

Date of submission:
Project title:

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SINAPSE PhD Project Proposal Template for PhDs starting in 2009

SINAPSE Centre (i.e. primary university to which this studentship will be attached*):

University of Dundee

First supervisor: contact details

Name: Professor Keith Matthews
Department: Centre for Neuroscience
Address: Division of Molecular and Translational Medicine, University of Dundee,
Ninewells Hospital and Medical School, Dundee DD1 9SY
Email: k.matthews@dundee.ac.uk **phone:** 01382 632121

Second supervisor: contact details

Name: Dr Mark Bastin
Department: Medical and Radiological Sciences (Medical Physics), Univ. of Edinburgh
Address: Western General Hospital
Crewe Road, Edinburgh
Email: Mark.Bastin@ed.ac.uk **phone:** 0131 537 2511

Third supervisor: contact details

Name: Dr Douglas Steele
Department: Department of Mental Health, University of Aberdeen **
Address: Clinical Research Centre, Royal Cornhill Hospital, Aberdeen
Email: d.steele@abdn.ac.uk **phone:** 01224 557 602

Speciality of first supervisor:

clinical psychiatry (mood disorder),
neuropsychology, neurosurgery for
mental disorder (NMD)

Speciality of second supervisor:

Neuroimaging computational physics
(DTI-tractography)

Speciality of third supervisor:

Neuroimaging (DTI, fMRI, etc) and
clinical psychiatry (mood disorder, etc)

** from 1/1/09 Dr Steele will be
Professor of Neuroimaging at the
University of Dundee

PROJECT

Title:

Exploration of white matter tracts in patients with chronic, refractory mood disorders treated by therapeutic lesions of the anterior cingulate and anterior internal capsule using probabilistic neighbourhood tractography (PNT) modelling of diffusion tensor imaging (DTI) data.

Planned start date (month/year):

August 2009

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Likely background of suitable student (eg. Neuroscience, MR Physics, Chemistry, Psychology) and essential skills required prior to starting this PhD:

The successful candidate will require a background in a quantitative science (e.g. physics, computing, engineering, mathematics) and will have a strong interest in developing and applying computational neuroimaging techniques to clinical neuroscience research. The successful candidate will not have to recruit study participants, nor be involved in their treatment or clinical assessment, as this will be done by clinically trained collaborators. However, they will be expected to assist with image acquisition. Computational modeling of DTI data involving tractography, and the statistical analysis of the data, will be a central feature of the project. Previous experience of DTI is not required as training will be provided.

*usually this would be the university in which the first supervisor is based.

Summary of proposed project (approximately 200 words):

The 'Advanced Interventions Service' (AIS) <http://www.advancedinterventions.org.uk/> is an NHS 'National Specialist Service' for severe and chronic treatment-refractory mood disorders and is based in Dundee. The AIS is hosted by NHS Tayside with several key clinical staff employed by the University of Dundee (e.g. Matthews).

One of the treatments provided by the AIS is Anterior Cingulotomy, which involves the creation of small bilateral thermal lesions in the anterior cingulate cortex, including the cingulum bundles. We have recently reported that there is a relationship between lesion characteristics (location and volume) and clinical outcome at one year (1). A similar, though less compelling, result was reported in a Swedish study of another procedure, Anterior Capsulotomy (2). Both studies used T2 weighted imaging which provided limited information on lesions. It is well known that when such a lesion is made in a white matter tract, distal degeneration may occur (3). The neuroimaging technique of choice for the investigation of white matter tracts is diffusion tensor imaging (DTI). The proposed study would use novel DTI-tractography computational methods to investigate hypothesised links between distal structural brain change and clinical outcome (symptom reduction and adverse effects). We propose to evaluate these relationships in existing AIS patients with Cingulate ($n > 10$) or Capsulotomy lesions ($n > 15$).

Output from tractography algorithms is often dependent on the choice of user-specified seed points. This limits confidence in the results. Addressing this limitation, probabilistic model-based neighbourhood tractography (PNT) is a novel method for automated seed point placement (4). PNT has been developed with particular reference to the tracts of interest (cingulum and anterior capsule) (4). The proposed study would, therefore, use data from matched controls as training data for the PNT technique before application to patient data. Development of the method to take account of lesions is a crucial aspect of the work.

Key references (up to five):

1. Steele J.D., Christmas D., Eljamel M.S., Matthews K. (2008) "Anterior cingulotomy for major depression: Clinical outcome and relationship to lesion characteristics" *Biological Psychiatry*, 63(7), 670-677
2. Rück C, Karlsson A, Steele J.D., Edman G, Meyerson B.A., Ericson K, Nyman H, Åsberg M, Svanborg P (2008) "Capsulotomy for Obsessive-Compulsive Disorder – long-term follow-up of 25 patients" *Archives of General Psychiatry*, 65 (8), 914-921
3. Mufson E.J., Pandya D.N. (1984) "Some observations on the course and composition of the cingulum bundle in the rhesus monkey" *Journal of Comparative Neurology*, 225, 31-43

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4. Bastin M.E., Piatowski J.P., Storkey A.J., Brown L.J., MacLulich A.M.J., Clayden J.D. (2008) "Tract shape modeling provides evidence for topological change in corpus callosum genu during normal ageing" *NeuroImage* 43 20-28

5. Steele J.D., Bastin M.E., Wardlaw J.M. and Ebmeier K.P. (2005) "Possible Structural Abnormality of the Brainstem in Unipolar Depressive Illness: A Transcranial Ultrasound and Diffusion Tensor Magnetic Resonance Imaging Study" *Journal of Neurology, Neurosurgery and Psychiatry*, 76, 1510-1515.

In what way does this PhD proposal meet the SINAPSE criteria as described in the call for proposals? (100 words)

This project seeks to build research capacity (establishing 'state-of-the-art' structural and functional clinical neuroimaging techniques in Dundee), fostering cross-centre academic collaboration between Dundee University and Edinburgh University Medical and Radiological Sciences, to establish patient access to clinical neuroimaging research in Dundee and, ultimately, to improve patient healthcare in a priority area – promoting the understanding and improved treatment of depression. Additionally, this proposal is supported by existing (guaranteed) funding for scanning, computing and clinical input. The proposal will build on existing computational modelling and clinical work and is fundamentally interdisciplinary in nature.

Please state the name of the local SINAPSE Centre Lead with whom you have discussed this project (Leads are listed on the Call for Proposals, applications submitted without prior discussion will not be considered.):

Dr Dick Lerski