

PSYNAPSE

ISSUE 1

RCPSYCH
NEUROSCIENCE
PROJECT

KEEPING YOU IN TOUCH WITH

NEUROSCIENCE

Welcome to the first issue of *PSynapse*, the newsletter that keeps you in touch with Neuroscience!

The Royal College of Psychiatrists (RCPsych) is running a 5-year programme to transform psychiatric training in the UK by integrating modern Neuroscience, with generous support from The Gatsby Foundation and The Wellcome Trust.

In its first phase, the focus of the RCPsych Gatsby/Wellcome Neuroscience Project was on the integration of modern Neuroscience in the Syllabus for the MRCPsych to ensure that it reflected up-to-date knowledge and understanding and was fit for purpose. Having achieved this in 2018, we embarked on a second phase of implementation, where our focus is on embedding these improvements and supporting the high-quality teaching of Neuroscience and a high-quality educational experience for trainees around the country. In parallel, we are encouraging the further integration of Neuroscience and Psychiatry, fostering the creation of regional networks and supporting collaboration.

PSynapse is a way to help you keep in touch with Neuroscience – the latest developments in cutting-edge research, the thoughts of leading researchers and clinicians, news and opportunities.

Visit [our pages](#) and stay up to date with all that's happening in Neuroscience at the RCPsych!



Trainees Online (TrOn) Neuroscience Trainee Editor

Are you a higher trainee in psychiatry with a passion for education and neuroscience? If so, we want to hear from you!

We are looking to appoint a Higher Trainee to the position of TrOn Neuroscience Trainee Editor to work alongside our existing Trainee Editors, Georgia Belam and Natasha Rishi, and our existing Neuroscience Trainee Editor, Jack Underwood. This is a fantastic opportunity to join the Advisory Board of this invaluable online learning resource produced by the Royal College of Psychiatrists. The successful candidate will be able to take on a hands-on approach while working remotely from anywhere in the UK or the Republic of Ireland.

We are currently inviting applications from all Higher Trainees interested in gaining experience in online publishing and passionate about education. This role will focus on development of the neuroscience aspects of modules in line with the revised neuroscience syllabus.

Applications from trainees who have not yet passed the MRCPsych examinations will be accepted provided they have a sound knowledge of and an interest in modern neuroscience, preferably gained from study or research outside of that undertaken in Core Training.

Further information can be found in the job description.

If you would like to be considered, you will need to submit a short CV (no more than 3 pages) and a statement (one A4 side) expressing interest and demonstrating experience to the Editor, Dr David Reiss, via email to: tron@rcpsych.ac.uk

Applications should be received **by 5pm on 30 September 2019** and interviews will be held in London in early October (date TBC).



Psychiatry Consortium: a strategic initiative to revitalise drug discovery in mental health

Medicines Discovery Catapult, MQ: Transforming mental health and Alzheimer's Research UK have announced the **Psychiatry Consortium**, a charity-industry partnership to accelerate innovative drug discovery in psychiatric diseases.

Supported by the Wellcome Trust, the **Consortium** of the two charities and six international pharmaceutical companies will focus on the identification and validation of novel drug targets for psychiatric diseases, including psychiatric symptoms associated with dementia.

Managed by Medicines Discovery Catapult, the **Consortium** will engage the global academic psychiatry community, creating opportunities for funding, collaboration and exchange of knowledge and skills between academia and industry.

Collectively, the strategic partners aim to provide approximately £3 million in research funding over a period of 3 years.

Despite the need, there has been a dramatic fall in psychiatric drug discovery over the last 10 years, due in part to the high failure rates of clinical trials in this field. However, advances in the understanding of disease biology combined with the emerging genetic data can inform new efforts in drug-discovery. The **Psychiatry Consortium** partners will share the high risks inherent in drug discovery and, as a collective, will work with academia to increase the number of new targets and screening assays, validated to industry standards, to support the discovery and development of new drugs.

The first call for proposals will be announced after the summer, and more information will be made available over the coming weeks at mdc.link/psycon.

Notes:

About the Medicines Discovery Catapult

Medicines Discovery Catapult is a national facility connecting the UK community to accelerate innovative drug discovery.

We provide unique scientific capabilities and act as a gateway to UK resources and expertise, supporting UK SMEs to drive the development and industrialisation of new approaches for the discovery of new medicines.

By validating new ways of discovering medicines and driving key talent and expertise across the sector, we will support the UK life sciences industry, SMEs and innovators to deliver growth for the UK economy and maintain the UK's heritage position as a global leader in medicines R&D.

Ultimately, new industrialised technologies are vital for delivering new medicines to patients, faster.

<https://md.catapult.org.uk/> [@MedDiscCat](https://twitter.com/MedDiscCat)

About Alzheimer's Research UK

Alzheimer's Research UK is the UK's leading charity specialising in finding preventions, treatments and a cure for dementia.

To help make breakthroughs possible, donate today by visiting www.alzheimersresearchuk.org or calling 0300 111 5555.

We are currently supporting pioneering dementia research projects worth over £31 million in leading Universities across the UK.

How can we challenge perceptions of dementia using only an orange? Find out more at www.alzheimersresearchuk.org/orange and help us share a better understanding about dementia. #ShareTheOrange

About MQ: Transforming mental health

MQ is the UK's leading mental health research charity, funding scientific research to transform the lives of everyone affected by mental illness.

MQ funds researchers investigating a range of conditions: depression, anxiety, schizophrenia, bipolar disorder, eating disorders and more. It brings together everything from cutting-edge neuroscience to social studies to find the answers needed.

MQ supports the next generation of mental health researchers to further understand how and why mental health conditions occur, in the effort to speed up diagnosis, improve the search for better treatments, and find ways to prevent mental illness developing.

MQ works closely with funders, charities and those affected by mental health conditions to build support for research and identify key priorities for action.

Find out more at www.mqmentalhealth.org or @mqmentalhealth



Championing Neuroscience in Scotland – The Journey Begins

Championing neuroscience in psychiatry in Scotland comes with a unique set of logistical and geographical challenges. Rather than trying to conquer this mountain blindly, we decided to try and gather some baseline opinions to help guide us through the journey.

A short electronic survey was sent out to doctors working in psychiatry in Scotland in April 2019, attempting to reach all training levels from core trainees to consultants in all four Scottish regions (North, East, Southeast and West). We had an impressive response with 142 doctors completing the survey over a 10-day period and the results have given us some interesting insights.

Participants felt that neuroscience was an important part of a career in psychiatry, with 97% agreeing that a basic knowledge of neuroscience was important for psychiatrists and 82% agreeing that keeping up to date with the latest in neuroscience research is important/ relevant for psychiatrists.

But the survey also highlighted a perceived lack of confidence with only 21% of core trainees agreeing that they had an adequate neuroscience knowledge base for their future psychiatric careers. Opinions on available resources varied widely across the different Scottish regions, although all agreed that more are needed: 19% of respondents in the North believed that there are adequate neuroscience-specific learning opportunities in their area, compared to 14% in the South-East, 11% in the West and 0% in the East.

A remarkable 92% of respondents were interested in participating in neuroscience-specific learning opportunities and 88% were interested in having access to more neuroscience-specific resources. When asked to select from a list of preferences, the most popular option was Scotland-based conferences/ seminars (81% of responders compared to 34% selecting UK-wide conferences/ seminars) followed by workshops (75%) and internet-based learning (68%). Qualitative data highlighted the difficulty sometimes experienced in attending London-based events. Additional ideas for learning opportunities, such as podcasts and video-linked forum discussions were also suggested by respondents.

Our survey shows that doctors working in psychiatry in Scotland value neuroscience as an important part of their profession and that there is a real demand for more local learning opportunities. The findings provide a foundation to devise strategies that champion neuroscience at a local level. We may be at the foot of the mountain – but we are now well equipped to pursue the summit.

Cinzia Giuntoli

CT2 trainee

RCPsych Neuroscience Champion for the West of Scotland



'Delegates gathered from around the UK for the eagerly anticipated Third Annual RCPsych Neuroscience Spring Conference in London. This year's event focused on the 'Genetics and Epigenetics of the Brain and Behaviour', promising a jam-packed day of cutting-edge Neuroscience with presentations from researchers at the forefront of their field from across the globe.

We saw how schizophrenia may share the same genetic risks with the early onset neurodevelopmental disorders such as intellectual disability, ASD and ADHD. This 'Neurodevelopmental continuum and gradient' is a major challenge to our categorical diagnostic system's validity and implies we should pay careful attention to our patients' early development during assessments.

We learnt that polymorphisms, such as retrotransposons ('jumping genes'), in the non-coding genome can affect gene expression patterns and responses to environmental challenges and are implicated in neuropsychiatric conditions.

We heard how significant advances in genomic studies of depression are helping our understanding of the underlying mechanisms in the development of depression and hopefully will support the development of more personalised therapies.

In a discussion around resilience to developing psychiatric disorders we learnt that fMRI studies reveal what could be a 'brain signature' for resilience to developing bipolar disorder in people exposed to high genetic and environmental risks. This has the potential to be harnessed to develop new, protective therapies.

Some fascinating, almost futuristic research with the potential to explain disorders of brain connectivity showed how 'mini brain' organoids from pluripotent stem cells enable *in vitro* modelling of neuronal migration, maturation and function in the human brain.

Meanwhile, data from behavioural studies demonstrated how adverse experiences in early life can manifest not just in altered and distressed behaviour, but also leave their mark on germ cells as an 'epigenetic footprint' that transcends generations, affecting descendants' behaviour despite them not being directly exposed to the trauma.

Event Reports

The day was an unmissable opportunity for interdisciplinary conversation between researchers and clinicians about how Neuroscience can advance our understanding of mental illness and shape patient care in the future. It inspired me to ask questions, such as 'What is the dynamic interplay between nature and nurture in the development of mental illness?' 'Why do relatives at high risk of mental illness not develop it?' 'How can trauma transcend generations?' and many others.

The conference also marked the launch of the RCPsych **Neuroscience Champions** scheme, developed and coordinated by Dr Gareth Cuttle. This group of Psychiatric trainees will form a network across the UK to ensure that Neuroscience is properly integrated into their respective deaneries. We were fortunate enough to receive a bursary to attend the conference, and it was a fantastic opportunity to meet likeminded trainees from different regions excited about shaping the integration of neuroscience in our respective localities.

The 2020 Neuroscience Spring Conference will be on Friday 13th March at the RCPsych in London. Watch out for news later in the year, sign up and join the conversation about how Neuroscience is shaping the future of Psychiatry!

Gabrielle Churchhouse
CT3 trainee
RCPsych Neuroscience Champion for Severn

A Psychiatrist among Neuroscientists

Through the generous support of the Gatsby Charitable Foundation, 12 Early Career Psychiatrists were immersed in cutting-edge neuroscience at the recent biennial conference of the British Neuroscience Association. Read how one of them experienced the event.



'The 2019 meeting of the British Neuroscience Association was undoubtedly a commemoration of neuroscientific knowledge, but the denomination of "Festival" was misleading: this was no party. Four days packed with sessions with a wide range of exhilarating, current and relevant themes. On top of this, the international panel of speakers did not miss a beat and were outstanding. The ability to be in two or more places at the same time would have been handy, but alas, I had to choose the sessions I felt would be most relevant for me.

To anyone thinking that a clinical psychiatrist would struggle with the content of a full-blown neuroscientific conference – this is not the case! The relevance of neuroscience in psychiatry is such that there were plenty of lectures available to meet the needs and curiosity of a psychiatrist. Amongst them was one of my personal favourites – a discussion of neurobiological candidates for the rapid antidepressant response to

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ketamine. This topic is very current and “hyped” at the moment and the discussion of the potential role of dopamine, glutamate and, surprisingly, opioid receptors in the antidepressant effect of ketamine certainly sparked my interest.

My highlight of the next two days was listening to Professor Essi Viding discussing psychopathy and the old debate of nature vs. nurture. It turns out we are all very bad at detecting lies, contrary to what some parents might want to believe!

Starting the final day with a discussion on sleep and the neuroendocrine system was particularly interesting taking into account that psychiatrists work nights and often ignore the impact of sleep disruption.

Appropriately, I left Dublin exhausted, but motivated by the advances happening throughout the neuroscientific community. Every psychiatrist should attend this type of conference from time to time.'

Soraia Sousa

ST4 trainee

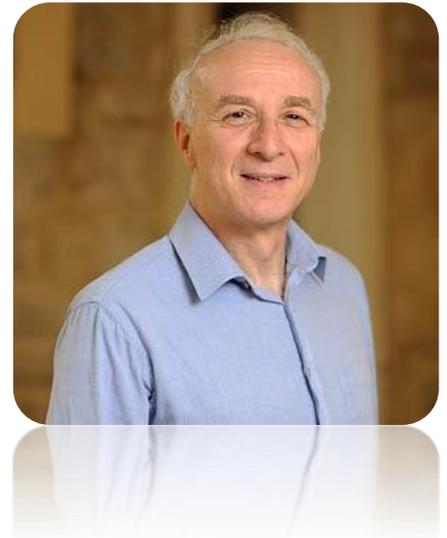
RCPsych Neuroscience Champion for Northeast England and Gatsby BNA Travel Fellow 2019



Two leaders in the field of ketamine use for depression in the UK

Angharad de Cates talks to PHILIP COWEN to understand more about the underlying scientific mechanisms, and Noura AlJuffali chats to RUPERT MCSHANE about transferring this understanding to clinical practice.

PROFESSOR PHILIP COWEN is an MRC Clinical Scientist and Professor of Psychopharmacology at the University of Oxford, and honorary consultant psychiatrist at Oxford Health NHS FT. He is recognised internationally for his outstanding research into mood disorders and their treatment, and is the lead academic clinician on a recently-awarded MRC grant to study ketamine in depression using an experimental medicine model framework.



Professor Cowen, thanks for talking to us today. To begin, why do you think it is still important to continue the search for new antidepressants?

First-line treatment of depression with medication is reasonably successful. However, when depressed patients have failed two drug treatments, the chances of subsequent response to another medication becomes quite low. Most of the antidepressants we use have similar actions on monoaminergic mechanisms. This suggests that we need medications with new modes of action to help people with treatment resistant depression (TRD).

With ketamine in particular, how do we think it might be producing an antidepressant effect?

The initial effect of ketamine is mediated through blockade of the glutamate NMDA receptor. How this then leads to a relatively prolonged antidepressant action (for many days after the end of the ketamine infusion) is not clear. Studies in animals suggest that NMDA receptor blockade leads to a surge of glutamate release thereby activating another kind of glutamate receptor, the AMPA receptor. Stimulation of AMPA receptors results in rapid increases in the formation of new dendritic spines and increased synaptic plasticity. Some people think that ketamine produces its antidepressant effect by an action on

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opioid systems. This is because in some but not all patients, the opiate receptor blocker naltrexone prevents the antidepressant effect of ketamine.

A meta-analysis from McGirr and colleagues in 2015 suggested that the 1-day response rate was 50%, and overall remission was 25%. Do we know why ketamine might not be working for everyone? And might there be population sub-groups for whom it might be particularly useful?

As with most antidepressant treatments ketamine is less effective in patients who are more treatment resistant, that is have failed many other treatments prior to receiving ketamine. Also, anxiety during the ketamine infusion probably predicts a poor response. But there are hints that ketamine may be more effective in depressed patients with a family history of an alcohol use disorder. And continued use of ketamine, for example up to 6 infusions over 2 to 3 weeks, increases response rates to about 70%.

And what about the typical symptoms that we associate with ketamine, such as the dissociation and euphoria – does a patient need to have these for ketamine to be working as an antidepressant?

Some studies suggest that the antidepressant response to ketamine is better in patients with strong dissociative reactions. However, in the naltrexone study mentioned above, when naltrexone blocked the antidepressant action of ketamine it did not block the dissociative effect. This suggests that dissociation by itself cannot explain the antidepressant effect of ketamine. The euphoria is a brief effect of ketamine and is not likely to be related to the longer lasting antidepressant action.

Do you think that the short-term effect of ketamine limits its use? And why does it only seem to have a short-term action with a requirement for continued dosing?

Most antidepressant treatments seem to require continuous administration for effectiveness to be maintained. This is presumably because the underlying pathophysiological process causing the depression is still going on. It is therefore not surprising that ketamine needs to be administered repeatedly in most patients for the antidepressant effect to be sustained. This makes careful observation for emerging adverse effects particularly important.

Professor Cowen, thank you so much for that succinct and easy to understand summary of the science behind ketamine. We'll look forward to hearing how the next phase of research into ketamine for depression develops.

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DR RUPERT MCSHANE is an Associate Professor at the University of Oxford, and leads the ECT and ketamine service at Oxford Health NHS FT. He is the chair of the Royal College of Psychiatrists special committee on ECT and related treatments. Professor McShane also ran the first international conference on ketamine treatments for psychiatric disorders in March 2018.



Professor McShane, thank you for talking to us. How did you first become involved in the field of ketamine therapeutics?

Well, the short answer is that Phil Cowen came in one day and said that there's this exciting research going on at Yale and that we should think about putting in a grant application. We then did a small case-series looking at the safety of giving ketamine on six occasions over three weeks. I was very fortunate that the first patients that we treated did very well. They were patients who had not responded to numerous other treatments. Subsequent to this, the faculty were supportive of our aspiration to develop a clinic to make ketamine therapy available.

Who benefits most from ketamine therapy?

We do not have good predictors for the people most likely to benefit except, perhaps, that people who are heavier benefit more. The reason for that seems to be that the doses have been calculated on a per kg basis so they are simply getting a higher dose. There are other unreplicated predictors that include having a family history of alcoholism and a more endogenous picture. Overall, however, we have yet to understand what predicts treatment response. In a way what is probably of more importance is predicting who is not going to respond. I know that seems like a fine-grained distinction but with most psychiatric drugs, because they tend to be rather widely applied, it is more helpful to have knowledge about who not to give it to and when to stop the drug. That is at least as important as knowing who to give it to and when to start it.

And are there any medical or psychiatric conditions that are contraindicated for ketamine therapy or certain individuals who you would feel would not be as responsive to ketamine?

It's a good question. Ketamine was originally used as an experimental model of psychosis because it induces some aspects of disruption in thinking that are similar to psychosis. So, people who have very high acute doses tend to develop

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hallucinations as they come out of their initial ketamine delirium, if you like. As a model for schizophrenia, I do not think it is a very good one because the symptomatology induced by the dissociative phenomenon of ketamine is really very different from those of schizophrenia.

So, should we use ketamine for people with psychosis? Well, we have certainly used it for some people who had depressive psychosis and what we have noted is that in just a few cases, the voices that people had (the depressive hallucinations) are acutely louder and more insistent during the infusion but that effect does not persist, and the benefit seems to accrue in that group as it does in other types of treatment-resistant depression. So, I wouldn't say that psychotic depression itself was a contraindication and also just to go back to the point about schizophrenia, I've seen some very preliminary evidence of people who've had depressive adjunctive symptoms in schizophrenia and where the report was of them benefitting.

There are certainly patients who I try to dissuade from taking ketamine and there are some whom I have refused to treat. For example, someone who had very prominent dissociative symptoms as a way of managing trauma was someone I did not think ketamine would be a very good idea for.

And have you noticed any adverse effects with ketamine administration?

There are a variety of acute adverse effects. A key issue in the field is whether it is necessary to have dissociative phenomenon to benefit and I am still undecided about this. There are patients who don't seem to need to dissociate to have continued benefit from low-dose ketamine but equally there are others who will, if they don't dissociate, say that this one (i.e. ketamine treatment) didn't work for me and when I see them a month later, they will say I had the worst month ever because the last one just didn't work. That of course could be due to placebo expectations and I really wouldn't want to dismiss that as a possibility but equally I'm reluctant to dismiss what the patients say. Some people would say that dissociation is certainly not an adverse event and that it is part of the experience.

Other things- sometimes people feel sick, dizziness is quite common, sedation, people feel tired afterwards. During the course of the infusion, people will sometimes describe body and mind feeling separate (i.e. dissociation) and that separation can extend to the point that they are having an out-of-body experience or further to having a near-death-experience and that can be extremely frightening.

One of the more common side effects is of a rather unpredictable anxiety/panic attack that occurs during the infusions and that has also been noted on an idiosyncratic basis with esketamine (intranasally-administered ketamine). What seems to happen is that people can have a series of ketamine or esketamine treatments without any particular problems and then one day they will get a

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panic attack and there does not seem to be any obvious reason for that so that just remains unexplained at the moment.

In your opinion and I suppose this would be very specific to the disorder being treated, how long, on average, does the ketamine effect last for in, for instance, treatment-resistant unipolar depression?

I think there is at least a decade's worth of research here so it's a good field to get into. In terms of duration, it is very variable. This is purely impressionistic, but I think that there is a group of patients who have a very rapid and acute benefit – almost within less than an hour. I think that may have a different mechanism perhaps from those who will wake up the following morning or sometimes the day following that and say 'actually, I woke up and just felt better' so that suggests a different sort of mechanism, doesn't it?

The mean duration is about ten days before relapse, but it's got a very wide variability so sometimes it is just for the day but equally we have patients who have a couple of months or longer.

It would be interesting to delineate the predictors of the rate and effect of ketamine response. How do you think ketamine compares to other pharmacological therapies on the market so far?

The short answer is we don't know because the only studies that have been done are based on the esketamine studies. In those studies, esketamine plus a new antidepressant was compared to a new antidepressant and a placebo intranasal spray. Those head-to-head comparisons haven't been done.

What I can say is that obviously some of the patients who have been treated have had depression that appeared to be resistant to many different classes of antidepressant so that's obviously an important, potentially attractive, feature of using ketamine or esketamine.

As an experienced organiser of ketamine clinics, what do you think are the basic logistics of running one?

You've tied up a lot of complicated issues in one question there. The most important one is to have supportive management in the hospital and it's worth getting very senior support first. So I think it will be important to know what the health economic data on this look like. NICE is due to deliver a decision on this in March 2020.

We have situated our ketamine suite in an NHS ECT clinic and I think this is a good place to do it because firstly, you've got staff interested in this sort of problem and secondly, it's an interventional procedure. You have to have a waiting room and somewhere for the patient to lie while they are having the potentially dissociative experience so I personally would like to see a model

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where people have a hub based on the ECT suite and potentially looking to have patients having longer term ketamine being administered in community settings.

And is this ketamine clinic funded by the NHS and is ketamine treatment in general funded by the NHS?

To my knowledge, there are only two other clinics in the country that administer ketamine (Middlesbrough and Northampton), but speaking for the Oxford Clinic, much of the largest stream of what we do is NHS self-funded. In other words, we work under the auspices of the NHS. I'm employed by the NHS and I don't have any extra income as a result of this, but the patients pay so there isn't an expectation that the clinical commissioning groups (CCGs) pay for this.

We set it up like that because with the evidence for ketamine it's not realistic to expect the public purse to pay for it. That might change once NICE has delivered its decision.

We also treat some Oxfordshire patients, alongside the ECT sessions, referred into the service as tertiary referrals and that's covered within the NHS but the numbers there are really very small.

Can anyone refer?

Yes, GPs and psychiatrists do refer to our clinic. The usual mechanism is that the patients have approached the GP or psychiatrist and asked for a referral. We then ask for substantial amounts of information describing the previous diagnoses and treatments.

One of my missions is to try to develop a registry in which patients are receiving both ketamine and esketamine medically and potentially also for those self-treating with ketamine. In that way, we would be able to track movement between these three options and also get a handle on the extent of abuse that develops and also any withdrawal phenomenon that might develop.

So, there's a lot that we don't know and it's only going to be established by routine data collection through registries. In my view, it's very important that clinics starting-up join in a national effort so that there is harmonisation of data-gathering procedures. We also need to involve patients in that, that's why the data collection system we use is called 'Patients Know Best' in which the patients actually control who can access their data.

Professor McShane, thank you so much for discussing this cutting-edge therapy; we're excited to hear more from you in the future.

*E*vents and *O*pportunities

2019

September 7-10

32nd European college of neuropsychopharmacology (ECNP) Congress
Copenhagen, Denmark

<https://2019.ecnp.eu/>

OFFERS TRAVEL AWARDS AND FREE CHILD CARE SERVICE

September 21-25

International brain research organisation (IBRO) World Congress of
Neuroscience

Daegu, South Korea

www.ibro2019.org/

OFFERS TRAVEL AWARDS

2020

March 13

4th Annual RCPsych Neuroscience Spring Conference

London, UK

<https://www.rcpsych.ac.uk/training/neuroscience-in-training/>

OFFERS TRAVEL AWARDS TO TRAINEE PSYCHIATRISTS AND MEDICAL
STUDENTS

March 28-31

28th European Congress of Psychiatry (EPA2020)

Madrid, Spain

www.epa-congress.org/

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Get Involved!

Want to advertise your event? Or publish an article? Contact us at Neuroscienceproject@rcpsych.ac.uk. **Please put 'PSynapse' in the subject line.**

Curious about what's going on in your region? Want to get involved, or organise an event? Contact your local **RCPsych Neuroscience Champion** to talk all things Neuroscience!

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Who We Are

The **Royal College of Psychiatrists** (RCPsych) is running a **5-year programme** to transform psychiatric training in the UK by integrating modern neuroscience, with generous support from **The Gatsby Foundation** and **The Wellcome Trust**. Our aim is that future psychiatrists will incorporate a modern neuroscience perspective into every formulation. We have evolved and invigorated psychiatric Core Training in the UK. A comprehensive programme of activities is proactively supporting excellent neuroscience teaching for trainee psychiatrists.



rcpsych.ac.uk/training/neuroscience-in-training

#GWNeuro