Investigating reproducibility of working memory effective connectivity

N. Goulden[1], S. McKie[1], J. F. Deakin[1], and R. Elliott[1]
[1]Neuroscience and Psychiatry Unit, University of Manchester, Manchester, United Kingdom

Introduction

Effective Connectivity is being increasingly used in an attempt to make inferences about brain function during certain tasks. Useful potential applications include increasing understanding of the nature of psychiatric illnesses through knowledge of disrupted connectivity. It may also be possible to make inferences regarding psychoactive drugs and better understand their mechanism of action. However, if we are to confidently make inferences regarding patient groups or psychoactive drugs, we need to ensure that healthy volunteers exhibit consistent effective connectivity. The reason there may potentially be a difference is because volunteers are likely to adopt different strategies for carrying out tasks, which will result in differences in the observed effective connectivity.

Methods

24 healthy right handed volunteers (12 males), age 18-23 were recruited. Two volunteers (1 male) were excluded from analysis due to poor task performance. The volunteers carried out an n-back task, designed to test working memory. Volunteers were presented with a sequence of letters and there were four ways they were asked to respond:
A: Rest - volunteers were presented with a fixation cross, and were not expected to do anything,
B: 0-back: Press when see X - volunteers were asked to respond if an 'X' appeared on the screen,
C: 1-back: Press if letter same as last – volunteers were asked to respond if the current letter displayed was the same as the previous letter e.g. A A,
D: 2-back: Press if letter same as one before last – volunteers were asked to respond if the letter shown was the same as the one before last e.g. A B A.
Images were acquired on a 1.5T Philips scanner with a multi-slice, single-shot EPI sequence, TR=2.1s/TE=40ms and analysed using Statistical Parametric Mapping (SPM5, www.fil.ion.ucl.ac.uk/spm). Time series were extracted from each individual's fixed effects analysis in the following brain regions which have been shown to be important for carrying out the n-back task (2): Dorsolateral Prefrontal Cortex (DLPFC), Posterior Parietal Cortex (PPC) and the Supplementary Motor Area (SMA). For each brain region, the time series for each subject were combined into a scan*subject matrix. We then performed principal component analysis on each matrix and used the first principal component as an input for Structural Equation Modelling (SEM) which was implemented using AMOS (www.spss.com/amos).
It has been demonstrated that good power can be obtained with 12 volunteers in a typical fMRI study (1) therefore in order to test reproducibility, the 22 volunteers were randomly divided into groups of 11 and the two independent groups were compared to each other. This was repeated 100 times. The model tested was a good fit to the whole group of 22 subjects ($\chi^2 = 0.295$, p=0.587) (Figure 1). We chose to assess the differences between groups since these are the typical results that would be reported.

Results

Our model was a good fit for 76.5% of groups tested and 30% of comparisons showed no significant difference between groups. The results for the mean, range, variance, skewness and kurtosis of each parameter, as well as the number of times an individual path coefficient was significantly different between groups is shown in Table 1.

	LDLPFC → SMA	RDLPFC→ SMA	SMA → RPPC	SMA → LPPC	LPPC → LDLPFC	RPPC → RDLPFC	LPPC → RDLPFC	RDLPFC → LDLPFC	RPPC → LPPC
Mean	0.0986	0.1323	0.2885	0.0928	0.3467	0.2344	0.2732	0.2795	0.5705
Range	0.89	0.91	1.53	0.73	1.16	1.14	1.28	1.29	1.74
Variance	0.041	0.047	0.163	0.022	0.06	0.053	0.055	0.092	0.146
Skewness	-0.39	-0.828	-1.222	-0.496	-2.054	-1.308	-1.605	-1.779	-2.905
Kurtosis	-0.527	-0.256	0.116	-0.128	3.867	1.511	2.842	1.932	7.152
No times sig diff	26%	27%	51%	13%	27%	24%	23%	23%	20%

Table 1: Results of effective connectivity reproducibility

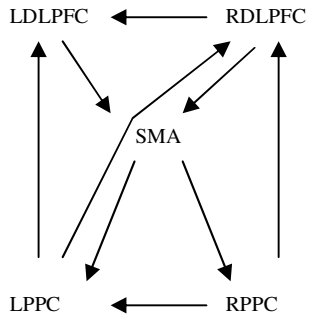

Figure 1: The model tested (L denotes Left and R denotes Right)

Discussion

The low variance for all parameters and relatively low kurtosis for the majority of the parameters indicates that there is a consistently moderate deviation from the mean, as opposed to occasional outliers. The one exception, where there is a particularly high kurtosis, is the RPPC→LPPC connection, where the large range seems to be due to infrequent large deviations from the mean, as opposed to consistent and moderate deviations.

Conclusions

We have demonstrated that 11 volunteers per group is not adequate for an effective connectivity analysis to be carried out using current SEM analysis techniques, especially when investigating group differences in path coefficients due to either psychiatric illness or drug action. With this number of volunteers there is a high probability of observing spurious significant differences between groups, although the overall model can be reproduced reasonably reliably. For this study we used a p-value of 0.05 as the criteria for declaring a significant difference. It may be worthwhile adopting a more stringent p-value, such as 0.001, to account for the high probability of observing spurious significant differences with such a low significance threshold. For our data this would mean that 11 further comparisons showed no significant difference between the two groups. We would suggest including more volunteers in a study where possible.

References

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2. McMillan KM, Laird AR, Witt ST, Meyerand ME. Self-paced working memory: validation of verbal variations of the n-back paradigm. Brain Res. 2007 Mar 30;1139:133-42.