Functional magnetic resonance imaging and glutamate spectroscopy of the n-back network in healthy controls, patients with schizophrenia and patients with bipolar disorder II

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BACKGROUND

Functional magnetic resonance imaging has previously been used to identify a canonical network of regions that respond to the n-back paradigm[1]. The contrast between the 0-back and 2-back conditions is optimised to probe working memory (WM) manipulation. This study aimed to assess how activity within this network is perturbed in schizophrenia (SCZ) and bipolar disorder II (BPII) relative to healthy controls (HC). Glutamate spectroscopy was used to elucidate n-back network activity in terms of both static and dynamic, task-dependent measures. Glutamatergic abnormalities have been shown to be influential in the pathophysiology of both SCZ and mood disorders[2,3].

METHODS

Fourteen patients with SCZ, 15 patients with BPII and 14 HC underwent functional magnetic resonance imaging (fMRI) and functional magnetic resonance spectroscopy (fMRS) n-back paradigms. For each participant mean voxel-wise fMRI values across the 2-back>0-back contrast were calculated in seven regions of interest (ROI) using SPM12 and MarsBaR. As a complementary measure, the mean difference in Glx (glutamate and glutamine) between the final spectra of the 0-back condition and initial spectra of the 2-back condition (ΔGLX) was calculated using TARQUIN in an anterior cingulate cortex (ACC) voxel. ROIs were based on a prior n-back meta-analysis as well as the fMRS ACC voxel location. Static Glx (GLX) was collected from a more dorsal ACC voxel tied to glutamatergic pathology in SCZ. Group contrasts were performed for each ROI. Correlations between ROI values and GLX were calculated. In multiple linear regression modelling, backwards elimination was used to select ROI independent variables associated with the functional glutamate dependent variable ΔGLX.

Table 1. Demographics and clinical characteristics

	SCZ	BPII	HC	F or χ^2 (dfs)	p
No of participants	15	15	14		
Age, mean ± SD	40.1 ± 10.0	33.8 ± 10.5	38.6 ± 10.6	1.442 (2,41)	0.248
Male/female	11/4	6/9	7/7	3.532 (2)	0.171
MADRS [mean rank]	[26.80] 9.0 ± 8.6	[26.47] 9.2 ± 12.0	[13.64] 2.1 ± 2.6	9.883 (2)	**0.007**
SANS	[34.97] 13.8 ± 9.0	[22.70] 3.9 ± 3.9	[8.93] 0.1 ± 0.5	31.054 (2)	**<0.001**
SAPS	[32.97] 29.0 ± 23.5	[21.60] 3.8 ± 3.5	[12.25] 0.8 ± 1.8	20.138 (2)	**<0.001**
YMRS	[22.83] 3.5 ± 4.4	[28.33] 4.7 ± 3.6	[15.89] 1.3 ± 2.4	7.246 (2)	**0.027**

MADRS, Montgomery-Asberg depression rating scale; SANS/SAPS, scale for the assessment of negative/positive symptoms; YMRS, Young mania rating scale

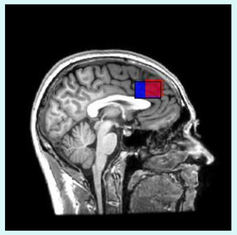


Figure 1. Voxel placement
MRS voxel
fMRS voxel

RESULTS

There was a pattern of greater activation in BPII than SCZ, with an insignificant trend to HC intermediate between the psychiatric groups. This suggests hyperactivation in BPII and hypoactivation in SCZ.

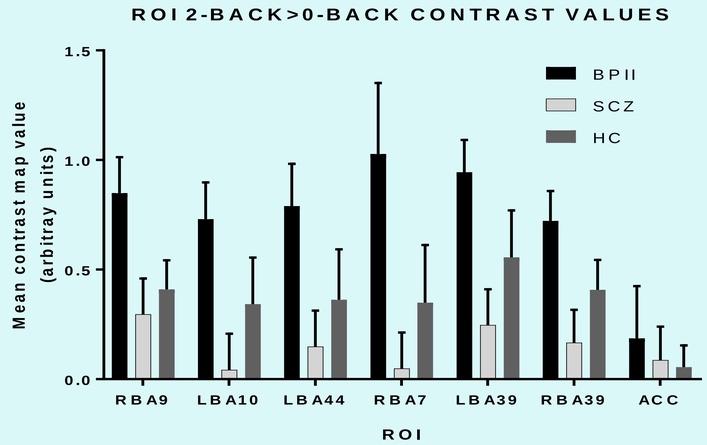
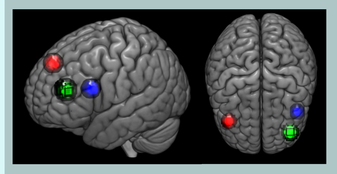


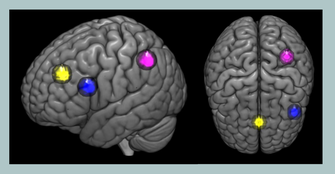
Figure 1. Mean contrast value by ROI and participant group. Error bars are SEM.

For subjects overall (OVERALL) GLX was inversely correlated with the mean 2-back>0-back contrast value in two posterior parietal cortex ROIs; right-BA7 (r=-0.353, p=0.026) and left-BA39 (r=-0.339, p=0.032). Backwards elimination revealed associations between n-back ROIs and ΔGLX for HC and BPII but not SCZ and OVERALL.

Table 2. Significant multiple linear regression models produced by backwards elimination, predicting ΔGlx

BPII	**HC**
R^2=0.636	R^2=0.748
F(3,9)=5.242, p=0.023	F(3,8)=7.916, p=0.009
ΔGlx is predicted by RBA9, LBA10 and LBA44	ΔGlx is predicted by LBA44, LBA39 and ACC





DISCUSSSION

The trend to BPII hyperactivation and SCZ hypoactivation of the n-back network is consistent with leftward shifting of the inverted-U WM n-back load response curves proposed by Callicott *et al*[4]. This is commensurate with reduced WM capacity in these conditions. Performance indices are suggestive of greater impairment in SCZ than BPII. Inverse correlations between GLX and two PPC ROIs may indicate that increased glutamatergic tone in the ACC inhibits WM response in these loci. However, these correlations may be an artefactual consequence of the concatenation of HC, BPII and SCZ data. Linear regression models suggest that the n-back network is eloquent in the expression of ΔGLX in healthy participants. This relationship persists in BPII but is ablated in SCZ. The deterioration of a relationship between the n-back network and ΔGLX in SCZ may be a result of heterogeneity within SCZ or generalised stochastic decay of this relationship. Power is a key limitation of this study.

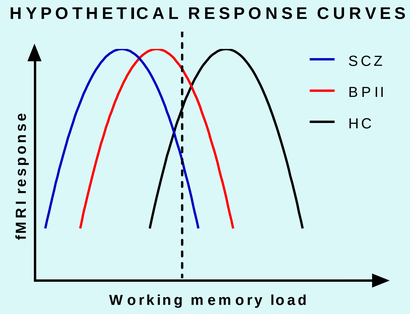


Figure 2. Hypothetical account of BPII hyperactivity and SCZ hypoactivity
Greater activation for BPII compared to SCZ and the trend to BPII>HC>SCZ may be accounted for by the depicted arrangement of hypothetical response curves. Curves are of the inverted U-shape posited by Calicott et al.[4] Dotted line indicates load corresponding to 2-back.

CONCLUSIONS

The trend to n-back hyperactivation in BPII is contrary to the pattern of hypoactivation observed in the only prior study to consider this population[5]. N-back network participation in the expression of ΔGLX is evident in HC and appears to be relatively preserved in BPII. It is deteriorated or lost in SCZ. Effective connectivity work with integrated glutamate measures is indicated to further address causal relationships between fMRI of the n-back and spectroscopic glutamate. Direct dynamic causal modelling (DCM) comparison of ΔGLX-fMRI networks is unlikely to be possible given the dissociation between groups demonstrated in this study.

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