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Verbal working memory and functional large-scale networks in schizophrenia

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ABSTRACT

The aim of this study was to test whether bilinear and nonlinear effective connectivity (EC) measures of working memory fMRI data can differentiate between patients with schizophrenia (SZ) and healthy controls (HC). We applied bilinear and nonlinear Dynamic Causal Modeling (DCM) for the analysis of verbal working memory in 16 SZ and 21 HC. The connection strengths with nonlinear modulation between the dorsolateral prefrontal cortex (DLPFC) and the ventral tegmental area/substantia nigra (VTA/SN) were evaluated. We used Bayesian Model Selection at the group and family levels to compare the optimal bilinear and nonlinear models. Bayesian Model Averaging was used to assess the connection strengths with nonlinear modulation. The DCM analyses revealed that SZ and HC used different bilinear networks despite comparable behavioral performance. In addition, the connection strengths with nonlinear modulation between the DLPFC and the VTA/SN area showed differences between SZ and HC. The adoption of different functional networks in SZ and HC indicated neurobiological alterations underlying working memory performance, including different connection strengths with nonlinear modulation between the DLPFC and the VTA/SN area. These novel findings may increase our understanding of connectivity in working memory in schizophrenia.

1. Introduction

Schizophrenia is a severely disabling illness that is characterized by positive and negative symptoms as well as cognitive deficits. It is thought that such cognitive deficits are often associated with working memory deficits (Bozikas and Andreou, 2011; Genevsky et al., 2010; Gold, 2004). Evidence comes from functional Magnetic Resonance Imaging (fMRI)[1] studies including functional connectivity (FC) and effective connectivity (EC) studies in verbal working memory in patients with schizophrenia (SZ) and healthy controls (HC). Such studies repeatedly reported cortical dysconnectivity in SZ when compared to HC (Birnbaum and Weinberger, 2013; Dauvermann et al., 2014; Deserno et al., 2012; Glahn et al., 2005; Schlosser et al., 2003a, 2003b, 2006; Schmidt et al., 2013, 2014).

Evidence from animal studies proposes that activity-dependent synaptic plasticity processes (Abbott et al., 1997; Rothman et al., 2009)

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[1] Abbreviations. ACC, Anterior cingulate cortex; ARMS, At-risk mental state; BMA, Bayesian Model Averaging; BMS, Bayesian Model Selection; BOLD, Blood oxygen level-dependent; *d'*, Sensitivity index; DCM, Dynamic Causal Modeling; DLPFC, Dorsolateral prefrontal cortex; EC, Effective connectivity; EST, patients with established schizophrenia; FC, Functional connectivity; FEP, Patients with first-episode psychosis; FGA, First-generation antipsychotics; fMRI, Functional Magnetic Resonance Imaging; HC, Healthy controls; IPL, Inferior parietal lobule; IPS, Intra-parietal sulcus; M1, Model 1; MFG, Middle frontal gyrus; NMDA – R, *N*-methyl-D-aspartate receptor; PFC, Prefrontal cortex; ROI, Region of interest; SZ, Patients with schizophrenia; SGA, Second-generation antipsychotics; SN, Substantia nigra; SPL, Superior parietal lobe; VTA, Ventral tegmental area; *Xp*, Exceedance probability.

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are modulated via nonlinear effects. These nonlinear and glutamatergic modulation processes encompass the meso-cortical and cortico-mesal connections (Pan and Zucker, 2009; Salinas and Sejnowski, 2001; Wang, 2010) and are implicated in working memory (Berends et al., 2005; Durstewitz and Seamans, 2002, 2008; Gao et al., 2003; Laruelle et al., 2005; Murphy and Miller, 2003; Neher and Sakaba, 2008; Pan and Zucker, 2009; Salinas and Sejnowski, 2000; Sun and Beierlein, 2011; Tseng and O'Donnell, 2004; Tzschentke, 2001; Volman et al., 2010), which also involve dopaminergic modulation processes (Coyle, 2006; Javitt, 2007; Tanaka, 2006). For human neuroimaging studies, it has been shown that the connection from the ventral tegmental area/substantia nigra (VTA/SN) area to the dorsolateral prefrontal cortex (DLPFC) (i.e. the meso-cortical connection) is implicated in working memory function (D'Ardenne et al., 2012; Murty et al., 2011). Furthermore, for SZ it has been proposed that blood oxygen level-dependent (BOLD) responses during working memory in SZ could be explained by underlying gating mechanisms of the meso-cortical connection when compared to HC (Braver et al., 1999; Braver and Cohen, 1999). In other words, observed changes in BOLD responses and cortical connectivity may be driven by altered connection strengths with nonlinear modulation of the meso-cortical and/or cortico-mesal connections.

The Dysconnection Hypothesis posits that the *N*-Methyl-D-aspartate receptor (NMDA-R) hypofunction model for schizophrenia could be underlying the pathophysiological pathways of altered synaptic plasticity processes and thus result in cortical dysconnectivity in schizophrenia (Friston et al., 2016; Friston and Frith, 1995; Stephan et al., 2006, 2009; Weinberger, 1993). In clinical studies, the non-invasive and indirect investigation of the NMDA-R hypofunction model can be modeled by Dynamic Causal Modeling (DCM) for fMRI. DCM is a biophysical modeling approach of neuronal dynamic processes (Friston and Dolan, 2010; Friston et al., 2003) that integrates functional large-scale models with Bayesian inversion methods (Daunizeau et al., 2011a; Friston and Dolan, 2010). DCM evaluates inter-regional EC through assessment of experimental modulation of a given experimental task (Friston et al., 2003) within *a priori* defined functional large-scale networks. Nonlinear DCM, an extension of bilinear DCM, allows for the inference about nonlinearities in fMRI data (Stephan et al., 2008).

We hypothesized that the connection strengths with nonlinear modulation from the VTA/SN area to the DLPFC would be altered in contrast to the connection strength with nonlinear modulation from the DLPFC to the VTA/SN as a potential measure of working memory disruption between SZ and HC. To test this hypothesis, we applied bilinear and nonlinear DCM for fMRI in separate analysis steps to investigate functional large-scale networks in the verbal "N-Back" task in SZ and HC.

2. Methods

2.1. Subjects

Sixteen SZ and 21 HC participated in the verbal working memory fMRI task. SZ and HC were recruited from the Royal Edinburgh Hospital, associated hospitals and the Scottish Mental Health Research Register (http://www.smhrn.org.uk/). Diagnosis of schizophrenia was based on interview using the Structured Clinical Interview for DSM-IV (First et al., 2002). SZ were also assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987), Scale for the Assessment of Negative Symptoms (Andreasen, 1989) and the Global Assessment of Function (Pedersen and Karterud, 2012). Inclusion criteria included (i) diagnosis of established schizophrenia as assessed, and (ii) no acute psychotic symptoms at the time of the scan. Exclusion criteria included (i) history of any major psychiatric illness other than schizophrenia, (ii) history of severe brain injury, (iii) history of a neurological disorder, and (iv) dependency or harmful use of alcohol or drugs during the last 12 months. Also, HC were excluded if they had a family history of schizophrenia. All participants provided written informed consent. The study was approved by the local Research Ethics Committee.

2.2. Functional experimental details

All participants performed the verbal "2-Back" task known to show a consistent functional large-scale network of BOLD responses (Owen et al., 2005). They were presented with a sequence of single capital letters (Broome et al., 2009). The experimental block design consisted of (i) the baseline or "0-Back" condition; (ii) the "1-Back" condition; and (iii) the "2-Back" condition. Behavioral task performance was analyzed with the sensitivity index *d'* (Eq. (1)) (Macmillan and Creelman, 1991).

$$d' = z(Hits) - z(Falsealarm \quad s)$$
$$z = \text{statistical } Z \text{ value} \tag{1}$$

Hits and false alarm rates were adjusted as previously reported (Macmillan and Kaplan, 1985). For the fMRI and DCM analyses, SZ and HC were selected based on comparable good behavioral performance level in the "N-Back" task to control for behavioral performance impairments on BOLD response (Eryilmaz et al., 2016) and EC measures. Briefly, the cut-off for good behavioral performance was set at $d' > 1.93$ which equals a hit rate > 85% and false alarm rate < 20% across all participants. *D'* values were entered in a general linear model with group as fixed factor and age and gender as covariates.

2.3. Functional scanning procedure

Brain imaging was carried out at the Clinical Research Imaging Centre at the Queen's Medical Research Institute (Edinburgh, UK) on a Siemens 3 T whole-body MRI Verio scanner (Siemens Medical Systems, Erlangen, Germany) using the matrix head coil with 12 elements. Structural scans, verbal "N-Back" EPI scans were acquired during the same scanning session in all participants.

An initial localizer scan was performed to measure the inter-hemispheric angle and the AC-PC line. The structural images were acquired using T_1-weighted, magnetization prepared rapid acquisition gradient echo images prescribed parallel to the AC-PC line, providing 160 sagittal slices of 1 mm thickness, 256 × 256 mm^2 FOV, matrix size 256 × 256 mm^2. Further scan parameters were TR = 2300 ms, TE = 2.98 ms, TI = 900 ms and flip angle = 9°. EPI scans for the "N-Back" task were acquired continuously during the experimental task (TR/TE = 1560/26 ms, matrix size of 256 × 256 mm^2; FOV 256 × 256 mm^2). Twenty six interleaved slices with 4 mm slice thickness were acquired. Each EPI sequence encompassed 293 volumes of which the first six volumes were discarded.

2.4. FMRI data analysis

FMRI data processing and statistical analyses were performed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab (version 7.1; The MathWorks, Natick, MA, USA). All functional volumes were spatially realigned, normalized to MNI space and spatially smoothed with an isotropic 8 mm full-width at half-maximum Gaussian kernel.

For the statistical analyses, the onset times for each condition were convolved using a canonical hemodynamic response function. For the design matrix, the temporal reference has been set to the middle slice in the EPI acquisition where the TR was set to 1560 ms. The main contrast of interest was defined as "0-Back" < "2-Back" with age and gender as covariates. From this second-level analysis, we generated statistical parametric maps of the *T* statistic and *F* statistic at each voxel SPM (Constantinidis and Klingberg, 2016), which denoted differences in activation for the main contrast of interest. The statistical parametric maps were thresholded at $p < 0.001$ uncorrected. Regions are reported that survived cluster-level correction for multiple comparisons across