Disrupted Functional Connectivity During a Working Memory Task Characterizes Negative Symptoms in Schizophrenia

Authors

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Abstract

Negative symptoms, such as avolition and anhedonia, are key components to understanding schizophrenia. However, much is still unknown about their etiology and the neural substrates that underpin them. We recruited a clinical sample of 50 schizophrenic patients with negative symptoms, of whom 27 had negative symptoms that were in remission, from the Institute of Mental Health, Singapore. Among them, 41 (16 non-remitters) completed a dual-modality working memory task with three memory load levels while undergoing fMRI.

To quantify behavioural performance, we computed load-specific discrimination indices (d') and conducted a two-way mixed ANOVA, controlling for age and gender. We found a significant (group x load) interaction effect ($p = 0.022697$). Post-hoc comparisons revealed that remitters outperformed non-remitters at all load levels (0-Back: $p = 0.0040619$; 1-Back: $p = 0.00045349$; 2-Back: $p = 0.015980$).

We also conducted subsequent paired t-tests between each pair of load conditions for remitters and non-remitters separately. As expected, remitters' ability to discriminate between stimuli decreased as a function of memory load ($p < 0.001$ for all comparisons). However, the data revealed a distinct pattern among non-remitters. While there was a sharp drop in their ability to discriminate between stimuli beyond the 0-Back condition ($p = 0.0032989$ when comparing 0-Back to 1-Back; $p = 0.0034654$ when comparing 0-Back to 2-Back), non-remitters performed just as poorly in both the 1-Back and 2-Back conditions ($p = 0.55554$). These findings indicate that patients with ongoing negative symptoms, relative to those in remission, exhibit disruptions in working memory performance.

To better understand the neural underpinnings of such behavioral deficits, we constructed load-specific functional connectivity matrices using Yeo's 144-ROI functional parcellation among a subset of participants (12 non-remitters, 22 remitters) who had minimal artefacts in the fMRI and T1 data. As an initial exploratory analysis, we ran, for each pair of ROIs, a linear mixed-effects model with functional connectivity as the dependent variable and with group, memory load and the (group x load) interaction as predictors while controlling for age, sex, and head motion. We found that remitters exhibited widespread increase in functional connectivity as a function of memory load. In contrast, the opposite pattern was observed among non-remitters where functional connectivity tends to decrease with increasing memory load. Within each network, these group differences were most salient in the intra-network connectivity within the default mode, control and dorsal attention networks, as well as within the subcortical regions. Similarly, we observe that the differences between remitters and non-remitters were most apparent in the inter-network connectivity of the subcortical regions, followed by the default-mode, dorsal attention, and control networks.

Taken together, these preliminary results show that negative symptoms in schizophrenia can be characterized by alterations in working memory at both the behavioural and neural levels. Future work can

examine how these findings can be interpreted at the level of specific networks and explicitly link these brain differences to the observed behavioral deficits.