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Reduced neuro-integration from the dorsolateral prefrontal cortex to the whole brain and executive dysfunction in schizophrenia patients and their relatives

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ABSTRACT

Executive dysfunction is one of the core symptoms of schizophrenia. Functional neuro-imaging studies have suggested an association between deficits in activating the dorsolateral prefrontal cortex (DLPFC) and executive dysfunction, but neuro-integration from the DLPFC to the whole brain remains unclear. Studies investigating the neuro-integration from the DLPFC to the whole brain in unaffected but genetically liable family members are scant. In this study, we report DLPFC neuro-integrative deficits correlated with executive dysfunction and family history of schizophrenia using resting-state functional magnetic resonance imaging (fMRI). Using seed regions in DLPFC, we examined resting-state functional connectivity in 25 patients with schizophrenia, 25 unaffected first-degree relatives (UR), and 25 healthy control (HC) persons. Schizophrenia patients and UR have impaired connectivity from DLPFC to its coordinated regions (ANOVA: $F = 7.316–10.974$, $p < 0.001$). These coordinated brain regions are distributed in the bilateral caudate, left middle/inferior frontal gyrus, left precentral gyrus, and right cerebellum. The individual functional connectivity strength between the left DLPFC and its coordinated regions was correlated with individual executive function performance among whole persons. (Pearson's $r = 0.244–0.366$, $p = 0.035–0.008$) Our findings support that distributed neuro-integrative DLPFC deficits reflect a genetic risk for schizophrenia and that these deficits are present, to a lesser degree, in unaffected first-degree relatives. Our findings also support that neuro-integration might correlate with a patient's executive function performance.

1. Introduction

Schizophrenia as a hereditary component is well established. Whereas the lifetime prevalence of the general population is approximately 1%, first-degree relatives of schizophrenia patients have increased risk of developing schizophrenia. In genetic-epidemiology family studies, a 31%–58% concordance rate exists in monozygotic twins, and a 6%–17% morbid risk exists among first-degree relatives (Tsuang, 2000). First-degree relatives of schizophrenia patients are considered a population with increased genetic risk of schizophrenia. Studies in this population highlight the genetic-risk characteristics of schizophrenia.

First-degree relatives of schizophrenia share certain neurocognitive deficits with schizophrenia patients. Executive dysfunction has been described in schizophrenia patients (Bozikas et al., 2006; Tan et al., 2006) and their first-degree relatives (Bove, 2008; Groom et al., 2008; Allen et al., 2009). Executive dysfunction is also associated with clinical manifestations of schizophrenia, including disorganization symptoms (Breton et al., 2011), social functioning (Xiang et al., 2010), and clinical outcome (Martinez-Aran et al., 2002).

The dorsolateral prefrontal cortex (DLPFC), executive function, and genetic-risk for schizophrenia are closely associated and inseparable in schizophrenia pathophysiology. DLPFC plays an important modulatory and integrative role in executive function (MacDonald et al., 2000; Rogers et al., 2000; Monchi et al., 2001; Konishi et al., 2005), and DLPFC dysfunction has been implicated in the pathophysiological substrates of schizophrenia (Perlstein et al., 2003; Holmes et al., 2005). The correlation between abnormal DLPFC connectivity and genetic-risk for schizophrenia has been proven in many imaging modalities (Whitfield-Gabrieli et al., 2009; Woodward et al., 2009; Jang et al., 2011; Rasetti et al., 2011).

Functional brain imaging has shown abnormal functional connectivity within the DLPFC in both schizophrenia patients and their relatives (Whitfield-Gabrieli et al., 2009). Diffusion-tensor imaging has also shown white matter integrity disruption in the left DLPFC related to inheritable schizophrenia risk (Hao et al., 2009). In resting-state functional connectivity studies, reduced-functional connectivity in

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the DLPFC was found in participants with high genetic loading for schizophrenia (Jang et al., 2011). In cognitive task-related connectivity studies, the right DLPFC showed a decreased functional connectivity with multiple brain regions is related to genetic liability for schizophrenia (Woodward et al., 2009). The compromised connectivity between the right DLPFC and hippocampus in patients and relatives was modulated by a single-nucleotide polymorphism in *ZNF804A* (Rasetti et al., 2011). These findings in schizophrenia patients and their relatives suggest that neuro-integrative deficits from the DLPFC to the whole brain are likely to be involved in executive dysfunction and the genetic risk for schizophrenia, but the association between heritability neuro-integrative deficits and executive dysfunction in schizophrenia has not been extensively explored in a single data set.

We examine the hypothesis that schizophrenia patients and their unaffected first-degree relatives have connectivity abnormalities from the DLPFC to the whole brain in the resting state, and that these abnormalities might correlate with executive function performance.

2. Methods

2.1. Participants

This study was conducted at National Yang-Ming University and Losheng Sanatorium Hospital in Taiwan. We recruited 25 patients satisfying the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia and 25 of their unaffected first-degree relatives (UR) from the Psychiatric Outpatient Department. Twenty-five healthy control (HC) participants without any known psychiatric family history were also recruited through advertisement broadcasts in the community. The institutional review board of National Yang-Ming University approved the study. Written informed consent was obtained from all the participants. Patients underwent structured clinical assessments by a senior psychiatrist who completed the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to re-confirm diagnosis and evaluate psychiatric comorbidity, and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for psychopathology evaluation. Mediation status was recorded and converted to chlorpromazine equivalents. HC and UR persons were sex- and age-matched to patients, with no history of neurological or psychiatric disorders confirmed by MINI interviews, and free of any medication at the time of study.

All participants were right-handed, which was determined by the Edinburgh Handedness Inventory (Oldfield, 1971). On the same day before the MRI scan, all participants underwent the Beck Depression Inventory (Beck et al., 1988) and the Beck Suicide Inventory (Beck et al., 1979) to measure depression and suicidal intention, and the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993) to measure executive function. Participants who had a history of meeting DSM-IV substance abuse, mental retardation, having any systemic, physical, neurological illness, brain trauma, unstable psychotic symptoms, or psychotrophic medication adjustment within 3 months preceding the study were excluded.

2.2. Image acquisition

MRI data were acquired using a 3 T MR scanner (SIEMENS TRIO, TIM system) at National Yang-Ming University. A whole-brain high-resolution T1-weighted sagittal 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired using the following parameters: 192 slices, TR = 3500 ms, TE = 3.5 ms, slice thickness = 1 mm, flip angle = 7°, inversion time = 1100 ms, FOV = 256 × 256 mm, and in-plane resolution = 1 × 1 × 1 mm^3. The functional images were obtained using an echo-planar imaging sequence with the following parameters: 43 axial slices, thickness = 4.0 mm without gap, in-plane resolution = 64 × 64, TR = 2500 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm. Two-hundred sequential images were obtained from each participant for a duration of 8 min 20 s.

2.3. Image processing

All participant data were identically processed. The first 10 time points in all of the functional MRI data sets were discarded to reduce instability of the initial MRI signal. The resting-state fMRI data were pre-processed using Statistical Parametric Mapping-SPM8 (http://www.fil.ion.ucl.ac.uk) and the resting-State fMRI Data Analysis Toolkit (http://www.restfmri.net). Pre-processing steps included slice-timing correction for interleaved acquisition and head motion correction. Participants with a head motion greater than 2 mm were discarded. The data were then co-registered to the person's high resolution T1 image using a rigid-body model (Collignon et al., 1995). The co-registered functional images were then spatially normalized to the echo-planar imaging (EPI) template in Montreal Neurological Institute (MNI) space using a nonlinear transformation, and all the images were spatially smoothed by convolution with an isotropic Gaussian kernel (FWHM = 6 mm). Finally, the resting-state fMRI Data Analysis Toolkit was then used to remove the linear trend of time courses and temporal band-pass filtering (0.01–0.08 Hz) to reduce physiologic confounding effects (Biswal et al., 1995; Lowe et al., 1998).

Nuisance signal regression was performed. To ensure that each time series data set represented regionally specific neural activities, several sources of spurious variances were removed. Eight predictors that modeled nuisance signals from white matter (WM), cerebrospinal fluid (CSF), and the six motion parameters were used for regression (Birn et al., 2006). We generated global signal variance by averaging across all voxels within the brain.

2.4. Within-group DLPFC connectivity analysis

Including the DLPFC, 39 regions of interest (ROI) were derived from the previous cross-study analysis and the coordinates established by Dosenbach et al. (2006, 2007). According to their reports, two spheres from the left and right DLPFC (±43, 22, 34), each 5 mm in radius, were used to identify the DLPFC regions. The averaged time course from each region was used to generate representative time series from the left and right DLPFC regions. The time series were then correlated with every voxel in the brain to determine the correlation coefficient. Individual correlation-coefficient maps were then transformed into Z-scores. Sample *t* tests of the patient, UR, and HC groups were performed on individual Z-maps of the functional correlation maps. The within-group statistical threshold was set at $|t| > 3.435$ ($p < .001$) and cluster size > 2064 mm^3, which corresponds to a corrected $p < .001$. This correction was confined within the whole-brain mask (size: 1,911,640 mm^3) and determined by Monte Carlo simulations performed by the AlphaSim program in Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). The resting-state DLPFC connectivity map of each group was then formed (Fig. 1; Table 2).

2.5. Statistical analysis

One-way analysis of variance (ANOVA) was used to compare the Z-maps of 3 groups with age, sex, and education level as covariates. Significant clusters were set at $p < .05$, as determined by the AlphaSim program in the Analysis of Functional NeuroImages (ANFI) software. Threshold was a combination of $p < .05$ for voxel level and a minimum cluster size of 1008 mm^3 (126 voxels with 2 × 2 × 2 mm) with the mask file.

The contrast of Z-maps among the 3 groups shows the 8 cluster areas (Table 3, Fig. 2). We determined the 8 cluster areas as 8 new ROIs (6 ROIs with seed in the left DLPFC, 2 ROIs with seed in the right DLPFC). To examine subject-specific differences in each of the schizophrenia patients, UR, and HC people, individual values of the