Seoul
CINP 2016

Featured article
Depression circuitry – an integrated approach

Professors Anthony Grace, USA, and Heon-Jeong Lee, Republic of Korea, co-chaired a fascinating first symposium on Sunday morning at CINP. Its aim was to give an integrated view of the latest thinking about the circuitry of depression and how imaging studies can help facilitate the development of more effective therapies.
Page 5

Read more

Interview with CINP President, Professor Shigeto Yamawaki

Interview

Professor Shigeto Yamawaki, President of the CINP

At the 30th international CINP congress in Seoul, Korea, we were privileged to speak with Professor Shigeto Yamawaki, President of the CINP, about changes and developments in the field and the value of medical education and knowledge exchange in the future.

→ **Read article online**

> The field of psychiatry is developing in a number of areas. Development of contemporary cognitive, affective and social neuroscience using neuroimaging are especially prominent.

Psychiatry is evolving as a profession. The number of patients with mental disorders in all life-cycle phases, from childhood to old age, is increasing all over the world and is responsible for enormous social and economic loss. The expectations for psychiatry as a profession are getting higher.

However, such complex and heterogeneous psychiatric disorders still cannot be classified and diagnosed precisely by diagnostic criteria such as DSM and ICD. Professor Yamawaki encourages us to establish objective diagnosis by utilizing findings of recent brain science research, and develop innovative treatments. If not, the expectation towards psychiatry may turn into disappointment.

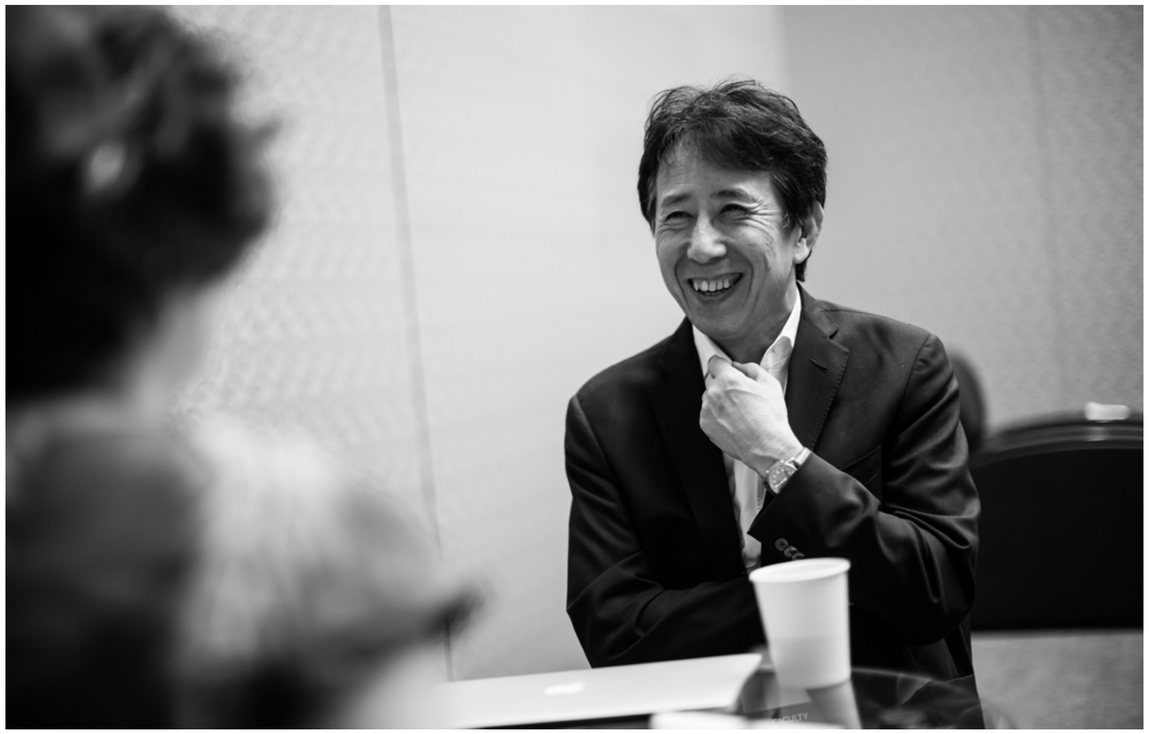
The field of psychiatry is developing in a number of areas. Development of contemporary cognitive, affective and social neuroscience using neuroimaging are especially prominent. Molecular target data are being accumulated using genome and epigenome research and proteomics; however, issues such as reproducibility have arisen. In order to elucidate the pathophysiology of complex psychiatric disorders with variant, heterogeneous conditions, and to establish objective diagnosis, we need large cohort studies which have incorporated brain function and biomarker measurements, as well as clinical evaluation.

While there are many hurdles to achieving breakthroughs in our field, the theme of the 30th CINP congress is one to strive for - Innovation Integrated with Neuroscience for Mental Health.

The CINP has made active efforts to accelerate the development of biomarker and objective diagnosis by precompetitive collaboration of public and private institutions - a collaboration of basic and clinical academia, pharmaceutical companies and regulatory agencies.

By applying every brain science approach such as genomics, proteomics and neuroimaging and data analysis techniques, he is confident that we will see breakthroughs in the future.
The full video interview with Professor Yamawaki will be posted on www.progress.im. Also, look out for our interview with Professor John Krystal, CINP President Elect, in which we hear about future plans for the CINP as he takes the position of CINP president.

Artificial intelligence offers new perspectives on psychiatric diagnoses



Computational neuropsychiatry is a new discipline exciting huge interest for its potential in diagnosis and possibly even management of psychiatric diagnoses. Progress in Mind had a unique opportunity to interview Dr Mitsuo Kawato, of the Advanced Telecommunications Research (ATR) Institute International in Kyoto, Japan ahead of his plenary lecture at CINP 2016 on this intriguing subject. We report on his presentation and shared insights.

→ **Read article online**

Neuroimaging biomarkers may soon become a clinical reality

Artificial intelligence is a term that conjures up images of robots and machines capable of intelligent thought. In the field of psychiatry, artificial intelligence principles and practices are being used to take neuroimaging data and develop biomarkers that could support a clinical diagnosis and quantify and describe that diagnosis.

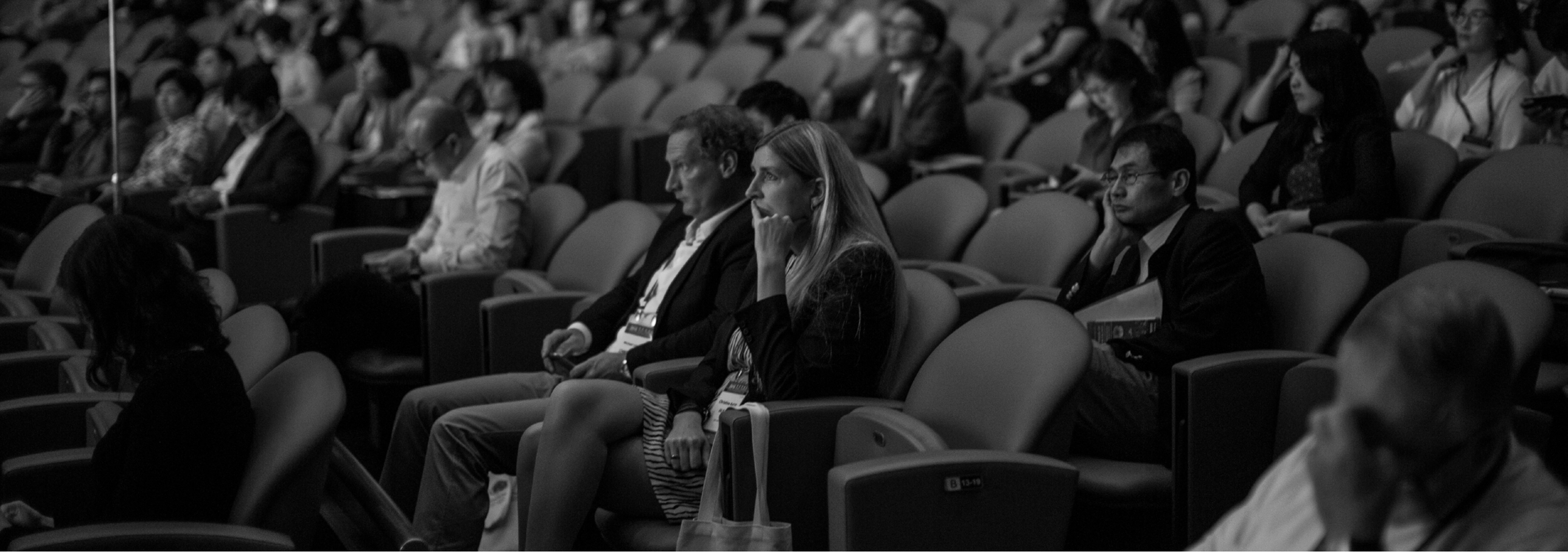
Neuroimaging biomarkers

Dr Mitsuo Kawato of the ATR Computational Neuroscience Laboratories in Kyoto, Japan has been involved in research that for the first time defines the biological dimension – an imaging dimension – of a psychiatric diagnosis. Research published by Dr Kawato and colleagues in Nature Communications in 2016 ranked among the top 1% of viewed scientific papers published in same period. Dr Kawato believes this is because the paper dealt with an artificial intelligence application that could define autism spectrum disorder (ASD) using neuroimaging-based classifiers – or biomarkers. The research team are using the application to define and create neuroimaging biomarkers for major depressive disorder (MDD), schizophrenia, obsessive compulsive disorder (OCD) and chronic pain syndromes.

Taking data from 200 patient samples, and looking at 10,000 neuroimaged connections and 140 brain regions, Dr Kawato said it had been possible, using sophisticated artificial intelligence algorithms, to select the 16 functional connections that are specific for and discriminate ASD from normal (typically developed) brains. He explained that this type of computational neuroscience allows the description of one scale – one dimension – that plots the Gaussian distribution for typically developed individuals and another that plots the distribution for, in this case, ASD. This biomarker tool therefore also allows for a quantitative assessment – or score for the diagnosis.

Distinctions and connections

What is more, Dr Kawato explained that these neuroimaging biomarkers being developed for different psychiatric diagnoses not only define and describe a specific diagnosis, but highlight distinctions between diagnoses and similarities and closeness of certain diagnoses. For example he said that the ASD neuroimaging biomarker could not distinguish MDD patients from their controls, but showed some ability to discriminate between patients with schizophrenia and controls. According to Dr Kawato, this closeness of ASD and schizophrenia is in keeping with historical views that these conditions shared some commonality and with genetic studies indicating common loci for schizophrenia and ASD. →



Dr Kawato believes that neuroimaging biomarkers will be a valuable support to clinical diagnosis and will become a reality of practice and diagnosis in the near future. He told Progress in Mind: “In other disciplines of medicine like cardiovascular medicine and oncology for example, it is common to examine biomarkers – be they blood biomarkers or imaging scans (fMRI and PET). But in psychiatry, we haven’t had that kind of quantitative measurement to support the clinical diagnosis.”

“We had two objectives. The first was to provide objective scales to support clinical diagnosis with neuroimaginging based biomarkers.” Dr Kawato then said that if these biomarkers prove to be really reliable, it may be possible to use these tools to explore and describe the neurocircuits and brain regions with correlates for predicting certain diagnoses.

Resting state data

Dr Kawato described how neuroimaging biomarker looks at resting state fMRI, with a 5-10 minute scan providing the data to allow a quantitative diagnosis. He said that in the future it might be possible, not just to diagnose one condition, but to use all the available biomarker scales to see if, in the case of ASD for example, a person has a condition more predominantly located between ASD and schizophrenia – or locate closer to the normal healthy position.

Biofeedback

These developments in neuroimaging biomarker research might also have applications in the management of psychiatric disorders. Dr Kawato said that real-time feedback based on imaging biomarkers might have therapeutic applications in some diagnoses. He explained: “We can define “ASDness” and then in real-time we can feed this back to our patient as a score. It’s something a bit like cognitive behavioural therapy or psychotherapy, although a little bit more high tech.” Dr Kawato said that pilot studies in ASD, MDD and chronic pain conditions, have been looking at this real-time feedback. According to Dr Kawato, outcomes may depend on the learning capability of a given patient and some conditions may be more amenable to reinforcement conditioning than others.

For the future, Dr Kawato said that neuroimaging biomarkers may soon become a clinical reality and he hoped that machine learning algorithms based on biomarkers might also find a place as another modality in the management of psychiatric disorders.

Depression
Depression circuitry – an integrated approach

Professors Anthony Grace, USA, and Heon-Jeong Lee, Republic of Korea, co-chaired a fascinating first symposium on Sunday morning at CINP. Its aim was to give an integrated view of the latest thinking about the circuitry of depression and how imaging studies can help facilitate the development of more effective therapies.

→ **Read article online**

> … the situation surrounding 5HT receptor binding in MDD is complex and much still remains to be discovered.

Serotonin in depression – a lesson from SAD perhaps?
In the first of four talks, Professor Gitte Moos Knudsen, Denmark, gave an overview of the serotonin system and its contribution to controlling intrinsic brain activity in humans. Of particular interest were the large number of Positron Emission Tomography (PET) studies that have sought to identify the influence of the various regions thought to be involved in depression and mood disorder.

A total of 34 studies investigating the effect of mood disorder on 5HT receptors are compiled in a recent review. Although in general it appears that post-synaptic $5HT_{1A}$ receptor binding potential is decreased in mood disorders, this finding was not consistent across all the studies included. This was also the case for $5HT_{2A}$ and $5HT_{1B}$, both pre-and post-synaptic. Likely reasons for such inconsistencies include use of different radioligands, poor statistical power, disease heterogeneity, medication associated differences between studies and cross-sectional data acquisition. This inconsistency of results between studies suggests the situation surrounding 5HT receptor binding in MDD is complex and much still remains to be discovered.

However, a longitudinal study that exemplifies nicely the influence of serotonin transporter (5HTT) binding on outcome considered seasonal affective disorder (SAD). Patients in Copenhagen were assessed both during the summer (when they were not affected) and again in winter. Patients with SAD appear unable to down-regulate their 5HTT binding globally. This was not the case when they were unaffected by SAD. The degree of lack of availability of 5HTT appears related to symptom severity. Thus, it may be possible to predict those most likely to be affected by SAD and possibly effect a specific therapy.

MRI – discovering hotwired networks
Several promising approaches in high-field functional magnetic resonance imaging (fMRI) in depression were presented by Professor Quiyong Gong, China. He explained how the circuitry associated with depression correlates with refractoriness in treatment-resistant depression and with suicidality. Such associations could facilitate diagnosis and likely response to antidepressant therapy in the future.

For example, diffusion tensor imaging studies, a type of MRI that facilitates examination and characterization of neural connectivity in the brain, have identified abnormal alterations in the frontal-striatal circuits that pass through the anterior limb of the internal capsule in suicidal patients with MDD. Additionally, such studies have identified functional connectivity differences related to responsiveness to treatment. Thus, patients with non-refractory and refractory MDD exhibit changes in their limbic-striatal-pallidal- thalamic and thalamo-cortical circuits, respectively.

Professor Gong also described brain connectosome studies in patients with MDD. Changes to core networks identified using resting fMRI are seen in this heterogeneous condition. It has been postulated that the default mode network, the salience network and the central executive network are linked together through the dorsal nexus and could explain how MDD symptoms arise in discrete clusters, such as rumination or excessive self-focus.

Thus, high-field MRI allows investigation of brain circuitry and connectosomal abnormalities, not only giving us a tantalizing glimpse of the underlying psychopathology of MDD but also a means of facilitating its early detection, assessment of prognosis and intervention. →

Dopamine - change of focus in depression
Professor Anthony Grace presented work in animal models of depression – but with a dopaminergic perspective.

Considerable evidence has now accrued supporting a role for dopamine in depression. For example, exposing laboratory animals to chronic mild stress (CMS) over a 4-6 week period generated behaviour, assessed using the forced swim test or learned helplessness, that mimics depression.

What impact do such stressors have on the dopaminergic system in these animals? Examination of activity in dopaminergic neurons through probes placed in the ventral tegmental area (VTA) showed a reduction in the number of neurons available to respond to reward stimuli when these were offered. Such a finding suggests that this response could be the murine equivalent to human anhedonia, a feature usually associated with depression.

What happens in terms of dopaminergic activity in the murine equivalent of Brodmann Area 25 - an area associated with MDD? Activation of the infralimbic prefrontal cortex (ILPFC) in normal rats suppresses VTA DA neuron activity, primarily in the medial VTA while activation of the lateral habenula (LHb) inhibits such activity in the central and lateral VTA. In stressed rats, however, only ILPFC inactivation restores VTA DA neuron activity – inactivation of the LHb had no restorative effect.

The effects of ketamine in rats exposed to learned helplessness has also been examined. In these animals, decreased DA neuron activity and long-term depression in the hippocampus-accumbens are noted. Thus, lack of hippocampal drive appears not to compensate for any ILPFC down-regulation. Just one dose of ketamine, however, restores hippocampal-accumbens drive, normalizes dopamine neuron firing, and reverses behavioural despair in the forced swim test.

Taken together, it appears that the ILPFC and LHb regulate different subpopulations of DA neurons within the mesolimbic system. Such differential regulation can help explain the unique restorative capacity of ILPFC inactivation in reversing the abnormal DA system hypoactivity observed in stressed rats.

DREADD and optogenetics – the way ahead in depression
Professor Alan Fraser, USA, is interested in ketamine. More specifically, he is interested in describing the circuits underlying the sustained effects of a single ketamine injection and understanding how ketamine impacts the ventral-hippocampal to medial PFC pathway.

Three pieces of evidence support the idea that the VHipp-mPFC pathway is needed for ketamine to elicit its anti-depressant effect:

- Bilateral lidocaine inactivation of the ventral hippocampus (vHipp) in animal models at the time of ketamine administration completely blocks the sustained anti-depressant response to ketamine at one week post-injection. (This anti-depressant effect was assessed using the forced swim test.)
- Optogenetic inactivation of the VHipp-medial PFC pathway completely reversed the anti-depressant-like effects of ketamine at the time of testing.
- DREADD-Gq activation of the VHipp-mPFC pathway but not the VHipp-NAC pathway produces an anti-depressant response.

Thus, the sustained anti-depressant-like effect of ketamine is mediated by activation of a circuit from the VHipp to the mPFC.
Is it possible to mimic ONLY ketamine's anti-depressant effect?

Potential selective inhibition of the α5-$GABA_A$ receptors in the hippocampus or activation of 5-HT_4 receptors present there produces a sustained anti-depressant-like effect. Ketamine's reinforcing effects, as shown by its being self-administered in animal experiments, likely account for its abuse-related properties. By contrast L655 708, a selective negative allosteric modulator of the α5-$GABA_A$ receptor, is not self-administered by rats, showing that ketamine's good and bad effects can be teased apart. This suggestion is reinforced when considering that, unlike the α5-$GABA_A$ receptor inverse agonists or RS67333, a 5-HT_4 partial antagonist, ketamine disrupts the inhibition of the acoustic startle response. Thus, it should be possible to develop new antidepressants that exhibit the beneficial effects of ketamine without the negative ones.

The field of psychiatry is developing in a number of areas. Development of contemporary cognitive, affective and social neuroscience using neuroimaging are especially prominent.

Depression
Circuit breakers – and why imaging studies are crucial to drug development

Interview
Professor Anthony Grace, Professor of Neuroscience and Professor of Psychiatry and Psychology at the University of Pittsburgh, Pittsburgh, Pennsylvania, US

Depression is no longer the sole province of serotonin-based research. Imaging studies have uncovered the role dopamine might play. We spoke with Professor Anthony Grace about the important reciprocal relationship between clinical and basic research in psychiatry, as well as finding out more about the session 'Uncovering the circuitry of depression and how it guides the development of novel treatment strategies' that he will co-chair at the CINP 2016 congress in Seoul, Korea.

→ **Read article online**

Is it important to draw from both clinical and basic research when trying to understand the circuitry of human depression?

It's essential! Clinical research, especially imaging studies, gives us an idea of where to look while basic research on drug effects tells us what potential pathophysiology there might be in depression. That leads us to animal models where we can try and find out what brain circuits normally do and how these might be disrupted in depression.

The give and take between the clinical information we have, the basic information we have and any treatment responses we can elicit enables us, in a co-ordinated manner, to find out what's wrong with the circuit and how best to fix it.

Why are human brain imaging studies (fMRI and PET) helpful in exploring depression circuitry and the pharmacology of depression?

Research into depression has mainly focused on serotonin, largely based on the nature of the antidepressants available and whose effects were discovered by chance. In rat models of depression, however, the activation of Brodmann area 25 [aka subgenual cingulate area and the rodent homolog, the infralimbic prefrontal cortex] in the frontal cortex decreases the responsiveness of dopamine neurons and elicits depressive signs. This suggests that the dopaminergic system is at least partly involved in depression pathogenesis.

Another lucky find is ketamine. In animal models of depression, ketamine (a type of N-methyl-D-aspartate glutamate receptor (NMDAR) inhibitor) normalises dopamine function by rebalancing two competing dopaminergic circuits – an overactive frontal cortex and an underactive hippocampus. Imaging studies in humans allow us to study these circuits and ascertain whether ketamine is doing the same thing in human brains as it is in animal models.

What key points and learnings can delegates at CINP hope to gain from attending session S1 on the 3rd of July?

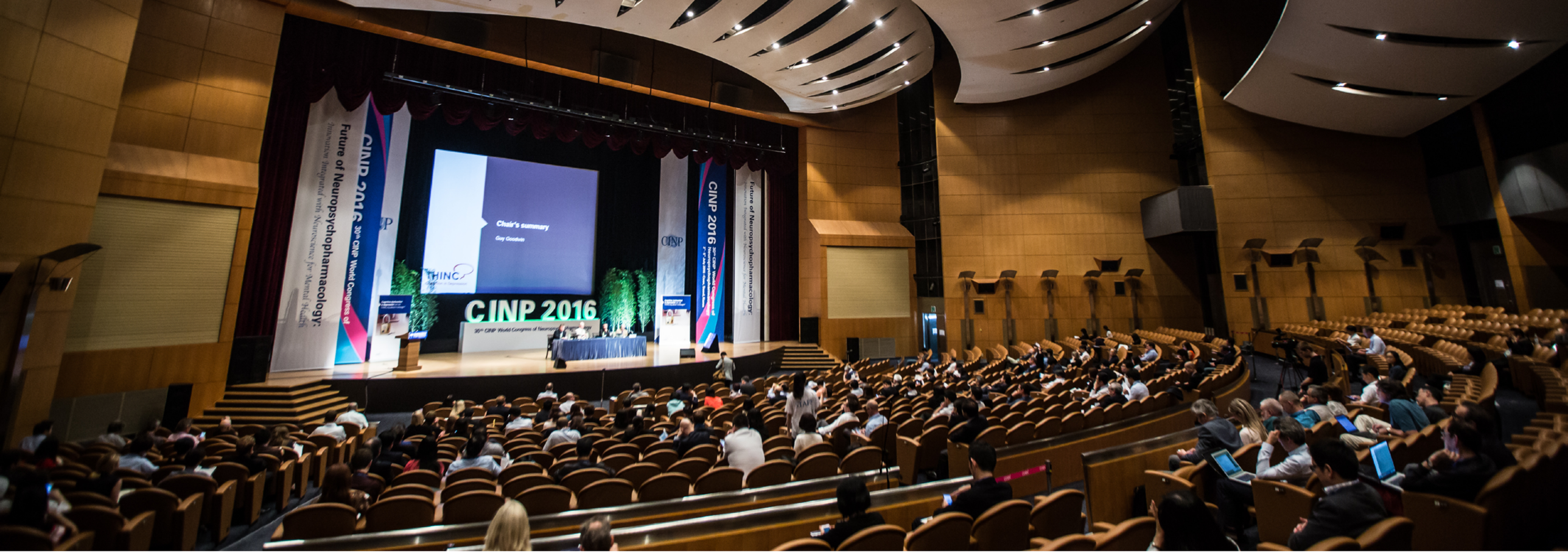
We hope to describe a circuit-based system that will allow the targeted treatment of depression. We'll do this by looking at some of the various clinical investigations and animal model studies in which specific areas of the brain have been identified as the sites of depression pathophysiology.

Thus, we've invited Gitte Moos Knudsen from Denmark to give an overview of the brain regions associated with depression and the connectivity of these areas. Qiyong Gong from China will describe how connectivity analyses in patients might predict therapeutic response. And my co-chair, Alan Frazer from Texas in the USA will describe the depressed brain's response to ketamine and the differences between the neuronal circuits underlying its acute and sustained effects.

Overall, the symposium will provide data that translate between human depression and animal models where the key circuits involved in the development and expression of depression have been uncovered. We'll also describe how the interactions among these circuits are regulated, and how novel therapeutic targets may help to restore the balance in the brains of individuals with major depressive disorder.

Why is it important for psychiatrists to keep abreast of depression research?

Keeping abreast allows psychiatrists to have a better understanding of depression beyond the textbook: much is so new it hasn't yet entered the text book. For example, the ways the dopaminergic and serotonergic systems interact and the role of dopamine in depression symptomatology. Also, psychiatrists need to know about new ways to treat depression, and how they work. →



What do we still need to know in order to improve approaches to treatment of depression?

Understanding brain circuitry will help a lot. We need to learn more about susceptibility to mental illness and also resilience – why some people become ill while others don't and why some people bounce back when others don't.

In psychiatry we are currently seeking to personalize medicine. To be able to do this we need clinical biomarkers of disease. If we can identify, for example, susceptibility markers, we may be able to intervene in a psychosocial way not only to treat but maybe to prevent illness.

Major depressive disorders are the 'common cold' of psychiatry. It's important to understand how patients become ill – what that disease state is – so that we can figure out how best to help them. The more we know about the biology of disease, the better we can understand where it comes from.

How do you see the evolution of psychiatry as a profession?

Currently, there is a big push to find clinical biomarkers - hard diagnostic criteria - that will allow diagnoses to be made beyond the diagnostic interview and that are reproducible. Personalized medicine will eventually allow us to diagnose patients and then give them medicines that are effective for their specific condition rather than trialling a variety of drugs in the hope that one of them will work.

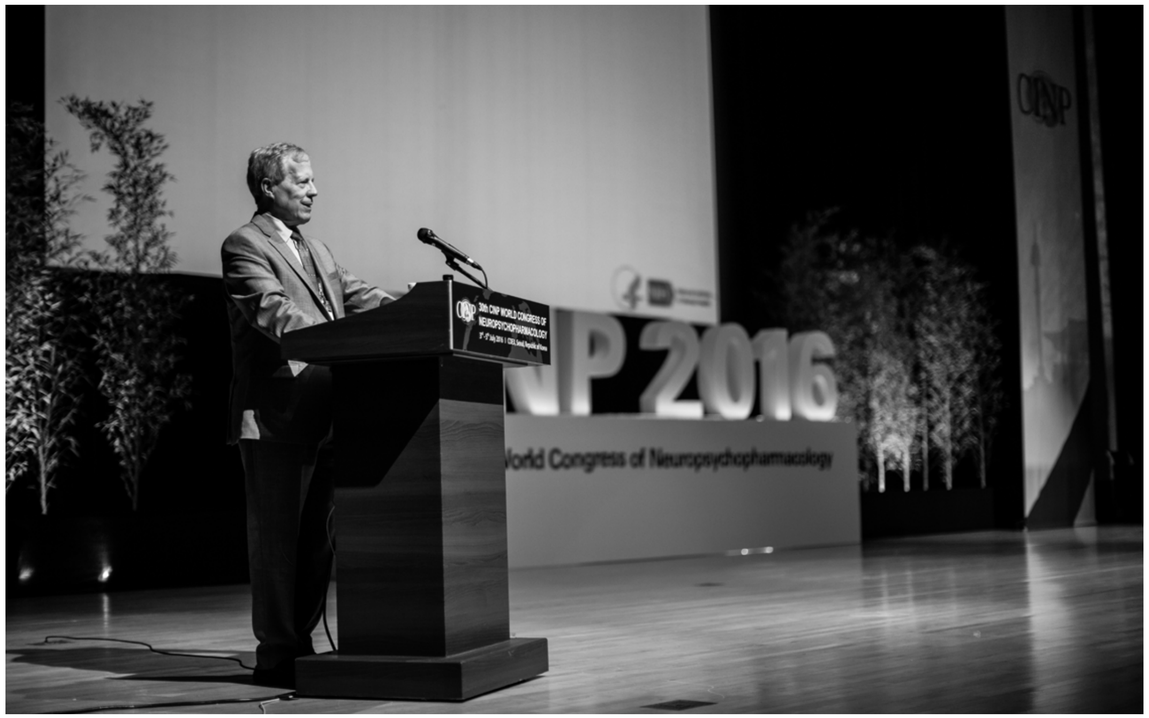
Hopefully, we will get beyond serendipity and not use drugs discovered by chance but which will act to actually fix whatever is wrong with the brain.

What do you think have been the most important breakthroughs?

Ketamine and its speed of action. Patients who are acutely suicidal cannot wait for drugs to work.
Also, imaging studies which have pointed to Area 25 and its hyperactivity. Now we have a target for further studies to determine exactly what is driving the pathology of depression.

> The symposium will provide data that translate between human depression and animal models where the key circuits involved in the development and expression of depression have been uncovered.

RDoC – entering the matrix



RDoC (Research Domain Criteria) is a new research framework for studying mental disorders. It integrates many levels of information (from genomics to self-report) to better understand the basic dimensions of functioning underlying the full range of human behaviour from normal to abnormal. Dr Bruce Cuthbert, the Acting Director of the National Institute of Mental Health (NIMH) and Head of the NIMH's RDoC Unit, gave a description of just how RDoC works and how it might influence 21st century psychiatric drug discovery.

→ **Read article online**

RDoC was devised because current practices in clinical diagnosis (DSM, ICD) are no longer optimal for contemporary research. For example, diagnosis currently is based on signs and symptoms, behavioural data do not align well with DSM or ICD categories, disorders are heterogeneous syndromes, almost all of which are dimensional in severity.

Research is categorical
The main problem researchers have in adopting the RDoC approach is that diagnostic categories drive the entire research system. However, things need to change. For example, in a plea to drop the term 'schizophrenia' it was pointed out that only 30% of those with psychotic illness have schizophrenia. Thus, not only are 70% of those with other psychotic illnesses being ignored, but the implication is that we really don't understand schizophrenia – if it exists as a single entity – at all.

Furthermore, with the marked advances in our understanding of the operation of the main brain circuits and the behaviours they implement, instead of continuing with symptom-based definitions, can we not understand mental disorders as deviations from the normal functioning of these brain systems, Dr Cuthbert suggested. Such is the overarching goal of the RDoC.

Enter the matrix – construct identification
RDoC aims to develop a research framework for studying psychopathology based on dimensions of observable behaviour and neurobiological measures. To do so, fundamental 'constructs' that span multiple disorders, e.g. executive function, affect regulation, must be identified. The full range of the variation within each construct then has to be determined using as many components as are available, be they genetic, neurobiological, behavioral, environmental or experiential. Crucially, reliable and valid measures of these fundamental components must be developed for use in basic and clinical studies.

Homogeneity is the key
Suffice to say, RDoC is not an alternative nosology – simply because as yet it isn't known exactly what an integrated multi-measurement diagnostic system looks like. However, it is a focused research initiative moving towards a new classification system. The idea underlying this is that by gaining a deeper understanding of the psychological and biological systems related to mental illness, it should be possible to identify new biomarkers and biosignatures for mental illness. These, in turn, should facilitate more homogeneous groupings for the underlying psychopathology and pathophysiology. The development of new, enhanced interventions and treatments should follow thereafter.

Always under construction
Dr Cuthbert was adamant that RDoC is a dynamic initiative. The matrix can be expanded with new research discoveries as these become available. For example, a motor construct domain and integration of new connectome data are planned for inclusion soon.

Of course, challenges exist to be overcome. Two of the key issues highlighted were granularity and biomarkers; granularity because determining the size of change to be assessed when defining normal and abnormal function is likely to be challenging, and biomarkers because it needs to be clear exactly what the biomarkers are marking – is it identification of a DSM/ICD disorder or of individual differences within a DSM/ICD disorder?

RDoC – a fruitful approach?
Already evidence from studies such as the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) study is mounting to show that the RDoC approach is likely to be fruitful in making homogeneous subgroups from a heterogeneous psychotic population.

And, there may also be movement on overcoming the requirement for clinical studies to classify patients based on the DSM diagnostic categorization. This follows the EMA and FDA approvals of cognition as an indication in depression and in schizophrenia clinical studies. Indeed, the FAST-MAS study was devised solely on RDoC criteria. Its aim was to recruit patients with anhedonia to examine their responses to kappa opioid antagonism and the primary outcome was to be the engagement of circuitry related to hedonic processing. Whether future studies will be undertaken using such an RDoC-inspired approach is keenly awaited.

Schizophrenia
Uncovering dopamine deficits in schizophrenia through advanced imaging

Interview
Professor Anissa Abi-Dargham MD,
Professor of Psychiatry and Radiology at Columbia University Medical Center and Director of the Division of Translational Imaging at the New York State Psychiatric Institute, New York, USA

Neuroimaging tools offer invaluable perspectives on the neurochemistry and function of the brain in schizophrenia. In the lead-up to the international CINP 2016 congress in Seoul, Korea, we spoke with Professor Anissa Abi-Dargham, from New York in the USA, about how imaging is revealing unexpected aspects of dopaminergic dysfunction to be characteristic features of schizophrenia.

→ **Read article online**

Can you describe how brain imaging techniques help our understanding of the neurochemistry of schizophrenia?

Imaging techniques allow us to examine anatomy and function of the brain in live subjects, which is a unique opportunity to understand how the findings in the brain relate to behaviour and function, as well as symptoms in patients.

What has positron emission tomography (PET) imaging revealed about circuitry and dopaminergic dysfunction in schizophrenia?

PET imaging allows us to look at receptors and neurotransmitters in a way that is not possible with magnetic resonance imaging (MRI). We are able to access and study dopaminergic dysfunction in patients with schizophrenia and we have confirmed that the condition is associated with excessive striatal presynaptic dopamine leading to excess D2 receptor stimulation. This in turn is associated with psychosis. But what has been harder to do is to examine other parts of the brain – like the frontal cortex – areas involved in cognition, executive functions and working memory. The latest PET imaging techniques now show us that there are actually profound deficits in cortical dopamine and that indeed there are dopaminergic deficits in many other regions outside of the striatum.

Why is it important to understand mechanistic changes in the schizophrenic brain?

Imaging techniques allow us to investigate changes in the very early stages of the disease, and can be used to assess effects of treatments for schizophrenia. There have been imaging studies of the prodromal stage of schizophrenia. Imaging studies are helping to show that our current treatments – based on D2 blockade – may not be enough to address the dopaminergic changes in schizophrenia. Now that we know there are areas of the brain where there is too little dopamine release – we may need to rethink our treatment approaches, and work harder to find treatments to enhance and manage these dopaminergic deficiencies.

What are the main key points and learnings for delegates at CINP attending your plenary lecture on the 3rd of July?

I hope delegates will get an update on the topography of dopaminergic dysfunction in schizophrenia, the nature of the dopaminergic dysfunction, and how the different aspects of dopamine dysfunction correlate with the symptom domains of schizophrenia. For example the striatal dopamine excesses appear to correlate with psychosis, while the cortical deficits seen on imaging appear to relate to abnormal activation during performance tasks and poor working memory capacity.

Delegates will also come to understand the dopaminergic changes in schizophrenia in the context of lots of other abnormalities and we will discuss whether the changes we see in schizophrenia are a downstream consequence or are more proximal to disease course.

We need to know more about the cellular and molecular events that bring schizophrenia about – and that will come with more study – looking at stem cells from patients with schizophrenia, studying extreme phenotypes, developing better animal models of schizophrenia, and tapping into the explosion in basic understanding of genes conferring risk for schizophrenia.

Schizophrenia
Multifaceted aspects of dopamine dysfunction in schizophrenia

Dopamine dysfunction is a fundamental feature of schizophrenia. Now advances offered by neuroimaging-research are helping clinicians and scientists scrutinize the crucial changes and aberrations that could hold the clues to improved disease management. In this feature article, we report and summarize the opening plenary lecture at CINP 2016, given by Professor Anissa Abi-Dargham from New York, USA, on this hot topic.

→ **Read article online**

Neuroimaging offers a powerful tool to dissect and potentially explain the functional and neurochemical processes at play in schizophrenia. Decades of research identify dopamine as a key player in the disease process, and now neuroimaging looks set to provide some new, much-needed, perspectives to fuel further research and potentially change approaches to patient care.

Shine a light

Why is neuroimaging so illuminating? According to Professor Anissa Abi-Dargham, the newly-appointed Professor of Psychiatry and Vice Chair for research in the Department of Psychiatry at Stony Brook University in New York, USA, it's the ability of neuroimaging to tease out the multifaceted aspects of dopaminergic dysfunction at play as schizophrenia evolves, emerges and progresses as a clinical entity.

Professor Abi-Dargham provided an exhaustive review of decades of research that has been seated in the idea that dopaminergic dysfunction is a downstream effect of many other alterations in the brain. Dopaminergic pathways and processes in schizophrenia have been implicated ever since it was shown that the dopamine antagonist chlorpromazine had antipsychotic activity.

DA deficits as well as excesses

Professor Abi-Dargham urged delegates to consider the evidence that shows that - beyond excessive striatal presynaptic dopamine levels and excess D2 receptor stimulation - schizophrenia appears to involve profound deficits in dopamine in the cortex and other extra-striatal regions.
There appears to be more to the condition than hyperactivity of transmission mediated by D2 receptors in the limbic system.

An interconnected and evolving process

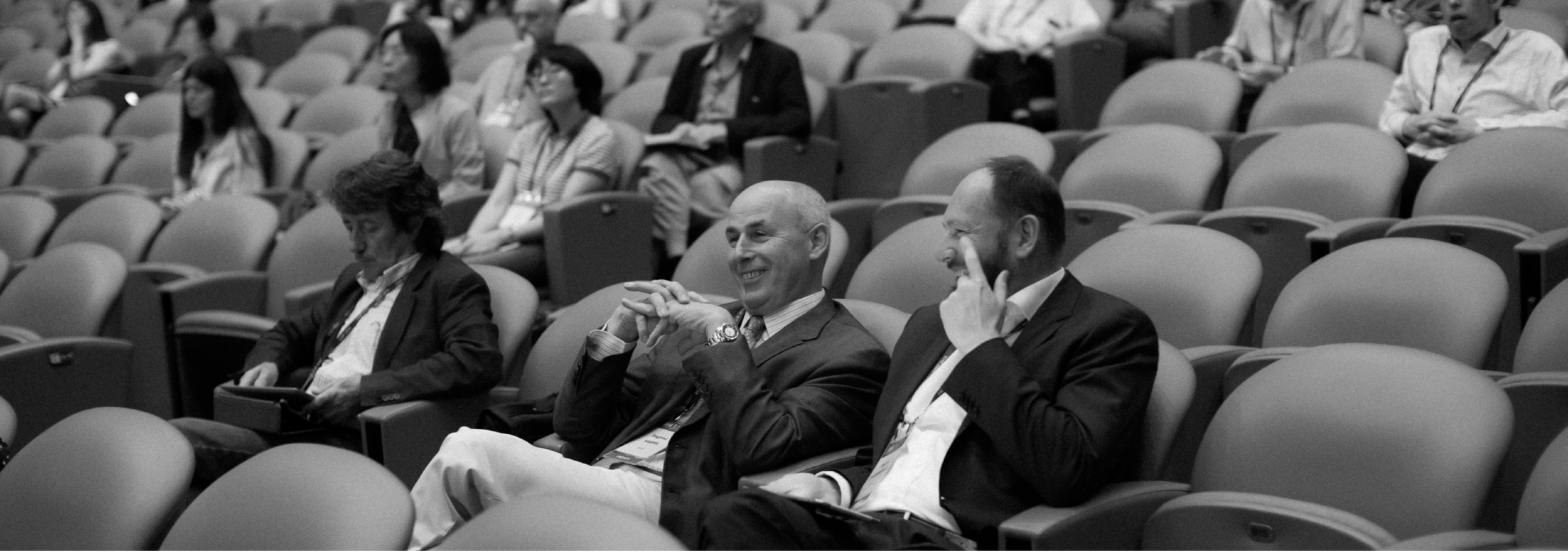
She also reminded delegates that many excitatory and inhibitory processes in cortical circuits are tightly modulated by dopamine, and that key aspects of dopaminergic function in these regions arise as a result of events and processes at play in adolescence and maturation.

Professor Abi-Dargham explained that changes in cortical inhibitory circuits in the juvenile cortex during adolescence are implicated in the transition to schizophrenia. Initially D1 receptor stimulation predominates, with D2 receptor stimulation becoming more prominent during adulthood.

Sensitivities also affected

Imaging studies have allowed researchers to measure the number and density of synaptic (pre and post) D2 receptors and their occupancy, and the impact of schizophrenia on dopamine uptake, synthesis and storage. The availability of radiolabeled ligands with different binding affinities for dopamine receptors allows for comparison of dopaminergic activity across different brain regions.

In schizophrenia, while there is excess dopamine release in the striatum, it appears from imaging studies that specifically, it is changes in the rostral caudate, and stimulation of dopamine receptors in this brain region, that may be linked with psychosis. Excessive dopamine appears to affect brain plasticity within the striatum, weakening the rostral caudate connectivity with the rest of the brain. →



Wide-ranging dopaminergic dysfunction
Professor Abi-Dargham said that it seems too little dopaminergic activity in the ventral striatum is linked with negative symptoms in schizophrenia, while too much activity might lead to psychosis. She said that dopamine appears to have less influence in the sensory motor striatum.

Not a level playing field
Imaging studies also suggest that some patients may not display the elevations in dopamine that are classically associated with the disorder – and as such may not respond as well as other patients to antipsychotic therapies that target and aim to block dopaminergic effects. Likewise, there may be some patients such as those with co-morbid substance abuse, who may have altered post-synaptic D2 receptor function, in the face of reduced dopamine release.

Dopamine and cognitive function
Professor Abi-Dargham described studies examining the neural correlates of working memory impairment in schizophrenia and their relation with dopaminergic dysfunction.

Research from her own group using PET fMRI suggests that there may be deficits in dopamine release within the dorsolateral prefrontal cortex (DLPFC) that are part of a widespread dopaminergic deficit affecting many cortical and extrastriatal regions, including the mid brain.

Expanding the hypothesis on dopamine and schizophrenia
According to Professor Abi-Dargham, neuroimaging studies – preclinical and clinical – are helping to expand ideas on dopaminergic dysfunction in schizophrenia. The striatum appears to be the only region of the brain with excessive dopamine release in schizophrenia, although it is not clear if this is due to a small subset or abnormally firing cells or linked with changes in local regulation of dopaminergic function. Professor Abi-Dargham said that there is evidence for extrastriatal deficits and she described mid brain dopamine deficits as puzzling.

Future areas that Professor Abi-Dargham said are ripe for exploration using neuroimaging include study of the evolution of dopaminergic dysfunction in schizophrenia to establish what changes are already brewing as a result of genetic predisposition, study of dopaminergic plasticity including changes in dopamine turnover and receptor expression and activity, and more investigation of the effects of other neurotransmitter systems on dopaminergic function. She added that stem cell research might offer new ways to explore the cellular mechanisms and connectivity changes that determine the machinery and pathways of schizophrenia. Professor Abi-Dargham said that new insights will help inform and improve approaches to treatment of schizophrenia.

For references please go to
http://progress.im/en/content/multifaceted-aspects-dopamine-dysfunction-schizophrenia

Nurture and networks – supporting the next generation of scientists and psychiatrists

Interview

Dr Sahoo is currently working as a Consultant Psychiatrist with Queensland Health, practicing at Ipswich Hospital in Brisbane Australia where he is also a Senior Clinical Lecturer in the School of Medicine at the University of Queensland. Prior to this he was a Clinical Fellow at the University of British Columbia, Vancouver, Canada.

Young scientists, brimming with ideas and eager to progress, are vital for the future of psychiatry. Ahead of the international CINP 2016 congress in Seoul, Korea, we spoke with Dr Saddichha Sahoo, a member of the CINP Young Programme Sub-committee about how he sees the evolution of psychiatry, and got his views on how upcoming psychiatrists and researchers can get ahead and contribute to advances in the field.

→ **Read article online**

Tell us a little bit about the CINP Young Programme

I've been associated with the CINP Young Programme for around 5-6 years now. CINP has been one of the organisations that supports young scientists in the field of clinical psychopharmacology. For the past year I've been involved a s coordinator of the Young Scientists group and we've tired to extent that inot having a session at the CINP 2016. This will be a mix of topics and an opportunity to speak about the experiences of young scientists. We have speakers who will talk about the challenges in being a young scientist and research fellow, getting academic positions, applying for grants and overcoming barriers to progress. I will also speak about the importance of achieving the right work-life balance!

How do you see the evolution of psychiatry as a profession?

I've been lucky enough to practice in three continents – I've worked in India, Canada and now Australia. And I think there has been greater and growing acceptance of psychiatry in general and within the medical fraternity. I'm really pleased that psychiatry as a whole has started to move away from just a descriptive science to a more evidence-based science, without loosing its humanistic touch.

In the future – I think we will aim to achieve more holistic treatments for our patients – rather than just targeting disorders with a single medication or cocktail of medications.

Is medical education in psychiatry changing?

Medical education will always be delivered in different forms. I'm a faculty member at The university of Queesland and I'm also involved with the education committee of the American College of Clinical Pharmacology – and increasingly we see that on-going medical education can be delivered on-line rather than through didactic lectures. Webinars and on-line learning mean that you can undertake education in your own time, and allows the integration of different topics and different branches of medicine within educational programmes. This makes things more interesting. Audiovisual advances also mean that on-line medical education is engaging.

What about the role of medical societies in supporting change in the field and medical education?

Medical societies like CINP are among the biggest supporters in motivating, fostering and financially supporting young researchers who would otherwise not have the opportunity ort carry out their ideas. Medical societies give us the platform and the financial backing to come to international congresses where the doyens of research and academia assemble. It helps and leads to networks which are essential to supporting the brightest young researchers move ahead in their careers. Young scientists can come back enriched and share their knowledge – helping to pay back some of the kind support and backing they get from their current institutions. I can use the learnings from meetings in my organization.

What are the main challenges facing young scientists and researchers today?

I think the biggest challenge is that lack of a network or a mentor to give a push in the right direction. And probably the fact that often you have to seek out the avenues available, all by yourself. CINP has become increasingly visible in recent years as trying to support young scientists and foster a network.

What else could happen to make things easier for young researchers in psychiatry and neuropharmacology?

Personally, I have benefited the most from having a very interested mentor. It can also be good to work with and have a group of mentors – maybe spanning different fields. This helps your research evolve. Four interested mentors who you can lean on and tap when you need advice – that would be ideal.

What are some of the hot topics at CINP and in the field in general?

Being a psychopharmacologist, I'm looking forward to seeing if there are newer methods of delivery of psychotropics – because in some ways we've reached a peak in innovation in psychopharmacology – but yet we need to have antidepressants and other treatments which are longer acting, psychotropics with lesser propensity for side effects, or combinations. If you think about cardiology – that's a field that was revolutionized thanks to use of combinations of drugs acting in different ways and on different risk factors and symptoms. If we could something similar in psychiatry, it might change the way we treat certain conditions.