About me:
I am a British national, trainee psychiatrist, and a 3rd year PhD student at the Institute of health and wellbeing at Glasgow University. Over the last 3 years, I have used MRI structural neuroimaging to show that circulating inflammatory markers explain significant variance in brain cortical thickness and topology of structural covariance networks in healthy adult subjects. I was awarded the Jim Gatheral fellowship 2012/2013 of £3000.

Aims of the fellowship:
To acquire expertise in the application of advanced mathematic modeling of functional connectivity of resting state functional MRI (rsfMRI) data using techniques described below.

1. Spatial independent component analysis (ICA), utilises a model free data driven approach. ICA decomposes fMRI time series into a set of linearly separable spatial modes, based on the assumption that fMRI brain image at any time is a mixture of spatially independent components. These spatially independent components are also thought to be components of independent biological systems. ICA is used to recover the estimates of these independent components.

2. Seed based correlation analysis (SCA), in contrast, involves extraction of time series data from a-priori regions of interest (ROI) (a priori model). This data will be then used as a regressor in a correlational or a general linear model in order to calculate voxel-wise functional connectivity maps of covariance with the seed region.

Host centre:
The Stanford Cognitive and Systems Neuroscience Laboratory (SCSNL) headed by Prof Vinod Menon, is a multidisciplinary brain research group in the Department of Psychiatry and Behavioral Sciences at the Stanford University School of Medicine. The group pioneers in using intrinsic functional and structural connectivity measures to investigate neurocognitive networks in the brain. [http://stanford.edu/group/scsnl/cgi-bin/drupal_scsnl/content/home](http://stanford.edu/group/scsnl/cgi-bin/drupal_scsnl/content/home); Duration: 10 weeks (2.5 months) (February to April 2013).
During the visit, Prof Vinod Menon and Dr Srikanth Ryali, both experts in Brain Networks, and functional connectivity, tutored me at the SCSNL.

An Example project at SCSNL: ICA
Due to patient confidentiality and data-sharing issues, I could not use my own data at Stanford. I therefore used an open-source dataset - COBRE the Mind Research Network - of resting state fMRI of patients with schizophrenia.
For the current analysis, the aim was to investigate the functional organization of three core intrinsic connectivity networks (ICN) within the brain - the Salience Network (SN), Central Executive Network (CEN), and Default network (DMN), and to test the hypothesis that intrinsic connectivity of the SN, in particular, is aberrant in patients with paranoid schizophrenia.

What are intrinsic connectivity networks (ICN)?
ICNs are functionally connected brain systems that can be identified from resting state fMRI data and that recapitulate networks observed during various task conditions. ICNs have emerged as fundamental, organizational elements of human brain architecture. Initial characterization of ICNs focused on two large scale anti-correlated networks- a ‘task positive’ network that featured regions that are largely activated during task related activities, and a ‘task negative’ or default mode network (DMN) - anchored in the posterior cingulate and medial prefrontal cortices - largely deactivated during task related activities.
Further work deconstructed the task positive network into the central executive network (CEN) comprising the functionally coupled fronto-parietal regions, and the salience network (SN) anchored in the anterior insula (AIC) and anterior cingulate cortex (ACC), suggesting that they may indeed serve different purposes.
These three ‘core’ networks have been shown to be fundamental in higher cognitive processes. In particular, SN activity is thought to be crucial in the process of ‘salience mapping’ - i.e. allocating attentional resources to external and internal stimuli (bottom up) and attributing salience to the stimuli (top down)

Group Independent components analyses (ICA) with Dual regression:
I used group ICA and dual regression approach implemented in FSL (http://www.fmrib.ox.ac.uk/analysis/dualreg/) to identify ICNs from a 5 minute resting state fMRI scan from 34 subjects with Paranoid Schizophrenia and age/ sex matched
ICA can identify coherent intrinsic connectivity networks by extracting structured signals that exist simultaneously in data. ICA can also separate key signals of interest (i.e., patterns of coactivation) from artifactual or physiological noise and head motion.

Pre-processed data (motion correction, slice timing correction, normalised, smoothed) from both groups (Schizophrenia and Controls) were concatenated and entered into a group ICA. Data was then decomposed into 30 independent components using MELODIC (http://www.fmrib.ox.ac.uk/fsl/melodic/index.html). Specifically, the pre-processed concatenated data were whitened and projected into a 30-dimensional subspace using Principal Component Analysis. The whitened observations were decomposed into sets of vectors, which describe signal variation across the temporal domain (time-courses), the session/subject domain, and across the spatial domain (maps) by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique. Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values.

Second, a dual-regression algorithm was applied to identify subject-specific time-courses and spatial maps. This procedure quantifies voxel wise connectivity estimates for each network while controlling for the influence of other networks. The dual regression consists of two steps. Firstly each group network map was regressed on to each subject’s individual resting state data. This resulted in subject specific time course for each network. In the second step, the resulting subject specific time courses from the first step, were regressed onto the individual subjects' resting state data to estimate spatial maps corresponding to each network. Here, the second temporal regression examines each voxel's connectivity with each spatial network while controlling for the influence of other networks, including potential artefacts.

Four ICA components corresponding to the triple network model (left and right CEN, SN, and DMN) were identified as described above (Figure 1). Between-group differences in spatial maps were computed using non-parametric permutation methods, using FSL-Randomise. Group difference maps from the permutation tests were analysed using threshold-free cluster enhancement (TFCE) at the threshold of $p < 0.05$. 

Figure 1: Triple network identified using independent component analysis (ICA). Data from 37 patients with paranoid schizophrenia (SZ) and 37 healthy controls (HC) were combined in-group concatenation ICA. The triple network - (A) Default mode network; (B) Salience network; (C) Left central executive network; (D) Right central executive network. Maps are displayed at z>2.3.

The results in brief:
The schizophrenia group showed stronger functional connectivity within the left CEN, SN, and DMN than did controls. Using leave-one-out cross-validation, I found the SN map best discriminated patients from controls with 82% accuracy (p=0.008), 95% sensitivity, and 70% specificity. The SN maps predicted the severity of positive symptoms score on the PANSS (p<0.0001), particularly delusions (p=0.003).

Impact of the scholarship:
I have now been awarded an Academy of Medical Sciences, Clinical lecturer starter grant, to explore the relationship between circulating inflammatory markers and functional connectivity using the techniques that I learned at SCSNL. The work I did at Stanford, led to the submission of abstracts to two conferences. I won the trainee research poster first prize at the Royal College of Psychiatrists International Congress at Edinburgh in 2013. The paper was also presented as a poster at the Academy of Medical Science Spring Clinical Lecturer meeting 2014, and was published as an abstract in the Lancet. doi:10.1016/S0140-6736(14)60328-7. The first manuscript resulting from the visit is currently under preparation for publication in a peer-reviewed journal.