Wellcome PhD Supervisors
Mental and Cognitive Health Theme

David M Clark

Social Anxiety Disorder: Cognitive Processes and Treatment

Abstract: Social anxiety disorder is one of the most common, disabling and persistent of the anxiety disorders. We have developed a cognitive therapy programme for adults, which specifically targets the maintaining factors outlined in Clark and Wells' (1995) model. Randomised controlled trials show that the treatment is highly effective. It is recommended as the first treatment option by NICE. However, there is room for further improvement. Key areas for research include: 1) adapting and evaluating the treatment for use with children and adolescents, 2) testing aspects of the cognitive model in children and adolescents, 3) understanding the mechanism of change, 4) developing an internet version of the treatment for fear of public speaking with associated experiments that characterise the cognitive processes distinguishing fear of public speaking from generalised social anxiety disorder. Students will be able to spend their day-a-week of clinical work in the Oxford Centre for Anxiety Disorders and Trauma supervised by Professors David M Clark, Anke Ehlers and colleagues. Other possible placements include research within a local IAPT service, or working with Christopher Fairburn's (eating disorders) or Daniel Freeman's (psychosis) clinical teams.

Philip Cowen

The role of inflammation in clinical depression

Abstract: Several strands of evidence indicate that inflammation plays a part in the development of clinical depression. For example, the cytokine interferon, when used as a treatment for hepatitis C, leads to significant depressive symptoms in about a third of the people receiving it. Conversely immune-modulating drugs such as TNF-alpha antagonists improve depressed mood in patients with rheumatoid arthritis over and above what would be expected from symptomatic improvement in physical symptoms.

The research project will take advantage of the expertise in Oxford in molecular immunophenotyping to identify particular depressed patients in whom immune mechanisms appear to play a significant role in illness. Neural correlates of inflammation will be identified using magnetic resonance spectroscopy and functional brain imaging. Finally, studies of the effects of a suitable immune modulator in patients with refractory depression will be conducted. This translational aspect of the work will be carried out in the Professorial mood disorders clinic which provides a world class expertise in the clinical assessment and treatment of patients with complex mood disorders.

Reference

Raison CL, Miller AH (2011) Is depression an inflammatory disorder? Curr Psych Rep 13: 467-475.

Drug repurposing to develop a lithium-mimetic

Abstract: Lithium is the mainstay of pharmacological treatment of bipolar disorder but its use is limited by poor tolerability and safety. A leading hypothesis suggests that lithium's mode of action in bipolar disorder is mediated by its ability to inhibit inositol monophosphatase (IMPase) and thereby decrease second messenger signaling. Work in the University Department of Pharmacology has identified an anti-oxidant drug called ebselen, previously developed for the treatment of stroke, as a potent IMPase inhibitor. Ebselen is known to be safe in humans and therefore offers an excellent opportunity for repurposing for the treatment of bipolar disorder.

The research project will involve a collaboration between the University Departments of Pharmacology and Psychiatry. The work will involve elucidating the neurobiological profile of ebselen in healthy participants using both neuropsychological and brain imaging (fMRI and MRS) approaches). Subsequent clinical work will develop a proof of concept study aimed at demonstrating therapeutic efficacy of ebselen as a mood stabilizer in patients with bipolar disorder. This study will be carried out through the Professorial mood disorder clinic which will provide specialized training in assessment and treatment of patients with bipolar disorder.

Reference

Singh, N., Halliday, A. C., Thomas, J. M., Kuznetsova, O. V., Baldwin, R., Woon, E. C., Churchill, G. C. (2013). A safe lithium mimetic for bipolar disorder. *Nature Communications*, *4*, 1332.

Philip Cowen and Rebecca Park

Translational investigation of novel pharmacological treatments and predictors of response in Anorexia Nervosa

Abstract: The prognosis for Anorexia Nervosa, particularly for adults, remains poor with few evidence based treatments and no beneficial drug therapies. To improve outcome a more innovative approach to drug discovery is required, making use of repurposing current therapies and pilot studies of efficacy in treatment-refractory patients. It will also be necessary to find neuropsychological and neurochemical predictors of response to specific pharmacological approaches.

A range of potential therapies are available for novel investigation including cannabinoids, partial dopamine agonists, and anti-compulsive agents. Treatment predictors will employ neuropsychological testing and brain imaging to assess functional responses in emotional and reward circuitry, and neurochemistry measured with magnetic resonance spectroscopy. The project allows experience in contemporary clinical neuroscience, using experimental strategies and neuroimaging. It will be co-supervised by Rebecca Park, Clinical Senior Lecturer in Eating Disorders and Philip Cowen, Professor of Psychopharmacology. Dr Park's expertise is in translational neuroscience applied to Anorexia Nervosa; currently using multimodal

neuroimaging and brain stimulation strategies. Professor Cowen's expertise is in translational neuroscience and drug development. Clinical placements, where biological findings will be used to guide novel treatment development, will be with Dr

Park in Oxfordshire's Specialist Eating Disorders Service, and Professor Cowen in the Professorial Mood Disorders clinic.

If you are interested in discussing the project please contact

Professor Philip Cowen: phil.cowen@psych.ox.ac.uk
Dr Rebecca Park : rebecca.park@psych.ox.ac.uk

Anke Ehlers

Overgeneralized fear responses in posttraumatic stress disorder

Abstract: Overgeneralization of conditioned fear responses is thought to contribute to the persistence of posttraumatic stress disorder. The empirical evidence for this hypothesis is relatively sparse. The project will explore a range of factors that may contribute to overgeneralised fear responses in this condition. A series of experimental studies with healthy volunteers and people who have experienced traumatic events will explore single trial associative learning, memory updating, and individual differences in perceptual and conceptual generalisation. Further experiments will compare the effect of different interventions on overgeneralisation.

Russell Foster (joint with Daniel Freeman and Colin Espie, see below)

Elaine Fox

The Role of Negative Cognitive Biases in the Understanding and Treatment of Generalized Anxiety Disorder

Abstract: Negative cognitive biases are a key feature of psychopathology. Thus, people with Generalized Anxiety Disorder (GAD) typically demonstrate a bias in their attention system so that threat-related events are given priority leading to persistent worry and rumination. Negative biases play a role in both the aetiology and the maintenance of psychopathology, and reducing these biases is an important component of psychological as well as pharmacological therapies. The development in basic experimental psychology of computerized tools to directly modify cognitive biases provides an exciting opportunity for translational research. These "cognitive bias modification" (CBM) procedures were developed initially to investigate the causal relationship between cognitive biases and mood states and some studies have investigated the potential of these techniques to reduce negative biases in clinical populations. There is now a real opportunity to develop more clinically appropriate CBM techniques that can be implemented via computer Apps. The aim of this project is to develop new CBM-like techniques that specifically target key cognitive features of GAD (such as negative attentional biases and persistent worry) and investigate whether these interventions can improve the effectiveness of standard clinical treatment, such as CBT. There may be opportunities to use brain-imaging methods (fMRI and EEG) as outcome measures in some studies in the project.

Daniel Freeman, Colin Espie and Russell Foster

Sleep and persecutory delusions: theory and treatment

Abstract: This project will combine the important areas of sleep problems and psychotic experiences. A series of studies have begun to establish that disrupted sleep may be a causal factor in the occurrence and persistence of paranoia. This thesis will have three aims: to establish the causal connection between sleep and paranoia (e.g. carrying out a sleep restriction study); to develop the treatment of sleep disturbance in people with paranoia (e.g. to test out new techniques for stabilising sleep); and to test whether sleep can enhance the benefits of behavioural tests for paranoia. The person will be based in the Oxford Cognitive Approaches to Psychosis Unit at the University Department of Psychiatry (where there will be clinical experience) and the new Oxford Sleep and Circadian Neuroscience Institute (SCNi).

See: Freeman, D., Startup, H., Myers, E., Harvey, A., Geddes, J., Yu, L-M., Zaiwalla, Z., Luengo-Fernandez, R., Foster, R., & Lister, R. (2013). The effects of using cognitive behavioural therapy to improve sleep for patients with delusions and hallucinations (the BEST study): study protocol. *Trials*, **14**, 214.

Colin A Espie

Insomnia as a disorder of selective attention: towards the development of therapeutic paradigms based upon modification of cognitive bias

Abstract:

Insomnia is the most common expression of mental dis-ease in men and women, of all ages and ethnic groups, worldwide. Traditionally thought of as a mere nuisance problem, or as a symptom of 'something else' (e.g. depression), it is now clear that Insomnia Disorder merits clinical attention in its own right (c.f. DSM-5) and that pre-existing sleep and circadian disturbance is a potent risk factor for a) the development of emotional ill health in the first place, and b) for relapse into poor mental health.

Psychological theory and practice has a great deal to offer in the management of persistent insomnia. Indeed, cognitive behavioural therapies are recognised by leading authorities as the treatment of first choice, based on a large literature comprising RCTs and meta-analysis. Consequently, there has been a growing research emphasis upon evaluating accessible forms of therapy, such as small group, therapist-assisted, and digital (web/ mobile CBT) methods of delivery.

Crucial to the science of the field, however, is further research into the pathophysiology of insomnia, and into predispositional, precipitating and perpetuating factors in the aetiology and maintenance of insomnia. One of the putative mechanisms that has been proposed and which offers a) an explanatory model for the most common form of insomnia (psychophysiological insomnia), b) a fresh understanding of existing psychological treatments, and c) the development of novel interventions, is that of

selective attention bias. Referred to as the ‘attention-intention-effort pathway’ this approach demonstrates how disadvantage to the automated and passive process of sleep engagement so typical of normal good sleep is greatly inhibited by cognitive bias

towards sleep and sleep related cues. Thus establishing a vicious, dysfunctional cycle that serves only to place sleep even further from the individual's 'control'.

Over the past 10 years we have developed, instrumented and tested Stroop, Dot Probe, Posner and Induced Change Blindness paradigms to provide experimental data on the A-I-E pathway, and we, and others, have published resultant data widely. Through this DPhil, and related externally funded projects, we seek to further this line of research. In particular, we wish to continue evaluation of cognitive behavioural change processes during evidence based psychological therapy, and to develop new interventions that specifically focus upon the modification of sleep-related cognitive bias.

The research will take place within the Sleep & Circadian Neuroscience Institute (SCNi) which is extensively funded by The Wellcome Trust, Sir Jules Thorne Charitable Trust, and the Sackler Foundation. There will be access to physiological monitoring equipment, cognitive testing facilities and to engineering/ digital health expertise, and a co-supervisor will be appointed to provide additional mentoring and support

References:

Espie, C.A., Broomfield, N.M., MacMahon K.M.A., Macphee, L.M. & Taylor, L.M. (2006) The attention-intention-effort pathway in the development of Psychophysiologic Insomnia: a theoretical review. *Sleep Medicine Reviews* 10, 215-245

Perlis M.L., Shaw, P., Cano, G., Espie, C.A. (2011) Models of Insomnia In MH Kryger, T Roth and WC Dement (eds) *Principles and Practice of Sleep Medicine*, 5th edition. Elsevier Saunders, NY

John Geddes

Enhancing self management of bipolar disorder by relating patient reported measures of mood instability to underlying neural mechanisms in bipolar disorder

Abstract: Our current model of intensive self management of bipolar disorder relies on weekly or daily self ratings of mood. The aim of this project will be to produce a more informative short-term assessment of mood variability than currently provided by investigating and validating more intensive and objective measures of activity, sleep and neural activity as usable measures during the initial training phase of self-management training. The project will be based in the University Department of Psychiatry with weekly clinical activity and training provided in the specialist bipolar clinic directed by Prof Geddes. The project will use the innovative .True Colours system for rating patient reported mood status and will sample from the existing OXTEXT cohort of intensively phenotyped and prospectively monitored patients with bipolar disorder.. Self reported mood ratings will be correlated with (1) high frequency temporal instability of brain function assessed by MEG in the multimodal OHBA neuroimaging facilities and (2) remote monitoring of activity and sleep using the Proteus patch. Validated clinical measures will be integrated into the OXTEXT self-management programme and developed/piloted as a more efficient self management intervention.

Catherine Harmer

Using a neurocognitive model to understand antidepressant drug action

The mechanisms by which antidepressants improve the diverse range of symptoms seen in depression have remained elusive. However, recent evidence suggests that antidepressants can target key psychological processes important for the maintenance of illness, including so called negative bias. This involves over sampling and processing of negative information at the expense of more positive cues. Antidepressants can reverse these negative biases very quickly in the treatment of depression (Harmer et al 2009) and are believed to lead to improved mood over time through interactions with the environment. The current project will involve testing whether these early changes in emotional processing (assessed with both behavioural and neuroimaging methods) can predict longer term treatment effects, as would be expected by this model. In particular, patients with depression will be randomised to receive a single dose of an antidepressant or placebo in a counterbalanced order before completing a battery of emotional processing measures. The ability of shifts in emotional processing bias with the drug treatment to predict clinical response after 6 weeks of treatment will also be assessed. This study will therefore contribute to our understanding of antidepressant drug action, using a cross-discipline approach, and have implications for the way in which we can detect and use information about early treatment response to improve treatment in depression. There will also be the opportunity to investigate specific neural mechanisms by which antidepressants affect the processing of emotional information which can be performed in healthy volunteers using MEG as well as fMRI.

Paul Harrison and Liz Tunbridge

COMT inhibitors as potential treatments for cognitive and addictive disorders: the influence of stress

Abstract: COMT is an enzyme which regulates cortical dopamine and thereby influences a range of dopamine-related phenotypes. COMT inhibitors are used in Parkinson's disease, and are being trialled in several psychiatric disorders. The effects of these drugs are predicted to differ between individuals due to a functional polymorphism in the gene ($Val^{158}Met$). We recently confirmed this experimentally, in terms of behavioural performance (Farrell et al, *Biol Psychiatry* 2012; 71:538-544) and using neuroimaging (unpublished). We are now interested in testing another prediction: that the effects of COMT inhibition will interact with stress. This experimental medicine study will use behavioural and neuroimaging (fMRI) methods to investigate this question in healthy volunteers, selected on the basis of their genotype, and randomised either to a COMT inhibitor (tolcapone) or placebo. They will undergo a range of cognitive and emotional tasks (in and out of the scanner) under either stressed or non-stressed conditions. Physiological stress will be measured using a novel device. The work will link with a new MRC-funded project, and will be based in the Neurosciences Building, University Department of Psychiatry, Warneford Hospital.

The clinical attachment will be in general adult psychiatry, in the Professorial

mood disorder clinic, on the same site.

Paul Harrison

Do calcium channel antagonists stabilise mood?
A genetically informed, placebo controlled, double blind, randomised experimental medicine study

Calcium signalling is central to current theories of bipolar disorder, for two main reasons. First, cellular calcium signalling is altered in people with the disorder. Second, recent data show that L-type calcium channel genes, especially *CACNA1C* (which encodes the $Ca_v1.2$ subunit), contribute to the genetic aetiology. L-type calcium channel antagonists are widely used to treat hypertension, and uncontrolled data suggest they may have some efficacy for the treatment of mania. However, there are no good studies showing whether these drugs stabilise mood, and none which have investigated their effect on brain function.

Forty subjects with high mood instability, and who have the *CACNA1C* bipolar risk genotype, will be recruited. After a 3 week assessment period (which will include remote monitoring of mood and activity, cognitive tasks delivered via an app, MEG and fMRI scans, and a range of biochemical investigations), they will be randomised to receive nifedipine (a licensed calcium channel antagonist) or matched placebo for a further 3 weeks. They will continue to be monitored closely during this time, and repeat neuroimaging and biochemical measurements taken. Both longitudinal and cross-sectional comparisons will be made.

The study will show whether and how calcium channel antagonists stabilise mood and, if positive, will provide a rationale and basis for large scale clinical trials in patients with bipolar disorder. The study also serves as an exemplar of how experimental medicine approaches can be applied to study of psychiatric disorders and their treatment.

The candidate will gain training in: psychological and cognitive assessments; multimodal functional brain imaging; design and execution of randomised clinical trials; genotyping; calcium biology; and bipolar disorder itself.

This project will be part of a large multidisciplinary study of mood instability and bipolar disorder called CONBRIO (http://conbrio.psych.ox.ac.uk/home), funded by a Wellcome Trust Strategic Award. It will be based in the specialist bipolar disorder research clinic situated in the Clinical Research Facility at the Warneford Hospital. Research assistants and research nurses will assist with the day-to-day running of the trial.

Potential applicants are welcome to contact paul.harrison@psych.ox.ac.uk for further information and informal discussion.

Glyn Humphreys

The neuropsychology of social cognition

Abstract: Problems in social cognition after brain lesion/degeneration are often profound and have a major impact on both the affected individual and his/her carer. There is currently no routine diagnosis of problems in social cognition, no readily

applicable clinical screen and few attempts to develop effective treatment. This project has the joint aims of (i) developing new, clinically applicable screens for impairments in social cognition in neuropsychological patients, and (ii) developing and evaluating novel therapies for impairments in social cognition – including the effectiveness of direct brain stimulation when used in conjunction with social learning procedures. The project will provide a training in neuropsychological test development, direct brain stimulation and imaging methods, and in the design and analysis of case-series based interventions.

Masud Husain

Motivation and decision-making in brain disorders

Abstract: Deficits of motivation and decision-making, e.g. apathy and impulsivity, are common clinical problems associated with many different kinds of brain disorder. They have a profound impact on the lives of people but currently there is little in the way of treatment for these complex conditions.
We're interested in understanding mechanisms that underpin such altered behaviours and developing programmes to treat them. Our experimental methods have been developed from basic cognitive neuroscience for application to patient groups.
We use behavioural techniques to assess sensitivity to rewards and the effort required to acquire them, as well as the ability to use feedback to learn from previous poor decision-making. We use structural and functional imaging to relate functional disturbances to alterations in brain networks.
We study patients with stroke, Parkinson's disease and Alzheimer's disease. Our intervention techniques include drug treatments and computerised training programmes to adaptively modulate behaviour.
If you're interested to learn more visit www.masudhusain.org .

Heidi Johansen-Berg

Impact of sleep quality on rehabilitation outcomes following stroke

Rehabilitation after stroke depends on processes of brain plasticity and learning. It is well established that sleep is critical for consolidation of certain types of learning, such as learning of new motor skills. There is some evidence that sleep quality is poor in older people in general, and in stroke sufferers and people in in-patient settings in particular. Therefore, improving poor sleep, and therefore maximising consolidation of new memories, is a potential 'back door' route to improving rehabilitation outcomes after stroke.
However, there is remarkably little research on the prevalence of sleep disturbance in individuals after stroke. It is unclear whether sleep problems are a risk factor or consequence of stroke. It is unknown whether sleep disturbance contributes to rehabilitation outcomes and whether interventions to improve sleep quality could enhance outcomes.
The proposed project would involve sleep quality assessments (using accelerometry, EEG, and questionnaires) in patients after stroke, in both home and in-patient settings.

Sleep measures would be related to impairments and to rehabilitation outcomes. Interventions (e.g., sleep therapy, melatonin) would be trialled.
The project would involve clinical placements in year 1 under the supervision of Dr Udo Kischka (Oxford Centre for Enablement).

Belinda Lennox and Camilla Buckley

Optimising treatment for psychosis and autoimmune encephalopathy

Joint supervisors: Dr Belinda Lennox (psychiatry) and Dr Camilla Buckley (NDCN)

We run a joint neuro-immunological and psychiatric clinical service for autoimmune encephalopathy with regional and national referrals. The proposed project will be based alongside this clinical service.

We have found that alongside the classical syndrome of encephalitis (involving seizures, cognitive impairment, movement disorder and autonomic disturbance), a proportion (6.5%) of patients with a primary psychotic illness, without other features of encephalitis also have antibodies against neuronal cell surface targets (including NMDAR, VGKC).

The project will involve characterising the clinical and neurocognitive phenotype of this new disorder, and the response to treatment with both psychiatric and immunological medications.

Charles Newton

Autism in children of immigrant parents

Immigration is recognised as a risk factor for the development of autism in the children born to mothers from Africa and Caribbean in particular. It is not clear the mechanisms of this risk. Possible explanations include: genetic susceptibility, higher incidence of brain insults, men seeking immigrant partners who are less aware of autism related social problems, difficulty in finding a partner with increased paternal age, selection bias of immigrants and low levels of Vitamin D in immigrant mothers. We want to examine the mechanisms that lead to increased risk of autism in children born to immigrant mothers.

Kia Nobre

Neural dynamics of regulatory mechanisms in cognition

Abstract: Our perception and cognition are shaped by numerous modulatory signals, related to our task goals, expectations, memories, motivation, and emotions. We are interested in understanding the neural mechanisms and dynamics of these various sources of biases, and in understanding how they are compromised during ageing and in neurodegenerative and neuropsychiatric disorders. Studies would be available looking at the integrity and dynamics of networks of brain regions derived from magnetoencephalography (MEG) data recorded at rest and during cognitive tasks. We are also involved in the Collaborative Network for Bipolar Research to Improve Outcomes (conBRIO,http://conbrio.psych.ox.ac.uk/home). Specifically, we are studying the influence of mood and mood instability on cognition using daily behavioural testing as well as its neural basis using MEG and structural and functional MRI.

For more information on specific projects and methods, please refer to the web sites of the Oxford Centre for Human Brain Activity (OHBA, http://www.ohba.ox.ac.uk) and the Brain & Cognition Lab (http://www.brainandcognition.org).

Michael Sharpe and Jane Walker

Psychological and psychiatric studies in the medically ill

Abstract: Clinical Unit: Psychological Medicine (psychiatry and psychology service) and relevant medical settings in the Oxford University Hospitals NHS Trust.
You will work with Professor Sharpe, Dr Walker and other members of the Psychological Medicine Research (PMR) team and members of the award winning the linked clinical services.
Projects available include:

(a) Secondary analysis of large descriptive and trial datasets of psychiatric illness in patients with cancer.
(b) Descriptive and intervention studies of very high users of general medical care who have psychiatric illness.
(c) Developing and evaluating interventions including the training of clinicians to deliver better psychological care to medical patients.

Research methods taught include:
Qualitative and quantitative descriptive methods, secondary analysis of large datasets, complex intervention design and clinical trial methods. You will also gain experience of working as a member of a multidisciplinary clinical research team whilst leading on an aspect of the work and writing it up for a DPhil.
[Access to clinical services agreed.]

Alan Stein

The Influence of Perinatal Psychological Disorders on Child Development

Abstract: Our main interest concerns the influence of perinatal depression and anxiety on parent-infant interaction and child development. We investigate the mechanisms underlying the relationship between parental disorders and child development and use this to develop targeted interventions.

The studentship will enable investigation of the pathway from parental disorder to child outcome. Of particular interest is the way in which disturbances in cognitions (including rumination and worry) can affect parenting capacities and how these different parenting capacities may in turn impact on child outcomes. The student could investigate aspects the three parenting capacities that have been hypothesised to mediate the effects on child cognitive and emotional development and behaviour:
1) Parental focus of attention to child's facial and vocal communications and the

associated contingent appropriate responsiveness and
2) Parental emotion scaffolding (principally comprising warmth, support and low levels of intrusiveness), particularly during potentially stressful situations to support infants to develop their own emotional regulation
3) Parental capacity to treat a child as a psychological agent (i.e. as someone with feelings and intentions).

Studies can include observational work, experimental studies or a brief intervention.