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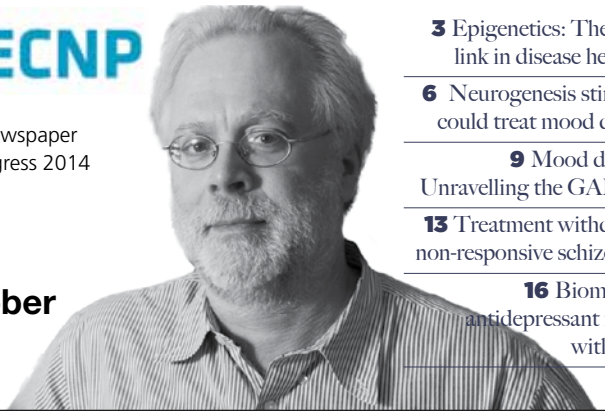

ECNP DAILY NEWS

Brain Prize winner Karl Deisseroth delivers scintillating keynote lecture

Karl Deisseroth (Stanford University, CA, USA) opened the 2014 ECNP Congress with a lecture on a number of critical leaps in scientific methods which are allowing us to look deeper into the brain with breathtaking precision.

His admirable career, which spans biochemistry, neuroscience and psychiatry, garnered broad acclaim upon his creating and developing both optogenetics and CLARITY (Clear, Lipid-exchanged, Acrylamide-hybridized Rigid, Imaging/immunostaining compatible, Tissue hYdrogel), two techniques which integrate basic methods in order to study normal and perturbed brain structure and function in living organisms as well as post-mortem tissue. The advantages: to control and monitor individual neurons and measure changes in real time in the case of optogenetics, and to produce highly detailed three dimensional images of brain volumes in the case of CLARITY.

"We try to do this in a way that keeps things intact, he said. "We nevertheless try to maintain high resolution and specificity for the sorts of interrogations of the system that we do. Of course, the human brain, with all of its mysteries, fragilities and complexities, is something I think about all the time.

"We use tools to control neural circuitry. We use different tools to look at the fine structure of intact brains, and yet other tools to observe in real time the activity of individual cells and components of neural circuitry. We are trying to make these not only compatible with behaviour in psychiatric disease models that are validated. We try to bring these tools together so that they are all operational at the same time. That goal may help us move towards a deeper understanding."

Optogenetics

Professor Deisseroth described the basis of optogenetics, which combines techniques in optics and genetics in order to track biological information processing in real time with millisecond-scale temporal resolution. "We were able to take a gene from algae and bring it into neurons," he explained. "This was a gene that allowed positive ions into the cell, and was triggered into doing so by blue light. This is a channelrhodopsin, and we found that we could flash blue light pulses and illicit action potentials in neurons in a very precise fashion."

> "We use different tools to look at the fine structure of intact brains, and yet other tools to observe in real time the activity of individual cells and components of neural circuitry."
>
> Karl Deisseroth

Although this initial achievement was made in vitro in cultured mammalian neurons, by 2007 the group had resolved most of the issues that had barred its translation into live tissue. Today, light can be delivered efficiently by fiberoptic directly into the brain, with the possibility of activating or inhibiting the action of specific cell types or brain regions. Genetic targeting strategies have been developed using cell-specific promoters or other conditionally-active viruses, which deliver the light-sensitive probes to specific populations of cells.

By affecting certain cell populations in this way, it has been possible to study the changes in activity that go on in specific brain regions as a result of behavioural expression. "We have since gone on to much more complex models, such as the forced swim test, where we have animals that are under optogenetic control of defined cells and projections during this very important behavioural test," said Professor Deisseroth.

Underscoring the value of basic science, he went on: "It is always important to highlight the fact that these microbial opsins were studied for decades by basic scientists interested in these proteins for their own sake and these organisms for their own sake," he continued. "The key principle for all of these being that there is a single gene encoding a single protein that both receives light and delivers ion flow. That single component turned out to be the crucial principle allowing optogenetics to work."

The engineering of rhodopsins involves the replacement of part of the ion channel with fluorescent proteins without altering the channel's function, allowing visualisation of morphology of these cells, as well as their axonal projections.

The group went on to look as aspects of motivated behaviour using the technique, explained Professor

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KEYNOTE SESSION

KL.01 **Keynote Session** Hall A4 **Saturday** 18:45 – 20:15

Keynote lecture

Continued from page 1

Deisseroth: "Early on we did experiments inhibiting cocaine conditioning, playing with patterns of activity to dopamine neurons, showing which patterns animals would work for in order to achieve a light pulse pattern, and so getting to the neural codes underlying positive conditions."

One of these experiments focussed specifically the ventral tegmental area, demonstrating that rats would perform a nose-poking task in order to receive activation of this neural region, thus picking out the causal role of a projection in a particular behavioural element. The ventral tegmental area, the origin of the mesocorticolimbic dopamine system, has been implicated in the reward circuitry and is an important element in motivational behaviour, as well as in psychiatric disorders such as addiction.

In other work, an anxiety model in mice was investigated using the elevated plus maze, with a focus on the various projections from the basolateral amygdala to different downstream structures including the central nucleus of the amygdala. These cells, when driven via fiberoptic delivery of light, elicited an anxiolytic effect upon the animal's behaviour. The animal, which under normal conditions would remain within the closed arm of the elevated plus, would venture into the open area of the elevated plus when the amygdala projections were driven. Importantly, this behaviour was reversible when light was halted.

CLARITY

Professor Deisseroth then moved on to a more recent method, CLARITY, a minimally invasive technique which enables high resolution imaging of whole brain or brain volumes, yielding unobstructed and detailed images of protein and nucleic acid structures when accompanied by antibody labelling.

Visibility through whole brain is limited by its incredibly dense nature, and to the network of lipid-water interfaces, which scatter entering photons by way of their differing refractive indices. In principle, the imaging of the brain in this way circumvents the issues that arise when analysing brain slices using pre-existing technologies – issues that severely impede the fine-grain analysis of whole brain.

CLARITY, explained Professor Deisseroth, is a method by which the brain is rendered transparent by the removal of lipids. The technique first employs the administration of a hydrogel to the tissue in order to create a mesh-like support network for the biomolecules that would otherwise lose their morphological integrity once lipids have been removed. The mesh provides a robust structure from which lipids can then be removed via methods such as electrophoresis, or passive shaking at slightly elevated temperatures, along with a detergent such as SDS.

This technique has allowed unprecedented access to large neural networks in human brain, from the superficial to deeper structures, which otherwise would be difficult to access non-invasively. This work is paving the way for robust study into the differences between the healthy and disordered brain states, noted Professor Deisseroth, with the ability to track individual axons from their origin to their terminal projections, using traditional and well-characterised phenotypic stains such as DAPI and parvalbumin. "It allows you to see in three dimensions and volumetric detail the relationship of the different elements," he added.

While the analysis of tissue was first performed with confocal microscopy, this technique had to be re-examined due to photobleaching of tissue that occurred due to the slow nature of analysis, and the large volumes of the samples. However, by the application of a far older technology – light-sheet microscopy – the group found they were able to scan quickly through a two-dimensional plane of the tissue, thereby presenting a fast, high resolution method of examining tissue in detail with low levels of bleaching.

While many issues have been resolved, Professor Deisseroth was keen to stress that these techniques are under continual development, a process that is sometimes arduous, but always rewarding. "We are working on speeding up the immunostaining," he said. "This takes a couple of weeks for an intact mouse brain. Not every antibody works, as in regular immunohistochemistry. We are working on a database of antibodies that work well."

Work that has emerged so far using this technique has been in the field of EAE, an animal model which demonstrates grey matter atrophy and is commonly used as analogous to multiple sclerosis in human. CLARITY has also been applied in Alzheimer's disease. Using human brain tissue analysed volumetrically in this way, it has been possible to illustrate senile plaques, neurofibrillary tangles and axons in three dimensions. It has also revealed the fascinating ladder-like pattern of neurons connecting to themselves and other nearby neurons, which has been linked with autism-like behaviour in animals. These are just a few of what are set to be the many applications of this emergent technology.

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> Karl Deisseroth

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PLENARY LECTURE

PL.04 **Epigenetics as a potential mechanism for intervention** Hall A4 **Monday** 13:45 – 14:30

Epigenetics: The missing link in disease heritability?

This year's series of esteemed Plenary Lectures continues this afternoon with an exploration of epigenetics as a potential cause of neuropsychiatric disease, and a new therapeutic approach.

Delivered by Art Petronis (The Krembil Family Epigenetics Laboratory, Centre for Addiction and Mental Health, and University of Toronto, Canada), the lecture will examine how new work in epigenetics can challenge the traditional interpretation of inherited and environmental components in disease etiology.

Speaking to *ECNP Daily News*, Professor Petronis began by commenting on the use of environmental studies of huge populations that aim to pick out specific environmental hazards that would predispose to disease. Although important, he cautioned that identifying an environmental association is one thing, but validating its causality is another. "For example, there is a very strong association between the carrying of matches or a cigarette lighter in one's pocket, and lung cancer," he said, noting that of course this is purely ancillary to the real association of smoking and cancer.

Moving on to discuss the genetic side of the coin, he continued: "The ultimate goal of biomedical research is to understand the primary causes of diseases. In some cases, researchers have been quite successful, such as, for example, classical genetic diseases, also called Mendelian diseases, like sickle cell anaemia, cystic fibrosis, or Duchenne muscular dystrophy. DNA sequence is really important, and the sequencing effort has attracted a big family of biologists, engineers, technologists, and venture capitalists.

"Frankly, the technology we now have is amazing. DNA sequence-based factors, i.e. specific genes, have been cloned, and specific mutations identified, and this has revolutionised our understanding about the disease origin. However, there are other categories of disorders – complex non-Mendelian diseases – where the story is less clear.

One of the problems in genetic studies of complex diseases, as Professor Petronis described, is the so-called 'missing heritability'. "DNA sequence analysis is technologically very powerful, but we still do not have a very good understanding about DNA sequence-based risk," he said. "The heritability in schizophrenia, for example, is very high – about 70% – yet genome-wide association studies can explain only a small fraction of that heritability.

"So it is an interesting situation. On the one hand geneticists can understand a lot of sophisticated processes in a cell, sequence genomes, and perform very powerful genome-wide association studies; they can investigate thousands and thousands of individuals and see how they are different, comparing those with diseases and controls. But on the other hand, the bottom line is that there is a feeling that the story is not complete."

While he conceded that not everyone may share this opinion, and perhaps a geneticist would argue that it is simply a case of more sequencing, and larger study populations, Professor Petronis believes the puzzle remains unsolved, and is in need of an epigenetic shift in focus.

"While traditional interpretation would be in terms of DNA and environment, from an epigenetic point of view it is not necessarily so," he said. "There are some other mechanisms at play that can describe inherited and non-inherited risk factors."

By way of example, Professor Petronis referred to the discordance between monozygotic twins, late age of onset, sexual dimorphism, parental-origin effects, and significant fluctuation of disease course which are very consistent with a putative epigenetic misregulation .[1]

Art Petronis

> "While traditional interpretation would be in terms of DNA and environment, from an epigenetic point of view it is not necessarily so. There are some other mechanisms at play that can describe inherited and non-inherited risk factors."
>
> Art Petronis

"The DNA sequence is not the full story," he said. "The DNA sequence has to be regulated, and all those 25,000 genes, and non-coding regions (a large chunk of the genome is non-coded), have to be regulated. And it is multiple layers of epigenetic factors that actually play a regulatory role in the cell.

"So we say okay, the DNA sequence provides the information as to how different amino acids must be added to each other, but actually the epigenetic factors control how much of a specific receptor, enzyme or structural protein (for example) are produced in each cell."

Indeed when one starts to think about the genetic variability in humans, the role of epigenetics becomes even more intriguing. Delving deeper, Professor Petronis noted that less than 1% genetic variability is seen between two non-related individuals, thus one could conclude that there must be more than genetics at play when looking at the vast array of predisposition to disease. However, perhaps the argument is not so simple: "Yes, 1% is a tiny fraction, but this 1% translates into millions of nucleotides, if you consider the whole genome, which is 3-billion nucleotides," he said.

"So if all those millions of nucleotides are different in two unrelated individuals, it will have a phenotypic impact. All-in-all we are running into this very unclear issue where you can find arguments to support any conclusion. One percent could be a lot, or it could be very little, but the fact is that unrelated individuals have relatively minor sequence variation, and that itself has been a surprise."

Moving on to discuss the work that he and colleagues are now performing to try and understand more about the role of epigenetics in disease, Professor Petronis described the large-

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PLENARY LECTURE

PL.04 **Epigenetics as a potential mechanism for intervention** Hall A4 **Monday** 13:45 – 14:30

Epigenetics: The missing link in disease heritability?

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scale epigenome-wide DNA modification studies undertaken: "We collected evidence that detection of epimutations can be confounded by epigenetic heterogeneity, large but uncommon epimutations, tissue- and cell-specific effects, epigenetic outliers, DNA sequence impact on epigenetic variation, age effects , and the presence of small epigenetic differences over extended genomics regions," he said.

Using tools that have not been previously applied to such studies (including DNA methylome networks, which may uncover systemic epigenomic changes in a diseased cell), Professor Petronis' lab have performed several studies differentiating the main types of DNA modification, and have ultimately found that such differentiation may be critical for the discovery of the molecular mechanisms of synaptogenesis and alternative splicing, and their role in psychiatric disease.[2]

Clinically, routine genetic tests for most conditions are a long way off, but Professor Petronis did allude to the usefulness of certain compounds that change epigenetic status. "For example, valproic acid. It has been used in clinical practice in psychiatry and neurology for decades," he said. "Its anti-convulsive effects mean it is used in the treatment of epilepsy, and it is also a mood stabiliser, so is also used for treatment of bipolar disorder (amongst others). Eventually, around 10 years ago or so, it turned out that valproic acid has several therapeutic effects, one being epigenetic.

> "There could be some other very fundamental non-DNA sequence-based mechanisms taking place in the organisation and configuration of genomes and cells, which we have very superficial understanding about."
>
> Art Petronis

"So now the thinking is, valproic is an epigenetic agent, so perhaps we can use other epigenetic compounds and achieve similar or different effects, and identify several indications. Thus there is a shift of opinion to try different compounds and see what they do in animal models of depression for example. But advancement has been very empirical. It is mostly trial and error, to a large extent because we have very superficial understanding about the epigenetic basis of complex diseases."

"At the moment we don't know what specific epigenetic targets we should be approaching, thus we try to make a sort of short-cut, and if we are lucky we may be able to identify them. But it still is not a very scientific approach. The scientific approach would be to find a target, and then try and come up with a "magic bullet" to hit that target, and crucially, that target alone."

Offering a snapshot of his main messages ahead of the lecture this afternoon, Professor Petronis began by stressing that the paradigm we're using now, either in traditional genetics or epigenetics, is built on numerous successful stories in Mendelian biology and diseases. He added that in both Mendelian and non-Mendelian disorders, there are some common denominators, like inherited predisposition, but a key question would be what does it mean in a molecular sense?

"This is still not very clear," he said. "So we should keep our eyes open, and think of alternative strategies. We should identify interesting anomalies. We do an enormous amount of research, and once in a while identify anomalies. What do we do then? We try to ignore them! But in fact we should take a magnifying glass to them.

"There could be some other very fundamental non-DNA sequence-based mechanisms taking place in the organisation and configuration of genomes and cells, which we have very superficial understanding about."

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2. Khare, T., Pai, S., Koncevicius, K., Pal, M., et al. 5-hmC in the brain: abundance in synaptic genes and differences at the exon-intron boundary. Nature Structural and Molecular Biology 19(10):1037–43, 2012.

ECNP

RU.01 **Regulatory update session: Latest developments in Alzheimer's disease** Room M2 **Monday** 19:00 – 21:30

The latest developments in Alzheimer's laid bare

This evening will place host to a special session that will explore the regulatory developments in Alzheimer's disease (AD). Jointly organised by The European Medicines Agency (EMA) and ECNP, this Regulatory update session represents a first for the annual congress.

Despite recent progress in understanding the neurobiology and pathophysiology of AD, only symptomatic treatment with overall limited clinical improvement in mild to moderate or severe AD have been approved so far. The current development of drug targets and therapeutics for AD is dominated by the conceptual framework of the amyloid cascade hypothesis. Unfortunately, many clinical trials with an Aβ-targeted mode of action failed so far to show symptomatic improvement or promising hints for disease modification in mild to moderate AD.

To find out more about the session, *ECNP Daily News* spoke to co-chair Manuel Haas (Head of Central Nervous System and Ophthalmology, Scientific and Regulatory Management Department, EMA, London, UK) who began by emphasising the importance of such a dialogue: "EMA values very much the contribution of our stakeholders to our work. But it is clear that we can do more to involve them in our activities, so we are making a lot of effort at this time to be even more open and communicative."

He added: "We only have symptomatic treatment with limited clinical efficacy for the treatment of mild, moderate and severe dementia. But there is growing evidence that there are some biological changes which start years before we see the first symptoms of AD. So now, the research targets patients at a much earlier stage of the disease, even sometimes in presymptomatic patients.

"This makes our guidance on the development of medicines for the treatment of AD outdated, because it does not address development in patients who are not demented yet. So we are updating it to include guidance on patient selection, choice of outcome measures to be used in the different stages of disease, duration of trials, and so on.

> "Now, the research targets patients at a much earlier stage of the disease, even sometimes in presymptomatic patients. This makes our guidance on the development of medicines for the treatment of AD outdated."
>
> Manuel Haas

"We got many comments from a public consultation on the Concept Paper announcing this revision earlier this year, and we are now drafting the updated guideline. As an integral part of this process, we want to exchange with the field to enrich this work."

Tonight's session will be followed by an EMA workshop taking place at the end of November. In addition to the guidance development, the meeting will focus on the diagnostic criteria in AD, the EMA scientific advice and qualification procedures, and some discussions of lessons learned from the recent failed AD trials.

Regulators like the EMA are best known as gate keepers, ensuring that only safe and efficacious medicines reach the market, but their work also extends back along the path, ensuring drugs are being developed in the best possible way: "We are also facilitators of drug development, and these two roles complement each other," said Mr Haas. "We have a battery of tools, including provision of scientific advice on drug development plans, or the qualification of novel methodologies, which led to several biomarkers being qualified for the enrichment of study populations in predementia clinical trials."

The EMA is also developing adaptive licensing, a novel approach to the authorisation of medicine, as part of efforts to improve timely patient access to new medicines. Access to medicine is another area where the EMA is very active, said Mr Haas, adding: "It is also about interacting with regulatory partners around the world, and with Health Technology Assessment Bodies, to facilitate global development, licensing and reimbursement decisions."

Tonight's session will be co-chaired by Manuel Haas, and David Nutt (UK)

EDUCATIONAL

E.02 **The sexual side effects of psychotropic drugs** Hall A8 **Sunday** 09:00 – 10:40

Antidepressant-induced sexual dysfunction under the spotlight

Yesterday morning gave delegates a chance to catch up on the latest research concerning the sexual side effects of antidepressants.

In a wide-ranging presentation, David Baldwin (University of Southampton, UK) discussed what recent studies reveal about the frequency and impact of sexual dysfunction brought about by SSRIs and lithium.

He began by noting how common sexual problems are in the general population, saying: "Sexual dysfunction is very common. We know this from very large epidemiological studies. Self-rated sexual problems are common in both men and women and in all societies. They are somewhat more common in older age groups, and certainly associated with chronic medical conditions.

"The most frequent sexual dysfunction in men is premature ejaculation, although that tends to be in younger age groups. Erectile dysfunction is almost as common, but becoming more so, in older age groups. And the so-called category of hypoactive sexual desire, using the old terminology, being the most common reported sexual dysfunction in women."

He continued: "But there's a very strong association with depression and with depressive illness and so much so that sexologists actually argue that depressive symptoms should be screened for when seeing patients with sexual difficulties."

Recent epidemiological studies have found that several factors are associated with sexual dis-satisfaction, including older age, being unemployed, having a lower level of education achievement, physical ill health and problems in childhood, including sexual abuse, said Professor Baldwin.

The number of depressive episodes also appears to affect the level of sexual dysfunction experienced. "If you have a history of a single depressive episode it has rather little impact on your sexual functioning," said Professor Baldwin. "But if you have a history of two or more depressive episodes then it does begin to have an adverse effect on self-reported sexual functioning."

Going on to discuss the effect of antidepressants on sexual function, he said: "Treatment of emergent sexual dysfunction with antidepressants occurs in 40 to 50% of patients. It worsens quality of life, adversely affects relationships and can persist after antidepressants are stopped."

Citing data from a study carried out by his own team, Professor Baldwin explained: "Looking at the relationships of self esteem and quality of life, and the quality of the relationships, the presence of sexual dysfunction was associated with a worsening of those aspects, so we controlled for severity of depression and those with depression plus sexual dysfunction, when compared to those with depression alone, described greater adverse effects on these aspects."

A recent meta analysis, [1] suggests that many second generation anti-depressants have a similar impact on sexual function, said Professor Baldwin.

"The researchers concluded that actually there was rather little difference between most of the second generation antidepressants in term of the proportion describing new sexual problems. They also commented that the evidence was a bit 'flimsy' for many drugs, but that that there was a relative advantage for bupropion and relative disadvantage for paroxetine or venlafaxine," he said.

Professor Baldwin proceeded to discuss why anti-depressants affect sexual function.

"If we think about the neurotransmitters involved in normal sexual functioning ... most of these have a role in anxiety or depression or the mechanism of the response to antidepressant drugs. So you would expect antidepressants to have interesting effects on sexual function and indeed that is the case," he said.

He went on: "It's a combination of central effects, and peripheral effects. There are quite a few neuroimaging studies into normal sexual response showing activation in widespread areas in both men and women whilst they engage in sexual activity. There are studies of the sexual response in depressed patients which compare the finding to healthy controls and you can see essentially lower levels of activation quite widely, but there are actually very few studies of the effects of antidepressants on sexual functioning."

He added: "We have some studies of depressed patients and some studies of patients with sexual dysfunction, but no comparison of depressed patients with and without sexual dysfunction."

Summarising what is known from a Korean-based neuroimaging study, he said: "Looking at activation of the anterior cingulate cortex in antidepressant treated patients, essentially there was reduced activation there, with both fluoxetine and with mirtazapine, although the reduction was less with mirtazapine than was the case with fluoxetine."

A second study comparing the effects of placebo, paroxetine and bupropion demonstrated that paroxetine had adverse effects and bupropion did not. The imaging findings showed that paroxetine was associated with reduced activation in the ventral striatum and the ventral tegmental area which was not seen with bupropion, said Professor Baldwin.

David Baldwin

"Actually there was rather little difference between most of the second generation antidepressants in term of the proportion describing new sexual problems."
David Baldwin

In his presentation, Professor Baldwin also touched on approaches to alleviating the impact of lithium on sexual function. "There is a recent placebo controlled randomised trial,[2] showing that aspirin can reduce the severity of erectile dysfunction and improve functioning on patients on lithium describing sexual difficulties," he said.

Moving on to how to manage patients on antidepressants who complain of sexual difficulties, Professor Baldwin explained: "There are many approaches. First of all prevention, by choosing an antidepressant that's less likely to cause sexual difficulties. There is waiting for remission, but usually that doesn't work. There is delayed dosing, which is when you take an antidepressant instead of in the morning you take it in the evening after sexual activity, which does work in some patients."

Drug holidays can also be effective, however this does not work with all medications, and the patient must also be in remission, he added.

Professor Baldwin also noted that the addition of, or substitution with, bupropion is a common approach. Viagra has also been shown to work in both men and woman, he said. "It may work partly by reducing depressive symptoms which his very interesting indeed and is an area of current research," he concluded.

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PLENARY LECTURE

PL.03 **Harnessing hippocampal neurogenesis to improve cognition and mood** Hall A4 **Monday** 11:00 – 11:45

Neurogenesis stimulation could treat mood disorders

René Hen

Stimulating adult hippocampal neurogenesis could play a future role in the treatment of patients with certain cognitive and mood disorders, delegates attending this morning's plenary session will hear.

René Hen (Center for Neurobiology & Behaviour, Columbia University, New York, USA) will discuss why the phenomenon affects the brain's ability to perform pattern separation and generalisation, and why it could be a factor in some types of anxiety-related disorders.

"Adult neurogenesis is an unusual form of plasticity in the sense that new neurons are being added in the adult hippocampus in all mammals, including humans, throughout life until old age. That's very different from the rest of the brain where, with a few exceptions, no new neurons are being added," Professor Hen told *ECNP Daily News* in advance of his talk.

"One of the questions that has haunted the field is, what's the function of these new neurons and why is that phenomenon just taking place in the hippocampus?" he added.

Now, Professor Hen may have found the answer, and with it, revealed a potential new therapeutic route for treating mood disorders, as he explained: "It takes often 30 days or even longer for selective serotonin reuptake inhibitors [SSRIs] to reach their clinical efficacy, so what interested us, about 15 years ago, is that a few groups reported that SSRI antidepressants increase neurogenesis in the mouse, in the hippocampus.

"That intrigued us, because that would be a mechanism that would explain why it takes a long time for these drugs to work; because when you produce new neurons from stem cells there are a whole series of growth-related events, from the proliferation to the differentiation and finally integration in circuits – that takes several weeks."

Professor Hen and his team decided to test whether there was a causal link between the effects of antidepressants on neurogenesis and their ability to change behaviour. In a key paper published in 2003,[1] they were able to show that blocking neurogenesis, by ablating young neurons from the hippocampus, prevented mice from responding normally to antidepressants in a number of behavioural tests.

Since then, the group have been investigating what the function of these neurons is, and why increasing their number produces antidepressant-like effects.

"As we delved into the functions of these neurons, it turns out, just like the part of the brain in which they reside, the hippocampus, they are involved in a collection of functions, some that are more cognitive, and some that are more mood related," explained Professor Hen.

It was while exploring the cognitive functions that he and his team came upon the phenomenon of pattern separation. "These new neurons populate a part of the hippocampus called the dentate gyrus," he explained. "And there is quite a bit of evidence, from an electrophysiological and computational neuroscience perspective, that the dentate gyrus is involved in the phenomenon of pattern separation."

> "Adult neurogenesis is an unusual form of plasticity in the sense that new neurons are being added in the adult hippocampus in all mammals, including humans, throughout life until old age."
>
> René Hen

Pattern separation is a term originally used to describe what neurons in the dentate gyrus do in terms of their electrophysiological activity and their influence on the local circuit. Along with some other groups, Professor Hen and his team went on to show that the young neurons in the hippocampus did modulate pattern separation, with more cells leading to better pattern separation and vice-versa.

"That leads us to what we call behavioural pattern separation, which is the behavioural consequence of the process of pattern separation," he explained. "And behavioural pattern separation is something that's actually related to a phenomenon that's often referred to in the psychiatric literature as generalisation."

He continued: "Basically, pattern separation is the opposite of generalisation; generalisation means that when you are confronted with similar experiences to the ones that you have already encountered, you do not discriminate between them. You generalise all the experiences that are similar. And that has consequences both in the cognitive domain and in the emotional domain."

For example, in the cognitive domain, generalisation is useful if you want to categorise similar experiences. However, if you generalise too much, you cannot distinguish between similar experiences in the present or the past. In the emotional domain, generalisation could also be very useful, he noted.

"If you see something dangerous that reminds you of a previous trauma, you are going to be very careful and avoid that situation. And this is very adaptive because it allows you to avoid potentially dangerous situations," he explained.

However, over-generalising could lead to the brain interpreting safe situations as dangerous, leading, for example, to anxiety or panic attacks.

"What we are proposing is that neurogenesis in the hippocampus may play a role in that phenomenon of over-generalisation," said Professor Hen. "Specifically, low levels of neurogenesis in the hippocampus may be responsible for some of the over-generalisation that is seen in anxiety disorders, and possibly in age-related cognitive impairments."

He added: "Individuals that may suffer from over generalisation could potentially be treated with manipulations that increase neurogenesis."

So far, the researchers have been testing their hypothesis in mice, as Professor Hen explained: "We have a number of manipulations both genetic, environmental and pharmacologic, that allow us to either increase or

decrease neurogenesis.

"As a result, we can assess the behaviour of mice in response to these manipulations. We also study, at the circuit level, what these manipulations do to the way the hippocampus functions. That allows us to correlate what's happening at a cellular level in the hippocampus to specific behavioural reactions to the mice."

Now Professor Hen is working on translating findings into new medicines by testing pharmacological compounds that might increase neurogenesis, in the hope that one day these compounds could be tested in humans.

The group is also interested in developing pattern separation tasks in humans, so that they can identify people who have pattern separation deficits or who over-generalise. Rather than recruiting patients with broad diagnosis like anxiety disorder, the team wants to focus future research on people who already have problems in the hippocampus.

> "Low levels of neurogenesis in the hippocampus may be responsible for some of the over generalisation that is seen in anxiety disorders, and possibly in age-related cognitive impairments."
>
> René Hen

"What we are proposing is to use more precise psychological and imaging tests to identify people who have a hippocampal dysfunction, as measured by a collection of behavioural tests as well as some imaging tools," said Professor Hen. "And then we may treat these individuals with compounds that stimulate neurogenesis. It's a way of stratifying the disorder and recognising that these are very heterogeneous disorders."

He went on: "If we can identify such individuals, and there is already quite a bit of evidence that people with cognitive impairments or with anxiety disorders over generalise, then we may be able to treat that specific symptom of their disease with manipulations that directly target neurogenesis."

René Hen will deliver his plenary lecture 'Harnessing hippocampal neurogenesis to improve cognition and mood' today at 11.00, Hall A4

References

1. Santarelli L et al. Professor Hen and his team began working on adult neurogenesis after initially investigating the effects of SSRIs, he explained. Science. 2003 Aug 8;301(5634):805-9.

ECNPHEADER BAR

Countries with developing economies

CDE Incentives

For people who are resident in a country with a developing economy (CDE), ECNP has installed a number of incentives to help ensure delegates from these regions are able to attend the annual congress.

Firstly, attendees from a CDE country pay lower registration fees. In addition, abstracts that are accepted from submitters based in CDE countries are also eligible for a CDE Grant, a new initiative that offers free registration to the Congress, and a fee (EUR 500) to cover travel expenses.

Close to 100 attendees were awarded the CDE Grant this year, and *ECNP Daily News* caught up with just a few of them to gather their perspectives on what it has meant to them.

Congratulations to all the recipients of this year's CDE Grants. More information about the Grants can be found on the Congress website.

Elisabeth Audi
(Maringá, Brazil)

I'm very happy to know that my study was selected. This grant was a wonderful surprise for me, and I believe that initiatives like this are important and encouraging.

The scientific activities of this congress are high quality. In addition, I think that the structure of the Congress is very productive. It is interesting for many professional disciplines, including clinical psychiatry and research. In my activities as a researcher, it incorporates all stages of research from preclinical, to interface, to clinical application.

I'm particularly interested in studies related to the 5-HT1A receptors role in the etiology and treatment of anxiety and depressive disorders. I also look for studies on other neurotransmitters involved in the etiology and treatment of these disorders. The 27th ECNP has bright speakers talking about this.

Janko Samardzic
(Belgrade, Serbia)

Generally speaking, the ECNP Congress represents the main conference for me every year, but it is not always easy to afford the necessary travel expenses. Therefore I think the new CDE Grant initiative is very supportive, especially for young scientists from Eastern Europe and other countries with developing economies. This year I am proud to be a CDE Grant winner!

At the ECNP Congress, I am always most interested in the Plenary Lectures, because they are a unique chance to hear from and meet the top scientists and leaders of neuropsychopharmacology. This year, I am also particularly interested in the Junior Scientists symposia, which are a great place for exchanging practical knowledge and for networking. The Congress always has a very professional program, great organisation and many opportunities.

Nikolay Bokhan
(Tomsk, Russia)

This year I was granted ECNP membership, and I am glad that my application for the CDE Grant was approved by organisers of the Congress.

The Mental Health Research Institute of Siberian Branch of Russian Academy of Medical Sciences, where I work, received four CDE Grants – two junior scientists were awarded and will arrive with me as well. It is very nice that a younger generation is engaged in research which is recognised at such a high level.

Respectable congresses such as the ECNP Congress convene together large groups of researchers, who, in lively discussion, can share their experience, their thoughts and ideas. This creates a unique atmosphere of academic communication which is needed.

Soraya Seedat
(Tygerberg, South Africa)

I'm both surprised and delighted to have received

CDE grants for two posters that I will be presenting at the ECNP meeting this week. I will be handing over both awards to the two postdoctoral researchers who work under my supervision, and who were instrumental in executing the work that is reflected in the posters. I will be encouraging them to use the awards to attend next year's ECNP Congress.

ECNP

Highlights from the Scientific Programme Committee

This year's congress highlights

Scientific Programme Committee chair Wim van den Brink (Academic Medical Center, University of Amsterdam, the Netherlands) spoke to *ECNP Daily News* about some of the Congress highlights this year, looking back over the last two days, and to the upcoming sessions, outlining the most exciting breakthroughs of this year in basic research, treatments and technologies in applied brain science.

The consideration in developing the scientific programme is not limited to novelty and clinical relevance, but also takes into account the scientific standing of the speakers and the balance of the programme in terms of gender, discipline and geography.

This year brings a number of new features, as Professor van den Brink described. "For the first time, we have the early morning career development sessions. We will offer these sessions to both young and mid-career people, with the possibility to have some training in how to give an effective talk, how to get EU funding and how to make an efficient webcast. This is a new opportunity."

Rapid-fire poster sessions, which essentially combine poster and oral presentation, are another new feature this year, allowing poster presenters the opportunity to get the message of their research across to a broader audience. "We have the normal poster sessions, but we selected for each day a few of the best posters that we saw," he continued. "These people will give a five minute presentation in the lunch period, and the presenters will be available for discussion after they gave their talk."

Today's Rapid Fire poster session will take place at 13:15–13:45 in Hall B poster podium.

The annual ECNP Congress will, for the third year, continue with six plenary lectures. Yesterday, Rainer Spanagel (University of Heidelberg, Mannheim, Germany) spoke on treatment strategies to reduce craving and relapse in addiction; in the afternoon, René Kahn (University Medical Center Utrecht, the Netherlands) reviewed the past twenty years of structural imaging in schizophrenia.

This morning, René Hen (Columbia University, NY, USA) demonstrates how stimulating hippocampal neurogenesis in the mouse by pharmacological and optogenetic approaches improves cognitive functions such as pattern separation and generalisation, and mood and anxiety-related behaviours. This afternoon, Arturas Petronis (University of Toronto, Canada) will explore epigenetics as a potential mechanism for intervention. Tomorrow, Francine Benes (Harvard University, MA, USA) will discuss the role of GABA neurons in schizophrenia, and in the final plenary lecture Christopher Gillberg (Gothenburg University, Gothenburg, Sweden) will speak on early symptomatic syndromes eliciting neurodevelopmental clinical examinations.

Another relatively recent instalment is the scientific cafés, which take place following afternoon sessions. "These are an excellent opportunity to have more intense conversations with the speakers of the sessions that go before them," explained Professor van den Brink. This afternoon sees cafés on a broad range of topics, including paediatric treatments, schizophrenia treatment, and biomarkers in bipolar disorder.

This year includes a number of featured topics, spanning the spectrum of behaviour, cognition and emotion, which reflect the changing atmosphere of research and clinical care. Speaking about what may be the most important symposia, Professor van den Brink continued: "On Saturday, there was something really new for most of us: recent findings on the Trace amine-associated receptor 1.[1] This is a receptor that may be very important in the future for disorders such as addiction and other impulsivity-related disorders.

"On Sunday, I would say that the most interesting thing from the more basic science was the increasing interest in the field of addiction for glutamatergic transmission."[2]

> "Psychiatry doesn't end at the border drawn by the DSM."
>
> Wim van den Brink

"We also want to emphasise that psychiatry doesn't end at the border drawn by the DSM. On Sunday afternoon, there was a very important session on two disorders that are becoming very prominent in the future: diabetes mellitus (DM) and Alzheimer's disease (AD). This is a new and very important issue."[3]

"Finally, this morning, there is a symposium on an issue that is very important to clinicians: personalised treatment in depression. In addition, there is a symposium on dysfunctional GABAergic networks in relation to stress and depression."[4,5]

References

1 S.04: Trace amine-associated receptor 1 (TAAR1): from cell to clinic; 16:50–18:30, Saturday, Room M1

2 S.08: Cocaine and glutamatergic plasticity; 09:00–10:40, Sunday, Hall A3

3 S.10: Type 2 diabetes and Alzheimer's; 14:45–16:25, Sunday, Hall A1

4 S13: Personalised treatment of major depression, 09:00–10:40, Monday, Hall A4

5 S.15: Dysfunctional GABAergic networks in psychiatric disorders, 09:00–10:40, Monday in Hall A7

Wim van den Brink

INTERFACE RESEARCH

S.15 **Dysfunctional GABAergic networks in psychiatric disorders** Hall A7 **Monday** 09:00 – 10:40

Mood disorders: Unravelling the GABA story

The notion that GABAergic systems have a role in the regulation of stress circuits is certainly well appreciated amid growing evidence in its favour, and this morning sees a session dedicated to the topic, with an examination of the latest explorations into the relationship of aberrant stress regulation with psychiatric disorders such as anxiety and depression.

Boldizsár Czéh (University of Pécs, Hungary), who will be speaking during the session, explained the mechanisms of the stress response in the context of his research, tying GABA in with adult neurogenesis and pathophysiology of depression.

While there are two classes of GABA receptors, GABA-A and GABA-B, it is the GABA-A receptors that are sensitive to environmental changes like stress. The stress response itself is modulated by a number of factors, explained Professor Czéh: "Apparently, acute stress can alter GABA synthesis and release, as well as the expression of specific GABA-A receptor subunits.

"But the direction of the changes seems to be influenced by the gender of the animals and also by the different stress-paradigm that is used. It is well known that certain steroids are potent positive allosteric modulators of the type-A GABA receptor, which may contribute to the stress effects and also to the significant gender differences in mood disorders.

"GABA-B receptors are also gaining increasing interest in psychiatric research, since both laboratory experiments and clinical data imply that a modification in GABA-B receptor expression and function may contribute to the symptoms of major depression and to the response to antidepressant treatment."

GABAergic neurons permeate the brain; hence, it is important to acknowledge the different ways in which GABAergic systems occurring in different brain regions behave in good health, and the different ways they respond in psychiatric disorders.

"For example, in the hypothalamus, there is a strong GABAergic control of the HPA-axis activity," continued Professor Czéh. "GABAergic neurons here regulate our stress response, which is a key behavioural function and often altered in psychiatric disorders. On the other hand, there are different classes of GABAergic neurons in the neocortex and hippocampus orchestrating the oscillatory activity of these higher brain areas. These interneurons have key roles in higher, more complex brain functions like cognition and emotional responses."

Professor Czéh's work centers on the role of GABA in another key element of the mood disorder puzzle: the hippocampus, whose association with mood disorders such as depression is well documented. Specifically, his recent findings demonstrate changes in function and structural integrity of a number of subtypes of hippocampal GABAergic neurons in response to various models of stress. These neurons form a relatively small population, but nevertheless their influence is critical and widespread.

Boldizsár Czéh

"Hippocampal volume decrease in depression is one of the best-replicated findings in biological psychiatry," continued Professor Czéh. "But whether it is cause or consequence of the disorder remains unclear. The continuous generation of neurons in the adult, mature hippocampus has also attracted plenty of attention and there are several theories on how this unique form of neuronal plasticity contributes to the pathophysiology of depressed mood or to the therapeutic actions of antidepressant therapies.

"It is known that GABA as a neurotransmitter is one of the key regulator of adult neurogenesis. What is the most interesting question to me at the moment is to explore how chronic stress affects the morphological and functional integrity of hippocampal and cortical GABAergic interneurons. We know that in these brain areas there are diverse subtypes of GABAergic interneurons and that they play a key role in hippocampal and cortical functions as they sculpt the firing pattern of a large number of pyramidal cells which represent distinct functional states, but relatively little is known on how these interneurons are affected directly by stress. Based on our experiments it seems that specific subgroups are selectively affected while others appear to be more resilient."

Professor Czéh will present data demonstrating the effects of chronic stress in reducing numbers of certain interneuron subtypes – parvalbumin, calretinin, neuropeptide Y and somatostatin interneurons – in the hippocampus. Further electrophysiological study, focusing on parvalbumin and cholecystokinin-expressing perisomatic inhibitory neurons, demonstrated alterations in the functional integrity of parvalbumin neurons, but not cholecystokinin neurons, in response to chronic stress, demonstrating that the loss is selective.

> "Acute stress can alter GABA synthesis and release, as well as the expression of specific GABA-A receptor subunits."
>
> Boldizsár Czéh

Hippocampus section immunostained for calbindin-positive GABAergic neurons

Animal models offer much information that human studies cannot, for obvious reasons. Indeed, the scope of models, from traditional to transgenic, broadens those discoveries further still. Speaking of transgenic lines, Professor Czéh continued: "It is truly an amazing world and I expect to see really interesting data coming out using the various GABAergic cell type-specific Cre mouse lines.

"But traditional models with rats or non-human primates have their important roles too, because these animals are much better suited for behavioural studies than mice. We, for example, work with normal Wistar rats and subject them to various stressors over a time period of several weeks and study the neurobiological changes in response to such chronic stress. This is a relatively simple experimental approach, but it can provide valuable insight and I think it mimics quite well our civilized human life, where we are subjected to a significant amount of stress almost every day."

While limitations of animal models are cited as a result of the arguable uniqueness of psychiatric disorders to humans, it remains probable that it is impossible to mimic in their entirety such conditions with experimental animals, explained Professor Czéh. "I also share this view to a certain degree," he went on. "Most probably we will never be able to produce a 'schizophrenic mouse' or a 'depressed rat'. But there are particular aspects of these disorders that we can model in animals.

"In animal experiments we can study only one or at best a few aspects of the disease. Afterwards, we should try to put these pieces together to get the complex picture. I also think that we should not abandon working with more complex experimental animals that have well developed brains and sophisticated social behaviours. I believe that for many aspects the best models are still the non-human primates.

"I know that if one says that we should experiment with monkeys, then the ethical concerns are the major issue. Still, I think we can learn most from our closest relatives in the animal kingdom and we do not necessarily have to do cruel experiments with them to gain valuable information. I think that the current trends, that we should do as much as possible in the culture dish or using mice is somewhat misleading in this type of research. We should not forget that psychiatric disorders have strong cultural aspects, and culture is unique to primates."

KEYNOTE SESSION

Welcome address / ECNP Neuropsychopharmacology Award / ECNP Media Award Hall A4 **Saturday** 18:45 – 20:15

Awards abound in **Keynote Session**

Saturday's opening Keynote Session began with a Presidential Address by Guy Goodwin, who welcomed attendees to the Congress, giving the audience a short account of the initiatives, messages and organisational teams behind this 27th edition.

"I'd like to start by looking at the name of ECNP, and what it really stands for," he said, adding: "Neuropsychopharmacology dates from a time when pharmacology was indisputably the core discipline for the study of particularly drugs in psychiatry, but also brain diseases more generally. But it has to be said that the kind of pharmacology done back then was pretty simple, and in fact you'd have to say it was relatively primitive.

"Now we have to move into an era which is really rather different, and where we have to accommodate some major, and I think revolutionary changes, in our understanding in relation: Neuroscience – and there will be a perfect example of that in the Keynote Lecture tonight; in genetics, where we've seen really landmark findings this year in relation to schizophrenia, with indisputable evidence for the genetic associations with at least 100 genes, published in Nature in July; and finally the challenge of big data – because of the wide availability of mobile phones and various technology, it is now going to be possible to get objective data from our patients, and I think change in a very important way how we define our diseases, and not simply rely on self rating.

"These are real challenges which mean that in thinking about the position of ECNP, and its identity, we have to move with the times, and reflect the change in science base that we are all working with, and excited by."

ECNP Neuropsychopharmacology Award

Alternating each year between basic and clinical science, the ECNP Neuropsychopharmacology Award recognises innovative and distinguished research achievements in neuropsychopharmacology and closely related disciplines.

Alongside an unrestricted prize of EUR 20,000, the Award carries with an invitation to give a Plenary Lecture at the Congress (held on Sunday), as well as an opportunity to submit a review article for publication in *European Neuropsychopharmacology* (to be submitted within six months after the award is granted).

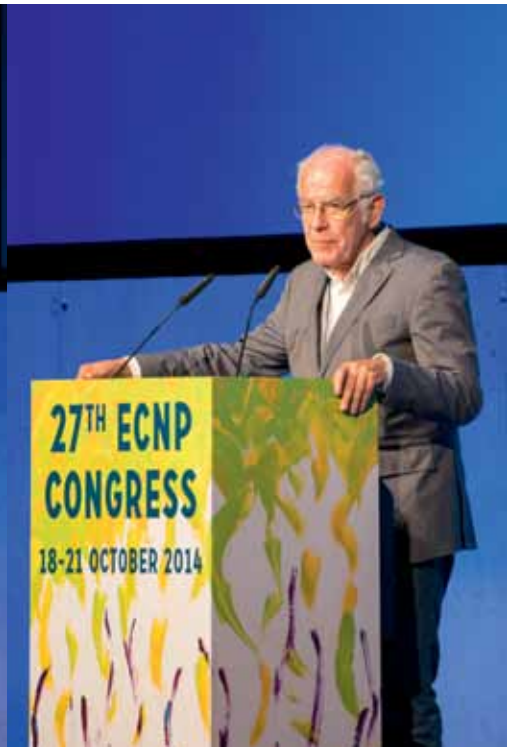
This year's recipient is René S Kahn (Head of the Division of Neuroscience at the University Medical Center, Utrecht, the Netherlands) for his lead role in several large European collaborative studies into the neuroimaging and treatment of schizophrenia.

Professor Goodwin introduced Professor Kahn during the session, stating: "I think he

ECNP Neuropsychopharmacology Award winner René S Kahn

Guy Goodwin welcomes delegates during the Keynote Session

Eduard Vieta



Dick Swaab accepts the ECNP Media Award

has made a unique contribution to our understanding of the structure of the brain in schizophrenia, and he has had a long-term vision which in part has been achievable through the great foresight of the Dutch medical establishment in having university medical centres that let people bring together research in a way that really works. He has been able to concentrate on schizophrenia and in particularly on twin designs that are informative in both the genetic and environmental contributions to brain structure.

"They are contributions that are really unparalleled in the world, so it is entirely right that he gets this Award."

Taking to the podium to accept his Award, Professor Kahn began by expressing his gratitude. "Thank you very much Guy, and thank you very much to the Committee for awarding me with this honour," he said.

"I am honoured because I am part of a long list of famous scientists that have preceded me in receiving this prize. I am very happy about that, and very proud of that."

Professor Kahn went on to express how humbled he was by the Award as well, especially given that he works with a large team at his centre who are themselves owed a great deal of thanks. "It is clear that all the work that I have done over the last 20 years is reflected in this Award, and their contribution has been essential," he said.

"It has been a privilege to work with them," he said in closing.

Media Award

Eduard Vieta, Chair of the Communication Committee of ECNP, introduced the Media Award during the session, which this year has been given to Dick Swaab (Netherlands Institute for Neuroscience, Amsterdam, the Netherlands), who was selected for his book *We Are Our Brains*.

The ECNP Media Awards celebrate the achievements of those who promote a better understanding of the complexity and impact of disorders of the brain, stimulate discussion, and challenge stereotypes and stigma in any medium, including journalism, literature, dance, film or theatre.

The awards may be given for a specific work, or body of work, published, broadcast or posted online within Europe, in any European language, and readily accessible to the general public. Preference is given to work that highlights the connection with scientific research and helps to make the science of disorders of the brain accessible to a wide audience.

"He has contributed, I believe in a very nice way, to the dissemination of neuroscience," said Dr Vieta, adding that the book has provided a fascinating exploration of the scientific basis of human behaviour, how the brain works and how its processes relate to emotions, to thoughts and to behaviour.

"Thank you very much: I am very honoured with this prize," said Professor Swaab as he began his acceptance speech. "I am especially glad because I have read people saying it has helped in the destigmatisation of brain diseases."

Paradoxically, the book's destigmatising message was censored so much in a number of countries that Professor Swaab refused to publish it. Sections regarding sex-based brain differences and homosexuality were just some of the parts of the book that had been removed during translation.

"There is still a lot of work to do in destigmatisation, and I think the best way that we all try to explain brain function in health and disease, and ECNP plays a very important role in this endeavour. I wish you all success, and thanks again for this prize."

CLINICAL RESEARCH

S.26 **Cognitive impairment in Parkinson's disease: role of molecular brain imaging** Hall A1 **Tuesday** 14:45 – 16:25

Mild cognitive impairment in Parkinson's disease

"There are a lot of questions we want to answer – what are the actual cognitive domains that predict dementia the best: is it a question of memory, or of executive dysfunction (planning, multi-tasking, alternating concepts)?"

Irene Litvan

Parkinson's disease (PD) research increasingly pulls focus towards non-motor symptoms, which, while not the principle initial clinical signs of the disease, nevertheless are a significant cause of morbidity and disability. Speaking to *ECNP Daily News*, Movement Disorder Society (MDS) advisory board member Irene Litvan (Director of the Movement Disorder Center at the University of California San Diego Department of Neurosciences, CA, USA) described her recent work in characterizing mild cognitive impairment in PD (PD-MCI), which she will be presenting tomorrow afternoon in a symposium dedicated to the topic.

Professor Litvan led the MDS Task Force that proposed diagnostic criteria for the identification of PD-MCI in 2012. Since then, the group has been working towards validation of these criteria, bringing the tantalising promise of slowing or even stopping the progression of MCI into dementia in PD.

"MCI is a gradual decline in cognition that is noted by the patient, the caregiver, or a clinician," she explained. "It does not affect the functional independence of the subject; that is, the ability to shop, to talk on the phone – those activities that are more sophisticated than the more basic activities of daily life, such as taking a shower or eating. These functions are the ones that really make a difference between what is dementia and what is MCI.

"MCI is a transitional stage, which is why, when subjects are tested, score values are still within the normal range – although obviously they are in the low end of normal, or within 1 or 2 standard deviations of normality. It is a clear decline, however not a significant enough one as to modify, say, driving and all of these more sophisticated functions."

The Task Force defined PD-MCI as specific to individuals that already have a diagnosis of PD, distinguishing it from MCI in the general population. As such, PD-MCI excludes that the abnormalities in testing could be due to certain comorbidities or conditions that are particularly observed in PD, such as severe motor impairment, anxiety, depression, or (according to certain data) psychosis. This circumvents the scenario in which certain observable changes in an individual may be mistakenly characterised as MCI, when they could in fact be due to a comorbid condition such as depression.

Reaching a consensus for the definition of the criteria for PD-MCI began, naturally, with a full review of literature and Task Force meetings, explained Professor Litvan. "Since then, we have worked together to form a consortium that is gathering data from several international centres that follow a large number of patients with PD longitudinally, and that have sufficient neuropsychological data, so that we could validate these criteria. Gert Geurtsen [Academisch Medisch Centrum, Amsterdam, the Netherlands] is the principle investigator of the consortium.

"The main effort is to really test how accurate and reliable it is to define MCI and if it predicts the development of dementia. In some ways that has already been shown for the abbreviated form of the criteria. It is still necessary to show whether the comprehensive criteria predict the development of dementia. We have two levels in these criteria: the first uses general scales that have been validated for PD, and this is an abbreviated form; the second is a more comprehensive level, in which we evaluate five cognitive domains.

"The comprehensive criteria have not been validated in any way, because its use is so much more difficult. We are really looking forward to validating it using this dataset. The dataset is actually phenomenal; it has about 4,500 patients and 1,000 controls, 1,500 of which have comprehensive neuropsychological evaluations. It is an incredible resource with which to look into all of the questions that are important for validating the criteria. There are a lot of questions we want to answer – what are the actual cognitive domains that predict dementia the best: is it a question of memory, or of executive dysfunction (planning, multi-tasking, alternating concepts)? These functions are certainly quite impaired in PD."

Cortical thinning and grey matter atrophy do correlate with PD-MCI. But, explained Professor Litvan, different features of cognitive decline could indicate distinct pathophysiologies. She continued: "First of all, there are the genes that are associated with dementia. One of them is the ApoE4 gene, which is associated with Alzheimer's disease [AD], and another is the tau gene. These two

particularly increase the risk of dementia, but there are probably other genes that we still don't know about.

"There is the idea that when the lesions are located more in the posterior part of the brain, they are associated more with AD, whereas if the lesions are more in the anterior areas – such as the ones related to executive function – then this would be more related to the same lesions that occur in PD, which spread to the cortex. The posterior lesions are those that give more problems with memory, language, visuo-spatial skills and the ones that are thought currently that best predict dementia in PD."

Perhaps the real crux of the difficulty of treating diseases such as AD and PD lies in the fact that characterisation is not achieved early enough. Screening tools largely entail neuropsychological testing, and therapies are usually applied when the disease is significantly advanced. The idea of this research, explained Professor Litvan, is that it would allow the diagnosis of impaired cognition before the precipitation of dementia. Only with this comes the possibility of stopping, or at least slowing, the development of dementia that is such a high cost both to the individual and to caregivers.

"The importance of having this concept lies in the fact that dementia occurs five times more often in the PD population compared to the general population," she concluded. "It is very important to be able to find ways in which we could identify this population that will develop dementia, so that we can treat them earlier."

Professor Litvan discusses 'The concept of mild cognitive impairment in Parkinson's disease,' tomorrow afternoon as part of the symposium 'Cognitive impairment in Parkinson's disease: role of molecular brain imaging,' taking place at 14:45 – 16:25 in Hall A1.

"The main effort is to really test how accurate and reliable it is to define MCI and if it predicts the development of dementia...It is still necessary to show whether the comprehensive criteria predict the development of dementia."

Irene Litvan

BRAINSTORMING SESSION

BS.6 **Under what circumstance ... discontinuation of antipsychotic drugs** Room M6 **Monday** 07:45 – 08:45

Treatment withdrawal in non-responsive schizophrenia patients

This morning begins with a brainstorming session that promises to feature a lively discussion on the thorny issue of when, or even if, antipsychotic medication should be withdrawn from actively psychotic schizophrenia patients who are not responding to their treatment.

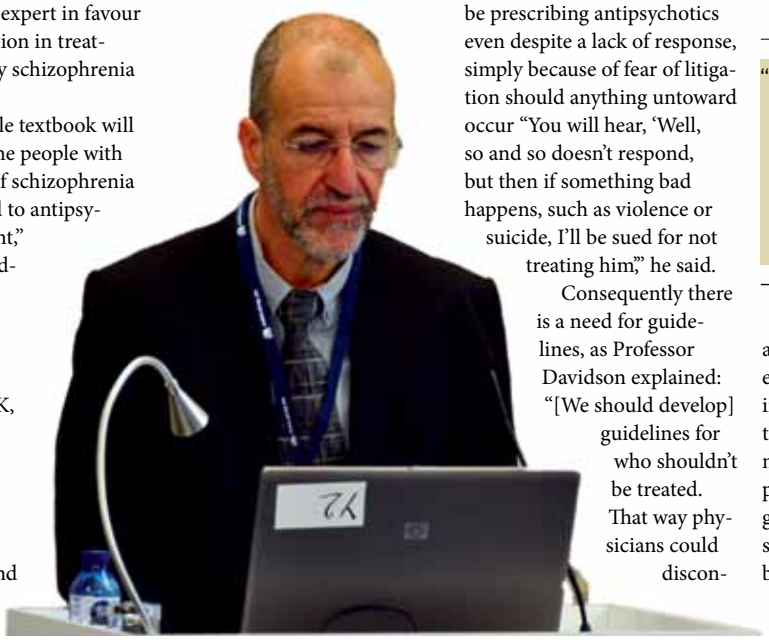
Michael Davidson (Chaim Sheba Medical Center, Tel Hashomer, Israel) will be speaking as an expert in favour of discontinuation in treatment refractory schizophrenia patients.

"Every single textbook will say a third of the people with the diagnosis of schizophrenia do not respond to antipsychotic treatment," Professor Davidson told *ECNP Daily News*.

However, if you go to any clinic, in the UK, in Israel, in the Netherlands, in the US, you will find that the physician attempts to – and maybe they are not successful – treat 100% percent of the people with schizophrenia."

"[In] oncology, at a certain point the physician turns around to the patient and says, 'Sorry, enjoy the quality of your life, whatever is left, but I have no treatment for you anymore. I think a psychiatrist should do the same."

Michael Davidson



One of the issues often cited is that predicting which patients will not respond is not possible, noted Professor Davidson. Others claim that, while a patient is not really responding, if you remove the medication they will get worse. However, this is not always the case. Professor Davidson added that physicians may also be prescribing antipsychotics even despite a lack of response, simply because of fear of litigation should anything untoward occur "You will hear, 'Well, so and so doesn't respond, but then if something bad happens, such as violence or suicide, I'll be sued for not treating him,'" he said.

Consequently there is a need for guidelines, as Professor Davidson explained: "[We should develop] guidelines for who shouldn't be treated. That way physicians could discontinue antipsychotic treatment in somebody who doesn't respond, and they can feel comfortable that if something bad happens, he can turn around and say 'I followed the guidelines.'"

Ideally, a large scale, prospective study would be organised to first demonstrate a lack of harm in removing medication from treatment refractory patients, continued Professor Davidson. "This is the good way, the scientific way, to do it. But this is very expensive … and it would probably take three to five years. Now if you are an insurer or the government you'd make the money back really easily."

He added: "Not everything has to be demonstrated in trials; there are a few things that either cannot be demonstrated in trials or are too difficult, therefore it's enough to survey many opinion leaders and practitioners and put together guidelines." In this way a consensus on the guidance could be reached.

"Every single textbook will say a third of the people with the diagnosis of schizophrenia do not respond to antipsychotic treatment."

Michael Davidson

Professor Davidson admitted that his views will not be accepted by everyone, and expects there to be some disagreement during the brainstorming session. "There will be very respectable people who say, "The people that don't respond, those are actually partial responders, not non-responders. If you take them off the drug they will get worse," he said.

But in fact, this has yet to proven either way, said Professor Davidson. "My main aim is to come up with guidelines," he said. "The same way as with oncology: at a certain point the physician turns around to the patient and says, 'Sorry, enjoy the quality of your life, whatever is left, but I have no treatment for you anymore. I think a psychiatrist should do the same."

Otherwise, the tendency is to continue care of treatment-refractive patients: "Physicians do what they know to do: they prescribe medication. Not prescribing medication is acknowledging the limits of your abilities. And who is going to acknowledging the limits of his or her abilities?"

Professor Davidson will be joined by Mark Weiser (Israel), and chair Lieuwe de Haan (the Netherlands) for the brainstorming session 'Under what circumstance (if any) should psychiatrists recommend discontinuation of antipsychotic drugs in a treatment refractory, actively psychotic, schizophrenia patient', held this morning at 07:45 in Room M6

CLINICAL TREATMENT

S.17 **TNM symposium – Unmet needs in paediatric psychopharmacology** Hall A4 **Monday** 14:45 – 16:25

Paediatric research – methodology on trial

This afternoon will see Christoph Correll (The Zucker Hillside Hospital, Psychiatry Research, New York, USA) take to the floor to discuss the methodological issues facing researchers in paediatric psychopharmacology today.

Speaking exclusively to *ECNP Daily News*, Dr Correll described the changes that the field needs to see in order to have the best evidence for making treatment decisions.

"In the past, the psychopharmacology in children and adolescents has been a neglected area," said Dr Correll. "We [relied] on extrapolation of data from adult trials."

He continued: "However, over the last decade, there have been a number of reasonably-sized, randomised controlled trials, particularly against placebo, for the main psychopharmacologic classes, and main psychiatric disorders in children and adolescents. These trials have been conducted mainly by pharmaceutical companies, driven by the requests from regulatory agencies to provide safety as well as efficacy data in children and adolescents for medications that are, once approved, very frequently used in this paediatric population."

The data shows that, though most pharmacologic classes are effective in children and adolescents, the efficacy signal is lower than that seen in adults for antidepressants and traditional mood stabilisers. But these aren't the only differences between child and adult responses to pharmacologics.

"The side-effect burden seems to be higher in children and adolescents than in adult samples, likely due to developmental differences, as well as a much shorter duration of psychopharmacologic treatment," explained Dr Correll.

"The big challenge in clinical trials right now, I think, has to do with reducing the placebo response that has been increasing in adult and paediatric trials over the past decades. This is particularly important for depression trials, where children and adolescents may react to psychosocial pressures, which express themselves as depressive symptoms."

One of the biggest problems facing the field is the lack of trials offering direct comparisons between treatments, as Dr Correll described: "We have a dire lack of head-to-head studies comparing medication classes, and even more so, individual agents within medication classes. This is important; this dearth of data is relevant because clinicians need to be able to choose among available options, balancing efficacy and safety."

He went on: "One of the medication classes that has increased in its use dramatically is antipsychotics. The reason for that is that they have been used, for the last 10 to 15 years, not only for psychotic disorders. After a discovery that they are effective for mood

Christoph Correll

> "Without this unified effort by the field, I doubt that we would be able to generate the necessary comparative effectiveness data that clinicians, families, patients and guideline-developing bodies, as well as societies, need in order to choose the most appropriate treatments."
>
> Christoph Correll

spectrum disorders, the use of antipsychotics has increased. Furthermore, currently, the use of antipsychotics in youth is mainly driven – particularly in the case of children – by their utilisation in aggressive spectrum disorders."

He added: "In fact, two-thirds of outpatient prescriptions in the United States for antipsychotics in children are for aggressive spectrum disorders. One-third of antipsychotic prescriptions in the ambulatory system in the United States in adolescents are for aggressive spectrum disorders."

As a consequence, trials in children and adolescents do not only need to focus on the efficacy of psychopharmacologic agents, explained Dr Correll. "It is of utmost importance to study the need for psychopharmacologic treatments after sufficient psychosocial interventions have been delivered, to compare psychosocial and psychopharmacologic interventions, and also to compare the addition of either medications to psychosocial interventions, or psychosocial interventions to medication treatment, once one of the two modalities have failed," he said.

Several challenges will need to be overcome in designing and conducting these trials, as Dr Correll explained: "Such challenges include the appropriate assurance that the diagnoses are appropriate; to obtain sufficiently large sample sizes; to reduce expectation and rater biases; to utilise assessment tools that are standardised and meaningful; and to employ not only rating scales for psychiatric symptoms, but also include patient-centred outcomes."

Patient-centred outcomes might include quality of life, subjective wellbeing, treatment satisfaction, and also interaction between children and adolescents and peers, as well as their caregivers, plus 'caregiver strain'.

"Such modern trials are hoped further to increase our understanding of the psychopharmacologic safety and efficacy of available agents, and help us also, hopefully, to develop new medications for this age group, that can improve psychiatric outcomes and functional levels," said Dr Correll.

Discussing how likely such changes in paediatric trials might be, Dr Correll commented: "Since the pharmaceutical companies are now required to conduct acute efficacy and longer-term safety studies with medications approved in adults, we will continue to see placebo-controlled trials informing us about the basic efficacy and safety of medications in paediatric populations.

"However, these trials do not have to be positive for pharmaceutical companies to get their patent extension. It would be important for the regulatory bodies to assure that the design, sample size and conduct of these studies is appropriate to being able to provide relevant signals."

He went on: "The more important issue is that pharmaceutical companies are not required to compare their own agent against other standard of care interventions. Therefore, such trials that need to enlarge, since they're active controlled, will require independent government funding. The problem is that this funding for clinical trials, and

> "We have a dire lack of head-to-head studies comparing medication classes, and even more so, individual agents within medication classes."
>
> Christoph Correll

for comparative effectiveness, is likely to be utterly insufficient."

Building larger networks and utilising trial methodology that moves from efficacy trials to effectiveness, with large pragmatic trials, is the way forward, said Dr Correll.

"Such large pragmatic trials that are added to usual care scenarios, would have two basic advantages," he explained. "Firstly, they would be much cheaper, as very little additional effort and assessment would be added to what is going on in usual care anyway. Secondly, these trials would bridge the efficacy to effectiveness gap by providing information, right away, about where these medications are being utilised; i.e. in the clinical settings where patients with severe mental disorders receive the medications and other interventions that are being compared against each other."

He concluded: "Without this unified effort by the field, I doubt that we would be able to generate the necessary comparative effectiveness data that clinicians, families, patients and guideline-developing bodies, as well as societies, need in order to choose the most appropriate treatments."

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CLINICAL TREATMENT

S.13 **Personalised treatment of major depression** Hall A4 **Monday** 09:00 – 10:40

Biomarker for antidepressant response within reach

André Tadic

> "If we could show with our trial that an EMC strategy is more effective than an antidepressant treatment strategy based on a traditional view, then depressed patients could be treated in a shorter period of time."
>
> André Tadic

New research to be presented in this morning's session on individualised management for major depression suggests that a biomarker predicting antidepressant response may soon be possible.

André Tadic (Department of Psychiatry and Psychotherapy, University of Mainz, Germany) will discuss data from his team's clinical trials that have investigated an early medication change strategy compared to treatment-as-usual (TAU) in patients with major depression. The researchers also investigated brain-derived neutrophic factor (BDNF) gene promoter methylation as a predictor for antidepressant treatment response.

The results suggest that a blood test that measures the methylation status of the BDNF promoter could rule out a response to certain antidepressants. Such a finding would allow physicians to focus on offering the antidepressant treatment most likely to be effective, as early as possible.

Dr Tadic will first detail a randomised clinical trial that was recently completed. "The clinical trial was to compare a new treatment strategy which, in case of non-improvement after two weeks of antidepressant treatment, scheduled an immediate change of antidepressant medication," he explained in an interview with *ECNP Daily News*. "Two weeks after this first change, in case of non-improvement there was a second optimisation, which was an augmentation with lithium,".

The treatment protocol was designed to test if it was possible to increase the rate of remission or to speed up the time until remission based on the assumption that it is possible to rate the onset of antidepressant action after 14 days of treatment, as Dr Tadic outlined: "This is based on several clinical studies which have been analysed, where the course of amelioration of depressive symptoms have been evaluated but so far only in a retrospective fashion.

"This is the first trial which uses a head-to-head design comparing an early medication change (EMC) strategy with TAU. It is based on a traditional idea which is called the 'delayed onset hypothesis'."

He went on: "The idea for many years was that antidepressants need several weeks to rate whether an antidepressant is effective or not. If we could show with our trial that an EMC strategy is more effective than an antidepressant treatment strategy based on a traditional view, then depressed patients could be treated in a shorter period of time."

Patients on the EMC arm received two weeks of escitalopram and two weeks of venlafaxine if they showed no improvement within 14 days. If patients continued to show no improvement, venlafaxine was augmented with lithium. Patients in the TAU arm received escitalopram and were switched to venlafaxine after four weeks if there was no response.

The trial, which included 889 patients across seven clinical trial sites, used the Hamilton Depression Rating Scale to compare treatment responses. Dr Tadic plans on presenting an in-depth analysis of the results during his presentation.

He will also discuss his team's work investigating the potential role of BDNF and BDNF expression on antidepressant treatment response.

The results suggest that a blood test that measures the methylation status of the BDNF promoter could rule out a response to certain antidepressants. Such a finding would allow physicians to focus on offering the antidepressant treatment most likely to be effective, as early as possible.

"I will present data for another idea – is it possible to predict the antidepressant treatment response by a biological marker?" said Dr Tadic. "This biological marker is the methylation of BDNF promoter IV. Specifically at CPG site -87, which is based on previous results from our and other laboratories," he explained.

Dr Tadic's lab and other groups have already linked the neurotrophin BDNF with both the pathology of depression and the action of antidepressants.

"There were some important findings described in the literature. The first was that this molecule BDNF is decreased in the blood in depressed patients compared to healthy controls. And then the second, it was observed that this concentration in depressed patients increases during antidepressant treatment," he explained. "And third was, the extent of the increase correlates well with the reduction of depressive symptoms."

However, the work from Dr Tadic's lab is covering new ground, as he described: "Our approach was to analyse the early course of BDNF in the blood during antidepressant treatment, and what we found was that the increase of this molecule in the first seven days of treatment was a necessary pre-requisite for a later response."

He went on: "We first tried to predict antidepressant response by analysing the course of BDNF in the blood in the first seven days of treatment, and we found that an increase of the concentration of this molecule was necessary for a later treatment response. On the other hand, if there was an increase, it was not a guarantee to be a responder after five or six weeks of treatment."

Then the team investigated the regulation behind BDNF expression. "We analysed the epigenetic regulation pre-requisite of whether it is possible that the concentration of BDNF molecule in the blood can be increased or not during antidepressant treatment," Dr Tadic explained.

"We therefore analysed the methylation status of a regulatory region of BDNF, and what we found was that methylation differences, especially at one site, are able to predict whether a patient will be a responder to an antidepressant treatment or not."

If the results are corroborated, the data point to a new biomarker for antidepressant treatment response.

"[Methylation status] may be even better than a protein measurement in the blood, because protein measurements can have several limitations," said Dr Tadic. "The measurement of methylation in a promoter seems to be rather stable as we found in our analysis, and so the general idea is to determine whether there is a methylation at a specific site in this promoter or not, and depending on the result, to decide whether the patients should be treated with monoaminergic antidepressants."

The team's initial data on BDNF methylation were gleaned from a smaller pilot study. However, the results were so remarkable that the team will now go back and apply their analysis to blood samples taken from the larger EMC trial.

"The molecular study was performed independently and before the EMC trial and the sample size was kind of a pilot study; it was a six week trial with standard treatments," he said. "Now we are trying to replicate the results from the first biomarker study; for this replication, we will use the biomaterial collected during the EMC trial."

Dr Tadic will present the full results of this analysis during his presentation, as part of the 'Personalised treatment of major depression' session this morning, beginning at 09:00 in Hall A4

PRECLINICAL RESEARCH

S.20 **Adult neurogenesis in anxiety and mood disorders** Hall A3 **Monday** 14:45 – 16:25

The HABs and the HAB-nots
New findings in anxiety and depression

A symposium on the relationship between adult neurogenesis and anxiety and depression takes place this afternoon, giving delegates an insight into the latest knowledge that has accumulated as a result of studies in both animals and humans.

Speaking to *ECNP Daily News*, Nicolas Singewald (University of Innsbruck, Austria) described the work he has been doing in deciphering the maze that connects anxiety and depression with neurogenesis and the hippocampus, with the hope that, in this way, it will be possible to improve the understanding and treatment of these conditions.

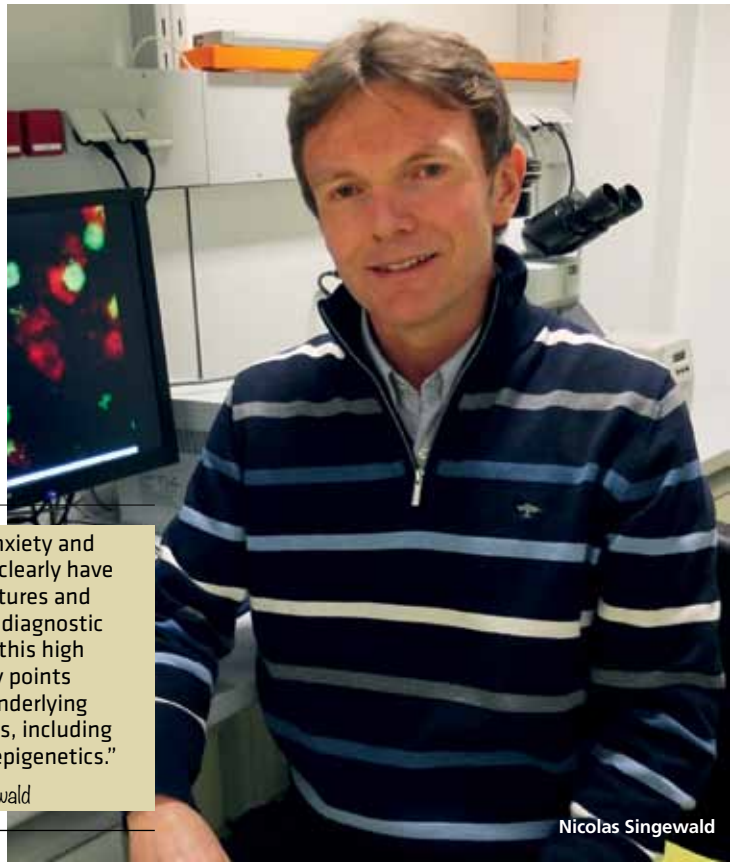
Along with fellow colleagues, Professor Singewald is involved in two Austrian network initiatives, SFB-F44 (Cell Signalling in Chronic CNS Disorders) and SPIN (Signalling Processing in Neurons), that take cross-disciplinary approaches to studying the involvement of mechanisms such as epigenetics, non-coding RNAs, and inflammation.

"The beauty there is actually that we have members that study completely different things to what we are classically studying in the anxiety and depression field. So you go into these questions with an unbiased approach. We came up with really interesting stuff that we would never have looked at had we not been in this network."

The principle of the lab, explained Professor Singewald, is to approach clinical reality as closely as possible by using psychopathologically-relevant animal models. The ways in which, for example, deficient fear regulation (evident in PTSD, phobia or panic disorder), could be rescued in a model via numerous pharmacological means provides valuable information as to the mechanisms involved in this recovery process.

"We have identified a number of pharmacological ways to rescue such deficits and build long-term fear inhibitory memories," he continued. "The idea is then to team up with clinicians and try to translate such findings into man. We were successful last year, showing that such a fear extinction-boosting approach that worked in mice also worked in humans."

The majority of experiments thus far that have looked at neurogenesis in mental illnesses such as depression, anxiety and schizophrenia, have used naïve animals under baseline conditions, noted Professor Singewald. He went on: "This was initially very important in order to find the basic mechanisms. I think the step forward now is to model risk factors for developing those disorders, rather than focusing on naïve animals. There has been a lot of work done on the stress side, for example, which we know is a triggering factor and an important epidemiological factor. But much less has been done with the genetic risk factors, and that is exactly what we are doing now."


Nicolas Singewald

> "Although anxiety and depression clearly have distinct features and are distinct diagnostic categories, this high comorbidity points to shared underlying mechanisms, including genes and epigenetics."
>
> Nicolas Singewald

Professor Singewald will present work on models of enhanced anxiety and comorbid depression, arguing that, because this comorbidity is the rule rather than the exception, it is necessary to take a deliberate look at them in tandem – in contrary to what most research thus far has done.

"This comorbidity has been shown to complicate therapy and worsen treatment prognosis," he said. "Although anxiety and depression clearly have distinct features and are distinct diagnostic categories, this high comorbidity points to shared underlying mechanisms, including genes and epigenetics.

"Experimentally, we have shown that nutritional issues can support the development of anxiety and depression, for example Mg2+ deficiency, and we have identified underlying mechanisms such as altered neuronal activation in key nodes of anxiety and depression-related circuitries, including the amygdala and paraventricular nucleus."

The group is studying a special rodent (both rat and mouse) model of trait anxiety and comorbid depression, the HAB (high anxiety-related behaviour) model, developed some years ago by Rainer Landgraf and colleagues at the Max Planck Institute of Psychiatry in Munich.

Twin, and twin versus separated sibling studies, along with other work, have demonstrated that complex gene-environment interactions are responsible for the expression of anxiety and depression-related disorders. Moreover, explained Professor Singewald, it has been estimated that the genetic contribution is indeed considerable (30-60%). Fraternal studies in twin populations with anxiety and depressive disorders have shown that nearly a third to a half (33-46%) of the variance could be explained by genetic factors alone.

These findings are pertinent when designing an animal model; such a polygenetic disorder in which each gene contributes in a small way to the phenotype can present difficulties, especially when only a small proportion of these contributing genes are known. "Therefore, we use a trick – selective breeding," explained Professor Singewald. "This is thought to accumulate relevant gene variants and produces a stable phenotype, in this case hyperanxiety with comorbid depression-related behaviour.

"An advantage is that the high anxiety/depression HAB mouse can be compared to mice with normal anxiety/depression (NAB) or even with low anxiety/depression mice (LABs), which all in principle have diverged from the same mouse strain. While a lot has been done looking into the environmental mechanism – in particular stress (a predisposing and triggering factor) – the effect of genetic risk and vulnerability for the development and maintenance of anxiety and depression symptoms is less studied.

"Due to the selective enrichment of the genetic risk factors related to anxiety across generations, the HAB/NAB/LAB mouse model is a robust system for studying genetically inherited behavioural extremes of trait anxiety and comorbid depression."[1]

The group and their collaborators found that HAB animals undergo a number of changes that reflect the progression of anxiety/depression patients. These include altered stress coping ability, anhedonia (a hallmark of depression in humans), altered effects of therapeutic treatments, altered anxiety-related physiology (e.g. heart rate responses, heavily fragmented sleep patterns), and dysregulated brain neurotransmitter systems (e.g. neuropeptides and the GABA system, particularly the GABA-A subunit).

Further investigations using brain imaging identified aberrant activation, including amygdala hyperactivity, and prefrontal cortex and dentate gyrus hypoactivity. "We wanted to go into this hypoactivity in the dentate gyrus in more detail, to see whether it can be modulated or normalised by successful treatment – by pharmacological and also environmental manipulations," explained Professor Singewald. "We also wanted to see whether there are morphological changes in this area and whether neuroplasticity and/or neurogenesis are altered in HABs, since the dentate gyrus is host

Continued on page 18

PRECLINICAL RESEARCH

S.20 **Adult neurogenesis in anxiety and mood disorders**
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The HABs and the HAB-nots
New findings in anxiety and depression

Continued from page 17

to the subgranular zone, the main neurogenic region of the hippocampus.

"Since comorbidity lowers the chances of remission from both anxiety and depression, the final aim was to investigate in this animal model whether long-term benefits of antidepressant treatment are observed – and if so, whether this is associated with long-term alterations in dentate gyrus activity."

A number of key findings emerged from the group's investigations. They showed that various antidepressant drugs with a high anxiolytic component (e.g. tianaptine, NK1R antagonist) can normalise both the hyperanxiety and enhanced depression-like behaviour of HABs, while not affecting the NABs, indicating that pathophysiologically deranged systems are a primary target of these drugs. Environmental interaction (both positive, such as environmental enrichment, and negative, such as stress), was found to normalize the anxiety- but not the depression-like phenotype in HABs as well as LABs – thus providing good evidence that even a strong genetic predisposition to anxiety can be influenced via environmental manipulations.

Noting further findings of the group, Professor Singewald explained that hypoactivation of the dentate gyrus was normalised by successful antidepressant treatment, as well as by successful deep brain stimulation in SSRI treatment-resistant HABs.

"In work performed by Anupam Sah in the lab, we found reduced hippocampal neurogenesis and impaired functional integration of newly born neurons in HABs, which may contribute to the hypoexcitability and hypoactivation of dentate gyrus neurons," he said. "In other words: selective enrichment of the genetic risk factors related to anxiety and possibly comorbid depression predisposes to reduced birth and integration of newly born neurons, with possible consequences like impaired pattern separation, cognitive disturbances, and anxiety/depression circuitry changes."

The fundamental finding that blunted hippocampal neurogenesis is not permanent, i.e. that it can be rescued by pharmacological and environmental interventions, provides an impetus to shift the emphasis of treatment approaches in patients with anxiety and depression.

While neurogenesis seems to be largely altered with changes in anxiety, the therapeutic modulation of depression-like behaviour is dissociated from changes in neurogenesis. This, explained Professor Singewald, indicates that neurogenesis may be an intermediate process followed by neurogenesis-independent processes governing the final antidepressant behavioural effect. He continued: "The therapeutic rescue of enhanced depression-like behaviour was associated with the normalisation of blunted dentate gyrus activity, indicating a close correlation with the ultimate behavioural response, rather than with (possibly intermediate) neurobiological changes.[2]

> "Positive experience in these predisposed animals – an enriched environment – rescues the blunted neurogenesis that we have seen that is associated with a strong genetic predisposition to anxiety. So that is good news, that it is not permanent."
>
> Nicolas Singewald

"What we can say from our data is that positive experience in these predisposed animals – an enriched environment – rescues the blunted neurogenesis that we have seen that is associated with a strong genetic predisposition to anxiety. So that is good news, that it is not permanent. We are investigating at the moment whether it helps to prevent the development of comorbid depression if we attenuate hyperanxiety by the identified means early on.

"There is more and more evidence that these patients should work out physically, because this also increases neurogenesis. We haven't got the causal link between these – it could be epigenetic – but it is really good news that you can do a lot with a positive experience, and by running or jogging to the extent that you might increase neurogenesis. The other positive aspect of this is that it may help to set the scene for better efficacy of other treatments you are using. In the future, this should be included much more in the therapy, because it is an easy thing to do. The step to boost neurogenesis pharmacologically as well in a specific and safe, well-dosed way, to ultimately possibly prevent hyperanxiety and depression in vulnerable patients, still needs a lot of joint basic work efforts."

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1. Landgraf et al. Candidate genes of anxiety-related behavior in HAB/LAB rats and mice: focus on vasopressin and glyoxalase-I. Neurosci Biobehav Rev. 2007;31(1):89-102. Epub 2006 Aug 28.

2. Sah et al. Anxiety- rather than depression-like behavior is associated with adult neurogenesis in a female mouse model of higher trait anxiety- and comorbid depression-like behavior. Transl Psychiatry. 2012 Oct 16;2:e171.

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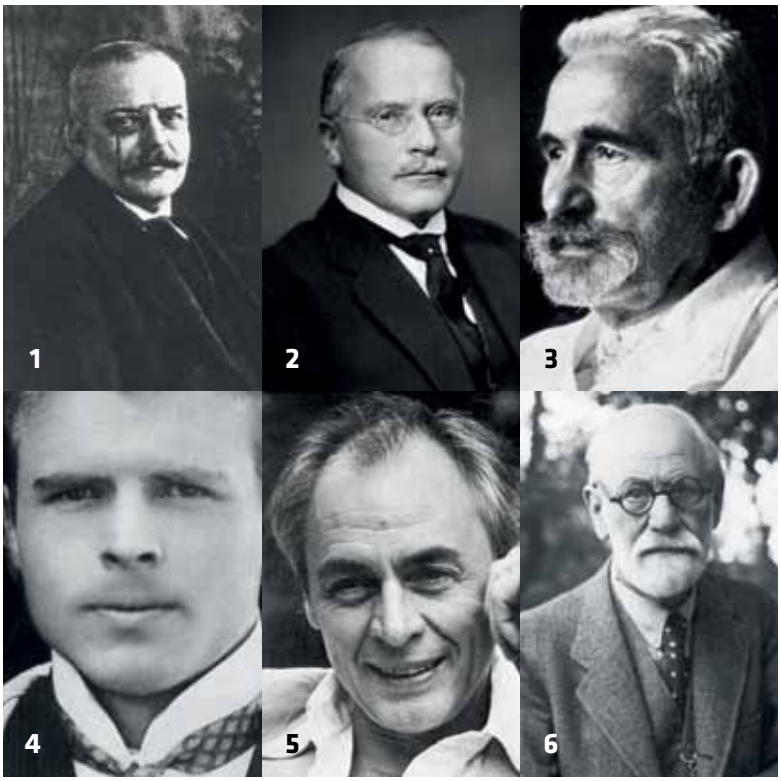

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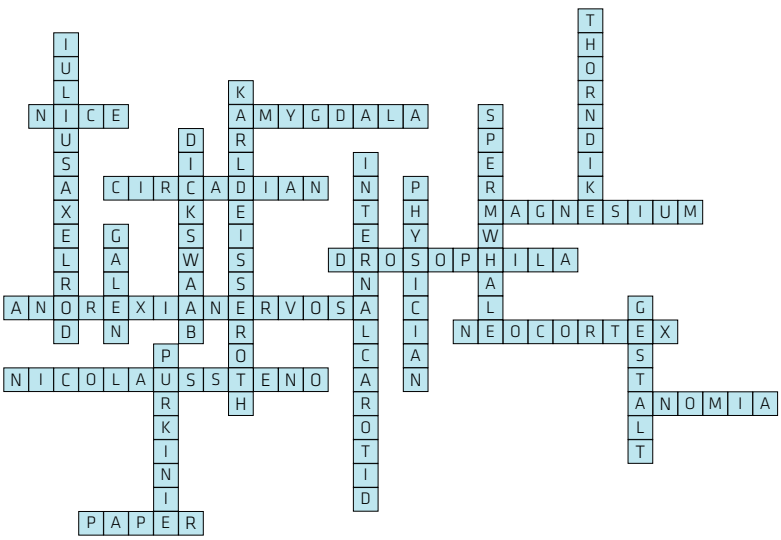
ECNP PUZZLES

Yesterday's crossword answers



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