METHODOLOGICAL ISSUES IN COMPARING BRAIN CONNECTIVITY BETWEEN GROUPS

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Introduction

The use of functional connectivity based approaches in resting state fMRI (R-fMRI) has recently received widespread interest. One approach involves the parcellation of the brain into a number of regions, where the mean time course in each is taken as a node, and a similarity measure, such as correlation, is calculated between every pair of nodes and is taken as an edge, allowing for network and graph theoretic techniques to be used. This step is usually carried out after a spatial normalisation to a standard space. A thorough review is given in [1]. Differences in functional connectivity have been examined between healthy controls and various groups, including those with autism, AD, schizophrenia, SAD, epilepsy, and ADHD. It has also been used to examine the effects of drug abuse, along with looking at differences between men and women, and young and old. Methodological issues surrounding functional connectivity have recently been explored, with the systematic effect of motion on functional connectivity network measures examined in [2]. This is especially relevant in comparing groups which would be expected to have systematic differences in motion as well as differences in network and structural measures. In the present study, we examine how the size of brain regions in their native space affects comparisons of functional connectivity between groups *even when there is no difference* in the underlying voxel time courses. Since the spatial normalisation step has little effect on the mean time course found for each ROI (due to the commutative properties of the averaging), those with more sampled voxels will appear to have a cleaner signal even if the underlying time course is the same. Therefore, a similarity measure, such as the correlation coefficient, will have a higher value between two regions in the bigger brain. When one performs a test to examine if the (transformed) coefficients are different between two groups it may show an apparently statistically significant result, due solely, or in part, to systematic differences in size or structure between the groups.

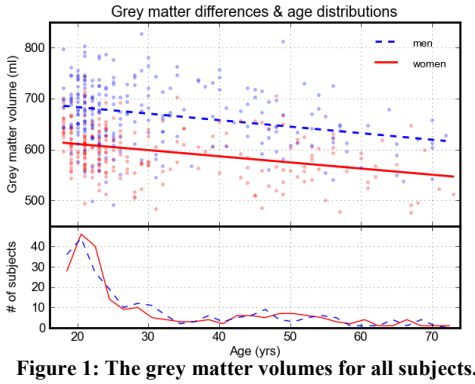

Figure 1: The grey matter volumes for all subjects.

Methods

Both structural and R-fMRI data of 484 subjects (242 female) aged 18-73 from 11 sites which contributed to the 1000 Functional Connectomes Project [3] were used. Distribution of age and grey matter volumes may be seen in Fig. 1. To find the regional volumes of 90 cortical and subcortical structures in each subjects' native space, the AAL atlas was brought into this space, for each individual, using a technique similar to the IBASPM method introduced in [4]. These 484 individualised atlases were used as the basis for simulated brain phantoms, with the signal before noise at every voxel in every brain being identical before adding Gaussian noise with a standard deviation 13 times the peak amplitude of the signal, forcing a correlation and coherence value of 0.58 between two mean sized regions in a male brain. Simulations were also constructed varying parameters such as the number of subjects involved and length of time scanned. For the real and the simulated data, both the correlation and coherence between each pair of regions was found for each individual/phantom. These were then compared between each group (male and female) to discover those connections that showed apparent significant difference after a full Bonferroni correction.

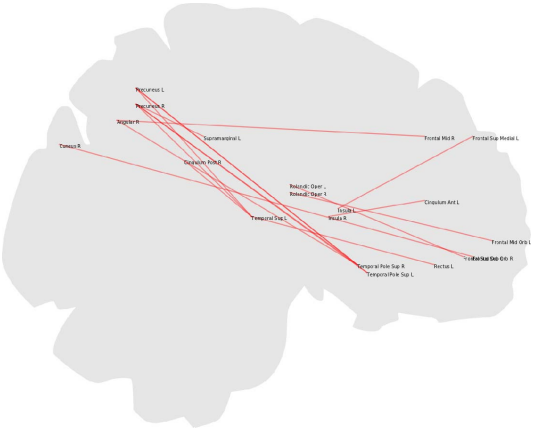

Figure 2: The coincident significant connectivity differences in both the simulated and real data.

Results

Men showed significantly higher absolute volumes before spatial normalization with increased grey matter volume compared to women of 11.5% in agreement with [5] who used data from an overlapping subset of the data examined here. After correcting for multiple comparisons, 799 significant differences were found when comparing the correlation values between the two simulated groups (all in the male direction). 119 significant differences were found when comparing the correlation values between the two real groups (75 in the male direction, 44 in the female direction). There are 16 pairs of regions which show significant difference in both the real functional and the simulated data. These are shown anatomically in Fig. 2. In the smaller simulations with varying parameters, Fig. 3 shows apparent significance arising when varying the number of subjects in a study, with the difference rising above threshold when around 300 subjects are in each group. Likewise, apparent significant difference emerges after 190 timepoints (almost 8 minutes in this simulation) and continues to rise as seen in Fig. 4.

Conclusions

This bias may often be hidden when the direction of the effect matches that which was predicted through other imaging methods such as DTI. More insidiously, it will also require edges between nodes in systematically smaller brains which have stronger intrinsic connectivity to have much stronger connectivity than would be expected to produce a detectable difference, leading to potentially important differences in connectivity being missed. Any regions which are calculated in a standard space will be susceptible to this form of bias, whether they be from an atlas, a sphere centred on a co-ordinate, or a cluster taken from group level functional task data. Since this problem is that of a systematic bias, it will become more apparent as a greater number of subjects are used or session length is extended. Coherence appears to be much less sensitive to this bias, though its use will depend on how association is thought of in a particular experiment.

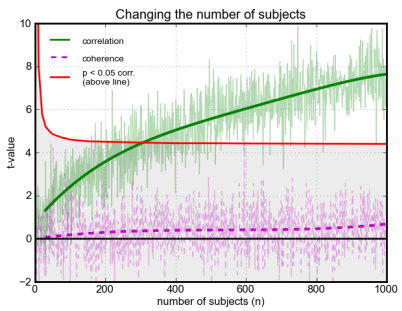

Figure 3: The effect of varying the number of subjects in the experiment.

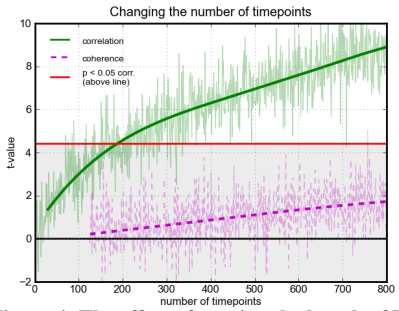

Figure 4: The effect of varying the length of R-fMRI session.

References

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