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ECNP

DAILY NEWS

Thank you for your support...

Our sincere gratitude for making
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success!

We look forward to welcoming
you again next year in
Amsterdam.



EU-AIMS driving the pace of research in autism spectrum disorder

A variety of presentations on new European research initiatives took place yesterday morning, covering the Innovative Medicines Initiative (IMI), and research networks PharmaCog, NewMeds, and EU-AIMS, whose endeavour it is to improve the understanding of disorder characterization and therapeutic options in Alzheimer's disease, depression and schizophrenia, and autism spectrum disorder (ASD), respectively.

Will Spooren (F. Hoffmann-La Roche AG, Basel, Switzerland) presented an update on the EU-AIMS project, launched in 2012, which seeks to enhance knowledge and hence treatment of ASD. Speaking of the need for such a concerted, well organised and robust approach to research, he noted that while much work is going on in identifying molecular pathways and targets, there is still a need for a translational model, mechanistic therapeutics, clinical outcomes and diagnostic biomarkers.

"On ASD, there was no real major



strategy defined within Europe, no major concerted efforts in drug discovery, no preclinical network, no clinical trial network, no regulatory strategy, late diagnosis, and poor diagnosis. Diagnosis tends to be between three and six years old, where parents are going from physician to physician for a diagnosis. There is poor knowledge of patients' needs across the life course. The needs of a ten-year-old are different from a thirty-year-old. There are a lot of treatments that are just trial and error – there is absolutely no evidence that they work"

Moving this field into evidence-based medicine would require a large scale concerted effort such as EU-AIMS, explained Dr Spooren. Seven companies as well as 14 academic groups under the leadership of Roche and King's College London are involved in the EU-AIMS consortium, encompassing more than 200 scientists from ten countries, focussing on preclinical and clinical networks.

The project is structured into six different work streams, including cellular assays, through to animal models, translational science, clinical research and genomics. The project began with the publication of numerous critical reviews, raising interesting questions on the factors involved in the emergence of the disorder. "The father plays, apparently, a very important role in the risk for being born with a neurodevelopmental disorder," explained Dr Spooren, referring to the work of Kong et al. published in *Nature* in 2012.¹

"The number of de novo mutations was found to increase with the age of the father, and this was associated with an increased risk of both schizophrenia and ASD, deleterious mutations having a putative involvement in the manifestation of these disorders."

The group went on to develop novel protocols for creating induced pluripotent stem cell lines (iPSCs), something that was demanded by the high anxiety experienced by many ASD patients. Dr Spooren continued: "You normally take a skin punch or draw blood. We set out to do a more simple approach that is new: to pull a hair. At the bottom of the hair there is a cell, a keratinocyte, that

"The number of de novo mutations was found to increase with the age of the father, and this was associated with an increased risk of both schizophrenia and ASD, deleterious mutations having a putative involvement in the manifestation of these disorders."

Will Spooren

can also be used to generate iPSC lines, but it has never been done. We use the keratinocyte to differentiate into iPSC lines and then to differentiate them further into neurons. We will be using that in our drug discovery efforts."

The group have also looked at a number of known genetic variations in this way, such as the SHANK3 deletion, in order to gain a deeper understanding of the sorts of morphological and functional changes that can contribute to ASD. Moving on to animal models, Dr Spooren described the *neurologin 3* knockout model, *neurologin* being a

synaptic adhesion molecule that has been linked to autism. "Using a mouse model we have identified a selective upregulation of *mglu1*," he said. "We have now validated that also in the rat, so we have generated a transgenic rat, which has a similar phenotype."

They group were hence able to demonstrate that multiple syndromes and disorders that emerge as a result of different genetic mutations shared the synaptic pathophysiology of upregulated *mglu1* receptor expression.

Moving on to the clinical work stream, Dr Spooren continued: "We are doing two studies, a high-risk sibling study and a longitudinal study in autism patients. This study is to identify early predictive biomarkers of ASD. We are doing that by prospective study of infants, where there is an older sibling with ASD. We are following in total about 400-500 patients, so these are very recent numbers."

The project takes a multimodal approach to data collection, including cognitive, behavioural, as well as neuroimaging and neurophysiological tests, relating these to symptoms and diagnosis of ASD at outcome. Subjects, who will be assessed at 5, 10, 14, 24 and 36 months, comprise either high risk (n=305) or low risk infants (n=100).

The second, longitudinal study includes 605 subjects between the ages of 6 and 30 years, who will undergo clinical phenotyping, MRI, eye tracking, event-related potentials, and -omics. "We do not know the course and the medical needs of the patients who have applied," said Dr Spooren, emphasising that this is something that

it is hoped the project will elucidate. "We will follow them for two to three years, evaluate them on a number of characteristics, and then see how these symptoms have developed over time. This is a very elaborate and deep characterisation. It is unprecedented in its magnitude as well as the level of

characterisation. Hopefully we will be able to, based on this, stratify patients for, for example, intervention."

Speaking of the genomics arm, he went on: "We are trying to sequence the whole genome of these patients. It will be possibly to stratify them, to divide this group into specific subgroups that are characterised by specific underlying neurobiology, and that can be used for, for example, testing compounds for their efficacy."

References

1. Kong et al. Rate of de novo mutations and the importance of father's age to disease risk. *Nature* 488, 471–475 (23 August 2012).

ECNP Daily News

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MediFore Limited

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Overlapping early symptomatic syndromes under the spotlight

This afternoon's plenary lecture from Christopher Gillberg (Department of Child and Adolescent Psychiatry, University of Göteborg, Sweden) explores the importance of diagnosing and managing so-called early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE).

"I first used this acronym ESSENCE in 2009, for the Royal College of Psychiatrists,

"There isn't one child in the world, or one adult in the world, who could be described as having only ADHD, or only autism, or only intellectual disability."

Christopher Gillberg

because I was asked at that time to summarise my own research and other clinical research relevant to my own research after a period of 40 years in the field," Professor Gillberg told *ECNP Daily News*.

"And when I thought about all these diagnostic categories that we currently use, things like autism, ADHD, Tourette's syndrome, language disorder, various counts of learning disorders – I also knew that all these names cover a number of overlapping areas. There isn't one child in the world, or one adult in the world, who could be described as having only ADHD, or only autism, or only intellectual disability."

In fact, there are usually a combination of various problems that exist across diagnostic category boundaries, noted Professor Gillberg. "If you have only the problems that we currently consider to be contained within the category of ADHD, that person would not be impaired in daily functioning," he explained. "But if there's another problem combined with it, such as slow language development, dyslexia, motor coordination problems, or autistic features, then the combination of the problems becomes handicapping – whereas each problem per se is usually not."

He continued: "This is particularly relevant currently in the field of autism, which has come from almost obscurity to perhaps now being the most talked about condition in psychiatry ... If you just have autistic symptoms or autistic features, you're very unlikely to ever come to the attention of any medical doctor if you're, say, under five. But if you do come to the attention of a medical doctor

it's 100% certain that you have lots of other problems, not just the autistic features."

And the other problems are often just as handicapping as the autistic features, added Professor Gillberg. "Most of the children currently being diagnosed with autism are actually those who have autistic features with ADHD, or with language disorder, or with intellectual disability and it's the other problems that are really even more handicapping," he said.

He added: "That's the whole idea with these overlapping disorders: they have no clear boundaries, even though we want to create them. And we can statistically show that, yes, these types of symptoms that we call autism, or ADHD, within each group the symptoms cluster together, but in order for anyone to become really impaired and in need of help, there is a combination of other neurodevelopmental problems that greatly drives the degree of impairment."

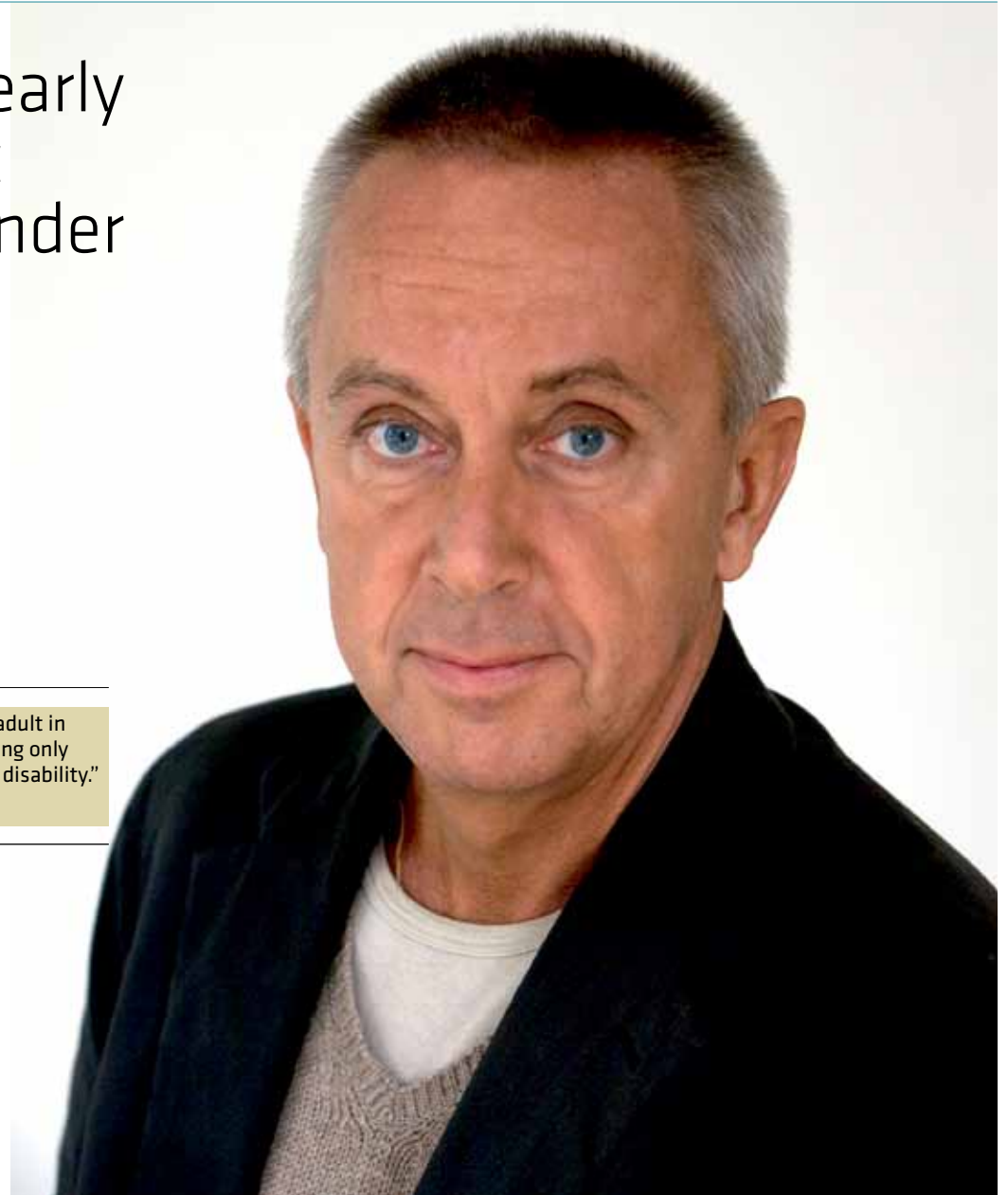
Professor Gillberg went on to discuss how this impacts physicians and psychiatrists.

"One of the clinical messages is, if you have a patient arriving in your clinic, regardless of whether it's a child or an adult, and you recognise the symptoms of ADHD, as a doctor you will then think 'I can make the diagnosis' if you look at the DSM or the ICD," he said. "... So you'll make that diagnosis, forgetting that [there are likely to be] more problems, and they will also need to be diagnosed and symptomatically intervened for."

As an example, Professor Gillberg noted that there are now a number of studies showing that ADHD is associated with being overweight in adult people. "It's strongly linked to anxiety disorder in adult women," he said. "And often times, when psychiatrists make the diagnosis of anxiety disorder, in a similar way they overlook the possibility that underlying the anxiety might very well be ADHD or another of these early symptomatic syndromes."

He went on: "It has a lot of other connotations, including the fact that, not only

Continued on page 4



Christopher Gillberg

PLENARY LECTURE

PL.06 **Early symptomatic syndromes eliciting neurodevelopmental clinical examinations** Hall A4 **Tuesday 13:45 – 14:30**

Overlapping early symptomatic syndromes under the spotlight

“It’s only in the past 20 years that enormous amounts of knowledge have developed in this field and so many of those who trained, even 10 to 20 years ago, have very little perspective on this.”

Christopher Gillberg

Continued from page 3

in clinical practice but in all research, one would have to take a different view on when one starts a new project, say about Tourette’s syndrome or about ADHD.”

Clinicians and researchers need to look at a range of related issues, not just the core symptoms, as Professor Gillberg explained: “That is the main message – that as soon as you get a patient where your first thought is ‘I recognise this pattern of problems as ADHD or Tourette’s syndrome or autism’, then you have to think – what else?”

“Patients should no longer have to come a specialised clinic. Many adult psychiatrists now in the United States and in the UK and elsewhere run specialist ADHD clinics, where

if you have ADHD and meet those criteria you know where to go. But it’s very likely that all the other problems that such a patient is likely to have will be missed unless you have this concept in your head.”

Professor Gillberg will also be discussing how early symptomatic syndromes or neurodevelopmental syndromes affect adult psychiatry. “They are present in more than half of all adult psychiatric patients that come for more than one visit to any psychiatrist,” he explained.

“Many of the so-called adult psychiatric problems – specifically depression, anxiety and personality disorder – are in a sense not new adult psychiatric problems. They were there from the very beginning of life in the vast majority of individuals with these problems.”

And not all doctors understand how common this phenomenon is, as Professor Gillberg stressed. “About 1 in 10 of all people,

in all societies, are affected by one or more (and it is usually more) subsets of these types of problems from the very beginning of life, and typically without treatment. They do not disappear with time, you don’t grow out of it, so a very large number of adults will still have these problems.”

He went on: “It’s only in the past 20 years that enormous amounts of knowledge have developed in this field and so many of those who trained, even 10 to 20 years ago, have very little perspective on this.”

“There is a need for further education for both adult psychiatrists, in particular, but also general practitioners,” concluded Professor Gillberg.

Professor Gillberg will present his Plenary Lecture ‘Early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE)’ today at 13:45 in Hall A4

PRECLINICAL RESEARCH

S.28 **Neuropeptides, obesity and addiction** Hall A3 **Tuesday 14:45 – 16:25**

Digesting the role of neuropeptides in food intake

Food intake, obesity and the link with mood, anxiety and depression will be examined this afternoon during a session tasked with neuropeptides, obesity and addiction.

“We are very interested in studying neuropeptides that regulate food intake, also because these neuropeptides are often also anxiogenic or anxiolytic,” Harriet Schellekens (University College Cork, Ireland) told *ECNP Daily News*. “The core of what we study is really the brain-gut axis, because of course most of these peptides that regulate food intake or are altered depending on nutrient status are produced in the gut. There is CCK [cholecystokinin], ghrelin and leptin in the stomach.

“They have a local effect modulating food intake, but ultimately they all signalled through the brain. They signal via the vagus nerve, converging on the brain stem, or they pass the blood brain barrier via the blood circulation and the hypothalamus.”

In her work, Dr Schellekens has been studying all of the neuropeptides in the brain-gut axis, looking at food intake and how the neuropeptides interfere with stress and mood. Her team then also study other brain regions which are involved in the hedonic regulation of food intake, i.e. the reward pathways – a topic which Suzanne L Dickson (Sweden) will also be talking about in the first presentation of the session.

“Because there is a real intricate and overlapping system of neuropeptides that regulate food intake versus those that regulate stress, we also wanted to study whether there was communication between the different receptors,” said Dr Schellekens. “Now, one of the particular neuropeptides that we are interested in is ghrelin, because this is currently the only one known to stimulate food intake that is orexigenic. All the others are anorexigenic, i.e. decrease food intake. It is also interesting because of the recent findings that ghrelin



is very important in stress-mediated food intake.”

Dr Schellekens also has been investigating if the ghrelin receptor would interact with other receptors important in food intake, such as 2C: “We started investigating this using several in vivo/ex vivo approaches, and we found evidence that there is potential interaction, crosstalk and even dimerisation of these receptors,” she said.

“This of course is very important because this could lead to combined treatments and combination therapies. For instance instead of using a drug only targeting the 2C receptors, such as the recently-approved lorcaserin, a 2C agonist.”

She added: “You could lower the dose if you had a combination treatment, and it even may be more effective, so that is what we are studying. The new interaction between the ghrelin receptor and the 2C receptor is very exciting in the field.”

Moving on to discuss the future clinical applications of her work, Dr Schellekens began by describing some of her published work in the last year, looking mainly at the overexpression of these receptors to show how they interact in their signalling pathways with each other, and whether they could be manipulated. “What we’re doing now is looking at in vivo animal models where we see what happens when we modulate one receptor, in terms of how it impacts on the signalling of the other receptor,” she said. “We’re looking at specific ghrelin receptor-modulated agonists and antagonists that we’ve identified as well from screening programmes with existing modulators of other receptors, so the ghrelin receptor to dopamine receptor, we’re looking at dopamine agonists and we’re also looking at lorcaserin to see if there is an impact there. And that is what I’ll be presenting at the ECNP Congress. This is not published yet, but there are some very interesting data that I will be showing.”

In her concluding remarks, Dr Schellekens stressed that emphasis is not solely on the homeostatic regulation of food intake, but also the aspect of the reward pathway and hedonic food intake. “So really the drive to eat,” she said. “Because that’s what makes the link between food and mood interesting.

“It has been shown that, for ghrelin, if you are very stressed, you have more ghrelin in your circulation, and you want to eat more food. And not only in terms of quantity, but more palatable food. Therefore the idea here is that in situations of acute stress, ghrelin has a protective effect, and will induce comfort eating to give you enough fuel to combat negative effect of stress, and also increase dopamine, making you feel better, and cope easier with the stress. But of course if it drives longer term, if it’s chronic, the ghrelin responsiveness decreases, and an imbalance develops, and the protective effects of ghrelin may actually drive towards obesity rather than imparting protective effects.”

“In situations of acute stress, ghrelin has a protective effect, and will induce comfort eating to give you enough fuel to combat negative effect of stress, and also increase dopamine, making you feel better.”

Harriet Schellekens

BRAINSTORMING

BS.8 Is ketamine infusions ready for clinical use in treatment-resistant depression patients M4 Tuesday 07:45 – 08:45

Brainstorming the use of ketamine in depression

The stimulating series of Brainstorming Sessions continues this morning with an exploration of whether ketamine is ready for routine use in patients with treatment-

Revital Amiaz



resistant major depression. “I think we can use it now, as long as we are cautious about the history of drug addiction, and about psychosis, and about other medical problems that may prevent the use of ketamine,” Revital Amiaz (Sheba Medical Center, Tel Hashomer, Israel) – who will debate during the session – told *ECNP Daily News*.

“But others will debate that it is not ready yet, and we have to wait more.”

Looking to the studies that support the use of ketamine in this setting, Dr Amiaz noted that there were over 10 open studies, and around seven controlled trials looking at the mechanism of ketamine, namely its elevation of brain-derived neurotrophic factor, or BDNF, the mechanism of quick response to antidepressant therapy such as ECT.

“There are two meta-analyses that claim ketamine improves depression with prominent results,” she said. “Research of ketamine add on to ECT and with other medications, and the interesting thing is ketamine improves suicidality, and we know that several hospitals around the world, especially

in the United States, use it in the psychiatric ER for suicidal patients, or acute major depression patients.”

She added: “So the question is why not to use it in our clinical everyday practice?”

One argument against its use that Dr Amiaz predicts will come up in the session is that ketamine is both a hallucinogenic, and may cause

“The question is why not to use [ketamine] in our clinical everyday practice?”

Revital Amiaz

addiction. Commenting on the addiction risks, she added that special selection can be used to try and reduce the possibility, although it is not always possible: “In research we take special patients. We know that they are major depression patients without a history of addiction, but in the ER we cannot take all of the information. So people may come to the ER and say they are depressed, and get ketamine. It’s complicated.”

She continued, addressing additional concerns that

some people may have about the cognitive implications of ketamine. She stressed that we must realise people who take ketamine recreationally also probably use other drugs like MDMA for example, and this clouds the issue of how ketamine may or may not affect the brain detrimentally. However, crucially, studies dedicated to ketamine only have shown no cognitive deficit.

“And patients with depression already suffer from cognitive deficit. So if their mood is improved with ketamine, their cognitive ability is also improved,” said Dr Amiaz. “We give it in major depression, and maybe for bipolar patients – although it is less effective for bipolar, rather than unipolar, depression.”

Dr Amiaz also touched upon how frequent ketamine treatment should be administered: “The process of improvement in depression ... the elevation of BDNF, and later neurogenesis, does take time. The effect of ketamine lasts up to seven days, and we have to give repeated treatment to maintain the improvement, and let the process start.”



ECNP

The ECNP Certificate

The ECNP Certificate

The ECNP Certificate is a recently-implemented initiative that ties together all of ECNP's junior-researcher programmes into a European-wide qualification, backed by Europe's premier scientific association for neuropsychopharmacology.

As such, it provides an ongoing structure for ECNP's many educational activities and provides formal recognition for the efforts of junior researchers in neuropsychopharmacology. The Certificate is designed to demonstrate a set level of knowledge and expertise in neuropsychopharmacology, and a clear commitment to the field. It does so in a way that is realistic and achievable for students and researchers across the spectrum of neuropsychopharmacology and its related disciplines.

The specific goal of the Certificate is to enable junior researchers to show that they have the competency to review the scientific literature critically and the capability either to carry out an original research project or to effectively disseminate knowledge on neuropsychopharmacology through writing a scientific literature review or organising an educational event.

ECNP Daily News spoke to the two recipients of this year's ECNP Certificate, who will receive their honour on Tuesday night at the ECNP dinner.

Florian Freudenberg

University Hospital of Würzburg, Germany

I think the Certificate really helps to build a professional network with senior scientist from the field. Moreover, I think it will make me feel more connected to ECNP. In addition, being approved by such an important organisation as the ECNP will help to shape my professional profile.

You have attended the Workshop in Nice, and

also last year's Congress in Barcelona. How have you found the experience so far?

These events were definitely very useful. I was able to interact and connect with people from the field, and was allowed to present my data twice in front of a knowledgeable audience, which was a very unique experience.

What was the project you proposed for the ECNP Certificate?

I proposed a project which involved designing and creating viral constructs that express peptides, which block interaction of a protein called nitric oxide synthase (NOS-I). NOS-I and its protein interactions have been suggested to be involved in schizophrenia. I tested the viral vectors in cultures of primary neurons and found that some of them caused disturbed growth of dendrites and dendritic spines, something that is also observed in patients with schizophrenia.

How have you found mentorship?

It was very helpful to have someone from outside to give input to the planned experiments and to have a look at the data created. I am very thankful to my mentor Jaanus Harro for his help and support.

What were you looking

forward to most before you came to the ECNP Congress here in Berlin?

A particular highlight was the Keynote Lecture given by Karl Deisseroth, but also the Junior Scientists symposia. Additionally, I am very much looking forward to the targeted network meeting on schizophrenia, which is not part of the official congress but takes place right after.

Marta Rapado Castro

Hospital G. Universitario Gregorio Marañón, Madrid, Spain

Being an ECNP certificate awardee has brought me closer to the scientific reality in terms of the opportunities, requirements and the expectations



to fulfil a successful scientific career. It has had a tremendous impact on the way I understand scientific reality today and has helped me to advance the understanding of brain development and its impact of cognitive function in early onset psychosis, which feels like a decisive achievement.

The ECNP Certificate has been such a positive and rewarding experience. I would encourage any European junior scientist to pursue it. They will not be disappointed!

What can you say about the mentoring you experienced?

I am thankful for the support and advice as well as the scientific guidance my mentor, Andreas Meyer-Lindenberg, has provided. It has been a crucial open-minded experience that I would recommend to all other young scientist in Europe.

You've been to quite a few events in recent times. What is it about the ECNP Congress and other events that you think are so attractive to attendees?

The ECNP Congress brings together a group of high profile scientists and supports the development of junior scientists including activities exclusively for them, such as Career Development sessions and a Best Practice session to stimulate high quality research among young clinicians and researchers, which constitutes an exciting opportunity!

The ECNP initiatives have given a decisive boost to my scientific career. Not only the discussed topics on these meetings were of high interest but the networking and mentorship opportunities that were available for young scientist have provided support on the formulation of new hypothesis, information on funding opportunities, possible career paths and internal guidance to success in strategically important areas of current research.



Marta Rapado Castro



Florian Freudenberg

EDUCATIONAL TRACK

E.06 **Diagnosis and treatment of the new obsessive compulsive and related disorders** Hall A8 Tuesday 09:00 - 10:40

New classification in obsessive compulsive disorder

This morning will see Dan Stein (University of Cape Town, Department of Psychiatry and Mental Health, South Africa) address the issues facing clinicians when diagnosing obsessive-compulsive and related disorders. "This is an educational overview of the current nosological classification issues in the obsessive-compulsive and related disorders, and looking at what DSM-5 has suggested, and what ICD-11 is suggesting, and discuss it from those two perspectives," he explained, speaking to *ECNP Daily News*.

DSM-5 has, for the first time, included a chapter on obsessive-compulsive and related disorders. It also includes a number of new disorders in this chapter; hoarding disorder and excoriation (skin picking) disorder.

Describing the two diagnostic systems, Professor Stein said: "I think the major issues are around the validity of the classification, in other words what the science is showing, and the other issue is the utility, in other words about the clinical usefulness of the systems.

"You could perhaps argue that DSM-5

is more focused on issues around validity, because all proposed changes to DSM-5 were really heavily weighted towards that issue. And you could argue that ICD-11 is more weighted towards the utility issues. That's been a big issue in those discussions. But there is useful crossover, because you can't have something that is useful if it's not valid."

ICD-11 is also likely to include a chapter on the obsessive-compulsive and related disorders, said Professor Stein. "It's still in the pipeline, but the ICD-11 reviews are in press, and field trials are under way," he explained.

Commenting on the potential for future amendments, Professor Stein said: "One of the issues is to look at the slightly different proposals in DSM-5 and ICD-11. To some extent, ICD-11 allows a review and a reconsideration of DSM-5 decisions. So what ICD-11 does differently to DSM-5 is of real interest to the field."

Professor Stein will be speaking in the session "Diagnosis and treatment of the new obsessive compulsive and related disorders" at 09:00 in Hall A8.



Dan Stein

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www.ecnp.eu/membership

EDUCATIONAL

E.07 Pharmacology-based nomenclature: a joint ECNP, CINP, ACNP and AsCNP Task Force Hall A8 Tuesday 14:45 – 16:25



Joseph Zohar

First phase of nomenclature project completed

Today at ECNP Congress brings an update on the new pharmacology-based nomenclature, the joint ECNP, CINP, ACNP and AsCNP project that looks to the cutting edge of neuroscience in the process of overhauling the existing nomenclature system. The session will provide a detailed examination of the pharmacological action of the various classes of psychotropic drugs, while Joseph Zohar (Chaim Sheba Medical Center, Tel Hashomer, Israel), who opens the session, will introduce the concept of the new nomenclature.

The completion of the first phase of the Taskforce on Nomenclature is accompanied by a book, which can be found in each delegate bag, as well as an app. Both of these provide an easy way for clinicians and scientists to manoeuvre through the new nomenclature system.

“We are going to meet with editors of journals and other individuals to make sure that what we are doing is going to be really useful and not just an academic exercise.”

Joseph Zohar



Scan this QR code for access to the Nomenclature App

Describing the book to *ECNP Daily News*, Professor Zohar said: “There are going to be different indexes in the book that you can access based on indication. You can access it via the new nomenclature, or the former nomenclature.”

Speaking of the app, he added: “People can download it and if they have any problems, they can go to the ECNP booth, where there will be people that can help them both with content and technical issues.”

“The book is going to be the first edition, and what we are going to launch is the beta version. The task force is going to continue in their work. We are going to meet with editors of journals and other individuals to make sure that what we are doing is going to be really useful and not just an academic exercise.”

Naturally, the nomenclature handbook and app will

evolve to reflect the latest knowledge. Indeed, the nomenclature project may well undergo another metamorphosis with the progression of the RDoC project. “We see this project as a Wikipedia-type of thing,” said Professor Zohar. “We expect to get a lot of feedback from our colleagues. We know that it is not perfect, that there will be some omissions, and that it is an ongoing project.”

“I talked with Tom Insel [National Institute of Mental Health, MD, USA] and we do see one of the next steps as being to incorporate the RDoC into this system. Focussing not on diagnosis but on pharmacological targets and mode of action is paving the way to looking and adding domain criteria into this nomenclature. We talked about this and it is on our list.”

Describing the process of decision-making for individual

drugs and trials, Professor Zohar went through each of the four axes of the system: “Axis 1 is related to the pharmacological target and mode of action. The members of the task force identify what they think is the most relevant pharmacological target and what is the mode of action. If we see that there is more than one, we put a primary one. Then we can say it is multifunctional (more than one target) or multimodal (more than one mode of action).”

“The second axis is approved indication. We put together indications that have been approved by the FDA or EMA. Axis 3 is the efficacy and side effects. We spell out exactly the criteria – if it is effective in a disorder but it doesn’t have an approved indication. We think this is very important, because the approved indication is a product of commercial interest of

the pharmaceutical company to licence specific medication for a specific indication. There are several examples where a medication may be effective in a specific disorder, yet there will not be a physical initiative for the pharmaceutical company to initiate the procedure.

“The best example would be an old medication such as the tricyclics. When they were

developed, the potential use in anxiety and panic disorder were not known yet. So the indication was as an antidepressant and this is why they are still called antidepressants, although almost all of them are used in anxiety disorder. And there are other examples of this. This is why we include in the efficacy something that includes the criteria.”

These three axes are followed by the committee note, which encompasses the collective wisdom of the committee. Then, Axis 4, which represents the neurobiology, was written via literature review.

The adaptation to the new system, explained Professor Zohar, ought to be much like the transition from one edition of the DSM to the next. “It is

“It is about adapting and thinking differently about different disorders. The last update of nomenclature was done 60 years ago, so it is about time that it is done again!”

Joseph Zohar

about adapting and thinking differently about different disorders. The last update of nomenclature was done 60 years ago, so it is about time that it is done again!”

Professor Zohar will present ‘Pharmacology-based nomenclature – Introducing the concept and the template’ today at 14:45 in Hall A8.

ECNP OFFICE

ECNP President

Interview Guy Goodwin

Since taking the mantle during the 26th ECNP Congress in Barcelona, ECNP President Guy Goodwin (University of Oxford, UK) has been at the helm for all of the year-round activities and forward-thinking plans of the College.

To that end, *ECNP Daily News* caught up with Professor Goodwin to ask him about some of the highlights, challenges and perspectives he has experienced in his first year as president.

What have been the challenges you have encountered in your first year of office?

For our field there are plenty, and their resolution will not be easy. The withdrawal of large companies from neuroscience will have an increasingly negative impact unless governments, foundations and industry find ways to fill the funding gap for translational research. We have to help make the case at the European level for pre-competitive funding for applied neuroscience. The EU’s Innovative Medicines Initiative has provided a great model but it is driven by industry. The societal costs of psychiatric disorder, demonstrated by the ECNP-European Brain Council study, argue strongly for the prioritization of our field (not its traditional marginalization) by policy makers.

I believe ECNP has the credibility and the people to make the case cohere in this area and we are working with a re-structured European Brain Council to get the message across in Brussels.

There must be a number of future plans and directions that you are keen for ECNP to pursue – both in terms of the Congress and the wider gamut of year-round events? Can you name some in particular?

We are developing an information strategy that I hope helps to get balance into the public debate on treatment in psychiatry.



That means being proactive in commenting on news stories and developing the ECNP’s media communication strategy so that the Congress itself can become more news worthy.

This relates to our increased responsibility as a ‘public interest serving entity’. The public, in one way or another, pays for research and we have to communicate with them about it. The Brain day for the public in Berlin immediately before the Congress was a first, which I hope we can repeat in all our host cities. Neuroscience is of interest to everyone, but neuroscientists are, as a tribe, slow to see an interest in its application to mental illness. That has to change: we need the most brilliant minds on humanity’s worst problems.

“We have to help make the case at the European level for pre-competitive funding for applied neuroscience.”

Guy Goodwin

What have been the key changes implemented this year for the Congress in Berlin?

Our new or expanded initiatives include:

- E-posters
- Regulatory Update Session
- Rapid-fire Poster Sessions
- Free registration if a poster is accepted for presentation for participants from developing economy countries (CDE)
- Up to 100 CDE grants of € 500
- Two Junior Scientist symposia – S.07 and S.12
- Six career development sessions
- ‘Junior Scientists’ café
- Awards: Six Fellowship Awards of € 1,500; 50 Travel Awards of € 500; 10 Poster Awards of € 500

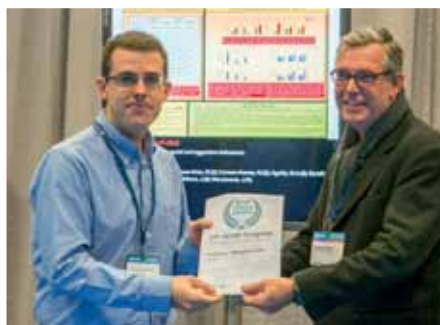
Is there any other exciting news on the horizon for ECNP that we can get a glimpse of?

We want to create a new style of one-day meeting in Nice to look at new areas of applied neuroscience. The first will be on diagnostics. Our aim will be to draw in people who might not immediately think of ECNP as providing a space for them. If it works, the topic can enter the mainstream of our interests. If not, so be it.

We are looking at how we can create an ECNP School for training in clinical research methods. There is clearly a need articulated by our junior colleagues.

Finally, our journal – *European Neuropsychopharmacology* – will have a new editorial team, which I find an exciting opportunity. They will inherit a successful journal and further define our identity as the premier organisation supporting applied neuroscience in Europe.

The last four years has seen immense organisational change for ECNP (much of which should not be ‘visible’ from the outside, but was very important). We have also created a host of new activities – the three ECNP Schools, the nomenclature project and greater input from junior colleagues are just three examples. I want these developments to be sustainable, so part of any exciting future has also to be the maintenance of an exciting past.



CONGRATULATIONS!

to this year's recipients of the ECNP
Travel Award and ECNP Poster Award!

Travel Award winners, Sunday

Amila Zuko	The Netherlands	P.1.c.001
Joanna Slusarczyk	Poland	P.1.d.002
Damiana Leo	Italy	P.1.g.030
Tamara Timic Stamenic	Serbia	P.1.j.011
Joeri Tijdink	The Netherlands	P.1.l.001
Inbar Zohar	Israel	P.2.a.001
Mara Seguini	Italy	P.2.a.006
Martina Balestri	Italy	P.2.b.013
Sarah Kittel-Schneider	Germany	P.2.c.001
Monica Morais	Portugal	P.2.e.003
Ivan Koychev	United Kingdom	P.3.b.007
Verity Pinkney	United Kingdom	P.4.a.005
Ravi Das	United Kingdom	P.6.b.004
Vanessa Coelho Santos	Portugal	P.6.c.001
Adeline Cathala	France	P.6.c.003
Moran Cohn	The Netherlands	P.7.a.001

Poster Award winners, Sunday

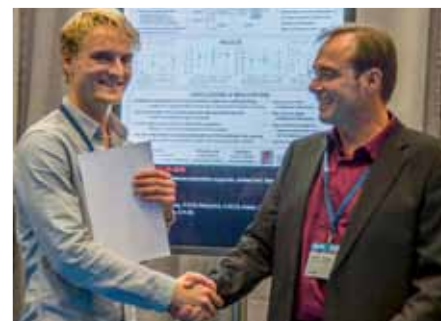
Catharine Mielnik	Canada	P.1.c.002
Marin Jukic	Serbia	P.2.c.003
Benedetta Vai	Italy	P.3.b.013
Moran Cohn	The Netherlands	P.7.a.001

Travel Award winners, Monday

Kristin Schmidt	United Kingdom	P.1.e.003
Adomas Bunevicius	Lithuania	P.1.e.004
Marc Udina	Spain	P.1.f.005
Marjan Popovic	Serbia	P.1.f.008
Tiffany Jeanson	France	P.1.g.039
Alexandra Alvarsson	Sweden	P.1.g.044
Francisco Navarrete Rueda	Spain	P.1.g.055
Laura Cremaschi	Italy	P.1.i.020
Andús Uribe-Mario	Germany	P.2.a.012
Irene Bollettini	Italy	P.2.d.037
Karen Ryan	Ireland	P.2.e.004
Marie Fitzgibbon	Ireland	P.4.a.009
Merce Masana Nadal	Germany	P.4.a.010
Marta Subira	Spain	P.4.b.017
Paul Kennedy	Ireland	P.5.f.005
Anastasia Olevska	Germany	P.6.c.009
Michael Bloomfield	United Kingdom	P.6.f.004
Nicolas Lucas	France	P.7.a.002
Covadonga M. Díaz-Caneja	Spain	P.7.b.009
Maria Goretti Moron-Nozalea	Spain	P.7.b.010
Maria Donovan	Ireland	P.7.c.002

Poster Award winners, Monday

Matthijs Bossong	The Netherlands	P.1.i.013
Roel Mockin	The Netherlands	P.2.b.031
Agata Antonina Rita Impellizzeri	Italy	P.5.a.006



Lithium's role in white matter protection uncovered

Lithium may prevent the degradation of white matter integrity that has been linked to bipolar disorder, new research suggests. The findings indicate that the drug, or others with a similar protective action, should be considered mandatory for the condition, as opposed to antipsychotics which do not carry out this potentially vital role.

Francesco Benedetti (IRCCS Ospedale San Raffaele, Department of Neuropsychiatric Sciences, Milan, Italy) presented his results, which were gained through a series of MRI studies using diffusion tensor imaging of white matter integrity, to delegates yesterday afternoon at the 27th ECNP Congress.

The research also suggests that adverse childhood experiences are linked to bipolar disorder and the disruption of white matter integrity in adults.

"These changes are not apparent on normal MRI scans because under normal MRI conditions white matter appears healthy. But they can be found by using these more sophisticated methods of measuring integrity of white matter," Professor Benedetti told *ECNP Daily News*.

His team have been conducting diffusion tensor imaging for several years, leading to some interesting results, as he explained: "It turned out that the patients with bipolar disorder, especially when they were in a depressive phase of illness, had a major change in measures of white matter integrity, and these changes were in a direction that suggested a disruption of myelin sheets because they had a reduction of fractional anisotropy without any change in the primary eigenvalues lambda one or factor diffusivity.

"These changes were paralleled by an increase in the so-called radial diffusivity, or diffusivity of water perpendicular to the myelin sheets around the axons, which is found in all the neurological illnesses which are paired with a disruption of myelin sheets."

This initial finding prompted a flurry of research, both in his and other research groups. Now it appears that changes in the integrity of white matter may be a major biological factor and therapeutic target in bipolar disease.

Professor Benedetti went on to explain that white matter disruption in bipolar disorder appears to cause reduced functional connectivity among brain areas, which then leads to an impairment in cognitive control of emotions and the experience of emotions.

Since the discovery, the researchers have been working to investigate what influences this reduction in white matter integrity. One factor, says the Professor Benedetti, is exposure to stress early in life: "It is now known that the breadth of exposure to stress is able to influence the wiring of the brain during the first stages of the neuro-



Francesco Benedetti

development," he said.

"Animal models showed that even when stressors are given to the mothers, the pregnant mothers, they are able to defasciculate core structures in the brain of rodents, such as the corpus callosum and other things."

"But data in human subjects clearly showed that even in healthy subjects, exposure to stress in the first year of infancy is able to cause changes in the connectivity of white matter tracts."

Extending their research to bipolar patients, Professor Benedetti and his team found a link between stress and white matter, as he summarised: "The disruption of white matter in our patients correlates with the severity of the stressors which they experienced in their first infancy going through their adolescence – we carried out a retrospective study of exposure to adverse childhood experiences which take from 5 to 15 years of age."

The team also investigated a number of biological factors that might influence the process. "One of these is the glycogen synthase kinase 3 beta (GSK-3 β) enzyme," continued Professor Benedetti. "This is a molecule which is at the crossroads of several pathways of signal transduction into the cells.

"In particular, it is equally affected by stimuli transduced from monoaminergic signaling coming from dopaminergic receptors on the membrane, or serotonergic receptors, and stimuli coming from other signalling cascades which are linked with the trophic factors such as BDNF or even insulin ... So it's a point of integration into the cell of factors affecting the cell cycle."

He went on: "It is also a core part of the

molecular machinery of the biological clock and we have published some papers showing that people who are carriers of a genetics variant in which GSK-3 β is less active ... have a less detrimental course of bipolar illness. They have less episodes, they have a later onset of illness and they have a better response to treatments, both to antidepressant treatments and to lithium."

GSK-3 β is one of the main targets of lithium, as Professor Benedetti noted. "Lithium inhibits GSK-3 β and we showed, in our data studies, that the administration of lithium correlates with a better integrity of white matter, and better directionality of water diffusion along fibres of white matter," he said.

He continued: "The hypothesis is that the benefits of the long-term administration of lithium come from the fact that it counteracts the detrimental effects

of both the bipolar illness and the exposure to early stress on the white matter integrity of the brain. So the long-term administration of lithium to the patients will lead to restoring the proper connection of white matter tracts among brain areas."

"In the long term this should improve the functional connectivity among these areas, making our patients able to have better control of emotions and of all the things pertaining to the cortical index connectivity in the frontal part of the brain."

Professor Benedetti will also be presenting new data on pro-inflammatory cytokines, which appear to affect white matter.

"[These] are known to be activated in patients affected by mood disorders, and so this probably point towards a role of pro-inflammatory monocyte macrophagic activation in the pathogenesis of these white matter abnormalities, and in this respect it should be noted that GSK-3 β is a core point in the activation of brain microglia. If you inhibit GSK-3 β you block the development of inflammation into tissues and into the brain ... activation of these inflammatory pathways is a known correlate of stress, both of physical and of emotional chronic stress in adult humans," he explained.

He added: "Lithium works towards normalising the white matter integrity in the brain, and probably does so by counteracting the effect of stress and blocking an enzyme, which is a core part of this transduction pathways for stressors and inflammation."

The findings could have a huge impact on the way bipolar disease is managed: "These

Continued on page 12

"The hypothesis is that the benefits of the long term administration of lithium come from the fact that it counteracts the detrimental effects of both the bipolar illness and the exposure to early stress on the white matter integrity of the brain."

Francesco Benedetti

INTERFACE RESEARCH

S.19 **Biomarkers in bipolar disorder** Hall A7 **Monday** 14:45 – 16:25**Lithium's role in white matter protection uncovered**

"These things were not known. If they are confirmed, this is a whole new target for treatment."

Francesco Benedetti

Continued from page 11

are the first studies to show that drugs affect brain integrity, and in particular white matter integrity," said Professor Benedetti. "This kind of information is not yet available, neither to the general public, to the patients, and neither to their physicians, and we have several treatments which might be acutely affective to treat bipolar disorders."

He went on: "For instance ... atypical anti-psychotics could be used for the acute treatment of patients, but in the long term,

modelling in macaque monkeys showed that they disrupt white matter integrity and reduced grey matter volumes. So probably they should be used for little amounts of time, and only when really needed."

The case for lithium, which is already known to have some neuro-protective effects by promoting BDNF and other neurotrophic factors, is now even stronger, stressed Professor Benedetti. "What we are showing now is that lithium actively promotes the correction, the restoring of the integrity of some core things

that may happen in the brain of patients, such as the disruption of white matter integrity. So it has a therapeutic effect which was not known and which goes against the detrimental effect of illness and of stress," he said.

Professor Benedetti concluded: "Based on these findings, I find it to be mandatory to begin patients on a long-term treatment with these kind of drugs, in order to protect them and to cure these aspects. These things were not known. If they are confirmed, this is a whole new target for treatment."

CLINICAL TREATMENT

S.21 **TNM symposium - Beyond blue** Hall A4 **Tuesday** 09:00 – 10:40**Early intervention for mental health in the young**

This morning's Targeted Network Meeting symposium on the possibilities available to European bipolar networks will feature a thoughtful presentation examining the issues surrounding early intervention in adolescent-onset mood, and what lessons can be learned from approaches used in psychotic disorders.

Jan Scott (Institute of Neuroscience, University of Newcastle, UK) will focus her talk on how physicians can improve the way that mood disorders are managed and researched by increasing their focus on younger patients in the early stages of illness.

"In the last 20 to 30 years, clinicians have recognised that if they can pick up people who are at very high risk of getting psychosis or are in their first episode, they can hopefully improve their outcomes, because they can offer them treatments but have a better benefit to risk ratio than the things that we give people when they're much older with long established illness," explained Professor Scott.

The core aim of such programmes is to reduce the length of time before people get access to services, and offering 'age and stage' appropriate treatments. "That's important for two reasons," she said. "One, because there is evidence that the shorter the duration of untreated illness, the better your outcome will be with treatment.

"Secondly, in psychosis they've started to look at whether or not you can find people who are very high risk of getting psychosis but don't have it yet. The idea is to identify these high risks groups, and then give the best possible treatment that's low risk and high benefit in the early stages of the illness and that takes into account that 70% of these individuals will not develop psychosis."

While early intervention in psychosis is widely accepted across Europe, similar protocols for mood disorders are lacking, as Professor Scott explained: "It's complicated in mood disorders because depression in young people is very, very common so lots of them get depressed: psychotic symptoms are actually relatively rare in comparison to mood symptoms."

The changing spectrum of symptoms is also an issue, she noted. "Seventy percent of people who eventually develop bipolar disorders start with a



"In medicine, what's happened is the treatment of each stage is different. That's what's got to change in psychiatry."

Jan Scott

depressive episode. You can't just say, 'Okay, my tactic would be to give antidepressant to all young people who get depressed,' and just go out, try and find them and treat them – because if you give antidepressants to the ones who are going to become bipolar, you

might actually precipitate an episode of hypomania or mania."

Professor Scott went on to discuss how the US and Europe are beginning to approach this issue in different ways. "In America they've gone down the route of specialised clinics looking for children with bipolar disorders. In Europe that's not so well accepted because there's a danger here of misinterpreting certain symptoms in childhood as if they were bipolar disorders," she said.

"The danger in the American model is a greater reliance on standard treatments, for example lithium may be used in very young children, some of whom

CLINICAL TREATMENT

S.21 **TNM symposium – Beyond blue** Hall A4 Tuesday 09:00 – 10:40

would benefit more from a different approach. One of the alternatives is what's happened as the next step after early intervention in psychosis, which is a Youth Mental Health approach. This means you try and get at young people no matter what their presenting symptoms are."

The aim behind Youth Mental Health approach is to identify people who are going to have certain types of illness trajectories. "You're trying to distinguish here between the ones who will go through periods of adolescent turmoil, possibly get depressed but whose problems will resolve and not come back, versus the ones where the depression is the starting point for one of several severe mental disorders," explained Professor Scott.

To achieve this approach, physicians need to consider their treatments carefully, ensuring that they work across the whole range of potential problems – such as psychosis, mania, and depression. It also requires planning each stage of treatment.

"What you're now trying to do is distinguish who is going to get psychosis from who is going to get recurrent depression, from who is going to get bipolar disorder. It changes what the research is about because it's cases versus positive controls. The treatment arguments have to change a bit and also how you think about what your research is going to be about to understand illness onsets, changes."

The Youth Mental Health approach lends itself to clinical staging models more akin to what is seen in general medicine, as Professor Scott explained: "Stage one is people who have a greater than average risk of developing a disorder and have also got some non-specific symptoms, so that might be depression in the cases I'm talking about. Stage two is where you get to symptoms that meet classic thresholds for diagnosis of illness. Now, in medicine, what's happened is the treatment of each stage is different. That's what's got to change in psychiatry."

She went on: "It's got real implications for what we think of as treatments ... We don't give a cardiac stent to people because they've got a risk of heart disease, we save that for a very small sub-group ... psychiatry needs to think more like this, about staging models, and this has major implications for diagnostic systems."

And early intervention should be considered a priority in mental illness, stressed Professor Scott. "If you look at all the data worldwide, mental disorders are the chronic diseases of young adults. 75 percent of severe mental disorders start before 30, in fact probably before 25."

She continued: "We don't pay enough attention to how we spot that, what we do about it and how we manage it. Eighty percent of our research money is spent on middle aged adults in specialist clinics. That's not to say it's wrong to want to investigate those treatments and improve the quality of life of those patients, but what they've done in medicine is ... they try and think much more about what can you do at an earlier stage that might reduce the risks further down the line."

The implication is that research strategies have to be re-thought if we're going to understand and change treatments for mood disorders. "We've got to design new treatments and you're likely to need to offer that to more people to prevent onset. The question is will that be cost effective – should you focus your

"What you're now trying to do is distinguish who is going to get psychosis from who is going to get recurrent depression, from who is going to get bipolar disorder. It changes what the research is about because it's cases versus positive controls."

Jan Scott

resources on the people with already very established disability," she said.

In her talk, Professor Scott will argue that to get the data they need, researchers have to follow up cohorts of young people with sub-threshold

symptoms, and widen the scope of the outcomes measured. Such studies could also help to identify biomarkers that could point to those at higher risk before the onset of symptoms or of diagnosis.

"We've got some genetics data and we've got data on established cases but we need the bits in the middle – why do some people make the transition to persistent or severe disorder whilst others may get to stage 1 but never to stage 2 or 3? That's what medicine has done. There is a model," she concluded.

Professor Scott will present her talk during the session 'TNM symposium – Beyond blue: new opportunities for European networks in bipolar disorder' starting at 09:00 today in Hall A4.



EDUCATIONAL

E.04 EPA educational update – Alcohol and suicidal risk Hall A8 Monday 09:00 – 10:40

Alcohol, the internet and suicide: correlations in adolescents revealed



Pathological internet misuse and alcohol are correlated in adolescents, delegates attending Monday's morning's education session heard.

Researchers also found an association between alcohol and suicidal ideation and attempts in the same study. Danuta Wasserman (Karolinska Institutet, National Centre for Suicide Research and Prevention of Mental Ill-Health, Stockholm, Sweden) began her talk by discussing epidemiological data showing a clear link between alcohol use and suicide in the former U.S.S.R.

"Gorbachev instigated a programme of diminishing of alcohol abuse in the former soviet society," she said. "It means that he cut

"Females have higher maladaptive rates because females are using chat rooms more. Boys use chat rooms less, but have higher pathological internet use rates."

Danuta Wasserman

production. He was trying to cut consumption but he also gave resources for treatment and rehabilitation for alcoholics.

"During that period of time – 1984 to 1986 – suicide for men decreased by 40% and in the workforce, in the very important age group of 24 to 54."

Studies have also demonstrated a link between alcohol and other causes of death, including homicides, external injuries, death from alcohol poisoning, cardiovascular diseases and other diseases, she added.

Professor Wasserman went on to discuss the link between alcohol and problematic internet activity. "The definition of pathological internet use, which is not classified

as a mental disorder according to DSM-5, is conceptualised as an impulse control disorder characterised by excessive or poorly controlled preoccupations or behaviours regarding internet use that leads to impairment or distress," she explained.

To investigate the connection between internet misuse and alcohol, Professor Wasserman and her team recruited 12,395 adolescents from 179 randomly selected schools across 11 European countries.

The researchers used assessed pathological internet use using the Young's Diagnostic Questionnaire.

"We classified internet users as adaptive users, maladaptive users, and pathological users," she explained.

The researchers also measured alcohol use with the Global School-Based Pupil Health Survey (GSHS) and suicidal behaviour with the Paykel Suicide Scale (PSS). Overall, 4.3 percent of adolescents were classified as having pathological internet use, Professor Wasserman said.

"Online activities included watching videos, using chat rooms, social networking as well as playing games," she added.

The team found that the correlation between alcohol misuse and pathological internet misuse was significantly higher among adolescents who consumed three or more drinks on a typical drinking day, who have had three or more instances of drunkenness or a hangover in their lifetime.

Professor Wasserman and her group found that pathological internet use was significantly associated with suicidal ideation and suicidal attempts. Suicidality was also linked with alcohol misuse, she noted.

Differences were also noted between genders, as Professor Wasserman explained:

"Females have higher maladaptive rates because females are using chat rooms more. Boys use chat rooms less, but have higher pathological internet use rates."

ECNP

Junior Scientists Science on the Rocks

Former ENP Editor reveals tricks of the trade

Junior scientists packed into the Homes Bar in downtown Berlin on Sunday night to witness former Editor of *European Neuropsychopharmacology*, Michael Davidson (Chaim Sheba Medical Center, Tel Hashomer, Israel) give an informal lecture about the ins and outs, best strategies and pitfalls associated with the publishing of scientific papers.

Organised by the ECNP Junior Members Advisory Panel (J-MAP), the Science on the Rocks event encouraged

open discussion, a chance to network, and of course an evening of social relaxation following the packed ECNP Congress programme.

"If you have good data, you will get published!" he began.

One of the aspects that Professor Davidson spoke passionately about the need to publish negative findings, assuming they are novel, important and as well-discussed as positive findings. "You should be committed to publish negative findings," he said, adding that

if good but negative data is rejected, he would blame the reviewer.

He added: "A rejection is not the end of the story. You should go back to the same editor and argue and haggle, and most editors – I hope – would reconsider. There is a new trend to publish negative data, and be open about it, although the reality is a little bit different."

Replying to an audience member who stated he had a paper rejected because of his country of origin, Professor

Davidson commented: "I don't want to offend you, but what about the possibility that your paper was rejected because it was not good enough?"

He cautioned that one should not look to which countries publish most, to then conclude that there is some sort of bias. "If you look at most of the literature, most of the accepted papers in the good journals are from the United States. But then, most of the PhDs, most of the science, and most of the money is from the United States, so

ECNP

Junior Scientists **Science on the Rocks**

there is no way around it.”

Referring back to the audience member's claim, he said: “It sounds to me very, very strange that they would not accept your paper.”

Moving on to discuss the whether he believed the author's names should be given to the reviewers, Professor Davidson said that perhaps in some cases it is useful to know their names, as the only real way to get a feeling of the validity of a seemingly ‘good’ study in many cases will be if they know the authors. Poor data, however, is much easier to identify.

On a similar topic of being able to choose one's reviewers, and whether this influences bias, he said. “You choose at least one or two reviewers, and then another reviewer you try to figure out who knows the area – but this is only one consideration. You also need to figure out who will respond fast enough.

“Remember, good, repu-

table, smart people receive around 5-10 reviews a week. Even the smartest, fastest most efficient person will take at least half an hour. It may take you two hours ... you don't get paid for it, and it is a lot of hours per week. So it's a balancing act. As an editor, you don't have

“If you have good data, you will get published!”

Michael Davidson

a lot of luxury to choose your reviewers. Particularly in subjects which are not mainstream.”

In his final moments of discussion, the topic turned to having authors on papers who carried a lot of weight, but were not actually involved in the project. “I think it is wrong!” he said. “I think it is cheating, non-scientific ... but don't ask me how to solve it!”



ECNP SCHOOLS

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AGENDA FOR 2015

- 1-6 March ECNP School of Child and Adolescent Neuropsychopharmacology
Venice, Italy
- 19-24 April ECNP School of Old Age Neuropsychopharmacology
Venice, Italy
- 5-10 July ECNP School of Neuropsychopharmacology
Oxford, United Kingdom

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ECNP neuroscience applied



Waking up to potential of novel insomnia treatment

Delegates attending this afternoon's session on managing sleep disorders will hear new research into orexin receptor antagonists that has paved the way for suvorexant, a novel treatment for insomnia recently approved in the USA and Japan.

Preclinical data, to be presented by Anthony Gotter (Merck Research Laboratories, Department of Neuroscience, West Point, Pennsylvania, US), suggest that dual orexin receptor antagonists (DORAs) could promote sleep without impacting cognitive performance and locomotor coordination.

"About 15 years ago the gene for orexin was identified as being responsible for narcolepsy, and really that induced a deluge of research, both on the academic side and shortly thereafter in the industrial side to identify antagonists that might be efficacious for promoting sleep," Dr Gotter explains.

Since then, he and his team have used genetic and translational animal models to successfully identify and optimise dual orexin receptor antagonists (DORAs) that, in pre-clinical trials, appear to offer significant advantages over the existing standard of care for insomnia, GABA-A receptor hypnotics.

"What our antagonists show is that first of all, they're effective at promoting sleep through a novel mechanism that antagonises the arousal-promoting effects of the orexin ligand. This mechanism of action is distinct from GABA receptor modulators, which increase the activity of an inhibitory receptor that basically promotes CNS depression," said Dr Gotter.

Dr Gotter and his team went on to carry out a number of other preclinical studies to examine the effect of DORAs on cognition, sleep patterns, and wakefulness. The results are promising, as he explains: "Orexin receptor antagonists do not inhibit or disrupt cognitive performance, both immediately after administering the drug as well as the day after. And those experiments have been done in both rodents and rhesus monkeys."

Interestingly, their data indicates that the quality of sleep produced by DORAs is essentially normal. "We have some new data on the sleep promoting effects which show that DORAs promote sleep that's very similar to normal inactive phase sleep," he said. "We also have some new qEEG data which shows that clinically there is a distinction between orexin receptor antagonists and GABA-A receptor modulators, and we're actually very excited about those results."

He continued: "The type of sleep that we observe pre-clinically includes both non-REM and REM sleep, the pattern of which looks very similar, if not identical, to what we see during normal sleep ... whereas with GABA receptor modulators, they suppress REM sleep."

Although the impact of abnormal sleep ver-



Anthony Gotter

"The type of sleep that we observe pre-clinically includes both non-REM and REM sleep, the pattern of which looks very similar, if not identical, to what we see during normal sleep."

Anthony Gotter

sus normal sleep is not yet fully understood, the findings open the door for future studies into sleep architecture and its effect on cognitive performance. Bypassing the CNS depression induced by GABA receptor modulators has other benefits, as Dr Gotter noted: "From the pre-clinical results that we have, they indicate that, at least in animals given GABA receptor modulators, you can't wake those animals up at a moderate dose that's efficacious at promoting sleep," he said. "Whereas with orexin receptor antagonists ... the animals will sleep through neutral stimuli but wake up to stimuli that they're conditioned to respond to."

This is a desirable outcome if the results carry through to humans, as Dr Gotter explained: "If someone were asleep under an orexin receptor antagonist, you might expect them to be able to wake up in response to salient stimuli [such as a baby crying or a fire alarm]. Those clinical trials have not been done so we can't say that that is absolutely something that we expect, but that's based on pre-clinical evidence."

In his talk, Dr Gotter will also contrast the pharmacokinetic aspects of DORAs with GABA-A receptor modulators. "With GABA receptor modulators you only need about 25 percent of the receptors to be bound by the drug in order for them to actually induce sleep. On the other hand, orexin receptor antagonists need to have 65 to 80 percent of the receptors bound in order to block the action of orexin," he

explained. "What that ultimately means is that you need to have more orexin receptor antagonist around in order to promote sleep."

This difference in mechanism is important for the timing of sleep efficacy. Dr Gotter went on to explain that an ideal insomnia therapeutic would exhibit initial rapid effects that are diminished later at expected wake times, and that the timing of sleep promoting efficacy is based on dose, pharmacokinetic properties and the drug's mechanism of action. For example, GABA-A receptor modulators effective at lower receptor occupancies require shorter pharmacokinetic half-life relative to orexin receptor antagonists active at elevated occupancies. "The way we look at orexin receptor antagonists, as far as the timing of efficacy is concerned, is a little bit different from GABA receptor modulators," he said.

Describing the research process that he and his team has carried out, Dr Gotter said: "It's a good model for how a CNS therapeutic can be developed rapidly for disorders that have a single gene being responsible for them, or a converse phenotype – in this case sleep induction – from a mutation of that gene. We can apply it to something like insomnia where we can antagonise that single gene product to be able to get a predictable physiological and behavioural result."

He added: "We've been able to make successful therapeutics where the pharmacokinetics and the properties and safety profile are ideal for moving into clinical trials, and to very selectively attenuate arousal and

"What our antagonists show is that first of all, they're effective at promoting sleep through a novel mechanism that antagonises the arousal-promoting effects of the orexin ligand."

Anthony Gotter

promote sleep."

In addition to developing novel therapeutics with clinical impact, compounds developed along the way have provided pharmacological reagents toward exploring the biology of orexin.

Regarding orexin receptor antagonists, Dr Gotter noted: "They've also been very useful for us to probe the mechanism of action, that is, identifying the function of those receptors both in sleep as well as other behaviours."

The role of orexin in neurological processes beyond arousal will undoubtedly be the topic of further study, Dr Gotter concluded.

Dr Gotter will present his talk during the session 'New treatment options for sleep disorders', held this afternoon at 14:45 – 16:25 in Hall A7.

CLINICAL RESEARCH

S.18 **New treatment strategies for schizophrenia** Hall A1 **Monday** 14:45 – 16:25

Anti-inflammatory strategies in schizophrenia

Novel treatment approaches in schizophrenia were placed centre stage yesterday afternoon in a session that outlined anti-psychotic, anti-inflammatory, glutamatergic and nicotine-based strategies.

Although she was unable to attend the session, with Metten Somers taking her place, Iris Sommer (UMC Utrecht, the Netherlands) spoke to *ECNP Daily News* to outline the role of the immune system in schizophrenia – a topic which is not entirely new, but which has only recently been gathering significant investigation. “We have known for a long time that children that have suffered an infection in their early years, or even in the womb, are at an increased risk for schizophrenia, but we never exactly understood how this is linked to the general pathology,” said Dr Sommer.

“The main hypothesis about schizophrenia usually involves neurotransmitters like dopamine, or others such as glutamate, and we didn’t really see how the immune systems would fit in. I think in the last 10 years, the pieces of the puzzle have started fitting together.”

She added that Denmark has been leading a lot of charge for research in this arena, harnessing data from large registries and linking together patient information and diagnoses. “Studies there have noticed that patients with schizophrenia have much higher prevalence of all types of autoimmune disorders, like diabetes type I, but also systematic lupus erythematosus and inflammatory bowel diseases – and many others had multiple sclerosis,” said Dr Sommer.

“And it is also the other way around. People with autoimmune disorders also have an increased prevalence of schizophrenia, and this is not only true for the autoimmune disorders, but also for atopic disorders such as asthma and skin allergies. So it seems that diseases that involve the inflammatory system are associated with schizophrenia, and bipolar disorder.”

Dr Sommer also described other important work that explored the link between human leukocyte antigen (HLA) genes and schizophrenia, saying: “The strongest genetic association with schizophrenia is found in the MHC region on chromosome 6, which has a putative role in the immune system. This suggests a primary involvement of the immune system.”

Alongside defence, the immune cells of the brain also have important roles in regulating brain development, for example axon guidance. With that in mind, Dr Sommer stressed that if those immune molecules are busy defending the brain from viruses and bacteria, they may neglect the regulatory aspect of their function, which could in turn lead to developmental disorders.

“Perhaps environmental influences can also be considered into this model,” she added. “For example if environmental stress



Metten Somers
speaking during
the session

increases, which could be for example by social isolation, or by traumatic events, then the stress levels – and the inflammatory processes – of the brain increases, and this may have disadvantage for development.”

Dr Sommer argued that in patients with schizophrenia, it may be the case that the immune system is more ‘trigger happy’, reacting to environmental circumstances more readily, and negatively affecting brain development. “That’s the theory, but it is not complete,” she said.

If the hypothesis is correct, it could open up a new class of treatment for schizophrenia, harnessing the wealth of agents that can influence the immune system. And, as development can be affected, the earlier the better for treatment: “In the trials that I have seen, they have been done with patients who have already developed schizophrenia,” she said. “But you can still see that there is some affect there. Not all of the inflammatory agents had an effect, but there was evidence that aspirin

interesting to look at high-risk individuals who have not yet acquired the diagnosis, as not all brain changes may have taken place.”

Dr Sommer also spoke about patient selection, i.e. when and how to intervene with therapies that could benefit the developmental process. One option, she said, would be to single out patients in which the immune system is most involved. “You can do that by profiling. Perhaps you can look at blood markers, or perhaps you can look at brain scans to see which patients have especially-increased levels of brain inflammation, and then provide anti-inflammatory therapies to these subgroups. We’ll be doing that in a study we just started. We haven’t included the first patient but we have obtained approval.”

She continued: “Another way to go is to use anti-inflammatory agents with very few side effects, and start as early as possible. Now, for that purpose we have selected simvastatin, which is of course a cholesterol-decreasing agent, but it also has anti-inflammatory capacities in the brain, and passes the blood brain barrier well. So we’re giving it to the patient as early as possible after diagnosis, and that has been running now for a few months. We’ve included the first 10% of patients, and we will be treating them for one year, which is quite extensive.

“The immune response may be most pronounced in the early stage of the illness. Mitigating this response may be advantageous not only for the symptoms of schizophrenia but also in preventing cognitive deterioration. Given the fact that cognitive dysfunction precedes the first psychotic episode, interventions to decrease the inflammatory response may be most effective during the prodromal phase. I think the way to go is to combine preventive strategies in reducing environmental stress in vulnerable youngsters with optimising the brains’ immune system to prevent cognitive dysfunction and the subsequent development of schizophrenia.

“We have known for a long time that children that have suffered an infection in their early years, or even in the womb, are at an increased risk for schizophrenia, but we never exactly understood how this is linked to the general pathology.”

Iris Sommer

at least has some effect on the severity of schizophrenia symptoms. I think that is very encouraging.

“The same as well for N-acetyl cysteine, which is actually an amino acid, so has very few side effects. There was one study that also showed some benefit. It is all still open, and I can imagine that it is important to start augmentation therapies with anti-inflammatory agents as early as possible. It would be very

“So it seems that diseases that involve the inflammatory system are associated with schizophrenia, and bipolar disorder.”

Iris Sommer

FUTURE MEETINGS

CONGRESSES

- 28th ECNP Congress** 29 August-1 September 2015, Amsterdam, The Netherlands
- 29th ECNP Congress** 17-20 September 2016, Vienna, Austria
- 30th ECNP Congress** 2-5 September 2017, Paris, France
- 31st ECNP Congress** 6-9 October 2018, Barcelona, Spain
- 32nd ECNP Congress** 7-10 September 2019, Copenhagen, Denmark

WORKSHOP

ECNP Workshop for Junior Scientists in Europe
12-15 March 2015, Nice, France

SCHOOLS

ECNP School of Child and Adolescent Neuropsychopharmacology,
1-6 March 2015, Venice, Italy

ECNP School of Old Age Neuropsychopharmacology
19-24 April 2015, Venice, Italy

ECNP School of Neuropsychopharmacology
5-10 July 2015, Oxford, United Kingdom

SEMINARS

31 October-2 November 2014, Turkey

14-16 November 2014, Serbia

28-30 November 2014, Georgia

OTHER MEETINGS

Biomarkers Meeting
15-16 March 2015, Nice, France

ECNP-ISCTM Joint Meeting on CNS Clinical Trials Methodology
28 August 2015, Amsterdam, The Netherlands

For more information and regular updates on ECNP initiatives please visit:

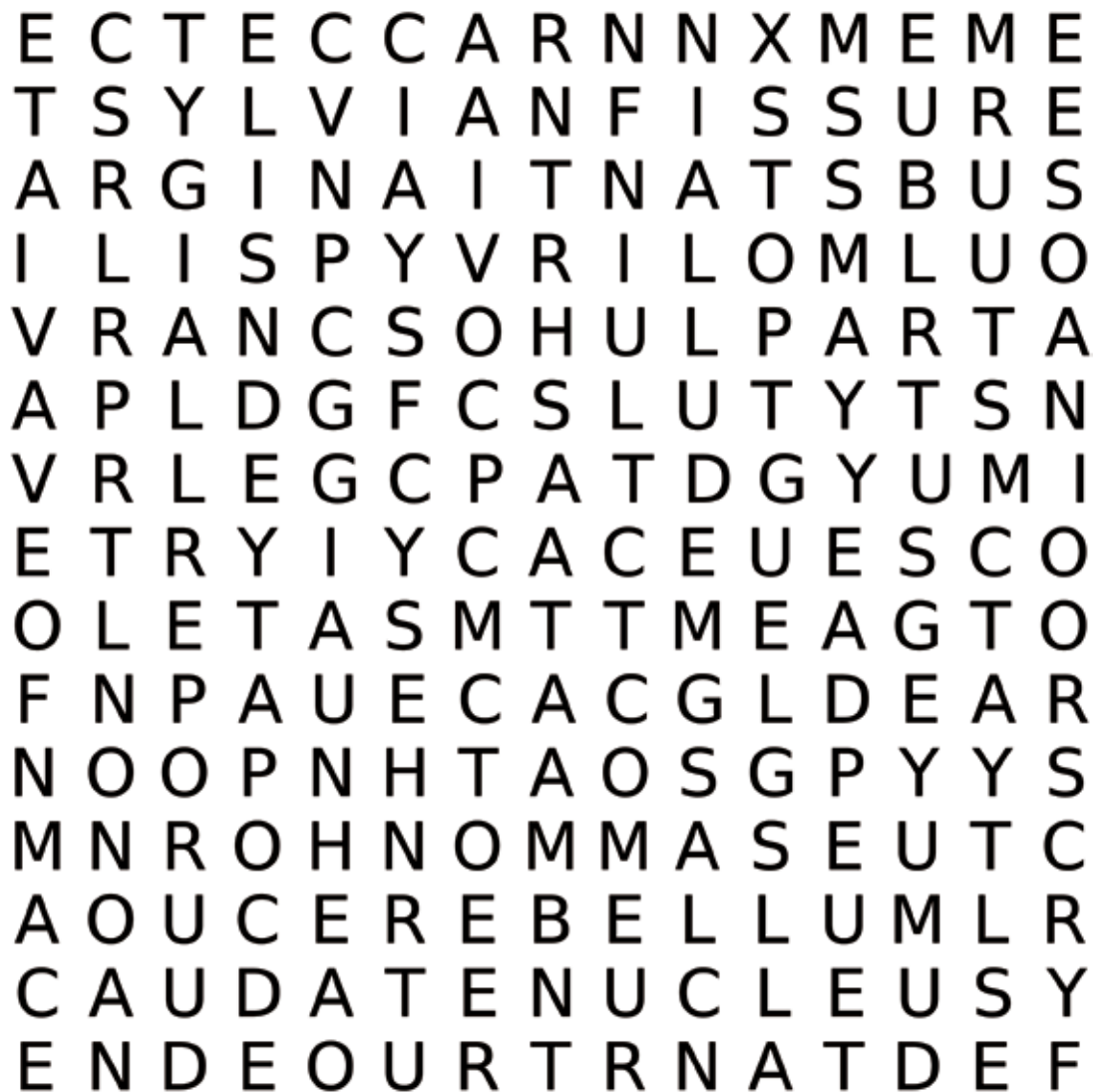
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Wordsearch

Find the words below in the maze of letters

- amygdala
- medulla
- sylvian fissure
- dentate gyrus
- corpus callosum
- optic chiasm
- caudate nucleus
- ammon horn
- cerebellum
- fornix
- putamen
- substantia nigra



ECNP PUZZLES

Famous faces



Could you name the famous faces from issue 2?

- | | | | |
|---|-----------------|---|-------------------|
| 1 | Alois Alzheimer | 4 | Hermann Rorschach |
| 2 | Carl Jung | 5 | R D Laing |
| 3 | Emil Kraepelin | 6 | Sigmund Freud |

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See you in Amsterdam!

28TH ECNP CONGRESS | 29 AUGUST-1 SEPTEMBER 2015 AMSTERDAM

FOR THE SCIENCE AND TREATMENT OF DISORDERS OF THE BRAIN

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- Oxytocin in schizophrenia
- Imaging markers for clinical use
- New medications for autism
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