (hallucinations, delusional ideas), negative symptoms (apathy, blunted affect) and disorganisation symptoms (disorganised speech)."

The study by the International Consortium on Brain and Behaviour in 22q11.2DS included 1,402 individuals from 6 to 68 years of age, bringing together a number of interesting patterns of lifetime prevalence and their associations with intellectual and adaptive functioning. Despite its highly variable expression of neurocognitive and psychiatric sequelae, the relative frequency of 22q11.2DS incidence offers the hope of picking apart risk-bearing and protective cofactors of the various psychiatric consequences of the syndrome.

During her PhD, Dr Schneider focused on the clinical expression of negative symptoms in adolescents and young adults with 22q11.2DS – a topic, she explained, that had never been properly investigated: "Negative symptoms are one of the hallmarks of schizophrenia, along with positive symptoms. They typically include manifestations such as social withdrawal, blunted affect, apathy, and motor retardation. Negative symptoms can be of clinical severity but can also be of subclinical severity in patients with 22q11.2DS."

She observed that negative symptoms are extremely frequent in patients with 22q11.2DS (finding that between 65 to 80% of adolescents and young adults experience negative symptoms of moderate to severe intensity). In bearing such an impact on daily-life functioning, they emerge as a key target for psychological intervention.

In relation to idiopathic schizophrenia, now appreciated to lay down its roots during childhood and adolescence, Dr Schneider explained that 22q11.2DS offers two major advantages over 'traditional' schizophrenia research.

"Patients are diagnosed with 22q11.2DS during infancy or childhood (in most but not all cases), years before the onset of the first psychotic symptoms," she said. "This enables us to follow cohorts of children that are at risk but not yet symptomatic and examine the risk factors that precede the development of schizophrenia.

"These risk factors can be different in nature: clinical, cognitive, biological (e.g. brain development), environmental, genetic, etc. Of note, the only other way to constitute a cohort of children at such high risk for schizophrenia is to recruit children of adult patients with schizophrenia, which is extremely complicated."

Interestingly, several papers in the field of 22q11.2DS have found that patients diagnosed with an anxiety disorder during childhood or early adolescence are at a much greater risk of developing a psychotic disorder later on than patients without an anxiety disorder.[2] Such findings, noted Dr Schneider, can be extended to the general population, with important clinical implications for child and adolescent psychiatry in general.

The second advantage of studying 22q11.2DS lies in the unique possibilities for translational research, she explained: "Indeed, there is a mouse model of 22q11.2DS called 'LgDel' that is characterised by a deletion on chromosome 16. This deletion encompasses the same genes that are also deleted in humans.[3]

"Studying patients with 22q11.2DS and LgDel mice together enables us to gain important knowledge in the biological mechanisms leading to the onset of schizophrenia. For example, several studies have found that 22q11.2DS is characterised by increased cortical thinning during adolescence in frontal regions. However, the biological mechanisms responsible for this excessive thinning are currently unknown and cannot be investigated in humans. Studying LgDel mice could help shed light on this question."

During the symposium, Dr Schneider will present a number of findings from her recent research, as well as that of others, suggest that risk factors such as cognitive decline can appear in some children from the age of seven years onwards. "We observed that atypical trajectories in some cognitive functions (executive functioning and verbal abilities) are associated with the presence of positive and negative symptoms of schizophrenia," she said.

"The clinical expression of schizophrenia in patients with 22q11.2DS is not fundamentally different from what is typically observed in idiopathic schizophrenia."

Maude Schneider

"Psychological interventions focusing on these cognitive functions (e.g. cognitive remediation) may contribute to reducing these symptoms."

Maude Schneider

"This aspect has important clinical implications because this suggests that psychological interventions focusing on these cognitive functions (e.g. cognitive remediation) may contribute to reducing these symptoms. In my opinion, this approach is particularly interesting and promising for negative symptoms, as we know that these symptoms respond poorly to medication and hence require psychological interventions. However, the impact of cognitive remediation has still to be examined directly in patients with 22q11.2DS."

Developing such remediation tactics to throw the development of psychiatric symptoms off-course is a much-anticipated consequence of Dr Schneider's research. Crucially, she concluded, such work demonstrates the importance of studying cognition in patients with psychiatric disorders: "Cognitive deficits are one (out of many) factors contributing to the emergence of clinical symptoms. This is particularly important in the field of schizophrenia, where the presence of cognitive deficits is clearly established, but also in other psychiatric disorders."

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CLINICAL TREATMENT

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

Medicines Chest circumvents 'brain drain'

The CNS drug development pipeline may be experiencing a period of slow growth, but pioneering shoots have sprung up alongside it, bridging the gap between academia and industry to reinvestigate and repurpose abandoned drugs of the past – and hopefully to revitalise the field of clinical pharmacology.

The opportunities offered by industry compounds that have previously failed in clinical trials for other indications will be discussed on Tuesday morning, during a symposium in which valuable experience from both Europe and the US will be shared. One key aspect that will be explored is the ECNP Medicines Chest[1], an initiative that assists clinical researchers in obtaining access to pharmacological tools important for the pursuit of their studies. Several pharmaceutical companies are already participating in the ECNP Medicines Chest, with a number of compounds already available to researchers.

"Destroying compounds and getting rid of the database is a bit like destroying original Shakespeare manuscripts so that no one can ever perform the play again."

David Nutt

Discussing the ECNP Medicines Chest during the session will be David Nutt (Imperial College London, UK), who will also be chairing a brainstorming session dedicated to the initiative on Monday morning. In an interview with *ECNP Daily News*, Professor Nutt began by outlining the other initiatives performing similar functions to the Chest: "There are interesting repurposing projects going on in Europe and the US," he said.

"In the US it is called NCATS [National Center for Advancing Translational Science], an NIH [National Institutes of Health] scheme to take compounds and to try them on new disorders.[2] The UK's MRC [Medical Research Council] has a similar scheme, but currently it is working just for AstraZeneca compounds – the company has made available some interesting compounds that they no longer wish to develop by themselves, so people have written MRC grants to work with these compounds.[3] Then AstraZeneca provides the compound and also takes care of the regulatory aspects such as adverse effects reporting."

"Pharmaceutical companies often don't know where to go with repurposing a drug."

David Nutt

While pharmaceutical companies have undertaken their own initiatives that put deprioritised drugs out to tender, there is perhaps greater strength in those collaborative efforts with academics, which are not directly driven by commerce: "When a compound fails, these companies do often try to license it out to other companies," explained Professor Nutt. "But the CNS field has become more constricted, and that is one of the reasons why we wanted to have the Medicines Chest. There is so little innovation in pharmaceutical brain science at present that we felt we may not get many new drugs – in which case it is vital to keep hold of the old ones, as that is all we have to work with!"

Shedding light on what the process of bringing back a proprietary drug might involve, Professor Nutt continued: "If a drug has recently been studied by a company and has failed in a clinical trial, if they are not going to use this drug for any other indications, and if they have supplies of tablets or capsules that remain stable for a year or two, then the company can supply the pre-formulated medicine to us and we can do further research."

But this is the dream scenario, he pointed out, because the vast expense of manufacturing capsules is avoided. A contrasting example would involve an extremely interesting and selective drug, developed but then dropped perhaps 10 or 15 years ago. As long as reports of the drug's toxicology and chemistry were still available, the drug could be resynthesized and studied.

While this approach can cost around 100,000 to 500,000 euros depending on the complexity of the synthesis, a far greater challenge is posed when pharmacology and toxicology data is absent or withheld. In these cases, the costs of resurrecting a drug would exceed 1 million euros.

The latter scenario might prohibit any reinvestigation, but drug repurposing can offer considerable advantages to both the academics and pharmaceutical companies involved in the process. The compounds in question have often undergone a considerable degree of industrial development at the point when they were shelved, which shortens their development time relative to virgin compounds.

Equally important to pharmaceutical companies is the prospect that an ECNP Medicines Chest investigation might discover some great utility of a compound, which the company could then develop themselves. Furthermore, as Professor Nutt noted, a certain amount of prestige can be gleaned by the simple fact that a company has engaged in 'important science'.

"There is a social commitment there too," he added. "Pharmaceutical knowledge is an important part of knowledge in general. Destroying compounds and getting rid of the database is a bit like destroying original Shakespeare manuscripts so that no one can ever perform the play again.

"Once the drug is gone, it is so hard to resurrect it. In fact, one of the things we want to do is to collate this old data, because companies might simply want to burn data after 10 or 15 years – and then it is gone forever."

When asked about the liability surrounding the drug once it is out of the pharmaceutical company's hands, Professor Nutt suggested that this poses a greater issue in the US than in Europe. "The sponsors are responsible for the assurances of the study," he said.

"American compensation laws are so broadly drawn, to the point that it is possible that anyone can sue for anything and this scares the company lawyers! European companies are a bit more flexible and pragmatic in realising that they would not be sued for having invented a compound which might be found by an academic to have some negative side effect."

Despite this, the success of such collaboration is rooted in the stronger backbone of knowledge and expertise it brings: "Pharmaceutical companies often don't know where to go with repurposing a drug," noted Professor Nutt. "So by putting it out to the community, you might just find someone who has use for that compound in a particular disorder that the company might never have thought of. So they are very interested in gaining new insights from academics."

Drug repurposing in the CNS will be discussed in greater depth on Tuesday morning between 9:00 and 10:40 in the Auditorium.

Professor Nutt will also be chairing a brainstorming session on the ECNP Medicines Chest, where he will be joined by speakers Trevor Robbins and Ann Hayes. The session takes place tomorrow morning from 07:45 to 08:45.

For more information about the ECNP Medicines Chest, the drugs available for study, and how to apply for a grant, please visit www.ecnp.eu/projects-initiatives/ECNP-medicines-chest.aspx.

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CAREER DEVELOPMENT

Career development sessions at the 28th ECNP Congress

Expert guidance for junior members

This afternoon marks the first of this year's roster of Career development sessions, with the first outing offering expert advice on how to produce an award-winning poster.

The Career development sessions are specifically designed to offer training and advice for junior scientists, but the topics can still offer interesting insights at all levels. Held at the Poster podium at 13:15–13:45 daily, each of the sessions will tackle a particular overarching topic. Along with this afternoon's discussion on how to produce a top-tier poster, tomorrow's focus will be on how to give an effective talk, with Tuesday wrapping up the sessions with a frank and open discussion of 'A job beyond research'.

Tackling Tuesday's industry-based career discussion will be Thomas Steckler (Janssen Research and Development, Beerse, Belgium) who, in conversation with *ECNP Daily News*, began by charting each session's basic underpinnings: "These sessions are really meant to be very interactive, and importantly they should take place in a very relaxed atmosphere, so that people do not feel inhibited in asking questions," he said.

"If you have too many experienced colleagues in attendance, then junior colleagues tend to be quiet. And we want to encourage active participation so we can maximise what people get out of it." To that end, emphasis on active participation is also mirrored in the rescheduling of each session from early morning to lunchtime, as well as their relocation to the more vibrant poster area.

Moving on to the specifics of his session, Dr Steckler offered a snapshot of what he and fellow speaker Mark J. Millan (Institut de recherches Servier, Croissy-sur-Seine, France) hope to address. "First of all I think it is important that we encourage an open and honest approach to the current job market," he said. "There are still a number of opportunities in great research positions in both academia and industry, but we also have to be clear that this is an extremely competitive area.

"So I think it is very wise, and useful, to explore alternatives, which I think there are many of, both in academia and industry."

One key message that Dr Steckler will be keen to get across is that candidates looking for a job in industry should realise that their existing skills are highly relevant, and very translatable. "The scientific industry requires a combination of expertise from different areas to be successful," said Dr Steckler.

"Industry is changing rapidly, in an aim to react to challenges. It requires employees who learn continuously and are flexible. And I think it is a place where we have a lot of different and exciting career opportunities. The point is that most people, in particular junior scientists who have not had any experience with industry, are not aware of those opportunities, and have no clear

view on what these positions are about. So that is one of the main goals in this session: to raise awareness of the different types of pharmaceutical opportunities."

He expanded more on the skillsets that go hand-in-hand with a successful career in industry: "Often these positions require a scientific background, even though they are not in science directly, and as such industry is a great area to look into because it really broadens one's horizon in an area that is scientifically-related."

By way of example, Dr Steckler listed several specific skills that can clearly be transposed from academia to industry, including teamwork, project management, resource management and quality control. "When you consider what constitutes an 'attractive' industry candidate, employers are looking for people who have analytical skills, problem-solving skills, experience of conducting research on a particular topic, etc., all the while being able to collect data and critically evaluate it," said Dr Steckler. "These are a set of skills that scientists already have in place as part of their education."

> "These sessions are really meant to be very interactive, and importantly they should take place in a very relaxed atmosphere, so that people do not feel inhibited in asking questions."
>
> Thomas Steckler

While Dr Steckler and Professor Millan will share more on the ins and outs of a career in industry during the session – including what strengths candidates should be confident in emphasising – Dr Steckler ended his conversation with *ECNP Daily News* with two final take-home points. "One; I think it is important for people to be motivated to go into these areas, because if you really want to be successful in your career, you should make these types of moves for the right reasons," he said. "Finally, candidates should see the opportunities to move in to other areas as a great chance in their careers, not a burden or something they 'have' to do."

There are three Career development sessions taking place at this year's ECNP Congress – each at 13:15–13:45 in the Poster podium area. Today's session will tackle 'How to make an award-winning poster'; Monday will explore 'How to give an effective talk'; and Tuesday will see Dr Steckler and Professor Millan take to the podium to discuss 'A job beyond research'.

EDUCATIONAL

E.05: **EPA educational session – The future of neuropsychopharmacology in Europe** Elicium 1 **Monday** 15:00–16:40

Closing the treatment gap: In conversation with **EPA President Wolfgang Gaebel**

An educational update session tomorrow afternoon sees the EPA sharing their perspectives on the future of neuropsychopharmacology in Europe. Making the case for the supplementation of national guidelines with Europe-wide guidelines in the field, Wolfgang Gaebel (Heinrich-Heine Universität, Düsseldorf, Germany) will discuss the ongoing EPA Guidance project that aims to fill the treatment gaps that are well recognised, both within and outside Europe.

"The few available studies in mental healthcare indicate that such gaps exist," explained Professor Gaebel in an interview with *ECNP Daily News* ahead of the session. "But we do need more studies with sound methodology and representative clinical samples to define and quantitate these gaps more precisely."

While such studies are necessary to developing a strategy that will overcome these treatment gaps, the EPA's Guidance papers form a prequel to this work by informing patients and other stakeholders about evidence- and consensus-based best practices in pharmacological treatment and mental healthcare. Unlike national guidelines, the EPA Guidance papers are not focused on individual diagnostic groups, dealing instead with aspects like quality assurance of mental healthcare, trust in mental healthcare services, the prevention and early treatment of mental disorders, and post-graduate training. The series also deals with severe mental illness, such as suicidality, and special care situations, including the mental healthcare of migrants and cultural competence training for psychiatrists.

These Guidances target two types of treatment gap that persist in mental healthcare: the qualitative and the quantitative. "The quantitative gap means that not all people with mental illnesses receive treatment," said Professor Gaebel. "And this may be due to many reasons, ranging from individual reluctance to use the available mental healthcare services to national problems like the non-availability of services. The other, qualitative gap addresses the question of whether the treatment received was optimal in the respective clinical situation."

Getting to grips with the complex manifold underpinning such treatment gaps will be valuable in understanding how to improve adherence from all sides of the care sphere. "One cannot expect that mental healthcare utilisation and quality will increase just by providing guidelines or guidance," said Professor Gaebel, noting that individual factors on the patient and provider side interact with broader, health-system-wide factors such as the non-availability of certain treatments.

> "EPA will use this chance to develop and implement indicators of mental healthcare gaps and to suggest plans to close these gaps."
>
> Wolfgang Gaebel

> "There are studies showing that guideline use in clinical practice can be improved, like through the use of computer-based treatment decision support systems."
>
> Wolfgang Gaebel

He continued: "Therefore the question arises, which factors are decisive for guideline implementation and guideline conformity? We know from several studies that knowledge transfer and experiences play a role, and that these can be improved by implementing guidelines – so the question arises of how the implementation of the existing guidelines may be improved.

"There are studies showing that guideline use in clinical practice can be improved, such as through the use of computer-based treatment decision support systems. We will need to devise guidance implementation programs using such techniques to improve EPA guidance implementation and evaluation, and the implementation methods that will be developed and successfully evaluated can then also be applied to national guidelines."

Strategy implementation hinges on working with individual countries to identify their educational, structural, traditional and financial resources and limits that constrain the healthy clamour for better mental health provision across Europe. "Here, the national psychiatric associations come into play," said Professor Gaebel.

"They have the experience and knowledge which is necessary for national efforts to improve the quality of mental healthcare. Many countries like the Czech Republic are reforming their mental healthcare systems and the EPA and its Council of National Psychiatric Associations – with 39 European members currently – will provide the psychiatric expertise to address the issue of national mental healthcare gaps in the framework of such reform actions.

"Both for countries undergoing mental healthcare reform and the established mental healthcare systems in other European countries, EPA will use this chance to develop and implement indicators of mental healthcare gaps and to suggest plans to close these gaps. One may not expect that one solution will fit all – on the contrary, it is most likely that country-specific strategies will need to be developed."

Three series of Guidance papers – 18 papers in total – have to date reached publication in European Psychiatry in the years 2012, 2014 and 2015. A fourth series is currently under development, which is expected to be published in 2016.

Professor Gaebel joins Patrice Boyer and István Bitter to discuss the future of neuropsychopharmacology in Europe tomorrow afternoon from 15:00 to 16:40 in Elicium 1.

ECNP

ECNP Fellowship Award

ECNP Fellowship Award honours excellence of junior members

The ECNP Fellowship Award was established to support the attendance of excellent European junior MDs and PhDs at ECNP Congresses. The Award is presented to individuals engaged full-time in clinical or basic research, training or teaching activities in the field of neuropsychopharmacology and closely related disciplines.
Consisting of a grant of EUR 1,500 and a commemorative certificate, recipients of the Award will have their posters on permanent display in the Award area of the congress. This year, six Award winners have been chosen, each of whom will receive their honour during the ECNP Dinner on Sunday 30 August, in the Cobra Museum in Amstelveen. *ECNP Daily News* spoke to each of the recipients to get a glimpse of the work they will be presenting in their posters.

Andreas Menke

University of Würzburg, Germany

In his work, Dr Menke has been investigating the effect of dexamethasone plasma levels on the outcome of glucocorticoid challenge tests of hypothalamic pituitary adrenal (HPA)-axis functioning. Speaking to *ECNP Daily News*, he began by noting that a dysregulation of the stress-hormone-axis (i.e. the HPA-axis) in patients with major depression is one of the most replicated findings in biological psychiatry. "However, the common tests assessing the function of this axis are not usually applied in the clinic, because some studies revealed problems with sensitivity and specificity," he added.

"One of these tests is the dexamethasone-suppression-test (DST), in which patients ingest 1.5mg of dexamethasone in the evening, and the next day cortisol plasma levels are measured. High cortisol plasma levels would indicate a non-suppression to dexamethasone and therefore a dysregulated HPA-axis. Another test is the dex-CRH test, where the DST is combined with an injection of corticotropin-releasing hormone (CRH). We wanted to investigate the impact of the plasma dexamethasone levels on the readouts of these tests.

"We actually could show that plasma dexamethasone levels time-dependently influence the readouts of the DST and the dex-CRH test in two independent samples of depressed patients. While there was no significant contribution of plasma dexamethasone levels to the readouts three hours after dexamethasone ingestion, the variance of the readouts increased from 5% to 14% in the DST, and from 28 to 37% in the dex-CRH test 16- and 21-hours post dexamethasone application. These findings indicate the importance of measuring the plasma dexamethasone levels in the context of the DST and dex-CRH test."

"I am very happy and proud that I was selected for the ECNP Fellowship Award, since this is significant award by a very distinguished organisation. With this award our research may gain more visibility and hopefully will be recognised and discussed in the field."

Andreas Menke

"From a professional point of view, the Fellowship Award represents an important, obtained goal that will improve my CV, and is personal compensation and reward for all of the daily hard work."

Annamaria Cattaneo

Annamaria Cattaneo

King's College Hospital, London, UK

Dr Cattaneo will share her work on inflammatory-related pathways and serum glucocorticoid kinase-1 (SGK1) as targets of early-life stressful events. "Stress and glucocorticoid hormones regulate hippocampal neurogenesis, but the molecular mechanisms mediating these effects are poorly understood," she told *ECNP Daily News*. "In a previous paper we have identified the glucocorticoid receptor (GR) target gene, SGK1, as one such mechanism.

"Using a human hippocampal progenitor cell line, we found that a small molecule inhibitor for SGK1, GSK650394, was able to prevent the cortisol-induced reduction in neurogenesis. Moreover, we also observed a significant increase of SGK1 mRNA in peripheral blood of drug-free depressed patients, as well as in the hippocampus of rats subjected to either unpredictable chronic mild stress or prenatal stress. Our findings suggest that SGK1 may represent a mediator for the effects of cortisol on neurogenesis and GR function, with particular relevance to stress and depression.

"In order to further characterise the molecular mechanisms underlying the stress-induced up-regulation of SGK1, we conducted further analyses (which I will present in the poster) in the hippocampus of rat subjected to prenatal stress as well as in the blood of clinical samples with a history of exposure to stress in utero or early in childhood."

She added: "We will now try to modulate in vitro the panel of miRNAs targeting SGK1 to see whether we could prevent the long lasting changes in SGK1 upon a stressful conditions."

Continued on page 10

ECNP

ECNP Fellowship Award

ECNP Fellowship Award honours excellence of junior members

Continued from page 9

Christina Dalla
University of Athens, Greece

"On a personal level, this award gives me strength and inspiration to continue my work with excitement and dedication. This is of particular importance for me and my research team in Greece because we often face several difficulties that we must overcome every day."

Christina Dalla

"Our research team in Athens focuses on sex differences in models of depression and antidepressant response," described Professor Dalla. "In this context, one research path that we pursue involves aromatase inhibition.

"The origins of the presented work lie in a study that we conducted back in 2002 with the University of Liege in Belgium, where I did a part of my PhD thesis as a Marie Curie fellow. There we showed that only female-, and not male-aromatase knockout, estrogen-deprived mice exhibited depressive behaviour and enhanced serotonergic activity in the hippocampus. Based on those findings, and after the recent establishment of my own research team, in 2014 we demonstrated that letrozole, an aromatase inhibitor, exerts acute antidepressant effects in female rats.

"Letrozole is widely used to treat breast cancer, and inhibits estrogen synthesis in all tissues including the brain. Interestingly, chronic treatment of ovariectomised female rats with letrozole exerts a pro-depressive effect. We are currently testing whether letrozole's effects are caused by neuroestrogen inhibition in brain areas involved in stress and depression, and plan to further analyse the neurochemical and molecular underpinnings. We will expand these findings through an ongoing observational study of women receiving aromatase inhibitors for cancer treatment, and also with a research collaboration with the Max Planck Institute of Psychiatry.

"Our future goal is to contribute to rapid and safe antidepressant treatments for both men and women."

Pick up a copy of *ECNP Daily News*, Issue 3 on Monday for interviews with the three other ECNP Fellowship Award winners: Eldar Hochman, Dina Popovic and Błazej Misiak.

ECNP

Expert Platform on Mental Health – Focus on Depression

A focus on depression

The Expert Platform on Mental Health – Focus on Depression[1] brings together key voices in mental health across Europe in order to support the implementation of the EU Pact on Mental Health and Well-being[2]. Led by Joseph Zohar, the initiative's aim is to highlight depression by bridging the gap between science and the public.

The Expert Platform is promoting solutions for change in early deduction of depression. They propose and are developing a depression app – Actograph Depression (iFeel), which analyses the user's social communication behaviour to detect significant deviations, which may indicate early changes in mood significant in depression[3].

The Expert Platform is also working to promote the idea that depression is not only highly prevalent, but perilous for individuals and society alike in terms of the hidden or clear disabilities it leads to. Along those lines, there is a special focus on collecting data and publishing it on depression in the workplace.

Another initiative of the Expert Platform is suicide prevention. The organisation initiated and supports a major review on updated evidence-based tools for suicide prevention. The review reached its final version and will be published soon.

As part of its promotional ambit, the initiative regularly confers its Media Award upon standout public communicators who contribute towards a better understanding of depression and stimulate its discussion. The most recent award-winner, Amos Oz, was honoured for his work in destigmatising depression during the 15th Conference of the Israeli Association of Psychiatrists (May 26-28, 2015). His widely-acclaimed memoir, *A Tale of Love and Darkness*, explores his mother's depression and ultimate suicide against the turbulent establishment of the State of Israel in the early 1950s.

"I have been thinking a lot about depression because I have seen a lot of it."

Amos Oz

Touching on his understanding of depression during his acceptance speech,[4] Amos Oz emphasized that depression is in of itself not an ailment: "Depression is an experience," he stressed. "An experience shared by the vast majority of the human race. If there are some people who have never experienced a moment of depression, I feel sorry for them; they are missing the experience.

"Depression becomes an illness when it is accompanied with despair. It becomes a dangerous, even deadly ailment with the combination of depression, despair and total loneliness. I have been thinking a lot about depression because I have seen a lot of it. I have reached the conclusion that we are not talking about a phenomenon, we are talking about a spectrum of phenomena such that depression, or depression plus despair is a family of illnesses.

"I am very, very grateful to the association of researchers of depression for honouring me with this distinguished award, and I can promise that I will go on studying human nature, including depression and despair, for as long as I can hold my pen between my fingers."

If you would like to make a nomination for the Expert Platform – Focus on Depression Media Award, send your ideas to secretariat@expertplatform.eu. More information can be found at www.expertplatform.eu

"I will go on studying human nature, including depression and despair, for as long as I can hold my pen between my fingers."

Amos Oz

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1. Expert Platform – Focus on Depression. http://www.expertplatform.eu

2. EU Pact on Mental Health and Well-being. http://www.mentalhealthandwellbeing.eu

3. Actograph Dep. http://www.expertplatform.eu/depfriend-app

4. Amos Oz accepts the third Expert Platform – Focus on Depression Media Award. https://www.youtube.com/watch?v=Mea646wsN74

CLINICAL RESEARCH

S.10: **Pharmacological fMRI for neuropharmacological assessment** Elicium 2 **Sunday** 15:00–16:40

Paediatric phMRI:
Detecting drug responsivity and developmental effects

Pharmacological magnetic resonance imaging (phMRI) techniques in research, and their applicability to the clinic, will be discussed this afternoon during a session on neuroimaging transmitter systems.

"Monoaminergic abnormalities underlie a wide variety of psychopathologies," Liesbeth Reneman (Academic Medical Center Amsterdam, the Netherlands) told *ECNP Daily News*.

Aberrant transmission in dopamine functioning is thought to be involved in ADHD, drug abuse and psychosis, and serotonin dysregulation with depression, anxiety and impulse-control disorders. "We have ongoing work in lesion models for clinical diseases such as depression (serotonergic system) and ADHD (dopaminergic system)," said Dr Reneman.

Researchers have gained direct insight into abnormal monoaminergic function in adults using single positron emission computed tomography (SPECT) and positron emission tomography (PET). Having approached phMRI from a nuclear medicine background, she explained her interest in the imaging modality: "I think the big difference between SPECT and phMRI is that with SPECT you are just getting the response at a particular receptor, but with phMRI you get the response of the whole orchestra, instead of just the first violin."

Dr Reneman went on to describe her group's phMRI studies on the monoaminergic system, in which animals were lesioned with either dexamphetamine or MDMA.[1] Their group also replicated SPECT-based results of dopaminergic activity using phMRI in dexamphetamine users. Results showed a blunted haemodynamic response in monoaminergic regions that tied in with indications for lower striatal DA release, D2/D3 receptor binding and DAT, and poorer behavioural measures.[2] These phMRI techniques were similarly validated when studying the effects of MDMA in both rats and humans (effects on the serotonergic system were detected[1], as had been seen previously with SPECT).

"Very little is known about the normal development of the neurochemicals of the monoaminergic systems in children."
Liesbeth Reneman

"... with phMRI you get the response of the whole orchestra, instead of just the first violin."
Liesbeth Reneman

Linking up the animal lesion work and human studies, Dr Reneman continued: "The brains are very different but the outcomes are similar in that there is disruption in the functioning of the dopaminergic and serotonergic systems. So they match quite well, and the conclusions are the same."

Dr Reneman's mission is to validate and advance phMRI in the clinic; she wants to exploit its non-invasive properties to study neurochemical imbalances and their development in paediatric populations. Unlike SPECT and PET, phMRI is non-radiating, so is ideal for researching neurotransmitter dysfunction in paediatric populations in order to investigate how drugs act on the development of monoaminergic neurotransmitter systems.

Antidepressants and ADHD treatments are increasingly prescribed to children and adolescents without a complete understanding of their neurodevelopmental effects. Many exert their beneficial actions though modulating monoamine transmitters, which raises important questions regarding their potential interference with brain development. Findings of significant age-dependent brain changes and differential responses after such drug treatment in rats in brain illustrate the necessity of developmental research in children and adolescents.[3,4]

Dr Reneman expanded on this topic: "Very little is known about the normal development of the neurochemicals of the monoaminergic systems in children, so that is the ultimate goal. phMRI may be a good stratifier to find responders and non-responders. This is important in children, because they are more vulnerable to the side effects of antidepressants and other psychoactive medicines."

Moving forward, Dr Reneman is currently undertaking a phMRI study of development of the monoaminergic system in a paediatric ADHD cohort, which she described: "The main question is whether a child's response to drugs is different to that of an adult, because their brains are still developing. I.e. do medications affect brain development? phMRI is the only technique we can use to test the monoaminergic system in children."

Due to enormous advances made in the field of phMRI since its inception, many data acquisition issues have been tackled, but now the challenge lies with taking data analysis to the next level. "Usually we do univariate analysis, but now we are looking at doing multivariate analysis. If we can show that this technique assesses what we think it does, as well as being robust, replicable and safe – the biggest challenge will be to integrate it into a clinical setting."

When asked why the transition to the clinic is taking so long, Dr Reneman commented: "It is strange that there has been so much pre-clinical animal work performed, but the clinical studies are very complicated. The step from pre-clinical to clinical study is very challenging and time consuming, particularly in studies that involve children and young adults."

She added that a multidisciplinary approach must be taken, ensuring protocols are developed and approved, utilising many scans and different drugs, and making sure medication-naïve subjects are recruited, and adhered to strict protocols, especially given that children are to be involved.

"Until now, there have been lots of different people in different groups working separately with very little translation between the two," said Dr Reneman. "We are trying to do both now."

Dr Reneman will share her experience in using phMRI for brain imaging of monoaminergic systems today at 15:50 In Elicium 2. For further insights into clinical neuroimaging, make sure you attend Monday's session entitled 'Neuroimaging as a clinically useful tool: the time has arrived', held at 15:00–16:40 in Elicium 2.

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TRANSLATIONAL RESEARCH

S.16: **Translational research on sleep and depression** Monday **09:00–10:40**

Memory deficits in depression are hormonally driven

The association between memory deficits and sleep disturbances in depression will be examined on Monday morning during a session on translational research on sleep and depression.

"The topic of sleep related memory consolidation has been a rather large topic in recent years," Martin Dresler (Radboud University Medical Center, the Netherlands) told *ECNP Daily News*, "but there has been very little on its effect in psychiatric patients, which is surprising since sleep complaints are one of the most prominent symptoms in depression."

Deep sleep and REM sleep are important for memory consolidation, REM in particular for consolidation of procedural memory (e.g. motor sequences such as learning to play the piano or riding a bike). REM sleep is not only altered in depression but most antidepressant medications have been shown to suppress REM sleep.[1] Furthermore, while declarative (verbal, episodic) memory is impaired in depression, procedural memories are not affected. Dr Dresler and co-workers investigated the extent to which sleep disruption in depression impairs memory consolidation. Subjects performed procedural and declarative memory tasks before and after a night of sleep with polysomnography and these (EEG) studies were corroborated with fMRI.

Explaining their findings, Dr Dresler said: "When we compared the wakefulness and sleep-related components of memory consolidation, we discovered a double dissociation: during wakefulness declarative memory was impaired but patients performed just as well as controls in procedural memory; the opposite was true when we looked at the sleep related components of memory consolidation: a strong impairment for procedural, but not declarative memory."

Given that deep sleep was thought to underlie declarative memory consolidation, and is typically impaired in depression, Dr Dresler was initially surprised by these findings. However, on closer inspection he found a paradox: patients taking medication that suppressed REM-sleep actually outperformed patients without such medication, and more surprisingly that patients taking drugs improving REM sleep performed worse showing that REM sleep is not related to procedural memory consolidation. Commenting on these findings, Dr Dresler said: "We don't know what the causal chain of mechanisms is, it is more complicated than we expected, we had expected that REM would be disturbed."

Whilst examining the EEG, Dr Dresler made yet another paradoxical discovery – unable to detect any robust sleep markers for these memory impairments he found that the sleep spindle (an EEG microfeature related to memory consolidation) was completely intact

in depressed patients, in fact more so than in healthy controls. The strong impairments in memory consolidation in depression were apparently unrelated to sleep processes per se, but instead are caused by hormonal disturbances.

Describing findings from neuroimaging studies, Dr Dresler explained that the most striking endocrine feature of depression was marked increases in stress hormones. "We found that if we studied multiple sclerosis patients who received high does of stress hormones (cortisone) that they showed strong overnight procedural memory consolidation impairments as with depressed patients; other multiple sclerosis patients who had different medication did not show this."[2] This led him to the idea that these memory impairments were driven by stress hormones rather than sleep disruption.

> "There has been very little on sleep related memory consolidation in psychiatric patients, which is surprising since sleep complaints are one of the most prominent symptoms in depression."
>
> Martin Dresler

Dr Dresler's group carried out other neuroimaging studies of depressed patients and showed that sleep-related procedural learning with fMRI was less efficient than that of healthy subjects (i.e. they had to make more effort, resulting in greater fMRI activation), indicating a lack of memory consolidation. He pointed out: "We also found that depressed patients showed disturbed connectivity, particularly in the motor system while performing in these motor tasks, and increased activity in the default mode network which is related to rumination."[3]

Dr Dresler described some other studies on hormones and sleep carried out with coworkers at the Max Planck institute in Munich, where he studied the temporal profiles of hormonal secretion during the night and their association with sleep stage. "We knew about cortisol but we also studied the peak and the lowest point of growth hormones," he said. "Hormonally speaking they were more active at night than in the day and we've only studied these indirectly."

Future studies include blood sampling during learning, during the night and again during memory retrieval the following day. This method might reveal how stress hormones are related to these sleep related memory deficits, and shed light on the day-bound procedural deficits and night-bound declarative deficits.

With regards to the spatial profile of the sleep related memory deficits, derivations from REM sleep EEGs, and data from neuroimaging studies, have shown that medial prefrontal cortex regions (MPFC) are hyperactive in depressed patients, especially during the night. Furthermore these can also be used as predictive markers of therapy response.[4]

Dr Dresler concluded: "We are also gathering data for sleep related memory deficits in the same subjects and we know that memory impairments are bound to the acute state of depression. As soon as patients are in remission, they show normal sleep related memory consolidation, so this might even be used as a biomarker of depressed state."[5]

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The ECNP Certificate

Formal recognition for junior research and education

The ECNP Certificate is a way for ECNP to officially acknowledge outstanding work undertaken by one or more of its junior researchers. At its core, the Certificate offers recognition of a recipient's level of knowledge and expertise in neuropsychopharmacology, along with their clear commitment to the field.

To qualify for the Certificate, potential applicants must participate in an ECNP Workshop, School, Seminar or other affiliated course, after which they will need to propose a research or educational project for consideration. Relevant projects could be a piece of original research, a comprehensive literature review, or the design and implementation of an educational activity. Whatever route is chosen, the final work must offer a meaningful contribution to neuropsychopharmacological research or education, and should span between 6 and 12 months if possible.

Before the project begins, candidates will need to pick a mentor from the list of ECNP Fellows, which will then be approved by the ECNP Educational Committee. This mentor will ideally reside in a different country to that of the applicant, and will be responsible for approving the initial project proposal, assisting throughout the entire process, and ultimately accepting the final submission of the project. Recipients will then be invited to the ECNP Congress to present their work as a poster, and receive their Certificate at the ECNP Dinner.

This year's ECNP Certificate has been awarded to Christian Imboden (Department of Psychiatry, Psychotherapy and Psychosomatics, Solothurn hospitals AG, Switzerland), who spoke to *ECNP Daily News* to share his experience leading up to the award.

At the time he applied for the ECNP Certificate, Dr Imboden already was in the process of putting together a project along with ECNP Fellow Edith Holsboer-Trachsler (Head of the Center for Affective, Stress and Sleep Disorders (ZASS), Psychiatric University Clinics (UPK) Basel, Switzerland), who then became his official mentor.

"She did a lot of encouraging … supporting me to go forward with the process," said Dr Imboden, adding: "We had contact by email, or if I was in Basel we arranged to see each other, just to see how the project was going, or to discuss any questions."

For his poster at the congress, Dr Imboden will be presenting work that has been focused on the evaluation of the effect of aerobic exercise on cognitive variables in depressed inpatients. In a randomised, controlled, multicentre trial, 23 depressed patients (first episode, recurrent and bipolar) were randomly assigned to either aerobic exercise (indoor cycling) or control (standardised stretching) regimes for three days a week, over a six-week period.

Alertness was measured at baseline and after intervention, and the results were very promising, with significantly decreased reaction times, and improved stability in alertness performance observed in the intervention cohort.

While these preliminary results lay some promising early ground, Dr Imboden is pursuing more extensive work in the field: "We now have to think about what we are going to do onwards," he said. "We are looking at a whole variety of variables: we look at sleep, we look at the stress system (mainly cortisol) … but there we just don't have the data yet."

He added: "But I think the cognition is one of the domains we should look into more thoroughly, and maybe also with further study. I think this is a very important variable in depression, and we see that exercise does have a beneficial effect on it, so it is a very promising candidate to keep looking at."

Discussing the personal benefits he feels he has taken away from the ECNP Certificate process, Dr Imboden commented: "I think it really encouraged me to commit myself to clinical research – to do a project together with someone who supports me, and also gives emotional support, which I think is very important because it is a lot of hard work, and there are times when you worry if it is going to work, if it's going to take too long, or whether you have problems with recruiting and so on."

> "[The ECNP Certificate] really encouraged me to commit myself to clinical research."
>
> Christian Imboden

On the very topic of the ECNP Congress, he continued: "I am part of a group of around four people who met at an ECNP School, and now we try to meet at the congress every year. I think that is a very nice way of keeping contact, and to also look at research together, and exchange views from different country perspectives, which I think is very important in psychiatry.

"I talk to Israeli friends, those from Belgium, the UK etc. – so I think it offers you the bigger picture, and it really strengthens the ties you have made to psychiatrists and researchers in other countries. I plan to go to the ECNP Congress whenever I can, because I think it is a very scientifically-outstanding congress."

Dr Imboden's poster can be found in the Poster Area, under 'P.2.f: Mood disorders and treatment - Treatment (clinical)'. For more information about the ECNP Certificate, visit www.ecnp.eu

How do I join the ECNP Certificate programme?

The application process has been designed to be as simple as possible. Prospective candidates should send the following to ecnp-certificate@ecnp.eu:

- A letter of application, indicating which ECNP Workshop or School, seminar, or affiliated course, you have attended
- A short description of your research plan (1–2 pages A4), including timelines and preferred mentor
- A curriculum vitae

If you have any questions about the programme, please contact us at the e-mail address above.

Join us in the poster area for the following daily activities

(Sunday, Monday and Tuesday)

10.40-11.15
Poster podium

Travel Award ceremony

Presentation of Travel Awards to junior scientists with the best abstracts for posters.

10.40-11.15

Poster viewing and coffee break

12.15-12.45
Poster podium

Rapid-fire poster session

The highest-scoring poster presenters present their data in a five-minute e-poster session.

12.15-13.45

Poster session

13.00-13.15
Poster podium

Poster Award ceremony

Poster Awards will be presented to poster presenters with the most outstanding posters.

13.15-13.45
Poster podium

Career development session

Engaging experts share their knowledge and experience. Topics are especially interesting for junior scientists, but sessions are open to all.

Sunday: **How to make an award winning poster**
Monday: **How to give an effective talk**
Tuesday: **A job beyond research**

PRECLINICAL RESEARCH

S.12: **Junior Scientists symposium – Novel concepts and targets ... CNS disorders** Emerald **Sunday** 15:00–16:40

Junior Scientists programme begins with exploration of

This year's roster of Junior Scientists symposia begins today, with a session that is focused squarely on novel concepts and targets for improving the treatment of CNS disorders. Featuring the best and brightest junior presenters – themselves chosen for their exemplary poster exhibitions at the annual ECNP Workshop in Nice, France – the session promises to be an eye-opening account of the kinds of works junior members are tackling head-on.

"I feel very honoured to have been selected for an oral presentation in the Junior Scientists symposium," Laura Neri (University of Modena, Italy) told *ECNP Daily News*. "It is a great opportunity for a junior scientist to present his or her work in an international context."

When she takes to the podium, Dr Neri will focus on the neuroprotective and neurogenetic effect of melanocortins in a transgenic mouse model of moderate Alzheimer's Disease (AD). Melanocortins – small protein hormones derived from the common precursor proopiomelanocortin (POMC) –regulate a variety of body functions, and include important members such adrenocorticotropic hormone (ACTH), which stimulates (at the level of the adrenal cortex) the production of mineralocorticoids.[1] "Equally famous is also the stimulation of melanocytes to produce melanin, carried out by α-MSH [α-melanocyte stimulating hormone]," noted Dr Neri.

"However, it was discovered and documented that melanocortins have a surprisingly large number of actions, in addition to the well-known stimulation of the adrenal cortex and melanocytes. In particular, the focus of the research conducted by Professor Salvatore Guarini's group [University of Modena and Reggio Emilia, Italy] in the last years was to study the protective effect of melanocortins against organ damage in several animal model of ischemic diseases, from cardiac ischaemia to cerebral ischaemia."

In her work, Dr Neri has demonstrated that treatment with a synthetic analogue of α-MSH is able to counteract the cerebral damage induced by ischaemia-reperfusion injury and, at the same time, increase the rate of physiological compensatory neurogenesis in the hippocampus leading to a better recovery even when the drug were administrated after several hours from the ischaemic event.

"That was the genesis of our present study," she continued. "We demonstrated that melanocortins have a protective and neurogenetic effect in an acute neurodegenerative disease, and we wanted to test if melanocortins were able to induce neuroprotection and neurogenesis also in a chronic neurodegenerative disease such as Alzheimer's disease."

For the work, Dr Neri used a transgenic mouse line with a moderate phenotype of Alzheimer's disease (Tg2576; Taconic, Hudson, NY, USA). These animals overexpress a mutant form of amyloid precursor protein that leads to the production of numerous Aβ plaques and cognitive impairment, characterised by an impaired learning at spatial tasks, working memory and contextual fear conditioning.

So far, results have been promising: "We have shown that chronic treatment with melanocortins leads to a better cognitive performance compared to a saline treatment group," detailed Dr Neri, adding: "Mice treated for 50 days with NDP-alpha-MSH [an analogue of α-MSH] had a comparable cognitive performance to the wild-type control animals without Alzheimer's disease. We also demonstrated a statistically-significant reduction in beta-amyloid deposits, and a marked increase of neurogenesis rate in the hippocampus of melanocortin-treated mice.

"It is important to stress that the newly-born neurons were active and fully integrated into the neuronal network. Altogether these results suggest that melanocortins could help in counteracting cognitive decline in Alzheimer's Disease."

Looking to the future, Dr Neri said: "The preliminary results of our study are promising, but to further assess the effect of melanocortins in counteracting the cognitive decline in Alzheimer's, we need to demonstrate if NDP-α-MSH is protective also in an advanced model of Alzheimer's disease. So what we are doing now is to study neuroprotection and neurogenesis induced by melanocortins in mice with a severe phenotype. Translated to a clinical context, this could allow clinicians to have a drug that is active both in the early and late stages of the disease."

Also speaking during the session will be Mona Nouhi (Karolinska Institute, Stockholm, Sweden), who will present her work in the modulation of NMDA receptors for the rescue of impaired synaptic plasticity in experimental Parkinsonism. "As we know, Parkinson's disease [PD] is a devastating brain disorder, which is characterised by severe movement disturbances associated with a dysfunction of the basal ganglia – a brain region that, amongst other things, controls motor function due to loss of dopamine," began Ms Nouhi.

> "[Our] results suggest that melanocortins could help in counteraction cognitive decline in Alzheimer's Disease."
>
> Laura Neri

> "We anticipate that our study will contribute to the development of tools that could be used to treat patients and/or to prevent further degeneration of dopaminergic neurons."
>
> Mona Nouhi

"For many years researchers have been trying to develop alternative treatments to the standard dopamine-replacement therapy for Parkinson's disease. One of the targets in finding new therapies is the NMDA receptor. However, dysfunctions of NMDA receptors, due to altered subunit composition in PD, have not clearly been demonstrated."

In her work, Ms Nouhi has been focused on the GluN2B subunit of NMDA receptors – a potential target for PD treatment that has shown promise for reduction of motor symptoms in animal models. However, she noted that clinical trials with GluN2B-selective antagonists have failed to provide clear benefit in patients afflicted with Parkinson's disease, thus she was prompted to carefully examine the subunit composition of NMDA receptors in the striatum, and identify functions and dysfunctions of these receptors attributed to specific GluN2 subunits.

Briefly describing the outcomes of this study, Ms Nouhi said: "We found that the subunit composition of NMDA receptors is altered in the striatum of a mouse model of Parkinson's disease. In particular we found that GluN2B is downregulated and GluN2D is upregulated in the dopamine-depleted striatum (Parkinson model). Based on our results we propose GluN2D as a novel candidate for therapeutic intervention in Parkinson's disease."

She continued: "Our research also has been investigating the possibility that subunit-specific compounds acting on GluN2 subunits, other than GluN2B, might have beneficial properties in the treatment of Parkinson's disease. We initially found that CIQ, a positive allosteric modulator of GluN2C/GluN2D-containing NMDA receptors, increases dopamine release from residual axon terminals

CNS disorders

in the partially dopamine-depleted striatum. Therefore, we have identified a novel way to enhance dopamine release in early Parkinsonism when a proportion of dopamine neurons are still functioning.

"We then decided to investigate whether CIQ could rescue other neurophysiological deficits, such as loss of long-term potentiation (LTP), in the dopamine-depleted striatum. Such a long term change in glutamatergic synaptic strength is a potential candidate for cellular mechanisms of learning and memory, and in the striatum is dependent on dopamine and NMDA receptors."

As she will outline during her presentation, the outcomes from this work have been positive, with a key finding being that CIQ, applied in the solution that bathes the brain slices, or administered intraperitoneally, rescues LTP in the dopamine-depleted striatum.

"We have identified a novel way to enhance dopamine release in early Parkinsonism when a proportion of dopamine neurons are still functioning."

Mona Nouhi

"This rescue occurs despite the absence of dopamine," she said, adding: "By using CIQ, we therefore bypass the need of dopamine for LTP induction."

As Ms Nouhi described, these observations, along with future study, will elucidate more on whether GluN2D could constitute a target for the development of effective treatments that have the potential to alleviate some of the symptoms of Parkinson's disease. Furthermore, it will shine a light on whether subunit-specific modulators could be considered for the management of Parkinson's disease.

"We anticipate that our study will contribute to the development of tools that could be used to treat patients and/or to prevent further degeneration of dopaminergic neurons," she said.

In her final comments, Ms Nouhi touched upon the Junior Scientists symposia format as a whole, concentrating on what particular benefits she believes the sessions embody: "Junior scientists can present their research amongst a diverse group of other juniors, as well as senior experts in the field, and then they can receive feedback on their work, and develop new ideas and approaches for their work back home," she said.

The first Junior Scientists symposium, 'Novel concepts and targets for improving treatment of CNS disorders', will take place this afternoon at 15:00–16:40 in the Emerald room. The second and final session, 'Dysfunctional brain circuits in psychiatric disorders: new clinical and preclinical insights', will be held at 09:00–10:40 tomorrow morning in the Forum.

References

1. Voisey J, Carroll L, van Daal A. Melanocortins and their receptors and antagonists. Curr Drug Targets. 2003;Oct;4(7):586-97.

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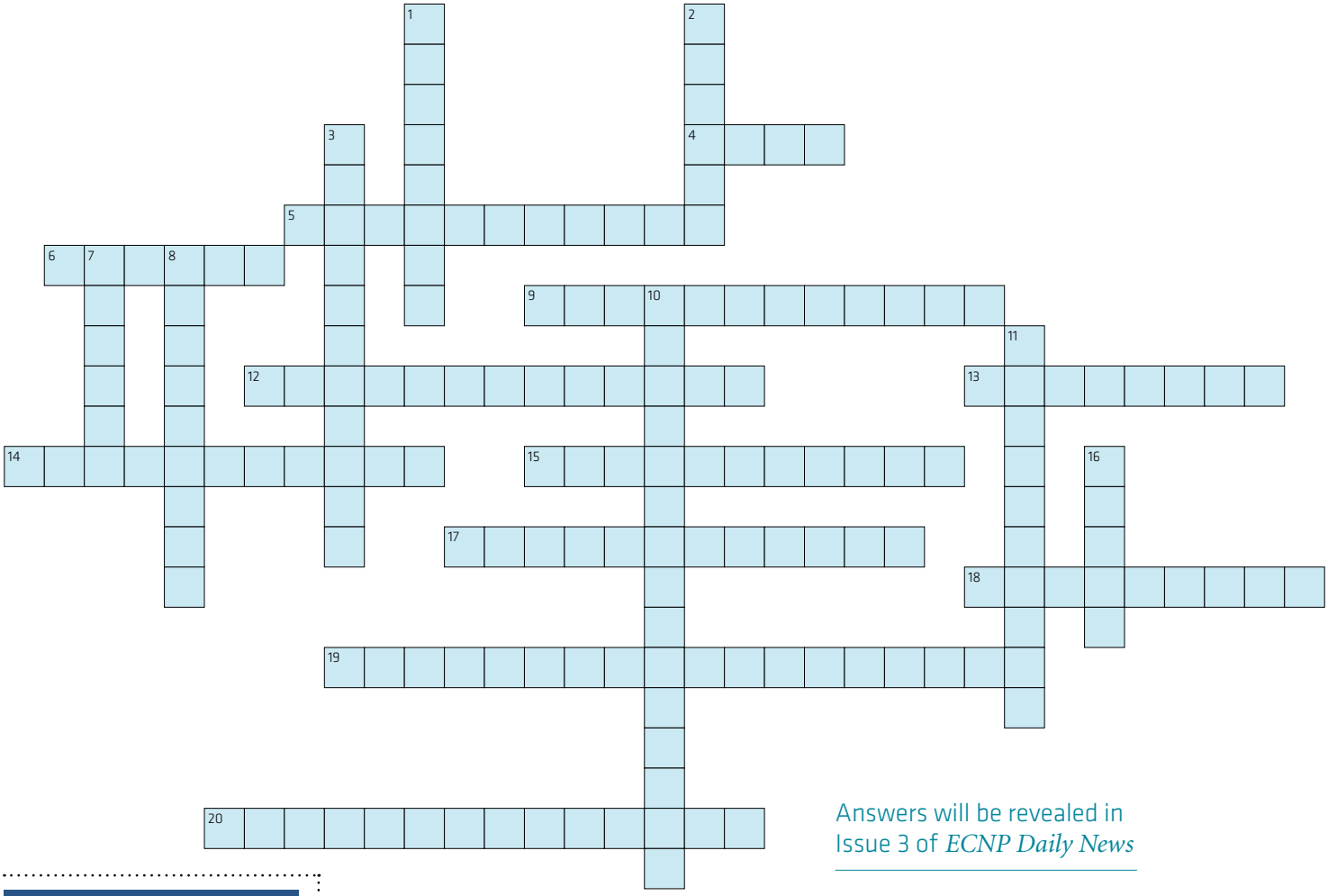
Puzzles and Games



Answers will be revealed in Issue 3 of *ECNP Daily News*

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ACROSS

4 ECNP Workshop for Junior Scientists takes p lace here

5 'Also sprach .....'

6 Gogol short story, 'Diary of a .....'

9 Name of famous Amsterdam houseboat rned cat shelter

12 Will be giving this year's Brain Prize award lecture

13 Coined the term 'collective unconscious'

14 Writer of the Bell Jar

15 Experimental therapy, a 'collaborative treatment involving the systematic assessment and modification of the environment to minimise the impact of any form of mental disorder on the individual or on society'

17 Using light to stimulate neurons

18 Lack of interest in once-pleasurable activities

19 Kurt Vonnegut's off-kilter exploration of PTSD following WW2 through his timetravelling protagonist 'Billy Pilgrim'

20 Proposed that "existence precedes essence"

DOWN

1 Recently deceased American mathematician whose struggles with schizophrenia were portrayed in film 'A Beautiful Mind'

2 Next year's congress takes place here

3 This year's keynote lecturer

7 River flowing through Amsterdam

8 Sleep disorder nootropic, students' smart drug of choice

10 CNS glial cell, wraps nerve cells in myelin

11 Limb-regenerating amphibian

16 '..... Circuit', early name for medial limbic circuit, named after the neuroanatomist who proposed it in 1937

Wordsearch solution

From Issue 1

DOPAMINE
GABA
GLUTAMATE
HISTAMINE
MELATONIN
OREXIN
OXYTOCIN
SEROTONIN
TRYPTAMINE
ACETYLCHOLINE

TODAY'S PROGRAMME SUNDAY

TIME	ROOM	SESSION
07.45 - 08.45		**Brainstorming sessions**
	D201	BS.1 Neuroinflammation in major psychiatric disorders: focus on bipolar disorder and schizophrenia
	D202	BS.2 Increasing signal detection in clinical trials: improving fidelity of instruments and patient selection
	D203	BS.3 Neurotransmitter interactions and cognitive function: can this optimally be studied in humans?
09.00 - 17.00	Exhibition area	**Exhibition**
09.00 - 10.40		**Symposia**
	Auditorium	CT S.05 Electroconvulsive therapy – achieving and maintaining the benefit
	Elicium 2	CR S.06 22q11.2DS deletion (velo-cardio-facial) syndrome: a multi-modal approach for the understanding of risk factors for schizophrenia
	Forum	TR S.07 Translational insights into compulsivity
	Emerald	PR S.08 MicroRNAs: leading actors in the scenario of mood disorders aetiology and treatment
	Elicium 1	ET E.02 Advances in ADHD research across the lifespan
10.40 - 11.15	Poster podium	**Travel award ceremony**
	Poster & exhibition areas	**Coffee break**
	Poster area	**Poster viewing**
11.15 - 12.00	Auditorium	**PL.01 Plenary lecture** – Neural correlates of chronic early-life stress
12.00 - 14.00	Poster & exhibition areas	**Lunch**
12.15 - 13.45	Poster area	**Poster session**
12.15 - 12.45	Poster podium	**RF.01 Rapid-fire poster session**
13.00 - 13.15	Poster podium	**Poster award ceremony**
13.15 - 13.45	Poster podium	**CD.01 Career development session** – How to make an award winning poster
14.00 - 14.45	Auditorium	**PL.02 ECNP Neuropsychopharmacology Award lecture** – Can we improve speed and efficacy of antidepressant treatments?
14.45 - 15.00	Poster & exhibition areas	**Coffee break**
15.00 - 16.40		**Symposia**
	Auditorium	CT S.09 Psychopharmacology of frontotemporal dementias – towards new therapies
	Elicium 2	CR S.10 Pharmacological fMRI for neuropharmacological assessment
	Forum	TR S.11 Gene-environment-brain interaction in the pathophysiology of psychosis
	Emerald	PR S.12 Junior Scientist symposium - Novel concepts and targets for improving treatment of CNS disorders
	Elicium 1	ET E.03 Mood dysregulation in children and adolescents
17.15 - 19.00		**Satellite symposia**
	Auditorium	C.06 New developments in schizophrenia treatment: emerging role of D2 partial agonists
	Elicium 2	C.07 Cognitive dysfunction in depression – are we THINCing about it enough?
	Forum	C.08 Schizophrenia – neurobiology and functional recovery. How close are we to personalised treatment?
	E104-E107	C.09 Interest in and enthusiasm for meta-analyses
	Elicium 1	C.10 Management of psychiatric emergencies in the 21st century

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