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Symptom recovery and relationship to structure of corpus callosum in individuals with an 'at risk mental state'

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ABSTRACT

Previous studies have revealed that changes in sub-threshold psychotic symptoms observed in individuals with an 'at risk mental state' (ARMS) are associated with biological changes in the corpus callosum (CC). To elucidate the biological background for resilience against transition to psychosis, we investigated the relationship between CC structural changes and recovery of sub-threshold psychotic symptom in subjects with ARMS who did not develop psychosis (ARMS-N). Sixteen healthy controls and 42 ARMS (37 ARMS-N) subjects participated this study. The volumes of five sub-regions of the CC were analyzed using MRI. The sub-threshold psychotic symptoms of the ARMS were measured using the Scale of Prodromal Symptoms (SOPS). Imaging and symptoms were re-administered in the ARMS group 52 weeks later. Significant baseline volume differences in the mid-posterior CC, central CC and mid-anterior CC were found between the controls and the ARMS-N subjects. These findings suggest that biological abnormalities are present in a so-called "false-positive" group of individuals. For the ARMS-N subjects, improvement in negative symptoms significantly correlated with an increase in the volume of the central CC at follow-up. This finding may suggest that a neurobiological 'resilience' is associated with symptom recovery.

1. Introduction

The corpus callosum (CC), which connects homologous frontal areas involved in cognitive functions associated with executive functions relevant to schizophrenia (de Lacoste, 1985; David, 1994; Pantelis et al., 1997; Crow, 1998), has been implicated in schizophrenia, with evidence of structural abnormalities observed across the various stages of illness (Walterfang et al., 2008a; Whitford et al., 2011). Recently, many studies have revealed that an increase in the severity of psychotic symptoms or deficits in cognitive functions are associated with progressive changes in the CC (Koutsouleris et al., 2010; Bleich-Cohen et al., 2012; Whitford et al., 2015; Walterfang et al., 2008a, 2008b). Nakamura et al. (2012) reported that lower fractional anisotropy (FA) values (measured using diffusion tensor imaging and reflecting white matter integrity) for the CC were associated with higher scores for avolition in subjects with schizophrenia. Serpa et al. (2012) reported that the CC volumes of subjects with recent-onset schizophrenia correlated with positive symptom severity at the time of a 1-year follow-up. Combined, these studies suggest that changes in the CC are associated with psychotic symptoms in general, and their findings raise the possibility that longitudinal CC changes may be linked to clinical changes over time in schizophrenia.

While transition to psychosis is defined by the expression of prominent positive symptoms, sub-threshold psychotic symptoms gradually develop before the onset of psychosis, and this increasing severity may be associated with progressive changes in multiple brain regions, including the CC (Pantelis et al., 2005; von Hohenberg et al., 2014; Saito et al., 2017).

In our previous study (Katagiri et al., 2015), we compared FA values using tract-based spatial statistics (TBSS) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) for the whole brain between normal controls and at risk mental state (ARMS) subjects who were followed over a 12-month period. We found significant FA reductions for the CC in ARMS subjects who did not subsequently develop psychosis (ARMS-N), as compared with the controls at baseline. This result raises the possibility that so-called "false positives" do not simply express sub-threshold psychotic

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symptoms, but that they manifest neurobiological abnormalities. However, the ARMS-N group showed significant improvements in sub-threshold positive symptoms at the 1-year follow-up, and these improvements were correlated with an increase in the FA value for the CC. These findings suggest that biological amelioration of the CC might contribute to the recovery of sub-threshold psychotic symptoms and might be associated with prevention of a transition to psychosis in ARMS-N. However, the TBSS method that we previously used has several limitations, including disregard of potential effects outside of the "skeleton" (the method only assesses a few voxels' thickness within the white matter tract) and evidence showing the tract-specificity of the skeleton projection step may be low for some fiber geometries (Zalesky et al., 2012).

For this reason, in this study, to confirm the association between neurobiological resilience of CC and amelioration of sub-threshold psychotic symptoms of ARMS-N subjects further, we used FreeSurfer V 5.2 (https://surfer.nmr.mgh.harvard.edu) to characterize the relationship between structural changes in the CC and recovery of the sub-threshold psychotic symptoms in ARMS-N subjects better. Based on our previous findings, we hypothesized the following: (i) at baseline, the CC volume would be reduced in the ARMS-N subjects as compared to controls; and (ii) the changes in the CC volume would be correlated with a change in sub-threshold psychotic symptoms. We also investigated the effect of antipsychotics on structural changes in the CC and recovery from sub-threshold psychotic symptoms.

2. Methods

2.1. Participants

Individuals with ARMS were recruited at the Toho University Omori Medical Center. The participants were diagnosed as ARMS using the Structured Interview for Prodromal Syndrome (SIPS) (Miller et al., 2003) at the time of the first consultation (baseline). Individuals with ARMS were treated at the Youth Clinic and at the Il Bosco day-care center intended for persons with early psychosis (Mizuno et al., 2009). Various intensive therapies conducted at Il Bosco are described in Nemoto et al. (2012).

Participants showing severe deterioration in clinical symptoms received antipsychotic medication even in the absence of apparent positive symptoms (Yung, 2007). Transition to psychosis during the term of the follow-up period was defined using the SIPS. After a 52-week follow-up, the ARMS subjects were divided into subjects who developed psychosis (ARMS-P) and subjects who did not develop psychosis (ARMS-N). To investigate the influence of antipsychotics on the ARMS-N group, we further divided the ARMS-N subjects into those who were not prescribed antipsychotics (ARMS-NN) and those who were treated with antipsychotics (ARMS-NA). The antipsychotic dosages were expressed as milligram equivalents of chlorpromazine (Wood et al., 2003), and these values were log10 transformed to reduce skewness (antipsychotics-log). Subjects were excluded if they had a history of alcohol dependence, substance abuse, or a neurological illness. Healthy control subjects were recruited from among students of a neighboring university, their relatives and acquaintances, and from independent sources in the community. Written informed consent was obtained from all the participants after the study had been explained in full. This study was approved by the Ethics Committee of the Toho University.

2.2. Grading the severity of sub-threshold symptoms

The Scale of Prodromal Symptoms (SOPS) is a 19-item scale designed to measure the severity of prodromal symptoms (Miller et al., 2003). The SOPS contains subscales for positive and negative symptoms. There are five positive and six negative items. We calculated the states of the sub-threshold symptoms of the ARMS subjects by separately summing five positive SOPS items (POS score) and six negative SOPS items (NEG score) at both baseline and 52 weeks. To use these values in a longitudinal analysis, the 1-year changes in the POS and NEG scores were calculated by subtracting the relevant baseline score from the score at 52 weeks (i.e., ΔPOS and ΔNEG).

2.2.1. Image acquisition

The ARMS and controls underwent magnetic resonance imaging (MRI; EXCELART Vantage, XGV 1.5 T; Toshiba Medical Systems, Tokyo, Japan) at the time of the baseline, and three-dimensional T1-weighted images were acquired. Imaging parameters were: repetition time, 24.4 ms; echo time, 5.5 ms; 2-mm-thick; matrix, 256*256; field of view, 250*250 mm; FA, 35; sagittal. We rescanned the ARMS group using the same MRI scanner at 52 weeks after baseline. One MRI data set for an ARMS-NA subject with severe artifacts on the baseline image was excluded.

2.2.2. Image processing

The structural scans were processed using FreeSurfer V 5.2 (https://surfer.nmr.mgh.harvard.edu) with default processing settings. FreeSurfer produces volume estimates of structures (in mm^3). To investigate the longitudinal volume changes in sub-regions of the CC, we used the volumes of five CC sub-regions (i.e., posterior, mid-posterior, central, mid-anterior and anterior) and the intracranial volume (ICV) at baseline and at 52 weeks, derived from the asegstats2table program (https://surfer.nmr.mgh.harvard.edu/fswiki/asegstats2table). The divisions of the CC are equally spaced in terms of distance along the primary eigen direction (approximately the long axis) of the CC. The default for the lateral extent of the CC was a thickness of 5 mm (https://surfer.nmr.mgh.harvard.edu/fswiki/mri_cc). The 1-year percent volume changes for each of the CC sub-regions (Δ sub-region of CC) were calculated as [(volume at second scan) – (volume at baseline scan)] / (volume at baseline scan) * 100 (%) (i.e. Δ posterior, Δ mid-posterior, Δ central, Δ mid-anterior, and Δ anterior of CC).

2.3. Statistical analysis

Data were analyzed using SPSS version 20 (www.spss.com). A p-value of < 0.05 was regarded as significant.

2.3.1. Cross-sectional comparisons at baseline

Based on our previous findings, we hypothesized that the CC volume would be reduced in the ARMS-N compared to controls at baseline. To confirm this hypothesis, we compared the volumes of the CC sub-regions among controls, ARMS-N, and ARMS-P using ANOVA. Subsequently, to confirm the demographic differences among controls and ARMS subgroups, ANOVA was used to compare the POS and NEG scores among ARMS-NN, ARMS-NA, and ARMS-P, and to compare the volumes of the CC sub-regions among the controls, ARMS-NN, ARMS-NA, and ARMS-P at baseline. Tukey's test was used for post-hoc testing. Furthermore, the volume of CC sub-regions in control group was set as a reference (standardized normal distribution), and those of ARMS-NN, ARMS-NA and ARMS-P groups were standardized using Z-score.

2.3.2. Longitudinal comparisons

The control group was not followed and thus, was not included in the longitudinal analysis. For the ARMS-P group, because only five individuals converted to psychosis (ARMS-P) during the follow-up period, and only three subjects underwent both MRI and SOPS at baseline and 52 weeks, our main results only relate to those who did not convert to psychosis (ARMS-N).

2.3.2.1. Longitudinal changes in symptoms (POS and NEG) and CC sub-region volumes in the ARMS-N subgroups. We examined the longitudinal changes in the POS and NEG scores and all the CC sub-region volumes, comparing those in the ARMS-NN group with those in the ARMS-NA group, by using a repeated-measures ANOVA that included a between-