Welcome to Berlin and the 27th ECNP congress

ECNP is an organisation directed to the understanding and translation of research for the benefit of patients, especially those patients with psychiatric disorders. It dates from a time when pharmacology provided the core discipline. We are in a new era where we have to accommodate entirely novel ideas from neuroscience, genetics and the emerging insights from big data. The congress is an event that brings together scientists, clinicians and industrial partners who must create a new fabric from this science to advance understanding of the brain, promote better treatment and enhance health.

The involvement of industry in medical congresses has become a subject of controversy. However, it started from the premise that without marketed drugs or devices, patients would experience little or no innovation. Without medical meetings that encourage the engagement of industry, doctors and patients would not know how to make use of such products. And historically, marketing budgets helped pay for the event and often brought people to it. This model is becoming controversial at exactly the time when its relevance is already much diminished.

Because neuroscience has proved so difficult, big companies have, with notable and important exceptions, turned away from our field. This means we have to provide an event that is really attractive to the individual participant whether a researcher or a clinician. We also want to look for a more creative relationship with those businesses that remain. Accordingly we will fund a meeting in Nice next March to look at the potential role of diagnostics in psychiatry; we are actively seeking ways to interest biotech companies in using ECNP as a vehicle for developing their applied neuroscience and we will re-ignite European interest in clinical trials by hosting a meeting of the ISCTM (International Society for CNS Clinical trials and Methodology) immediately before the next congress in Amsterdam.

The programme of this congress is exceptional: I am sure you will both enjoy it and be enriched by it, which is always a good combination.

Guy Goodwin
ECNP President

Shifting focus in addiction treatment

The first plenary lecture of the 27th ECNP Congress will be held this morning in Hall A4, diving straight into a discussion of novel targets for the treatment of addiction, with a particular emphasis on alcohol.

“First I want to give an evolutionary perspective on the question of why do we drink alcohol,” Rainer Spanagel (Central Institute of Mental Health, Institute of Psychopharmacology, University of Heidelberg, Mannheim, Germany) told ECNP Daily News. “It is a little bit surprising that more than two billion people drink alcohol; yet most of them know that it is not really doing them any good.

“We know that alcohol consumption, even that which we describe as ‘low’ amounts, is still unhealthy. There is little ‘good’ that alcohol is doing for us: It is a major risk factor for premature mortality, and for many diseases. So the question is how can two billion people be engaged in something knowing that it is not good for their health? After all, it is identified besides tobacco smoking as one of the major risk factors for global disease burden.”

Following his planned introduction during the lecture, Professor Spanagel will then head straight to the topic of addiction, touching first upon what preventative or relapse management strategies have been used in the past. While the meat of this issue will be reserved for the lecture itself, Professor Spanagel did give a glimpse of the current pharmacological strategies he plans discuss, which will include naltrexone, disulfiram and last but not least, nalmefene.

“When it comes to nalmefene, in Europe it is just being introduced now,” he said. “Scotland was the first country where it was introduced, at the beginning of this year, and in September it was introduced in Germany, but by the end of the year all member states will have introduced it into the market.”

Crucially, it is the harm-reduction concept that is of particular impor-

PL.01 New targets for the treatment of addiction Hall A4 Sunday 11:00 – 11:45

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Shifting focus in addiction treatment

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tance, and this represents a paradigm shift from more ‘traditional’ addiction management strategies. ‘I have been praying for this for years and years,’ said Professor Spanagel. ‘I have been strictly against the concept of complete abstinence, because the core of the disease of addiction is relapse. It is just a natural thing that one relapses’.

“So how can you tell someone who has the disease that they should not present the core symptom? This would be like giving treatment to a primary cancer patient and then telling them, ‘OK, now you will not show any metastasis in the next couple of years.’ But we all know it may happen, so how can you give a stigma to this? Similarly, if an addicted patient relapses, this is actually in line with the disease, so you cannot give negative feedback to the patient and say, ‘Oh, you did not succeed in the treatment programme’.

Whether a patient is suffering from alcohol addiction – or smoking, or drugs – this would mean even if a patient had stayed abstinent for months, or even years, relapse could be described as a failure in treatment. “It has been a major mistake to say you are only successful in the field of addiction treatment if there is abstinence,” continued Professor Spanagel. “This is an almost unreachable goal. This goal, set out to achieve for decades now, has been almost impossible for most patients to achieve.”

Therefore, he added, shifting the focus to reducing harm, and understanding that someone who cuts down from, say, 300 drinking days a year to 100 drinking days, for example, could still be described as a ‘success’, is a welcome shift. “Or a smoker that cuts down from 40 cigarettes to 5 cigarettes a day,” said Professor Spanagel. “They are still addicted – and still need cigarettes – but we know that just by drastically reducing the number of cigarettes they smoke, there is a linear decline in cancer rates, cardiovascular events, and a major improvement in more than 200 co-morbidities.”

He added: “Yes, it is better being completely abistent, and we should all still aim for it, but always trying to reach it is impossible.”

Professor Spanagel also added that a boost for the clinician was also part and parcel to the harm-reduction concept. With a clear-cut ‘abstinence-only’ concept, as soon as a patient has a relapse, there is danger of the clinician feeling like a failure, and this is not a healthy perspective to take. But, with the introduction of nalmefene, times may now be changing: “It might be a complete change in paradigm,” he said.

Moving on to discuss non-pharmacological strategies for addiction treatment that are emerging, Professor Spanagel focused on work with Deep Brain Stimulation (DBS), which is gaining traction in the discussion of alternative therapies. “You have to be extremely careful with the introduction of such a treatment approach, and this is what we see now in our newest experiments, because we do not know the system we are targeting,” he said.

“We do not know the brain hubs that are important to be targeted. Is the nucleus accumbens, for example, the right place to put stimulation electrodes in? And also, what should the stimulation protocols be? What are, from a neuro-biological perspective, the alterations? What are the pathological network changes we would like targeted? “In fact, Professor Spanagel warned of the results surfacing from a preliminary venture into models using alcohol-addicted animals that present very much the same systems that a human alcoholic would. “If we chronically stimulate in the nucleus accumbens, animals drink much more alcohol, and relapse much more heavily, so it is just the opposite effect,” he said. “This just shows how little we know.”

“There have been several case reports presented by the University of Magdeburg, Germany. They have been the pioneers, and now in other parts of Germany several other centres have a consortia that work on deep brain stimulation in alcoholics. This work – all unpublished – has produced extremely mixed results. So at the moment you cannot really say that for alcoholics DBS is founded. “It is also extremely difficult to recruit patients. If you are suffering from major depression, and completely treatment resistant, you are more open to treatment. But if you are a drug addict, even if you run through several unsuccessful therapies, what is the real motivation to enter a treatment programme when you undergo deep brain stimulation? There is still a point of exit, namely, taking the drug. A drug addict always has an exit point: just continue to take the drug. Therefore it will remain a major problem to recruit those patients.”

Professor Spanagel added that, for now at least, DBS may have more application in particular niche areas of addiction, including heroin or other similar compounds, but data are either limited or poorly constructed. “The bottom line here is that it is premature to offer such treatment to patients,” he said.

“I’m not saying that this is not an alternative approach; it is a clever approach – if we hit the right hub in the pathological brain network, and if we do the right stimulation, we might be very successful. But we still do not have the knowledge to do so. Therefore I would warn that we should not do an extensive clinical trial with a lot of patients, which may then fail at the end of the day, as then we may have to drop what could be a good treatment, simply because it was still too early. We need more research, and indeed in my lecture I will demonstrate very mixed and opposing results. I am not saying this is a misleading concept, just that we are only slowly understanding what we should do.”
TAAR1: From ‘Breaking Bad’ and beyond

The ECNP Congress began yesterday afternoon with five concurrent sessions looking at a range of cutting-edge translational neuroscience topics.

Among these was a symposium dedicated to trace amine-associated receptor 1 (TAAR1), during which invited experts gathered to discuss the discovery, therapeutic application and future study of this intriguing protein.

Speaking first during the session was David Grandy (Oregon Health and Science University, Department of Physiology & Pharmacology, Portland, USA), who offered a potted history of TAAR1. “My role is to share with audience how we came to discover this receptor,” he told ECNP Daily News ahead of the session.

TAAR1 was discovered in 2001 when two groups using different (but related) methodological approaches reported identification of a G-alpha-s (Gαs) protein-coupled receptor that is activated by trace amines.1

While initial biological understanding of TAAR1’s role in health and disease was hindered by a lack of appropriate animal models, antibodies and selective pharmacological tools, more recent establishment of taar1−/−-deficient mouse lines – and the development of a TAAR1-selective agonist, EPPTB – has opened up the possibility if in vivo investigation.2

EPPTB has been developed by F Hoffmann-La Roche (Switzerland), who have been part of a new push to move the field forward.”They in particular have developed tools that pharmacologists can now use,” said Dr Grandy. “But overall I think this field has really caught fire, especially in Europe.”

In his work using an in-house EPPTB compound, Dr Grandy and his team have pursued a translational approach in exploring the contribution of TAAR1-mediated signalling to the physiological and behavioural effects of cocaine, methamphetamine and bupropion. “Knock-out mice in particular provide a valuable background to evaluate off-target affects,” he said.

Looking at methamphetamine specifically, Dr Grandy’s work has identified that methamphetamine-activated TAAR1-mediated signalling constitutes around 70% of the drug’s stimulatory effect on locomotion in mice, with the remaining 30% due to its interference with dopamine transport. “This is in support of our two-hit hypothesis of methamphetamine action,” he said.

With this observation to hand, Dr Grandy colloquially refers to TAAR1 as the ‘Breaking Bad’ receptor, paying homage to the recent, hit television series that placed the drug’s stimulatory effect on locomotion in mice, with the remaining 30% due to its interference with dopamine transport. “This is in support of our two-hit hypothesis of methamphetamine action,” he said.

With this observation to hand, Dr Grandy colloquially refers to TAAR1 as the ‘Breaking Bad’ receptor, paying homage to the recent, hit television series that placed methamphetamine centre stage. From his perspective, the discovery has been important in promoting new thinking, as he explained: “The people who have studied amphetamines in the last 30 years have focussed on the dopamine transporter. This has been the target, thus it could be a little difficult for some people to actually accept there was a second target.

“When I think is important is that the textbooks get re-written, because it is still the case that people don’t get that this receptor is turned on by amphetamine-like compounds. They are made naturally in the body. They have important modulatory roles. And here is a receptor that is mediating that.”

He added: “I think this is an important direction for medication development for the treatment of stimulant abuse.”

“Touching upon the limitations still present in the field of TAAR1 study, Dr Grandy stressed that a primary concern is a lack of understanding of the underlying biology of TAAR1. “This is a challenge that we really need to address: we haven’t synthesised it into something that can be easily understood,” he said.

“I think it is a basic receptor in most cells, at a low level, and I think the antagonists, the agonists and the partial agonists developed by F Hoffmann-La Roche are really exciting compounds, because now they offer good bioavailability. There is key work emerging now using partial agonists and agonists for self-administration, and I think this is an important direction for medication development for the treatment of stimulant abuse.”

Moving on to describe the overall impact of having a dedicated TAAR1 session at this year’s ECNP Congress, Dr Grandy commented: “It is wonderful; it has been very difficult for the last six/seven years, because research in this field just didn’t catch on, and then the funding ran out. But we have made progress in spite of that.

“I think it has been a paradigm shift, and it’s taken people a while to get it, and I think it is really magnificent that we are able to be a part of it.”

Also speaking during the session was co-chair Per Svenningsson (Karolinska Institute, Stockholm, Sweden) whose presentation focused on the role TAAR1 in the treatment of Parkinson’s disease and depression. “For Parkinson’s disease we know of course that it is a disorder where the dopamine system degenerates, and we treat patients often with levodopa, the precursor of dopamine,” he began.

“What happens in many patients is that they develop sensitisation after a few years of this treatment – a side effect that can be quite troublesome, and which there is no good treatment for.”

With that in mind, Dr Svenningsson’s work has explored TAAR1 – abundant in dopamine neurons – as a novel way of modulating dopamine transmission. “Specifically for Parkinson’s disease, we have found that when we treat mice with a TAAR1 agonist, we can reduce this sensitisation – and dyskinesia – developed after treatment,” he said.

“This is unpublished data, but we have been studying this for a while now. We think that it may be due to indirect actions (or actions that we don’t exactly know) that modulate the glutamatergic neurotransmission. It seems that TAAR1 agonists in Parkinson’s...
TAAR1: From ‘Breaking Bad’ and beyond

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models decrease this neurotransmission. Overall, TAAR1 is very interesting, especially in modulating dopamine transmission.”

For the treatment of depression, Dr Svenningsson noted that alongside this strong dopaminergic component, identification of TAAR1 receptors in the raphe nuclei has also focused attention on the serotonin system. “But I would still say that it is mainly the dopamine system that is affected,” he said.

Looking to future studies that may shed more light on the therapeutic power of TAAR1, Dr Svenningsson commented: “It is still an area where more basic research is needed. The hard data in terms of what exactly is happening is not there yet.”

Per Svenningsson

With several high-profile papers from leading TAAR1 experts now published, and with primate models already undertaken in the industry, Dr Svenningsson feels that human studies are within near reach. “We must be very, very close to clinical trials,” he said in closing.

References

Don’t miss...

Junior Scientists symposia: Today!

Two Junior Scientists symposia will be held in Berlin this year, one scheduled in the preclinical track (S.07, Sunday, 09:00, Hall A7) and one in the Interface track (S.12, Sunday, 14:45, Hall A7).

All eight speakers in each symposium have been selected following poster presenters at the ECNP Workshop on Neuropsychopharmacology for Junior Scientists in Europe, which is held every year in March in Nice, France, chaired by Mark Millan (right).
Modelling DA-5HT network involvement in bipolar disorder

A Junior Scientists symposium taking place this afternoon raises various promising novel targets of psychiatric disorders, including bipolar disorder, the spontaneous mood fluctuations of which have evaded comprehensive characterisation due to the complex genetic and environmental influences involved in the condition.

Yet, recent work by Marin Jukic (Ben-Gurion University of the Negev, Beer-Sheva, Israel) and colleagues has demonstrated the phenotypic expression of such mood fluctuations by overexpression of transcription factor Otx2 in mouse. The group then went on to demonstrate the relevance of the affected neuronal systems in human bipolar disorder.

"The principle feature of these mice is aberrant development of dopaminergic and serotonergic neurons," said Mr Jukic, in an interview with ECNP Daily News. "The former is upregulated, meaning that there are more dopaminergic neurons; and the latter is downregulated, meaning that there are less serotonergic neurons."

Dopamine and serotonin are of course involved heavily in mood control and, hence, the expectation was that some sort of mood-related phenotype would emerge. But the basis of the aberration is down to the Otx2 transcription factor, which, although involved in many aspects of normal brain development and regulation, has previously been reported to be associated with bipolar disorder.

The study compared a group of mutant mice with controls. While control mice demonstrated relatively unwavering patterns of locomotion, the mutant mice went through extended periods of either elevated or reduced activity. This behavioural shift was present at six weeks of age (early adolescence), and became apparent at 12 weeks (i.e. adulthood). Differences were also significant in relation to intra-individual fluctuations in locomotion, habituation, risk-taking, social interaction and hedonic behaviour. Interestingly, the group were able to stabilise the behavioural fluctuations in mutant mice with mood stabilisers.

While there are many other animal models of manic and depressive symptoms, perhaps pharmacologically-induced or transgenic, this particular model possesses the fluctuation of mania and depression that forms the clinching factor in a bipolar diagnosis in human. "These mice spontaneously change their affective parameters, such as activity-related behaviour and hedonic behaviour – the former being associated with mania, and the latter with depression," explained Mr Jukic. "In various behavioural tests, the animals fluctuate in their affect over long periods of time. That would be the principle finding of the research."

So how is Otx2 overexpression related to these mood fluctuations? "Otx2 is one of the genes orchestrating the specification of dopaminergic and serotonergic neurons in brain development," explained Mr Jukic. "Overexpression of Otx2 leads to aberrant specification of these neurons affecting their neurotransmission in adulthood; this can lead to the impairment in the balance of mood."

Indeed, the influence of Otx2 over this set of genes that specify neurons as either dopaminergic and serotonergic was previously demonstrated. Furthermore, overexpression of Otx2 tipped the balance, increasing the number of dopaminergic neurons while decreasing the number of serotonergic neurons.

"The dopaminergic and serotonergic systems influence each other," continued Mr Jukic. "They are always in tight balance. Serotonergic neurotransmission can increase or decrease dopaminergic neurotransmission, while dopaminergic neurotransmission usually activates serotonergic neurotransmission. In conditions where there are more dopaminergic neurons to fire, and less serotonergic neurons to fire, this balance can become a little bit loose and it can cause spontaneous behavioural fluctuations."

"Otx2 is a gene involved in bipolar disorder, and this was the driving force for the whole project. In the original publication, in which Otx2 was associated with bipolar disorder, there were a few hundred patients for the one gene. But genome-wide association studies offer tens of thousands of patients looking throughout the whole genome."

And the group did just that, by way of an interval-based enrichment analysis tool for genome-wide association studies, which tests for enriched associations of gene sets, in this case specific to the networks involved in the specification of dopaminergic and serotonergic networks during development. "We found that both of these networks are showing aggre-gated association to bipolar disorder, but not to other disorders such as depression and schizophrenia," said Mr Jukic. "From there, we concluded that the translational potential of this model is quite high."

"There is a clinical implication of such an animal model: whatever pharmacological agent could stabilise these fluctuations in the mouse could stabilise them in humans as well. So the model could serve as a tool for preclinical studies and drug screening. We also observed that serotonergic 5-HT2C antagonists, which are candidate drugs for novel antipsychotics, are reducing the hyperactivity of the mutants. This could provide an extra validity for the potential use of these medications in bipolar disorder."

Like any model of psychiatric disorder, this one is limited in the extent to which it can be compared to the elements of higher thought processes that contribute to bipolar disorder in man. Nevertheless, these findings are thought-provoking, and have served as a springboard for future work in characterising the molecular mechanisms surrounding the development of the dopaminergic and serotonergic neurons. Amongst other plans, Mr Jukic and colleagues hope to examine the effects of stress on the phenotype, taking a cue from the link between it and the development and course of bipolar disorder, in an effort to precipitate the shift in affect-related behavioural parameters in mice.

Identifying the molecular mechanisms underly-
Modelling DA-5HT network involvement in bipolar disorder

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ing these fluctuations is another important direction of the group’s future research, as Mr Jukic described. “We will be focussing mainly on serotonergic neurotransmission and transcription patterns. Keeping in mind that the shifts in mood states happen over the course of days and weeks, we hypothesize that the slow changes in the expression of distinct genes in the brain are responsible for them. We will be mostly focusing on the genes coding serotonergic and dopamine receptors and the genes involved in circadian control. Circadian genes control physiological mood oscillations throughout the day, and they can be behind the increased mood fluctuations in En1+/- mutants as well.”

Mr Jukic will present ‘Aberrant development of monoaminergic neurons is implicated in mood fluctuations and bipolar disorder,’ this afternoon during the Junior Scientists symposium ‘Novel targets for improving the treatment of psychiatric disorders’, 14:45 – 16:25, Hall A3.

References


ROAMER report emerges

ROAMER is a three-year project funded by the European Commission under the Seventh Framework Programme (FP7)1 with the aim of developing a consensus-based roadmap to promote and integrate mental health and well-being research in Europe. Til Wykes (Institute of Psychiatry, King’s College London, UK), who leads the writing work package of the project, provided an update at the ECNP Congress yesterday afternoon. To that end, ECNP Daily News caught up with Professor Wykes to delve deeper into the project’s scope and aims.

What does the ROAMER project encompass?

ROAMER is structured into several scientific work packages covering all areas within the mental health research field (biomedicine and neuroscience, psychology and treatments, clinical aspects, social and economic aspects, public health, and funding, infrastructures and capacity building). It also includes the active participation of stakeholder groups.

We made particular efforts to include all relevant stakeholders in the project – individuals with mental health problems, families, caregivers, academics, industry, public health associations, and healthcare professionals (psychiatrists, psychologists and primary care physicians). Indeed, up to now, more than 600 researchers, about 200 stakeholder associations and dozens of policymakers and representatives of funding agencies for research from across Europe have participated in numerous meetings, scientific workshops and surveys organised by ROAMER.

At what stage is the ROAMER project currently? We have completed the initial work on identifying the state of the evidence in each area within mental health and well-being research. This allowed us to identify a large number of key research priorities: nearly 120, spanning the six scientific work packages. Through an iterative process, we were able to produce 20 integrated priorities that represented the concerns of all work packages. Then, most recently, this list of 20 priorities went out in a widespread survey of stakeholders and researchers, in order to establish the six main priorities which can be solved in Europe in the next 5-10 years and which will have the greatest impact on individuals, services and society both in terms of health and the economy. We have just finished compiling the results of this survey, which is very good timing as the European Commission is preparing for the next set of health funding calls for 2015-16, which we hope to influence.

Could you summarise the knowledge gaps that the first phase of the project identified? Have there been any surprises here? The individual ROAMER work packages generated a list of 20 priorities – each of which was targeted to address a gap in current research or understanding. This wasn’t justice to all the 20 priorities, but these can be summarised as five main areas: The need to support mental health for all through research evidence; the need to take account of societal values and concerns in research; the need for a life-course perspective on mental health problems; research aimed at developing personalised care; and the need to patients and scientists? The project has been surprisingly easy, as all those involved came together with a clear commitment to the project and with a keen interest in the data we would be able to produce. Many scientists do not have that much contact with policymakers so those contacts were particularly surprising, and really influenced our priority setting, as the policy context was part of the evaluation. The feedback from policymakers and service users was also sometimes challenging as they were demanding research data for evidence based policy that we didn’t have in the literature. This again led to considerations for the final priority list.

References


to build capacity for international and interdisciplinary research. What may or may not be surprising (depending on who you talk to) is the fact that there seemed to be such a strong consensus between researchers and non-researchers (service users, healthcare workers, policymakers, industry, etc.) on the final set of priorities generated by the project.

Two of the more striking conclusions from the consensus meetings and the ROAMER Europe-wide survey were how strongly people felt there was an immediate need for life-course research into mental disorders (especially focusing on childhood and adolescence), and the need to set up and maintain international and interdisciplinary networks for mental health and well-being research in Europe.

**What are the next steps for ROAMER and how can people get involved?**

At this stage we are in the process of finishing off the final ROAMER report, together with some other smaller reports and outputs. The next step will probably be getting the word out once the report and any other briefs are published. So the best way to get involved will be to take the ROAMER reports and ideas as jumping off points for specific future European projects, and closer collaborations between researchers, service users, healthcare workers and policymakers on research that will best inform robust policy down the line. We of course need to win the hearts, minds and pockets of both policy-makers and funding bodies so they get on board with the ROAMER priorities, so we will be urging all neuroscientists to speak out and disseminate them to anyone of influence. As mentioned before, the timing is critical in that the European Commission are currently putting together their health funding calls for 2015-2016. We think that now really is the time to argue the case for more mental health research that will impact patients and their families – we have done most of the work it is now up to researchers to do their bit.

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**Figure 1. The 20 priorities generated by the ROAMER project (above left), and the ROAMER process (right).**

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**Don’t miss... Book signing**

This year’s ECNP Media Award recipient, Dick Swaab (Netherlands Institute for Neuroscience, Amsterdam), who will be signing copies of his book ‘We Are Our brains’, this afternoon at the ECNP Plaza.
Early intervention could head off psychotic remission

Low IQ and poor Premorbid Adjustment Scale (PAS) scores are associated with a greater risk of non-remission in patients with non-affective psychotic disorders, new research suggests.

The findings, which were presented by Wiepke Cahn (University Medical Center Utrecht, the Netherlands) in Saturday’s session on the impact of schizophrenia in the long-term, indicate that early intervention could be vital in order to improve the course of the illness.

In her talk, Dr Cahn detailed the results from the Genetic Risk and Outcome (GROUP) project, which is a large prospective study in the Netherlands. “We started about six years ago and we included more than 1,000 patients, 1,000 siblings, their parents and healthy controls,” she told ECNP Daily News. “GROUP has been designed to examine which factors are related to the vulnerability and resilience of non-affective psychosis.”

The patients, who had an average age of 28 at enrollment, were recruited on a diagnosis of non-affective psychosis. The researchers did an extensive clinical assessment, including the Positive and Negative Symptom Scale (PANSS), Premorbid Adjustment Scale (PAS) and IQ. “We followed these subjects up and measured them again after three and six years,” said Dr Cahn.

The team were able to determine the remission status of 803 patients after the three year follow up, and 641 after six years, using the PANSS remission tool.

Dr Cahn continued: “Quite a few papers have already been written on the GROUP project. I am focusing on the results on the remission status of non-affective psychosis, and factors that are associated with – and/or predict – this status.”

“First we examined the factors associated with drop-out. What we’ve found is that patients with more symptoms, as measured with the PANSS, and those with a lower IQ at baseline, were more likely to drop out during the six years follow up compared with those that remained in the study.”

“We also found that among patients that stayed in the study, those patients with the diagnosis other than schizophrenia, with higher functioning, better quality of life, and a higher IQ at inclusion, are more likely to be in remission,” said Dr Cahn.

She went on: “Actually about 60 percent of patients with psychotic disorder are in remission six years after inclusion. Interestingly, we also found that those patients who had reduced pre-morbid functioning in childhood were less likely to be in remission.

“So it appears that patients who show problems in intellectual functioning early on in life are more likely to have a worse outcome.”

The study is unique, and not only because of its large sample size, said Dr Cahn. “It’s unique because we examine patients as well as their siblings. Furthermore, it’s unique because we have followed them up for such a long period of time,” she explained.

While these results are concerned solely with patient remission, Dr Cahn and her team plan to analyse the six-year follow-up data with respect to siblings as well.

“What we would like to examine is whether patients who have siblings with subclinical symptoms actually are less likely to be in remission after six years,” she said. “Essentially, is there a worse outcome if it runs in the family?”

The team are also planning to investigate the patients from a genetic perspective. “We’ve done quite extensive clinical phenotyping, and besides the phenotyping we’ve performed genotyping,” said Dr Cahn.

She went on: “We further looked at the effects of different types of medication over time and examined the side effects. We might present some of the data on that too,” she added.

Going forward, Dr Cahn and her team are hoping to extend the study, as she explained: “Unfortunately the present funding has come to an end, but we are looking for additional funding to follow the GROUP subjects for an even longer period of time.

“What we’re trying to do is to get data on subjects by using web-based questionnaires and measurements. We’ve assessed them face-to-face until now, but we might be able to get even more detailed information by using internet applications.”

References

Type 2 diabetes and dementia link explored

This afternoon at the ECNP Congress will see Rachel Whitmer (Kaiser Permanente Northern California Division of Research, USA) take to the stage to present a fascinating discussion on type 2 diabetes and its links with dementia.

As a lead researcher at Kaiser Permanente – an integrated medical care delivery system – Dr Whitmer has access to tens of thousands of electronic medical records, and she and her team have been rigorously analysing this data to glean what they can about how and why dementia and cognitive decline appears to be so prevalent in the type 2 diabetes population.

Speaking to ECNP Daily News, Dr Whitmer outlined the current and future burden of these diseases: “As I’m sure most people are aware, we are in the midst of an epidemic of both type 2 diabetes and dementia, and in the next 50 years there will be a tripling of cases of dementia,” she said.

“Type 2 diabetes is something that we’ve been looking at for a long time. We have a large group of elderly patients with type 2 diabetes and it’s been shown in many, many studies that people with type 2 diabetes have double the risk of dementia, and we’re trying to really understand why that is. We know people are at double the risk but we want to be able to understand what things make people at a higher or a lower risk after they have type 2 diabetes,” she added.

Dr Whitmer and her team have primarily been focusing on glycaemic control and the vascular complications of type 2 diabetes, as she described.

“We published a study in JAMA1 a few years ago where we went back and looked at 20 years, retrospectively, collecting information from our elderly patients with type 2 diabetes who had a severe episode of hypoglycaemia – that would be an episode that was severe enough that they had to go to the emergency room or to the hospital.

“And it turned out that these people had more than double the risk of dementia compared to their peers with type 2 diabetes who did not have very severe low blood sugar episodes.”

Dr Whitmer added that it is already well understood that, with other complications of type 2 diabetes such as neuropathy and nephropathy, how well you control your blood sugar is directly linked to the likelihood of developing them.

“But we’re really interested in trying to understand what role that plays in the brain, and keeping the brain healthy,” she continued. “We’ve seen in our data that people with both high blood sugar levels – and this is evaluated with glycosylated haemoglobin of 10 percent or greater – have a 20 to 30 percent greater risk of dementia. People with very low blood sugar, a glycosylated haemoglobin of five percent or less, are also at a much higher risk of getting dementia.”

Dr Whitmer and her team have also found that the levels of fluctuation in blood sugar is also a strong predictor of developing microvascular complications, as she described: “It’s not only looking at mean levels of blood sugar, but how much it varies over time and whether that is associated with a greater risk of being diagnosed with dementia.”

As well as examining the links between blood sugar control and dementia over the long term, Dr Whitmer and her team have been heavily involved in developing a validated prognostic risk indicator for trying to predict the risk of dementia in patients with type 2 diabetes.

“Since people with type 2 diabetes have double the risk of dementia, we wanted to focus on a risk score that was specifically about characteristics of type 2 diabetes,” she explained.

Dr Whitmer went on: “We looked at all of our information about patients with type 2 diabetes and looked to see, in a number of different models, what combination of risk factors was the most predictive of being diagnosed with dementia in the next 10 years. You can actually calculate whether you have a low, medium or high risk.”

After developing their test, using data from the Kaiser Permanente Northern California diabetes registry, the team validated it in another population of older patients with type 2 diabetes, from Group Health in Seattle, Washington.

“We’re really excited about this score,” said Dr Whitmer. “This is something that a primary care doctor, or even an endocrinologist, can very quickly calculate. When a patient with type 2 diabetes comes in for a check-up, they can simply ask a couple of questions, look at their co-morbidities, and then they can come up with what their likelihood of getting dementia is in the next 10 years.”

As well as examining the links between type 2 diabetes and cognitive decline, Dr Whitmer and her group have also been looking at depression. As Dr Whitmer notes, the...
Type 2 diabetes and dementia link explored

Continued from page 9

issue of whether depression is a true risk factor for dementia, or a very early symptom, is a controversial issue in her field.

“We went and looked back over time, at when people were diagnosed with having depression. And this is work that we’ve done in our older patients, overall, not just specifically in a type 2 diabetes population. We found that having depression at mid-life is strongly associated with all cause dementia and vascular dementia. Whereas with Alzheimer’s disease we’re only seeing that it’s depression a bit later in life.”

The researchers also looked specifically at data from patients with type 2 diabetes, as Dr Whitmer explained: “We know that people with type 2 diabetes are more likely to have depression and we know that depression is a risk factor for dementia. So we really carefully took into account other risk factors for dementia, but we found that depression is very largely associated with risks of dementia even in a type 2 diabetes population. People who have depression are more than double the risk of getting dementia even in the context of type 2 diabetes.”

But why is type 2 diabetes seemingly so intrinsically linked with dementia? Dr Whitmer and her group have also been examining the role that microvascular complications are playing with its onset. “Post-mortem pathology studies that have looked at people with type 2 diabetes, and looked at their brains after death, are not suggesting that people with type 2 diabetes have a higher burden of Alzheimer’s disease pathology,” she explained. “It looks like they have a much higher burden of vascular disease in their brain so it could be that that is part of the story of why this group is at double the risk of dementia.”

Nevertheless, looking back over some 30,000 records over 20 years, the researchers were able to find that type 2 diabetes patients with diabetic retinopathy had a much higher risk of getting dementia. Dr Whitmer may also be presenting data linking end stage renal disease in type 2 diabetes patients with dementia. In this work, researchers found that these patients have a 2.5-fold greater risk for dementia. “This evidence is coming together that type 2 diabetes patients who also have these complications where their small blood vessels are compromised, seem to have a much greater risk of dementia, and the ones who don’t have a lower risk,” said Dr Whitmer.

“We’re really just trying to understand – we know these people have double the risk of cognitive impairment and dementia, but why? And what’s really unique about the data is that we have enough. With such a huge sample of people with type 2 diabetes, we have the statistical power to look at the complications of diabetes and look at their glycaemic control, and see who is at higher or lower risk.”

Rachel Whitmer

Interview Bru Cormand

A growing body of research on the persistence of ADHD into adulthood is set to bring about leaps forward in both diagnosis and treatment, as well as in the ability to predict which children are most liable to persist. This topic will be discussed in depth this morning at the ECNP Congress, in a session dedicated to the latest understanding of the neurobiology of the condition across the lifespan.

Settling the foundations of such improvements has relied on large international collaborations in multiple disciplines including imaging and genetics. In an interview with ECNP Daily News, Bru Cormand (University of Barcelona, Spain) described how he and others go about deciphering ADHD genetics, which, by revealing key mechanisms, may well be becoming clinically invaluable in the future.

What have we learned about adult ADHD and how it can be distinguished from childhood-only ADHD (i.e. ADHD which is extinguished once that individual enters adulthood)?

Although twin and family studies have shown that the heritability of ADHD is very high, around 76%, we have not yet been able to resolve the genetic landscape of the disorder, neither for the childhood-only (or remitting) form, nor for the adult (persistent) form. So far, genetic association studies have been the major source of potential susceptibility genes for ADHD. Some of these studies have investigated children with ADHD, whereas others have focused on adult ADHD samples, identifying genes that appear in both samples but also others that show association only in the childhood group or only in the adulthood group.

The adult ADHD samples consist of patients with ‘persistent ADHD’, and have allowed identification of several genes potentially involved in the continuity of the disease across the life span. In contrast, children’s samples are more heterogeneous, as they include both remitting patients (subjects where the disorder will remit in adolescence or in early adulthood) and persistent patients. So in this case it is more difficult to draw conclusions. In this regard, it would be very interesting to perform genetic studies in remitting individuals, not reported so far (to my knowledge).

If one presented with ADHD symptoms during adulthood, would the assumption in this case be that the individual probably had ADHD symptoms throughout life?

The estimated prevalence of ADHD among adults is below that of children. In children and adolescents, the prevalence of the disorder is around 5%, and it
persists into adulthood in at least 30% of subjects diagnosed during infancy. This is a childhood onset disorder, so adults with ADHD have had symptoms throughout life. However, the nature of the symptoms may vary across the lifespan, usually with more hyperactivity in early stages and more attention deficit later in life.

We have already seen interesting differences in, for example, brain structure, to distinguish cases of ADHD that persist into adulthood from childhood-onset cases. Could you describe any genetic findings that point to the origin of these traits?

We have performed several case-control association studies focused on specific candidate genes or pathways that include both children and adult ADHD individuals from Spain, and have identified shared and specific risk factors in these two groups. For example, BAIAP2, a gene that is asymmetrically expressed in the two brain hemispheres, was found to be associated with adult ADHD but not with children ADHD, supporting a possible contribution to the continuity of the disease across the life span. Other genes that we have found associated with ADHD only in adults in the Spanish population are STX1A and MAOB, the first involved in the regulation of neurotransmitter release and the second in the metabolism of neuroactive amines. On the other hand, we have detected children-only associations (NTF3, NTRK2, DRD1) and genes associated with the disease in all age groups (SYT2, LPHN3, CNTRF, SHT2A, DDC). However, the scene is still puzzling, as many of these genes have been ‘usual suspects’ in hypothesis-driven association studies but they are not among the top hits of the reported genome-wide association (GWA) studies.

You mention in your presentation abstract that no significant GWA findings have been identified. What kinds of methods are being now employed to identify ADHD-associated genetic variants? What work is your group doing, and how does this relate to the work you are involved in on investigating the genetic relationship between five psychiatric disorders estimated from genome-wide single nucleotide polymorphisms (SNPs)?

The ADHD scientific community walks in different directions to identify both common and rare variants for the disorder. Recent studies by the Psychiatric Genomics Consortium (PGC) support a significant contribution of common genetic variants (SNPs), which would account for 28% of the liability variance. These studies have also shown that some genetic risk factors cut across different psychiatric disorders, whereas others may be specific. So, although no genome-wide significant hits have emerged yet from GWA studies on ADHD, they have to be there, possibly hidden by the limited sample size (only 4,000 cases in the best case) or by confounding factors such as comorbidities or genotype-environment (GxE) interactions. The example of the search for genetic risk factors in schizophrenia, with more than 100 genome-wide significant hits identified in a sample of around 40,000 patients and 100,000 controls, emphasises the importance of collecting more samples for analysis.

With regard to rare variation, ADHD research is just taking the first steps, with exome sequencing projects running now in multiplex families and by genotyping thousands of variants in thousands of individuals with the Exome Chip and the Psych Chip. The first reports will come soon.

The Barcelona group, which is part of the PGC, the ADHD network and the International Multicenter Persistent ADHD Collaboration (ImpACT), has contributed 600 GWA studies adult ADHD individuals from Spain to these multicentres studies, and is currently genotyping some additional 400 patients. In parallel, we perform association studies focused on specific candidate genes or pathways, with emphasis on miRNAs. Transcriptomics in blood cells and methylation studies are also our current focus.

Regarding the search for rare genetic variants, how far are these generalisable, i.e. what can we learn from them?

Most existing genetic studies on ADHD have focused on common variation (SNPs; VNTRs, variable number tandem repeats; CNVs, copy-number variants) and have used case-control association approaches to identify potential susceptibility variants. Still far from having established in detail the common genetic contributors to the disease, we are now starting to explore the role of rare variation. The first studies have focused on rare CNVs, but efforts to identify rare SNVs (single nucleotide variants) through whole-exome sequencing (WES) or by using the so called Exome Chip and also the Psych Chip are currently under way. Regarding rare CNVs, around ten genome-wide studies have been reported, three of them reporting a greater CNV burden in cases than in controls, with an excess of CNVs in glutamate receptor genes, in the PARK2 locus and encompassing genomic regions previously associated with other psychiatric disorders such as autism spectrum disorder or schizophrenia. And about SNVs, only one WES study has been published so far, in a single family, and further preliminary results on SNV’s have been (or will be) presented in the XVI World Psychiatry Association meeting (WPA) and the XXIInd World Congress of Psychiatric Genetics (WCPG).

Interestingly, polygenic risk studies that combine common (SNPs) and rare (CNVs) variants suggest that the genetic architecture of ADHD comprises both types of variants, although it is still not possible to establish the relative contributions at the moment.

Dr Cormand will present ‘The genetics of ADHD across the lifespan: tales and reality of common and rare genetic variants’, as part of the session ‘Neurobiology of ADHD across the lifespan’, beginning today at 9.00 in Hall A1.
Unmet needs remain in treatment of SAD

This morning’s session on schizoaffective disorder (SAD) features an in-depth analysis of the unmet needs usually faced by physicians operating in the field.

In his talk, Andrea Murru (Bipolar Disorders Unit, Department of Psychiatry, Hospital Clinic, Barcelona, Spain) will focus on examining the key points to be considered when developing an individualised treatment plan for SAD, whilst discussing why the field needs further research in order to allow physicians to make evidence-based decisions for their patients.

“I think that SAD is a field of great interest because, despite being a clinical entity known since the beginning of the last century, and first described by Kraepelin himself, it has been, for a number of reasons, a topic historically neglected by scientific literature,” Dr Murru told ECNP Daily News.

“Despite a growing amount of evidence produced in psychiatry over the last 30 years, there’s a significant gap regarding this very specific disorder,” he added.

SAD remains a research challenge because patients often present with a mixed set of features, ranging from purely psychotic to affective symptoms. This may have held back research, noted Dr Murru.

“The limits shown in scientific literature just reflect the limits in the criteria currently used for diagnosing schizoaffective disorder,” he explained. “As a consequence, the evidence for treatment of schizoaffective disorders is limited.”

Dr Murru added that physicians often choose treatments that rely on various classes of drugs that have not been specifically tested in SAD, saying: “The truth is that, nowadays, the evidence we have is mainly focused on atypical antipsychotics. But there are a number of unanswered questions.”

For instance, the evidence for atypical antipsychotics comes mostly from data tested or pooled from trials with schizophrenic or bipolar patients. Hence, the degree of evidence is still controversial.

“There is absolutely no evidence for combination therapies and we don’t know which ones can be used in schizoaffective disorders,” said Dr Murru. “Of course, the lack of clinical trial data causes a lack of treatment algorithms or clinical guidelines.”

He went on: “This is a difficult issue because, by definition, schizoaffective disorder is maybe the most pleomorphic entity in clinical practice. Moreover, the pharmacological management of SAD usually assumes the same dosages deriving from schizophrenia or bipolar disorder studies.”

Further, the concept of predominant polarity has not been validated in SAD patients, cautioned Dr Murru, making it difficult to choose the treatment option best suited to manage every single case. However, dimensional assessment may help to choose which symptoms should be considered as therapeutic targets. Lithium and other mood stabilizers may also play a role, especially in the prevention of affective relapses and cyclicity, he added.

Another area which deserves more research in SAD is cognitive rehabilitation, as Dr Murru explained: “Tailoring a combined approach integrating both evidence-based drug treatments and population-specific psychosocial interventions becomes a major need with conceptual grounding of their possible effectiveness. So, for instance, we should consider using a specifically-designed cognitive remediation program.”

Moving forward, Dr Murru plans to focus his research on schizoaffective populations in an effort to fill this existing gap of evidence in the field. His previous works, which examined treatment adherence in SAD patients, highlighted the importance of working with specific patient populations.

“We identified high prevalences of poor adherence to pharmacological treatment, but the variables associated to this phenomena were quite unique and somehow surprising,” said Dr Murru.

“Some elements which we thought could be of interest in poor adherence were actually found not to be related in the schizoaffective population.”

As for the clinical and diagnostic properties of SAD, further research is badly needed, as Dr Murru stressed: “In order to create a profitable debate on SAD, the main need is to carry out research in this specific population. Current evidence is only supported by mixed samples. But specific research is the only way to understand and produce treatment algorithms.”

He went on: “This is not the only situation in which the clinical practice of psychiatric populations is yet to be supported by concluding evidence; there is a need to better define specific subgroups of treatment-responding subjects, especially by better defining longitudinal issues. This could be the case for bipolar disorder, with predominantly manic, or predominantly depressive, polarity patients.

“Finally, real phenomena are usually continuous and this collapses with our intention of building up categories.”

Andrea Murru will present his talk during the ‘Schizoaffective disorder: construct and treatment’ session today at 9:00; Hall A4

The first ECNP Brain Day finds an enthusiastic audience
The first ECNP Brain Day finds an enthusiastic audience

looking at where neuropsychiatric disorders come from and how life events are mapped onto the circuitry of the brain. Peter Falkai (University of Munich) followed by demonstrating how research on animals is teaching us about the physiological basis of disorders of the brain, even in such elusive disorders as schizophrenia.

In the afternoon session, Henrik Walter (Charité, Berlin) explored how research is translating – despite the brain’s daunting complexity – into new treatments and greater hope for patients.

Andreas Meyer-Lindenberg looked at how our developing understanding of the ways in which genes, environment and lived experience interact is leading to new pathways in diagnosis and treatment. Andreas Reif (University of Frankfurt), charting the history of psychiatric research, plotted neuroscience’s journey to progressively better diagnosis and treatment, a journey that very much continues. Andreas Heinz (Charité, Berlin) closed by reviewing the science and treatment of disorders of the brain in Berlin, one of Europe’s pre-eminent centres for neuroscience and clinical research.

Reactions to the day were uniformly positive, with the level of engagement and the quality of discussion being particularly remarked upon. "This has been a great experiment in public outreach for us," said ECNP President Guy Goodwin. "It’s terrific to see the day was such a success. Andreas Heinz, the chair of the Brain Day Programme Committee, must be congratulated for putting together such an outstanding roster of topics and presenters, and we are very grateful to him and his speakers for making this such an excellent event."
Putting a STOP to youth suicidality

The STOP (Suicidality: Treatment Occurring in Paediatrics) study developed a set of web-based tools for children and adolescents to track suicidality over time, in order to identify the factors that make some young people more vulnerable to suicide. Paramala Santosh (Institute of Psychiatry, Psychology & Neurosciences, King’s College London, and Maudsley Hospital, London, UK) described the innovative monitoring and treatment strategy yesterday afternoon, as part of a broader session on the topic of pharmacotherapy in child and adolescent psychiatry.

In an interview with ECNP Daily News, Professor Santosh spoke about the origins of the project and the impact of the interactive HealthTrackerTM system, which children use to participate in the STOP. Professor Santosh is also one of the two co-inventors of the HealthTracker system and a Director of HealthTracker Ltd, an SME (small and medium-sized enterprise), which is part of the STOP consortium.

“The STOP study surfaced at a time when people were worried about side effects arising from medication use in children, especially the side effect of suicidality,” he began. “At that point in time, there was quite a lot of preoccupation as to whether medications such as anti-depressants and other medicines increased suicidality.

“The project aimed to develop a web-based suite of measures of suicidality, its risk and protective factors, as well as a scale which specifically looked at side-effects of medicines that would increase the likelihood of suicidality, so that we could develop it for the purposes of pharmacovigilance. This would then mean that for new medicines that are started in children in the future, this web-based system could be used to monitor whether there is suicidality emerging.”

The participant begins by answering a set of initial screening questions. If returning positive, the tool then goes on to capture more information about suicidality and possible underlying causes.

“The web-based system is currently being tested out in four groups of children as part of the STOP project,” continued Professor Santosh. “One group are children who are depressed; half of them are individuals who are being treated with medication such as fluoxetine, and half of them are receiving psychological interventions. Another group are with psychiatric problems being treated with anti-psychotics. The third group is a chronic illness group, with bronchial asthma or respiratory allergy, and the last group is normal controls. This way, we can see that the web-based STOP suite of measures that we have developed can be used for all of these groups, and therefore that it can be used properly in the future.”

STOP also did an in-depth analysis of one of the largest databases of side effects in the world – the WHO database – by which it was possible to identify drugs commonly associated with suicidality and side effects that co-occurred with it. With further literature review the group were able to identify other side-effects which, when an individual is suicidal, increase the likelihood of suicidality. This data was then used to develop the STOP Suicidality Medication Side-Effect Scale on the HealthTracker system.

The STOP project also developed scales to measure the intensity of suicidality, along with another scale for risk factors and protective factors. Currently, all of the individuals in the four test groups are being measured along each of these three STOP scales at multiple points across a 52-week period. The project completes in April 2015.

The hope, explained Professor Santosh, is that the STOP Suite of Suicidality Measures on the HealthTracker system will be shown to be suitable to be used in the four groups. Data will be explored to identify if any pattern will emerge in each of the four groups regarding suicidality and the profiles that might predict whether someone is more likely to end up expressing more suicidal ideation or behaviour. “The whole focus is not about proving whether one drug produces more suicidality or not; it is actually to prove whether these measures that we have developed are going to be applicable for use in children and adolescents across a wide variety of problems so that this can then...
become a standard pharmacovigilance tool for the future.

“We are going to be able to identify what is the likelihood of this kind of thinking in the ‘general population’ control group of children, compared to the rest of the groups. That would allow us to look at it from the perspective of identifying whether there are trends in terms of how children without any problems start thinking about suicide, versus those who are prone to it because of either a chronic mental health problem, including a disease like depression, or even in those with a chronic problem, including a disease like depression because of either a chronic mental health problem, including a disease like depression, or even in those with a chronic problem, including a disease like depression, because of either a chronic mental health problem, including a disease like depression, or even in those with a chronic problem, including a disease like depression.”

New study comes at a time where updated DSM-5 criteria for compulsive disorders has, for the first time, separated it from previous categorisation as an anxiety disorder.

“This is useful in that it focusses the attention of clinicians and researchers on the common aspects between these disorders, but on the other hand I see, from clinical practice, that obsessive compulsive disorder is also an anxiety disorder, so it is a bit of a crossover,” said Professor Veltman. “The former classification used to stress the similarity with other anxiety disorders, and now the focus has shifted to compulsivity. But I don’t think this is the last word!”

He continued, delving deeper into newer comparisons of OCD with both other anxiety disorders, and other compulsive disorders. “There have now been a number of studies comparing those in a single design, rather than just comparing OCD with healthy controls. If you just compare OCD with healthy controls then you will find differences, but you don’t really know if any difference is specific to OCD, or specific for people who take antidepressants, etc., so I think we are doing a better job now. We are more specific, and because studies have tended to become larger in size, there are lots of metaanalyses, some of which we have done ourselves, and I think the results we are getting are more generalisable to the population on the whole.”

Indeed, some of the latest meta-analyses that Professor Veltman referred to has included close to 2000 patients and healthy controls, thus he was confident that the results would be solid. “I don’t think it is very likely that someone will come up with some other results in the future that totally contradict what we have found,” he said.

Importantly, a main message during Professor Veltman’s presentation at the Congress will be how sophisticated analysis can be used to extrapolate data from groups results and apply it to an individual. Key to this is the use of machine leaning - a statistical technique where systems that can learn from data. “It allows you to obtain rules that differentiate between two groups, which you can then use to classify novel individuals on a single-subject basis,” he explained. “This has been done, for example, in Alzheimer’s and schizophrenia, but there are also now studies on their way on OCD.”

Professor Veltman will explore compulsivity imaging techniques – and the links from group to individual – during the session ‘Compulsivity – transdiagnostic perspective: new models, disorders and treatments’, held at 14:45 – 16:25 today in Hall A4.
5-HT1A-FGFR1 heteroreceptor complexes modulate neuroplasticity and depression

The balance of 5-HT1A autoreceptor homomers versus the FGFR1–5-HT1A heteroreceptor complex could be a crucial factor in determining whether or not you have depression coming up partly due to a dominance of inhibitory 5-HT1A autoreceptor function. Kjell Fuxe

5-HT1A-FGFR1 heteroreceptor complexes present in the hippocampus and midbrain, delegates attending yesterday’s session on 5-HT1A and depression heard.

In his talk, Kjell Fuxe (Division of Cellular and Molecular Neurochemistry, Department of Neuroscience, Karolinska Institute, Stockholm, Sweden) detailed the research that he and his group have been conducting into the formation and impact of heteroreceptor complexes comprised of fibroblast growth factor receptor 1 (FGFR1) and 5-HT1A mono-homodimers.

“It’s becoming more and more accepted by almost all groups that in fact these heteroreceptor complexes do exist with direct interaction, and the field has moved from monomers to homo-heterodimers and higher order heteroreceptor complexes. And of course also interacting with the G-protein interacting proteins,” Professor Fuxe told ECNP Daily News.

This is a dramatic change in thinking about how then the integration of signals can occur in the brain, noted Professor Fuxe. “We discovered that the FGFR1 could become linked to the 5-HT1A receptor. It has a major impact for novel strategies of treatment of depression. These FGFR1–5-HT1A receptor complexes change the function of the participating protomers,” he said.

The team used the proximity ligation assay to provide indications for the existence of 5-HT1A-FGFR1 heteroreceptor complexes also in the brain and not only in cellular models. “We have realised that 5-HT1A receptor pharmacology and function may be substantially changed in different heteromers versus 5-HT1 mono-homomers,” said Professor Fuxe. “It participates in a number of complexes with other types of receptors, and some of them are more exciting and more interesting. It gives a novel understanding of how one can play and modulate this receptor, which everybody would agree plays a major role in mediating antidepressant effects of drugs.

“We have the evidence that in fact there are also direct allosteric interactions in the 5-HT1A-FGFR1 heteroreceptor complexes which produce an enhancement of FGFR1 signalling, and this is of particular interest since there are indications of hippocampal atrophy in major depression.”

He added: “We believe that an increased growth and function of hippocampal neurons takes place when giving FGF2 and 5-HT1A receptor agonist together intracerebroventricularly (i.c.v.) in animals, and can contribute to the antidepressant actions observed.”

Describing the formation of the 5-HT1A-FGFR1 heteroreceptor complexes, Professor Fuxe said: “The two protomers can directly interact with one another and produce increased effects on brain plasticity. This could be a major event in understanding the mechanism for the ability of SSRIs to produce antidepressant effects which could involve increased structural plasticity and function of different types of hippocampal neurons, especially after chronic administration.”

The increased participation of 5-HT1A and FGFR1 homodimers and recruitment of β-arrestin-2 was demonstrated in the FGFR1–5-HT1A heteroreceptor complexes upon coagonist treatments, added Professor Fuxe.

Using the proximity ligation assay, the team went on to demonstrate the existence of the 5-HT1A-FGFR1 heteroreceptor complexes in the rat hippocampal formation, and also within the caudal midbrain raphe region, which is the major origin of the ascending 5-HT projections to the forebrain. They did not see these complexes in the cerebral cortex, noted Professor Fuxe, but selectively in the raphe-hippocampal 5-HT neuron system and its target area, the hippocampal formation.

“We could observe that in fact this heteroreceptor complex is increased in number with combined treatment with FGF2, which is the basic fibroblast growth factor, and 8-OHDPAT, the 5-HT1A agonist. This was observed in primary hippocampal cultures and in raphe RN33B cell cultures,” he said.

“The co-treatment in hippocampal primary cultures markedly increased the protrusions, the formation of large growth cones and the number of neurites or extensions per cell. Thus, there appeared a marked increase in the structural plasticity of the hippocampal nerve cells. Also in the hippocampus we could demonstrate that co-treatment produced an enhancement of the transactivation of FGFR1 and the signalling of the ERK1/2 pathway as seen from their increased phosphorylation.”

He went on: “The most exciting thing was that we obtained a behavioural correlate. In the forced swim test we could observe a marked enhancement of swimming time and a reduction of immobility time by the combined i.c.v. treatment of FGF2 and the 5-HT1A agonist, both acutely and chronically.”

Professor Fuxe described how the raphe 5-HT1A autoreceptor underwent an increased recruitment to the FGFR1–5-HT1A heteroreceptor complex in raphe cell cultures upon combined incubation with FGF2 and the 5HT1A agonist. Such an event may have a beneficial role in depression by assisting in the recovery of 5-HT nerve cell trophy from a state of atrophy, including increased 5HT synthesis and storage as shown in the raphe 5-HT cells.

“We conclude that a major restructuring of our ideas on the 5-HT1A autoreceptors is required,” said Professor Fuxe. “They are certainly important for inhibition of the firing rate of the 5-HT raphe cells, but they can also be recruited into being part of the FGFR1–5-HT1A heteroreceptor complex in the raphe 5-HT cells. In this receptor complex they can have a trophic role in the central 5-HT neurons, and have a major role in restoring the activity and survival of the 5-HT neurons in the raphe area in depression. Here we have a major change in the understanding of the regulation of the ascending raphe-hippocampal 5-HT neuron system.”

He added: “The balance of 5-HT1A autoreceptor homomers versus the FGFR1–5-HT1A heteroreceptor complex could be a crucial factor in determining whether or not you have depression coming up partly

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**5-HT1A-FGFR1 heteroreceptor complexes modulate neuroplasticity and depression**

Continued from page 16

**We conclude that a major restructuring of our ideas on the 5-HT1A autoreceptors is required.**

Kjell Fuxe

Due to a dominance of inhibitory 5-HT1A autoreceptor function.

Discussing the potential impact of the research, Professor Fuxe explained: “We believe that this could be a very interesting and novel target for antidepressant drugs. We don’t have any data with SSRIs yet, but they are forthcoming and we have also a lot of dynamic studies on these complexes. We have seen that they change their stoichiometric features especially upon the combined agonist activation. You can increase the recruitment of β-arrestin-2 to the 5-HT1A protomer upon co-treatment and also demonstrate an increased presence of the 5-HT1A homodimers in the FGFR1–5-HT1A heteroreceptor complex. The dynamics of this receptor complex is impressive.”

Summarising the findings, Professor Fuxe continued: “We would like to underline that these complexes exist both in the raphe-hippocampal 5-HT pathway and its target, the hippocampal formation. We conclude that co-activation of its FGFR1 and the 5-HT1A protomers in the hippocampus may contribute in rapid and robust antidepressant actions. Prolonged treatment is postulated to counteract hippocampal atrophy in depression that may develop in time leading to prolonged antidepressant effects.

“As to the SHT1A autoreceptor-FGFR1 heteroreceptor complexes in the midbrain raphé cells, we postulate based on our studies that synergistic allosteric receptor-receptor interaction induced upon coactivation of the two protomers can also contribute to acute antidepressant actions without having to wait for a couple of weeks to see the action. I think counteraction of atrophy in the raphe hippocampal SHT neurons can be one major event for the long term antidepressant actions.”

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**The ECNP Congress: A matter of spinning plates**

Planning each edition of the ECNP Congress requires a great deal of forward thinking, organisational flair and – for this year at least – faith that the congress venue would even be finished: “The organisation of the Congress has been even more challenging this year due to the fact that the congress venue that was chosen was not even built at that time!” Melinda Spitzer, Project Manager for Congresses & Meetings in the ECNP Office, told ECNP Daily News.

“Two years ago it was decided that we would host the Congress in Berlin instead of Helsinki. While normal preparations for a congress would have started three years in advance, the ECNP Office faced great challenges to have everything up and running in time.”

With floor plans from the venue being constantly updated in the final stages of construction, the ECNP Office faced a real organisational challenge, with only a few months of preparation available in-house once the CityCube opened in May of this year.

“But in the end, excellent cooperation between the congress venue, our various suppliers, our organis ing secretariat (Colloquium Brussels), the ECNP Committees and of course the dedicated team at the ECNP Office has meant that the Congress has been able to go full steam ahead, with even more content, innovative features and improved design this year,” said Ms Spitzer.

As always, the Congress will place exploration of the latest research in translational neuroscience centre stage, but one immediate difference this year is that the scientific sessions began on Saturday rather than today, bringing the Congress to a close one day earlier. “We are also introducing new sessions this year, including ‘Rapid-Fire’ posters sessions, e-posters, a Regulatory update session on the ‘Latest developments in Alzheimer's disease’ and several Junior Scientist initiatives,” added Ms Spitzer.

Indeed symposia and activities for Junior Scientists have been given quite a substantial boost in emphasis this year, with new initiatives that include: Career development sessions – early morning training sessions each featuring an engaging expert in the field, specifically invited to share their wealth of knowledge and experience; Best practice session – giving attendees the unique opportunity to interact with ECNP leaders and share their perspectives as to the needs and challenges of a junior scientist in Europe today; and the Junior Scientist’s Lounge – a relaxing area to exchange ideas and experiences.

Of course the ECNP Congress forms just part of the ongoing activities that ECNP holds year-round, with workshops, schools, seminars and many other activities on the calendar. Participants at these events are always encouraged to establish links with other members, or mentors, and then use the annual congress to re-join their colleagues to continue discussions, collaborations and social bonds that will form an important part of their careers as they progress. “The ECNP Congress is an important networking platform,” said Ms Spitzer.

In her closing remarks, Ms Spitzer underlined the ongoing drive of ECNP to always improve and adapt to the needs of its members, saying: “The key message we always want to put across is that ECNP is an ever-evolving, dynamic and service-driven organisation that puts its members, their expertise and their development, centre stage.”

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Melinda Spitzer
ACROSS

4. The 2015 ECNP workshop, on the topic sleep circadian rhythms and timing of neurobiological processes, takes place in which French city?

5. Brain region linked with ‘reading’ emotions and trustworthiness in another’s face.

9. From the Latin for “about a day,” this is the rhythm of wakefulness and of sleep.

11. Dietary trace mineral and N-methyl-Daspartate receptor blocker with suggested anti-depressive effect.

13. Winged creature, a stalwart of laboratory life.


16. The newest part of the cerebral cortex, which is believed to be responsible for the development of human intelligence.


19. This word describes when you can almost, but not quite, remember a word.

20. Papyrophobia is the fear of what?

DOWN

1. One of the founding fathers of behaviourism.


3. Keynote lecturer at this year's ECNP congress


7. Winner of 2014 ECNP Media Award for his book “We are our brains.”

8. Major cerebral vessel lateral to the chiasm.

10. The word ‘psychiatry’ is derived from the Greek ‘psyche’, meaning soul, and ‘iatros’, meaning what?

12. Emperor Marcus Aurelius described him as “Primum sane medicorum esse, philosophorum autem solum” (“first among doctors and unique among philosophers”; Praen 14: 660).

15. Theory of Mind from the Berlin School, whose central principle is that mind forms a global whole with self-organising tendencies.

17. In 1837, he gave the first description of neurons using microscopy.

Answers will be revealed in Issue 2 of ECNP Daily News, available on Monday!
<table>
<thead>
<tr>
<th>TIME</th>
<th>SATURDAY 18 OCTOBER</th>
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<tbody>
<tr>
<td>07:45-08:45</td>
<td>Registration (09.00-20.00)</td>
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<tr>
<td>08:00-10:00</td>
<td>Brainstorming sessions:</td>
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<tr>
<td></td>
<td>BS.1 Decision-making in psychiatry</td>
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<td>BS.2 Overlap depression and pain</td>
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<td>BS.3 Experimental Medicine Networks</td>
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<tr>
<td>10:00-12:00</td>
<td>Exhibition</td>
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<tr>
<td>11:00-11:45</td>
<td>Plenary lecture PL01: New targets for the treatment of addiction</td>
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<tr>
<td>11:45-13:15</td>
<td>Lunch and poster sessions</td>
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<tr>
<td>13:15-13:30</td>
<td>Coffee break</td>
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<tr>
<td>13:30-14:15</td>
<td>Satellite symposium - C.01 Depression: more than low mood</td>
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<tr>
<td>14:45-16:00</td>
<td>Rapid-fire poster sessions</td>
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<td>Plenary lecture PL02: Award lecture: Structural brain changes in schizophrenia</td>
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<td>what we have learned over the last 20 years</td>
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<tr>
<td>14:45-16:25*</td>
<td>Symposium</td>
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<tr>
<td></td>
<td>S.06 Compulsivity across disorders &amp; scientific café</td>
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<td>S.08 Diabetes and Alzheimer’s &amp; scientific café</td>
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<td>S.11 Autism and schizophrenia &amp; scientific café</td>
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<td></td>
<td>S.12 New treatment targets in psychiatry &amp; scientific café</td>
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<td></td>
<td>E.03 Treatment of tic disorders &amp; scientific café</td>
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<tr>
<td></td>
<td>Satellite symposium - C.02 Optimizing care in schizophrenia</td>
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<td>C.03 Imaging of cognition in depression</td>
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<td>C.04 Mania with depressive symptoms</td>
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<tr>
<td>16:00-18:30</td>
<td>Symposium</td>
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<td>S.01 Medication and child psychiatry</td>
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<td>S.02 Schizophrenia: long-term outcomes &amp; scientific café</td>
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<td>S.04 TAAR1 cell to clinic &amp; scientific café</td>
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<td>E.01 Mental health in Europe</td>
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<td>17:03-19:45</td>
<td>Satellite symposium - C.05 Depression and motivation</td>
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<td>C.06 Treating adults with ADHD</td>
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<td>C.07 Agitation in psychiatry</td>
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<td>C.09 Nature of schizophrenia</td>
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<tr>
<td>18:45-20:16</td>
<td>Keynote session incl. Keynote lecture</td>
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<td>KL01 Circuit dynamics of motivated behaviour</td>
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<tr>
<td>18:00-21:30</td>
<td>Welcome reception</td>
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</tbody>
</table>

**CLINICAL TREATMENT TRACK** **CLINICAL RESEARCH TRACK** **INTERFACE RESEARCH TRACK** **PRECLINICAL RESEARCH TRACK** **EDUCATIONAL TRACK**
* Scientific café (16.25-16.55)  ** Junior Scientists symposium