

October 2018



Neuropsychiatry Newsletter

Conference 2018
edition

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Editorial

New Beginnings: More of the same

by

Dr Kevin Foy

Editor of Neuropsychiatry Newsletter

Consultant Neuropsychiatrist,

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Rule 41 in Robert Greene's masterclass in management skills, 'the 48 laws of power' suggested that it is unwise to step into a great man's shoes. For the past 7 years my predecessor, Norman Poole, has steered the ship of this publication. During that time we changed from being a Special Interest Group to being a Faculty. Our membership has also increased dramatically, so that the Faculty of Neuropsychiatry now has well over 5000 members. Such success is down to the hard work of countless general and Executive Committee members of the Faculty over the years. Norman however, deserves special praise and mention in his work as former Editor of this publication. It's a testament to his skills that he has gone on to bigger things and is now Editor of the Psychiatric Bulletin. In taking up this post as Editor, I am delighted to be assisted in the task by a Deputy Editor, Dot Bindman, who will have a special role in ensuring that we adequately communicate and advocate on behalf of trainees.

The Neuropsychiatry Newsletter has many aims and goals. Encouragement of research and researchers is one of them and this edition publishes articles from prize-winners at the conference.

Special congratulations goes to Abigail Swakowski, Mark Smith, Mohanbabu Rathnaiah, Laurence Astill Wright and their colleagues on their winning research.

Communication of the latest developments within neuropsychiatry-

both nationally and internationally - is another role of the newsletter and a digest of the proceedings of the recent conference is included.

A great deal of work occurs behind the scenes at the Faculty on a daily basis. Much of that work, though unnoticed, has an incalculable effect on service development and the prospects for neuropsychiatry within this country. An overview of some of that work is presented in the news from the Executive Committee section.

Finally, we look forward to further conferences in the future. At the AGM Business Meeting the membership voted in favour of the meeting staying at the College for the next three years. Although the number of delegates is constrained by the capacity of the College premises, it was agreed that members identified with the College building and it was cost effective to hold meetings there.

Any publication is only as good as the contributions that it receives from its readers. As I begin the journey as Editor, I wish to let readers know that we at the Neuropsychiatry Newsletter will be delighted to receive articles, essays, original research and news on forthcoming events.

Conference Digest

This year's Faculty of Neuropsychiatry conference has been the largest yet with a total of over 400 attending during the two days.

The conference was opened by Professor Joyce and began by our President, Professor Wendy Burns, updating attendees about the Gatsby/Wellcome Neuroscience project. Dr Paul Johns gave a tour de force talk on the amygdala. During the talk he discussed the various roles of this vital and often misunderstood part of the brain. Dr Nandini Mullatti discussed the role of neurophysiology in mental health settings and Dr Oliver Robinson reviewed the history of functional MRI of mood and anxiety disorders in the context of seemingly contradictory findings.

A regular contributor and friend of the Faculty, Andrea Cavanna, reviewed the evolution of the limbic system and roles of the basal ganglia in mammals and ultimately humans. The tone of the proceedings then turned distinctly philosophical with a talk from Professor Lisa Bortolotti on delusions and rationality and mathematical with Professor Karl Friston discussing the computational psychiatry of psychosis.

Dr Ken Barret introduced Professor Andrew Lees who gave a compelling and very personal account of the mentor he never met, William S. Burroughs. This talk looked at the role of psychedelics in medicine and how increasing regulation means that universities no longer offer the oasis for investigation and free thinking that they once did when Professor Lees was a student.

Professor Ray Tallis in the next talk pointed out the limitations of the current trend towards all thing 'neuro'. In doing

so, he discussed the complexities of the human spirit and limitations of much of the functional imaging studies.

Day two of the conference commenced with a review of frontal lobe epilepsy. In a practical session, Dr Aileen McGonigal looked at the semiology of frontal lobe seizures, Dr Chris Derry looked at the link with parasomnias and the genetics was relieved by Professor Sameer Zuberi.

Ms Rachael Hansford spoke eloquently about the devastation at a family level caused by acquired brain injury.

The conference came to a close with a session on functional cognitive disorders by Dr Stoyan Popkirov. Dr Nick Medford discussed the complexities of MDT input for difficult functional neurological disorders. Professor Mark Edwards discussed FND and service development.

On both days, a series of seminars gave practical advice on management of various neuropsychiatric conditions.

Trainee Update

By Dot Bindman

Deputy-Editor

SpR in Neuropsychiatry, The National Hospital for Neurology and Neurosurgery, Queen Square, London

Exciting developments are afoot for aspiring neuropsychiatrists. There was an enthusiastic response to our call for views on a Neuropsychiatry Higher Trainee Special Interest Programme, with over 80 trainees registering their interest. Sincere thanks to those trainees who contributed to the questionnaires. The exercise gave valuable input into the type of content and structure that trainees are seeking.

Our hope is now to design programmes that offer the experience to equip the next generation of neuropsychiatrists. Several centers around the UK hope to take trainees from early 2019.

Trainees and new consultants at the conference were keen to discuss the issue of formal accreditation for Neuropsychiatry training. This has been a key priority for the Faculty over the last few years. Following discussions with the GMC, the route of obtaining a Credential in Neuropsychiatry seems the most promising. This process is already underway in several other subspecialties and we await with interest the outcome of those credentialing pilots.

Development of a curriculum and a syllabus continue in the meantime. To strengthen the neurology content of the syllabus, Professor Adam Zeman, a consultant neurologist with a keen interest in developing joint training in

neurology and psychiatry, will join the Faculty credentialing working group. The College Neuroscience Commission is another area the Faculty have been involved in and with further funding agreed by the Gatsby Foundation and

Wellcome Trust, we are pleased to continue our support to its new incarnation, the Neuroscience Board. The Faculty has already contributed new neuroscience questions to Paper A, as well as suggestions for updating TrOn modules.

List of Prize winners

Podium Presentation:

Prize: £500 and a College certificate

Dissociative seizures: are there any facts behind the phenotype myths? A large-scale case-control study of mental, physical and social factors associated with Non-Epileptic Attack Disorder

Miss Abigail Swakowski



Abigail Swakowski awarded prize by Professor Eileen Joyce for best oral presentation.

Poster Presentation:

Prize: publication in the Neuropsychiatry Newsletter and a College certificate

- 1. The In Vitro Pharmacological Properties of MT-45 and its Fluorinated Analogues on the μ -Opioid Receptor**

Dr Mark Smith, Medical Student



Dr Laurence Astill Wright and Dr Mark Smith awarded prizes by Professor Eileen Joyce for best poster presentation.

- 2. In vivo Measurement of glutamate metabolism and neuroenergetics in schizophrenia using ^{13}C -magnetic resonance spectroscopy**

Dr Mohanbabu Rathnaiah,
Higher Trainee



- 3. Pharmacological prevention of post-traumatic stress disorder: a systematic review and meta-analysis**

Laurence Astill Wright, CT1

Dr Mohanbabu Rathnaiah

Dissociative seizures: are there any facts behind the phenotype myths?

A large-scale case-control study of mental, physical and social factors associated with Non-Epileptic Attack Disorder

Abigail Smakowski, The Institute of Psychiatry, Psychology & Neuroscience Kings College London (IoPPN) and Dr Jacob S. Bird, Consultant Neuropsychiatrist, Kent & Medway Partnership Trust and Honorary Senior Lecturer IoPPN.

Dissociative Seizures are paroxysmal episodes of behaviour which arise from complex psychological mechanisms. Individuals with dissociative seizures, or 'Non-Epileptic Attack Disorder' (NEAD) often feel stigmatised by healthcare professionals and the general public. The bulk of scientific literature has focused on factors differentiating NEAD from epilepsy. Remarkably little research has investigated the phenotypic differences between NEAD and other mental disorders. Clinically and pragmatically, this would be useful in allowing identification, education, and possibly be a focus in management of the symptoms. The dearth of research into the commonalities and differences between NEAD and other mental health disorders is all the more striking given that the mainstay of treatment is psychiatric and psychological.

However, all studies to date have used moderate, possibly un-representative, sample sizes, making it difficult to extrapolate findings to a larger population. To rectify this, we aimed to collect a large-scale case-control sample in order to: clarify the socio-demographic characteristics of the NEAD population and to identify any medical predictors of its development. The full study will be written up and submitted to the scientific literature imminently.

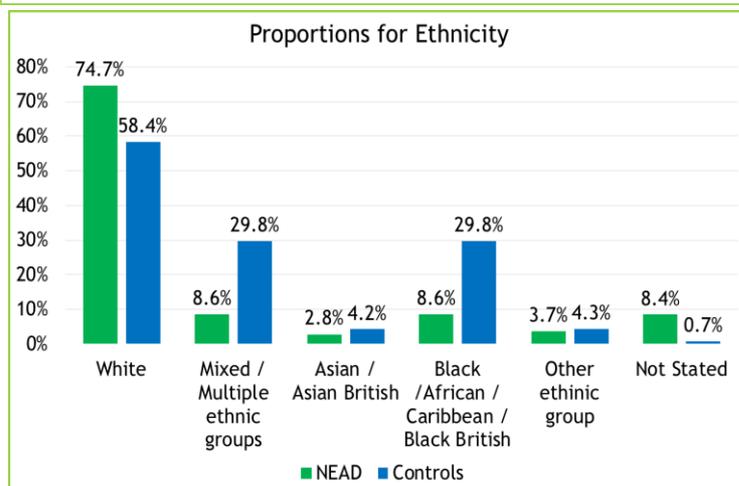
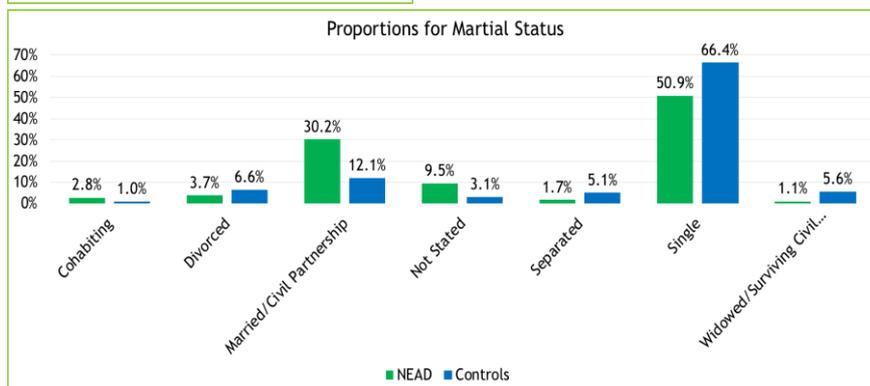
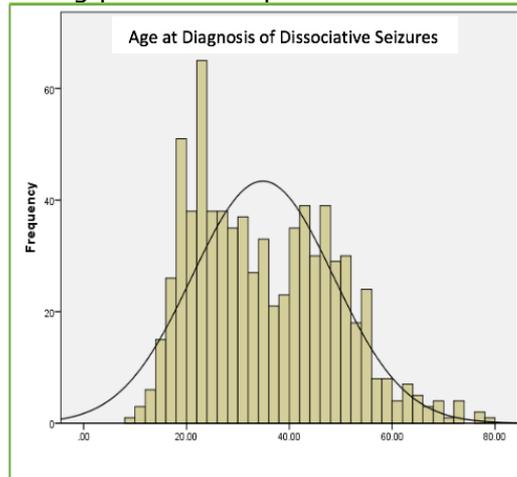
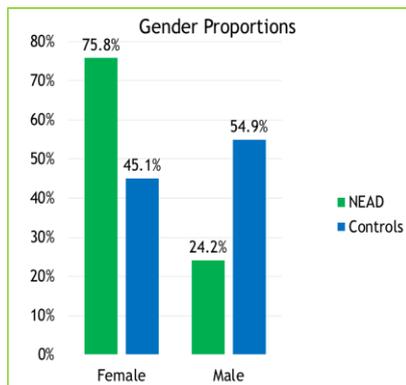
Methods

To do this we used the Clinical Record Interactive Search (CRIS) database which contains reliable de-identified data from over 250,000 psychiatric patients from the South London and Maudsley (SLaM) hospitals. Between the 1st Jan 2007 to 31st March 2017 we selected patients with a primary diagnosis of 'dissociative convulsions' (ICD-10). Controls were psychiatric patients in SLaM who received a diagnosis on the same day as a patient at our NEAD/ dissociative convulsions clinic. This gave us a total of 748 patients with dissociative seizures compared to 1496 controls (1:2 ratio). Comparison variables that we examined included: gender, age, ethnicity, social-economic status, service use information, marital status, concurrent psychiatric diagnoses, past medical history, medications and A&E visits in the year before primary diagnosis.

Results

The majority of patients were female, lived in areas of good-moderate social economic status and tended to be of white ethnic background. However, we found that although the majority of patients were single, as previous research suggests, they were actually less likely to be single than the psychiatric controls and more likely to be married. Secondly, the dissociative seizure group's use of A&E in the year before diagnosis was similar to that of the psychiatric control group, which disputes the view that these patients utilise more healthcare resources and are more difficult to manage than many other psychiatric patient populations. A peak age of diagnosis occurred in the patient's early 20s, but interestingly, there was also a second peak in the late 40s. And importantly, this finding is unlikely to be attributed to a diagnostic delay (thought to be

between 5-7 years). These results are novel findings with important implications for clinicians when it comes to assessing patients for potential dissociative seizures.



With regard to patients' psychiatric and general medical history, the greatest predictor for developing dissociative seizures was having a history of, or a concurrent secondary diagnosis, of a disease of the nervous system. The next greatest predictor was having a concurrent secondary diagnosis of a personality, or neurotic/somatoform disorder. Other vulnerability factors included having a history of neurological or musculoskeletal disease, or symptoms and signs not classified elsewhere. Unfortunately, due to the limited time frame allowed on this project we could not investigate the specific types of psychiatric or medical diagnoses within the categories mentioned; however, we intend to explore this further and will be including this information when we submit to the scientific literature.

<i>Table of significant medical/psychiatric predictors of NEAD</i>	<i>Odds Ratio</i>
a history of G00-G99 Diseases of the nervous system (HES data)	11.181
a current secondary diagnosis of G Diseases of the Nervous system (CRIS data)	7.284
a secondary diagnosis of F60-69 Disorders of adult personality and behaviour	6.163
a secondary diagnosis of F40-49 Neurotic, stress-related and somatoform disorders	3.651
a history of R00-R99 Symptoms, signs and abnormal clinical and laboratory findings (not elsewhere classified)	3.183
a history of M00-M99 Diseases of the musculoskeletal system and connective tissue	1.909

Conclusions

This research has begun to finally question some of the deep-rooted beliefs and myths regarding the dissociative seizure population. Up until now, studies have had too small of sample sizes to provide robust evidence which gives robust evidence for the typical characteristics of this patient group at a population level. The absence of such information has contributed to the ongoing confusion over semiology of the condition and diagnostic delay. By conclusively identifying the typical socio-demographic characteristics and medical predictors of dissociative seizures we hope this research will help at-risk individuals and sufferers to be swiftly identified, better educated, and subsequently treated.

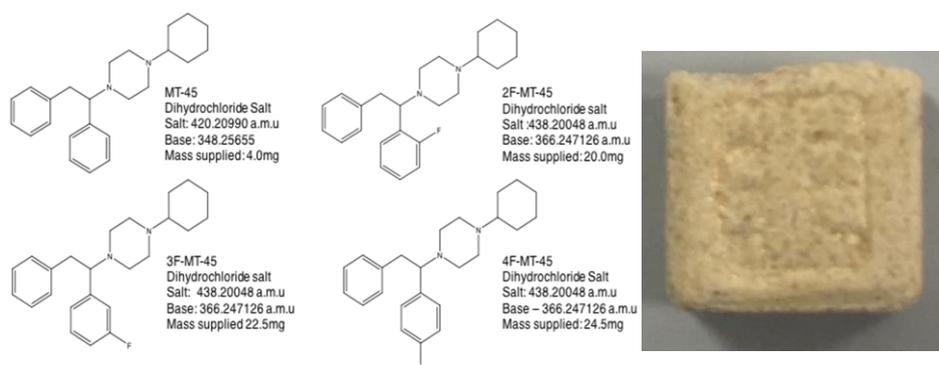
The Pharmacological Properties of the Illicit Fentanyl Derivative MT-45 and its Fluorinated Analogues on the μ -Opioid Receptor

by

M. Smith, D. Baptista-Hon & T. Hales

Institute of Academic Anaesthesia, Division of Neuroscience, School of Medicine, University of Dundee, UK

Opioids are some of the most frequently prescribed drugs by physicians and their efficacy as analgesics has long been recognised. However, their harmful side-effects including abuse potential are major draw-backs. MT-45 was first synthesized in Japan in the 1970s as a morphine-replacement but its production and subsequent research was abandoned by 1983. MT-45 re-emerged as a recreational novel synthetic opioid (NSO) in 2014 causing deaths in Sweden and Germany. Outlawed in Britain in 2015, fluorinated analogues appeared to evade pre-existing legislation and a seizure of these was made in Manchester in 2016. The emergence of NSOs was aimed at averting legal restrictions on controlled drugs by making minor alterations to their chemical structure (MT-45 is a Class A substance - Misuse of Drugs Act 1971).



It was unknown if these alterations caused changes in cell signalling. In response to the threat of NSOs, the British government legislated for the Psychoactive Substances Act 2016 which the analogues now fall under. However, as similar legislation is lacking in many European nations, illicit laboratories mainly located in Asia continue to produce a vast array of analogues for the market. Gaining a detailed insight into the drugs pharmacological traits *in vitro* will enable clinicians to better understand its potential *in vivo* effects and harm-inducing potential.

Methods

Chinese Hamster Ovary cell-based assays using Glosensor and PathHunter technology were used to investigate MT-45 and its analogues ability to accumulate cAMP and Beta-arrestin2 at the μ -opioid receptor respectively. At a cellular level, β -arr2 pathways have been linked to opioid-induced side-effects, whereas G-protein pathways relate to

analgesia. With these two comparative assays, the delineation of pathway bias - favouring activation of one pathway over another was possible. Potency and efficacy parameters were derived and then compared using a one-way ANOVA with post-hoc Bonferroni correction. All data are presented as mean \pm SEM or mean \pm 95% confidence interval where stated and the cut-off significance value (P) 0.05 was adopted. $\Delta\log(E_{max}/EC_{50})$ analysis was used to delineate pathway bias. MT-45 and its analogues (2-F, 3-F and 4-F) were also compared to clinically used opioids morphine and fentanyl in addition to the synthetic peptide DAMGO as a reference agonist.

Results

MT-45 was significantly less potent ($P = < 0.0001$) and efficacious ($P = < 0.0001$) compared to DAMGO, morphine and fentanyl in the β -arr2 assay. In the cAMP assay, MT-45 was significantly less potent ($P = < 0.0001$). When compared to its fluorinated analogues, MT-45 displayed near identical efficacies in both assays. However, it was significantly less potent than its analogues in both assays ($P = < 0.0001$). The bias factors for fentanyl and morphine correlated with previous published reports as in favour of G-protein pathways and neutral respectively. MT-45 displayed a trend of bias towards G-protein pathways compared to its analogues which were neutral.

β -arr2 assay:

	EC ₅₀ (μ M)	Efficacy (%)	Hill slope
DAMGO	0.15	78.39 (\pm 3.47)	0.97 (\pm 0.11)
Morphine	0.36	32.75 (\pm 1.93)	1.0 (\pm 0.16)
Fentanyl	0.09	53.53 (\pm 5.97)	1.04 (\pm 0.29)
MT-45	23.34	16.54 (\pm 1.07)	1.59 (\pm 0.33)
2-F	0.13	9.76 (\pm 0.51)	1.26 (\pm 0.51)
3-F	0.42	12.48 (\pm 1.05)	1.14 (\pm 0.33)
4-F	0.09	15.98 (\pm 1.99)	1.03 (\pm 0.37)

cAMP accumulation assay:

	EC ₅₀ (μ M)	Efficacy (%)	Hill slope
DAMGO	0.00075	79.82 (\pm 4.46)	0.87 (\pm 0.11)
Morphine	0.0029	78.05 (\pm 5.98)	0.68 (\pm 0.16)
Fentanyl	0.0016	73.59 (\pm 6.71)	0.70 (\pm 0.15)
MT-45	1.2	74.39 (\pm 8.15)	0.88 (\pm 0.15)
2-F	0.020	69.48 (\pm 7.80)	0.55 (\pm 0.12)
3-F	0.035	74.91 (\pm 5.02)	0.68 (\pm 0.11)
4-F	0.010	69.75 (\pm 6.24)	0.58 (\pm 0.21)

Conclusion

The results raise the prospect that MT-45's primary effect is not via the μ -opioid receptor due to its low potency. Previously, when compared to morphine, MT-45 has been shown to be 3.5 times more potent in the mouse tail-pinch assay; it also possesses over 10 times more potent an LD₅₀ in rodents. This contradicts the data from the cAMP accumulation assay in this project. By that factor alone, MT-45 should be less potent than morphine *in vivo* – giving credence to the theory that it may have more widespread receptor activity such as at the NMDA receptor. This would correlate with both drug-user reports and original research of it being a dissociative acting through the NMDA or κ -opioid receptor unlike traditional opioids. The differing properties of the analogues versus their parent drug also raises the spectre of how difficult it will be to characterise novel psychoactive substances and their *in vivo* effects. The fluorinated analogues of MT-45 displayed alternative pharmacological characteristics compared to their parent drug. It was striking how fluorination could alter the degree of pathway bias. The increased potency of the illicit forms of MT-45 in these assays may make them more dangerous to the recreational user. Fluorinated derivatives of fentanyl exist such as brifentanyl; they are both potent and short acting. This may aid in explaining why fluorination caused a leftward shift in the concentration-response curves of the analogues in both assays. This encapsulates the difficulties in attempting to understand the *in vivo* effects of "legal highs". A minor change in chemical composition can potentially alter cell signaling, which may in turn translate to different *in vivo* effects for the unwitting user.

In Vivo Measurement of glutamate metabolism and neurogenetics in schizophrenia using ^{13}C -magnetic resonance spectroscopy

by

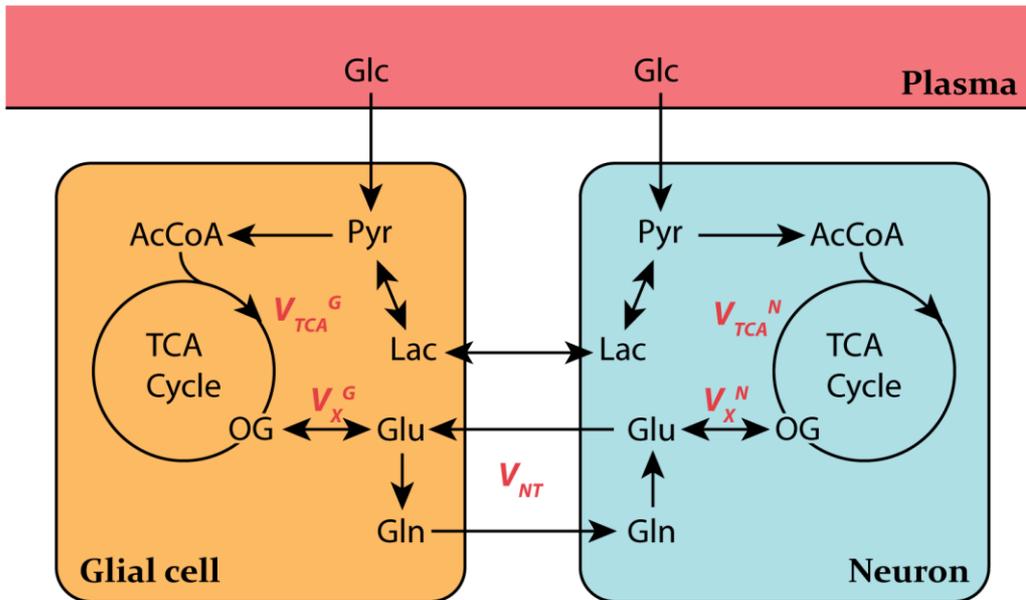
Dr. Mohan Rathnaiah* and Dr. Mohammad Zia Ul Haq Katshu* and Dr. Sudheer Lankappa and Dr. Kate Bransby-Adams and Prof. Peter Liddle, Institute of Mental health, University of Nottingham, Nottingham
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*Both authors contributed equally to this work.

Introduction

Patients with schizophrenia show elevated glutamate levels in anterior cingulate cortex (ACC) in the early unmedicated phase of illness, and reduced levels or no change in the later medicated stages. However, these static glutamate measurements provide little information about glutamate metabolism which is closely coupled with the tricarboxylic acid (TCA) cycle – a measure of neuronal activity levels. Both glutamate and glutamine are involved in multiple metabolic processes in the brain. For a clear understanding of the metabolic disturbance in the brain, study of dynamic process of glutamate synthesis and conversion rate of glutamate to glutamine is crucial. During glutamatergic transmission, glutamate is released into the synaptic cleft and subsequently taken into astroglia, where it is converted to glutamine in preparation for recycling back to glutamatergic neurons

-In vivo ^{13}C Magnetic Resonance Spectroscopy (MRS), has been used to measure the rate of oxidative glucose metabolism by measuring the rate of label incorporation into glutamate C-4 position from $[1-^{13}\text{C}]$ glucose. Because brain glutamate is of predominantly neuronal origin (from glutamatergic neurons), it effectively acts as a trapping pool for ^{13}C labels of the neuronal tricarboxylic acid (TCA) cycle through fast exchange with α -ketoglutarate (α -KG) via transaminase and mitochondrial and cytosolic transporters. This allows determination of the glutamatergic neuronal TCA cycle rate by measuring the time course of $4-^{13}\text{C}$ glutamate.

We used ^{13}C MRS to quantify the glutamate metabolism and TCA cycle in ACC in early and chronic stages of schizophrenia



Two-compartment modeling of [$1-^{13}\text{C}$] glucose brain metabolism (Gruetter 2001, Sibson et al., 2001), v_{TCA}^G - Glutamatergic TCA cycle rate in Glia, v_{TCA}^N - Neuronal Glutamatergic TCA cycle rate

Methods

SPRING research study:

The study of psychosis and the role of inflammation and GABA/Glutamate (**SPRING**) is a U.K multi-centre study conducted at Manchester, Nottingham and Cardiff. The three sites each recruited the similar number of participants (=60), but undertook different complementary imaging techniques to investigate the research objectives:

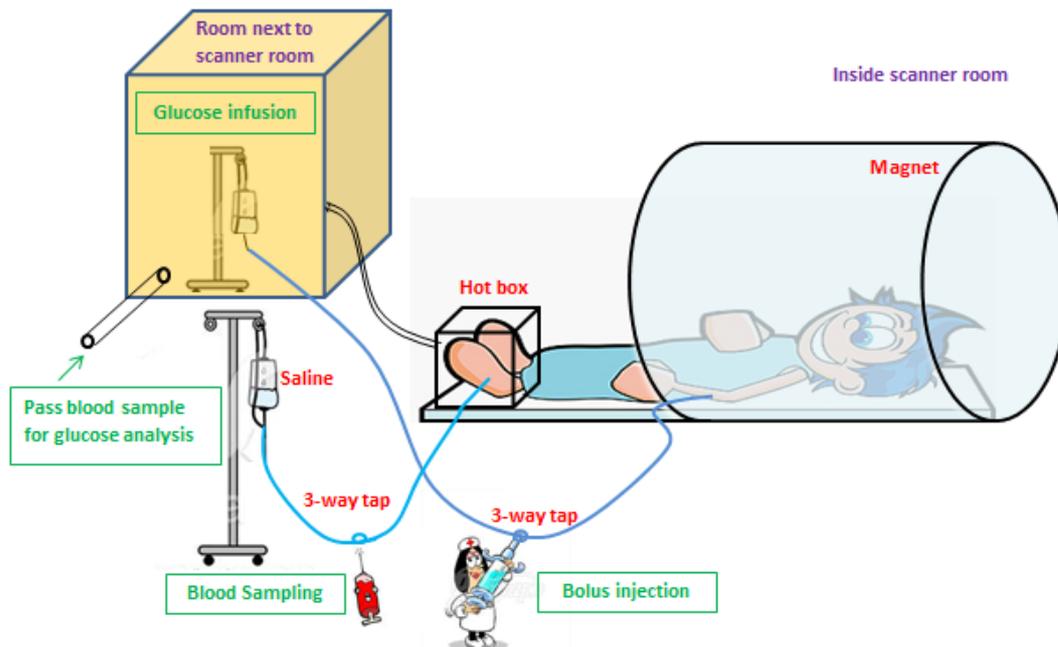
1. Cardiff University – 3T H^1 MRS, and Magnetoencephalography (MEG).
2. University of Manchester – 3T H^1 MRS, 3T C^{13} MRS, and Positron emission tomography (PET).
3. University of Nottingham – 7T H^1 MRS, 7T C^{13} MRS, and Magnetoencephalography (MEG).

Here we discuss the preliminary results from Nottingham site

Nottingham site ^{13}C -MRS:

Participants:

12 recent-onset patients (<5 years diagnosis, <3 months antipsychotic treatment; mean age $27.1 \pm$ standard deviation [S.D] 6.7, 1 Female [F]) and 10 established patients (>10 years diagnosis; mean age $39.5 \pm$ S.D 6.4, 2F) and 13 healthy controls (mean age 27.8 ± 6.4 , 2F) completed the study



Overview of ^{13}C -glucose clamp and infusion procedure

Acquisition:

Participants were scanned on a 7T Philips Acheiva MR System using a $^{13}\text{C}/^1\text{H}$ volume coil. After an overnight fast, participants received intra-venous cannulation in the dorsal foot vein from which arterialised blood was taken at 5 minutes intervals. Foot remained in a heated foot-warmer (temperature 50–55 degree centigrade) through-out the sampling period.

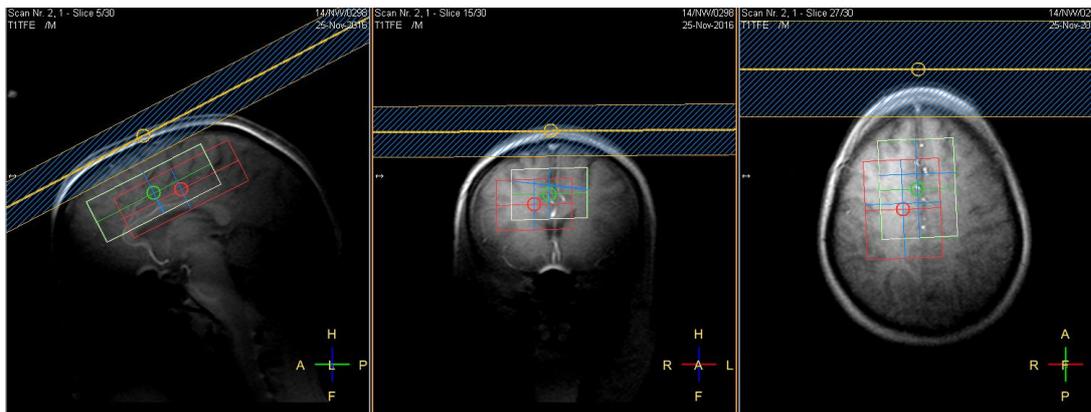
[1- ^{13}C] glucose (20% mass/volume, 99% enrichment) was infused through ante-cubital vein for 60 minutes. The infusion was a primed-continuous infusion to achieve blood glucose levels of 10-11mmol/L in a short time frame and these levels were constantly maintained during the course of neuroimaging acquisition

Preliminary Analysis:

^{13}C MRS data were quantified with AMARES algorithm. Absolute quantification was performed using an external reference method (glutamate phantom), using formic acid signal used as correction for effects of coil loading. Preliminary interpretation of the group averaged ^{13}C turn-over curves was undertaken using a one compartment model of TCA metabolism and glutamate/glutamine cycling

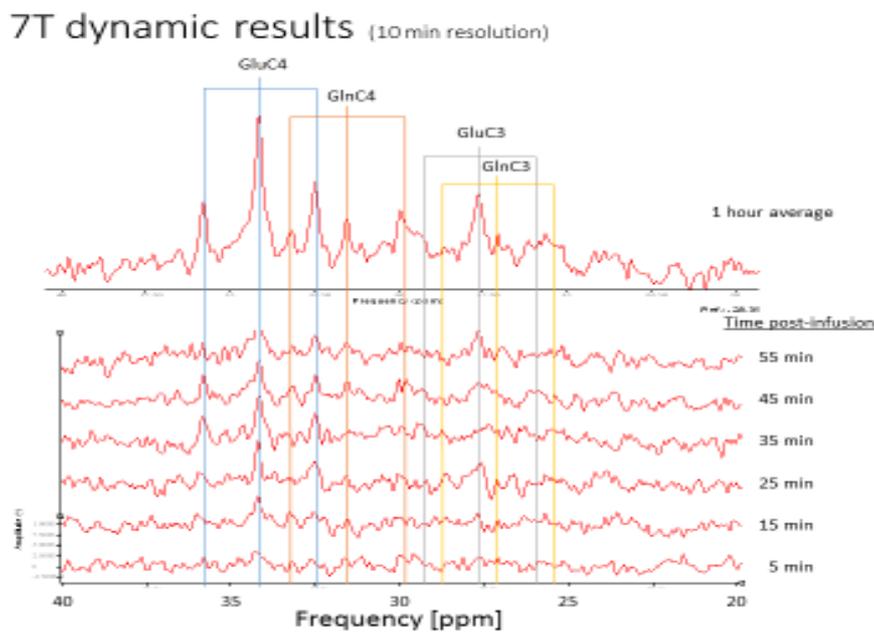
Results

Voxel positioning is shown as in Figure 1:



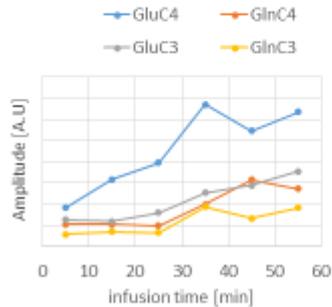
A typical ^{13}C MRS dynamic series acquired in vivo is shown in Figure 2:

Figure 2
Single subject example



The triplet patterns of the C4 and C3 resonances of glutamate and glutamine consistently appeared after about 15 minutes, with low contamination of lipid signal, as also confirmed by a baseline scan. The quantification results in the same dynamic series are displayed in Figure 3, with GluC4 having the faster turnover followed by GlnC4, while the C3 of glutamate and glutamine appeared above the noise level at a later stage, consistent with the delayed metabolic labelling of these positions. Analysis of group differences between early phase and established phase of schizophrenia compared to healthy controls is currently in progress

Figure 3
Single subject example



Conclusion

Recruitment and study set-up was challenging but we were able to successfully complete the recruitment and completion of neuroimaging acquisition. The scan procedure was well tolerated despite the need for fasting, two intravenous cannulas and over an hour and a half scanning time. Our study shows the feasibility of ^1H -localized polarization transfer ^{13}C MRS dynamic acquisitions from the ACC region in the frontal lobe of the human brain. It was possible to overcome the technical challenges encountered in this deep region. Our study is the first one, to our knowledge, to successfully measure glutamate synthesis and neuronal glutamatergic TCA cycle rate in schizophrenia patients at 7T MRS

Pharmacological prevention of post-traumatic stress disorder: a systematic review and meta-analysis

by

Dr Laurence Astill Wright, CT1, Avon and Wiltshire Mental Health Partnership NHS Trust; Professor Marit Sijbrandij, VU University Amsterdam, Associate Professor; Mr Rob Sinnerton, Cardiff University, Medical Student; Professor Jonathan Bisson, Cardiff University, Professor of Psychiatry.

Background

Post-Traumatic Stress Disorder (PTSD) is a common mental disorder associated with significant distress and reduced functioning. Its occurrence after a severe traumatic event and association with characteristic neurobiological changes make PTSD a good candidate for pharmacological prevention and early treatment.

Many psychological interventions to prevent the development of PTSD have been found to be ineffective¹⁰ and some, such as psychological debriefing after trauma may even be harmful¹⁴. Treatments incorporating both psychological and pharmacological intervention have also failed to show significant benefit²¹. There may, however, be a role for trauma-focused cognitive behavioural therapy in treating individuals with acute traumatic stress symptoms¹³. Newer preventative psychological interventions such as prolonged exposure therapy in the immediate aftermath of trauma also appear to reduce post-traumatic stress reactions¹⁵.

Research has also focused on pharmacological interventions to prevent PTSD. It is likely that memory consolidation is particularly vulnerable to disruption in the six hours after trauma¹⁷. Shifts in neurobiological activity during these 'golden hours'²³ has the potential to be a promising target for pharmacological intervention¹.

Early research found the effects of benzodiazepine administration to be largely ineffective⁵. Later research has focused on B-blockers, such as propranolol, and their ability to disrupt post-synaptic norepinephrine receptors¹². Studies have suggested that human participants who received propranolol have decreased recall of emotionally stimulating material, possibly due to the blocking of memory consolidation⁸ and subsequent studies have explored the efficacy of propranolol as a preventive agent¹¹.

Other studies have found an association between low cortisol levels following motor vehicle accidents and subsequent PTSD^{9, 2}. Both human and animal studies suggest that glucocorticoids attenuate heightened fear response⁷ through increased removal of fear inducing memories¹⁸ resulting in interest in the potential preventive effects of hydrocortisone.

This study assessed whether pharmacological interventions result in a clinically significant reduction/prevention of PTSD symptoms when compared to placebo/other pharmacological/psychosocial interventions.

Methods

A systematic search was undertaken to identify randomised controlled trials (RCTs) which used early pharmacotherapy (within three months of a traumatic event) to prevent and treat PTSD in adults. Using methodology advocated by the Cochrane Collaboration, RCTs were identified and rated for risk of bias. Available data was meta-

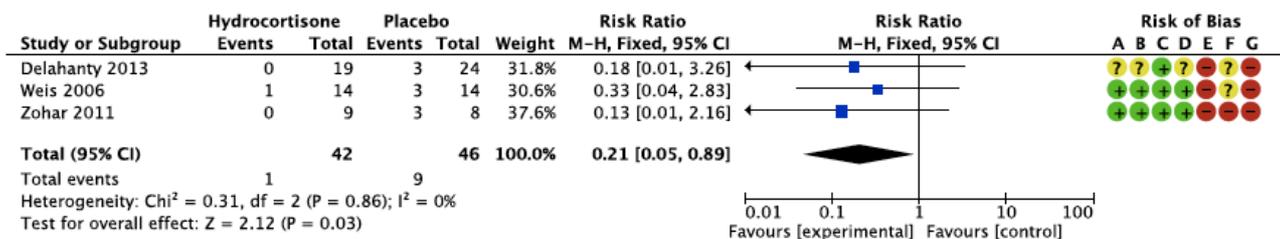
analysed to calculate risk ratios (RR) for PTSD prevalence and standardised mean differences (SMD) for PTSD severity.

Results

The search produced 7,639 papers. We examined the full text of 111 papers and there were 15 adult RCTs (n = 929) which met the inclusion criteria. The methodological quality of most trials was low. Only hydrocortisone was found to be superior to placebo (3 studies, n= 88, RR: 0.21 (CI 0.05 to 0.89) although this was in populations with severe physical illness, raising concerns about generalisability. No significant effects were found for the other pharmacotherapies investigated (propranolol, oxytocin, gabapentin, docosahexaenoic acid, fish oil, escitalopram, imipramine and chloral hydrate).

Pharmacotherapy	Outcome	Comparisons	Participants (n)	RR/SMD (95% CI)	I ²	GRADE Judgement
Hydrocortisone	PTSD 3-6 Months	3	98	RR: 0.21 (0.05 to 0.89)	0%	Low
Hydrocortisone	PTSD Severity 3-6 Months	1	43	SMD: -0.63 (-1.25 to -0.02)	N/A	Very low
Propranolol	PTSD 3-6 Months	3	96	RR: 0.75 (0.31 to 1.83)	0%	Low
Propranolol	PTSD Severity 3-6 Months	2	52	SMD: 0.06 (-0.49 to 0.61)	0%	Low
Escitalopram (treatment not prevention)	PTSD 3-6 Months	2	92	RR: 1.05 (0.61 to 1.79)	0%	Low
Escitalopram (treatment not prevention)	PTSD Severity 3-6 Months	2	68	SMD: -0.01 (-0.49 to 0.47)	0%	Low
Gabapentin	PTSD 3-6 Months	1	32	RR: 0.80 (0.18 to 3.59)	N/A	Very low
Oxytocin	PTSD Severity 3-6 Months	1	107	SMD: -0.24 (-0.62 to 0.14)	N/A	Very low

Table 1: Effects of pharmacotherapy for PTSD prevention in adult participant RCTs

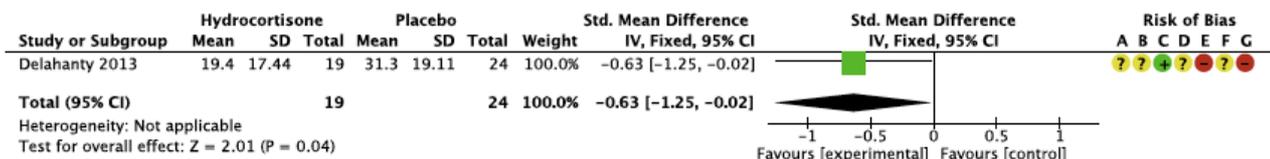


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 1: Risk ratios of hydrocortisone versus placebo in 3 studies measuring PTSD incidence with risk of bias assessments.

Conclusions



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 2: Standard mean difference of hydrocortisone versus placebo in 1 study measuring PTSD severity with risk of bias assessment.

Initiating a therapy within the first six hours post-trauma is thought to be crucial to impeding the disruption to memory consolidation that occurs within this period. Eight studies initiated therapy within 12 hours^{3, 4, 6, 11, 16, 19, 22, 24} - two of propranolol^{6, 11} and six of hydrocortisone^{3, 4, 16, 19, 22, 24}. Five of these hydrocortisone trials^{4, 16, 19, 22, 24} initiated therapy within the “golden” six hours, while Delahanty et al.³ administered hydrocortisone within a 12-hour window and their results suggest that hydrocortisone may still be effective in preventing PTSD outside of a six-hour window.

Pragmatically, it is difficult to identify, consent and enrol a participant into a RCT within six hours of an unexpected trauma, with many studies thus instead investigating expected trauma (e.g. ITU admission, cardiac surgery). Hydrocortisone remains a potentially promising intervention for PTSD and is particularly well suited to trauma that necessitates prompt presentation to a hospital setting such as severe injury. Furthermore there is scope for large scale administration of hydrocortisone in a low resource setting, given its widespread availability as a WHO essential medicine²⁰ and its low cost. Given this, it is likely to be much better suited to a low resource or disaster setting than a psychosocial intervention.

Our work supports additional research investigating the preventative effect of hydrocortisone, but there remains insufficient evidence to recommend its administration routinely. Our research was hindered by the small number of studies evaluating certain

therapies, and by the methodological limitations of many RCTs raising concerns about possible risk of bias. Larger, high quality RCTs are necessary to establish the most efficacious use of hydrocortisone, in particular the dose, dosing window and route. There is currently a lack of evidence to suggest that other pharmacological agents are likely to be effective.

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List of Posters Presented

1. Could sleep dysfunction lead to neurodegeneration?

Mr Damian Amendra, University of East Anglia, medical student, Mr Mihail Dimitrov, King's College London, MSc. Neuroimaging student, Mr Nisar Sherzad, Keele University, medical student, Miss Circé LaMache, King's College London, Mr Kelechi Aofolaju, King's College London

2. A rare case of post-stroke bipolar affective disorder

Dr Clara Belessiotis-Richards, East London Foundation Trust, CT1; Dr Waleed Fawzi, East London Foundation Trust, Consultant

3. Opiates and Benzodiazepines - predictive prognostic factors in Functional Neurological Disorders?

Dr Fabian Bonello, Mount Carmel Hospital, Matla.

4. A Cross-sectional survey of referrals for 'Medically Unexplained Symptoms' to Paediatric Liaison Service within a Tertiary Children's Hospital

Dr Laavanya Damodaran, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, Consultant Paediatric Liaison Psychiatrist

5. Sleep consolidates landmarks in long-term memory facilitating spatial working memory recall

Dr. Mohammad Zia Ul Haq Katshu, Institute of Mental Health, University of Nottingham & Nottinghamshire Healthcare NHS Foundation Trust, Specialist Registrar & Clinical Lecturer; Dr. Giovanni d'Avossa, School of Psychology, Bangor University & Betsi Cadwaladr University Health Board, Consultant Neurologist & Lecturer

6. The Cambridge Centre for Paediatric Neuropsychological Rehabilitation 2009-2018: A service evaluation

Dr Robyn McCarron, Cambridgeshire and Peterborough NHS Foundation Trust (CPFT) and the University of Cambridge, Academic and Clinical Fellow in Psychiatry ST2; Dr Suzanna Watson, CPFT and NIHR CLAHRC East of England, Consultant Clinical Psychologist; Dr Fergus Gracey, CPFT, NIHR CLAHRC East of England and the University of East Anglia, Consultant Clinical Neuropsychologist and Senior Research Fellow

7. The Scottish Epilepsy Centre: Service evaluation of outcome for patients diagnosed with Non-Epileptic attack disorder (NEAD)

Dr Jonathan McLaughlin ST4 Dr Maria Oto Consultant Psychiatrist Dr Karli Dempsey ST5

8. Neuropsychiatric Symptoms in Stiff Person Syndrome

Mark Paramlall MRCPsych, South London and Maudsley NHS Foundation Trust
Himanshu Tyagi MRCPsych, University College London Hospital NHS Trust

9. The clinical characteristics of patients undergoing NMDA and VGKC antibody testing in a psychiatric hospital

Dr Rollo Sheldon¹, Dr Sarah Davies¹, Dr Jane McNulty¹,

¹Millview Hospital, Sussex Partnership NHS Foundation Trust, Brighton, UK.

10. Polydipsia and neuropsychiatric symptoms in a rehabilitation service

Prof Graeme Yorston, Consultant Forensic Neuropsychiatrist, University of Chester and St Matthew's Healthcare; Katie Walsh, Occupational Therapist and Michelle Evans, Deputy Nurse Manager, St Matthew's Healthcare, The Dallingtons Hospital, Northampton

News from the Executive Committee

The executive committee meeting had a full agenda, stimulated by a fantastic conference programme. We celebrated progress by past and current committee members and welcomed our newly elected representatives. Mr Paul Rees, the Chief Executive of the College, gave an update on how the College is developing its strategy, including engaging stakeholders and enhancing the experience of members. As part of this, he announced that the Faculty of Neuropsychiatry can have its own Twitter feed, watch this space for more details!

A major breakthrough announced at the meeting was the finalisation of NHS England's commissioning arrangements for Specialised Neurosciences, which, thanks to the hard work of committee members, includes a requirement for every Regional Neuroscience Centre in England to have dedicated neuropsychiatry support. There will be a public consultation stage before the agreement is finalised. This is a significant step forward, both for the specialty and for patients; congratulations to all involved. We also heard good news about the Faculty outcome measures project (FROM-NP; Framework for Routine Outcome Measurement in NeuroPsychiatry), which has now been ratified by the College. It is envisaged that this framework can guide the collection of more consistent and higher quality outcome measures on neuropsychiatry patients nationwide. The document, along with many other useful resources, will be available on the Faculty

webpage of the new College website going live on 23rd October [LINK].

Financial statements are rarely cheerful and even less often delivered with panache, but our Finance Officer, Dr Czarina Kirk, managed both this year! Our balance sheet shows a healthy surplus and the committee agreed to use this money to create bursaries for junior doctors and medical students. Although increasing numbers of trainees are attending the annual conference, we wish to encourage more. Our academic secretary, Dr George El-Nimr, who created the diverse and stimulating conference programme, discussed plans for future conferences and other, regionally-based events. Although it seems most financially viable to continue to hold the annual conference at the College, the Faculty is very keen to support other events around the country, including in the devolved nations.

Enabling training in neuropsychiatry, and contributing to education in Clinical Neuroscience more generally, are key aspects of the Faculty's strategy for the coming years. We discussed an update from the GMC regarding our efforts to formalise neuropsychiatry training and members reported on progress in other areas of our education strategy. The section 'Trainee Update' in this newsletter has more details of the committee's work in this area - do check it out. If anything in this section has piqued your interest, please send comments, questions and suggestions to Kevin Foy, our new editor.

Forthcoming Events

December 7th to 9th

The British Neuropsychiatry 2018 Teaching Weekend at the Mathematical Institute Oxford with accommodation in St Anne's College. This traditional event hosted by the BNPA provides an excellent overview of pertinent topics in neuropsychiatry and behavioural neurology for SpR's in Psychiatry and Neurology. Registration fee costs £435 and covers accommodation, breakfasts and dinner on Friday as well as all lectures. For further information contact the BNPA on www.bnpa.org.uk

March 7th and 8th 2019

The 32nd Annual General Meeting of the BNPA will take place at Kings Place, London. The main symposia this year will focus on epilepsy, functional neurological disorders and global neuropsychiatry.

March 20th to 23rd 2019

The 30th Meeting of the American Neuropsychiatry Association in Chicago, Illinois. For further information see www.anpaonline.org

September 19th and 20th 2019

The Faculty of Neuropsychiatry Annual Meeting will take place again at the Royal College of Psychiatrists in London.

The external events listed here are not organised or endorsed by the College.