

Neuroimaging research paper analysis



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Brüne, M., Özgürdal, S., Ansorge, N., von Reventlow, H. G., Peters, S., Nicolas, V., & Lissek, S. (2011). An fMRI study of “ theory of mind” in at-risk states of psychosis: comparison with manifest schizophrenia and healthy controls. *Neuroimage* , 55 (1), 329-337.

Brüne et al. (2011) utilised functional magnetic resonance imaging (fMRI) to identify neural activity in the Theory of Mind (ToM) network of subjects at-risk of developing schizophrenia. This analysis aims to undertake a critical analysis of the study’s rationale, design and conclusions.

Rationale

ToM impairments predict poor social functioning in patients with manifest schizophrenia (Bora et al., 2006); given deterioration in social functioning is a critical criterion for diagnosing at risk states of schizophrenia, Brüne makes a strong argument that ToM deficits should be present within the at-risk patient group, and this deficit should be reflected neurologically. However, this argument is undermined by the paucity of research demonstrating differential ToM performance at behavioural and neural levels across patient groups. Of those cited, only one demonstrated a significant difference in at-risk patient performance on ToM tasks (confined to non-core subsets). This issue persists within the neurological research; only a single study demonstrates differential activity in ToM neural correlates in at-risk patients.

Despite this, the authors hypothesise that at-risk patients should exhibit differential activity in the neural regions known to index ToM. The form and direction these deviations take is not stated however, although prominent citing of the Marjoram et al. (2006) study might suggest they are seeking to

identify similar activation patterns. As the aim is to identify localised neural activity, fMRI is an appropriate tool for this study given its high spatial resolution. Inclusion of manifest schizophrenic patients also allows for observation of the changes in neural functioning over the stages of the disorder. However, the fMRI paradigm utilised is a bespoke design tested solely by the author's research team (Brüne et al., 2008; Lissek et al., 2008) and therefore lacks independent experimental support.

Design

Three participants groups were recruited – healthy controls (N = 26), manifest schizophrenia patients (N = 22) and “ at-risk” patients (N = 10). Whilst participant numbers for the control and schizophrenia groups are appropriate, the “ at-risk” group is substantially undersized. Further, statistical power analysis has not been considered in the selection of the sample, potentially limiting the statistical power of the study (Cohen, 1992). Inclusion and exclusion criteria for each group were extensively reported. Groups were effectively matched on age and sex distribution (with suitable chi-square statistics reported). However, no attempt was made to match the groups on other performance-biasing factors such as education level and IQ. This is concerning in the context of evidence that suggests IQ modulates performance on mentalising tasks (Brüne, 2005; Doody et al., 1998) and that IQ in schizophrenic populations is typically 0.5 standard deviations below that of healthy controls (Woodberry et al., 2008).

The task appears to address the stated aim of the study. Participants were presented with cartoon stories during whole-brain fMRI scanning, with

sequences either in order (ToM condition) or out of order (control condition), in conjunction with questions prompting perspective-taking (ToM) or attention to physical aspects of the scenes (control). A paper version of the design was utilised as a behavioural task. Conditions were presented in an alternating blocked design. Block designs provide significant statistical power (Friston et al., 1999) but are reliant on appropriate control blocks to ensure an optimal contrastive baseline. Control conditions in this study are adequate; the use of jumbled variants of the ToM condition stimuli avoids confounds arising from the use of ambiguous baseline resting-periods (Stark & Squire, 2001) but utilising near-identical stimuli across conditions risks minimising the distinctiveness of the control and reducing the contrastive power of the design. Furthermore, instructing participants at outset to focus on the ‘story’ of a sequence risks the emergence of perspective-taking during the control condition and the emergence of ToM related neural activity – potentially minimising differential neural activity between conditions. Finally, no differentiation is made between sequences depicting cooperation and deception, despite the fact that these are known to recruit different subsets of the ToM network (Lissek et al., 2008).

Analysis

Single-subject preprocessing was undertaken in SPM prior to the calculation of individual contrast images, with methods clearly stated and normalisation using an appropriate EPI template reported. Thresholding was not reported for the calculation of single-subject contrast images, presumably as these were to be utilised in the second-level multi-subject analysis. Second-level analysis was correctly undertaken on the individual contrast images utilising

a single-sample t-test, to identify ToM activation across all subjects. Cluster-based extent thresholding of uncorrected $p = 0.05$ with voxel extent of 10 is extremely liberal, presumably utilised to increase the apparent robustness of identified clusters given the small, underpowered nature of the study.

However this minimises the spatial specificity of neural activity (Woo et al., 2014) and risks the emergence of Type 1 errors (Bennett et al., 2009).

Group activation differences were analysed via two-sample t-tests to contrast controls, at-risk and manifest groups on specific regions of interest (ROI); again, liberal thresholding and arbitrary voxel extent reduce confidence in this analysis. ROI were derived from whole-brain data (via the MARSBAR toolbox); by utilising the same dataset used for the whole-brain analysis to determine the specific voxels for the ROI analysis (eschewing the use of an independent dataset) the authors have double-dipped the data, potentially leading to distorted and invalid statistical inference (Vul et al., 2009).

Results

Initial whole brain contrasts for the entire dataset identified a number of regions recruited during ToM tasks. Further fMRI contrasts (utilising two-sample t-tests) on specific ROIs demonstrated differential activation profiles across groups, with at-risk participants evidencing enhanced activation in left inferior frontal gyrus, temporal-parietal junction, superior / middle temporal gyrus and others in comparison with both controls and manifest schizophrenics, with additional enhanced activation in other areas for at-risk compared to controls only. However, all contrasts suffer from the adoption of

uncorrected p values which heighten the potential for Type 1 errors, and also from circular analysis resulting from the use of the same dataset for the selection and analysis of regions of interest. Statistical analysis for the behavioural task was not reported; however no group differences were observed suggesting the groups were functionally identical in their ToM ability, undermining further the argument for representative samples.

Discussion

The authors conclude that at-risk participants differ in the recruitment of their ToM network compared to manifest schizophrenia patients, a conclusion supported by data showing markedly different activation levels across groups in ToM-indexed locations. However circular analysis within the comparisons limits the robustness of these findings.

Furthermore, interpretation is muddled by unexpected patterns of activation; for instance, the heightened activation of the posterior cingulate region in at-risk participants. The authors discuss this in the context of evidence supporting its role in evaluating emotionally salient stimuli (Maddock, 1999), employing reverse inference to suggest the recruitment of the PCC in this task reflects heightened emotional arousal in the at-risk patients. The alternative explanation of compensatory over-recruitment avoids reverse inference by contextualising the data alongside similar activations observed in other tasks (Marjoram et al., 2006) but relating these activations specifically to the utilised task. Although the researchers posit that over-recruitment may be indexing a form of ‘hyper-mentalising’ (Walter et al., 2009) they correctly limit the interpretation of this by noting that the current

design was inappropriate for testing this theory, and that further analysis is required.

In citing the Marjoram et al. (2006) study as a point of reference, the authors attempt to suggest their current study as directly supports it. However, inconsistencies in methodology and outcome limit this conclusion, including differences in classification of at-risk participants and in particular divergences in the neural areas activated during the ToM condition. Given this, the study provides support for the broader conclusions of previous research (i. e. differential activation and over-recruitment in at-risk patients) but fails to replicate their specific patterns of neural activity.

Conclusion

Brüne et al. present a novel study demonstrating differential neural activity in ToM related areas in at-risk participants compared to healthy controls and manifest schizophrenics. However methodological issues, circular analysis and poor thresholding reduce the robustness of the findings.

Word count: 1320

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