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ORIGINAL ARTICLE

Volume Reduction of the Dorsal Lateral Prefrontal Cortex Prior to the Onset of Frank Psychosis in Individuals with an At-Risk Mental State

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Abstract

Although some individuals with at-risk mental states (ARMS) develop overt psychosis, surrogate markers which can reliably predict a future onset of psychosis are not well established. The dorsal lateral prefrontal cortex (DLPFC) is thought to be involved in psychotic disorders such as schizophrenia. In this study, 73 ARMS patients and 74 healthy controls underwent 1.5-T 3D magnetic resonance imaging scans at three sites. Using labeled cortical distance mapping, cortical thickness, gray matter (GM) volume, and surface area of DLPFC were estimated. These measures were compared across the diagnostic groups. We also evaluated cognitive function among 36 ARMS subjects to clarify the relationships between the DLPFC morphology and cognitive performance. The GM volume of the right DLPFC was significantly reduced in ARMS subjects who later developed frank psychosis (ARMS-P) relative to those who did not ($P = 0.042$). There was a positive relationship between the right DLPFC volume and the duration prior to the onset of frank psychosis in ARMS-P subjects ($r = 0.58$, $P = 0.018$). Our data may suggest that GM reduction of the DLPFC might be a potential marker of future onset of psychosis in individuals with ARMS.

Key words: at-risk mental state, dorsal lateral prefrontal cortex, magnetic resonance imaging, psychosis, schizophrenia

Introduction

Accumulating evidence suggests that individuals with psychotic disorders, such as schizophrenia, suffer not only from psychiatric symptoms but also from difficulty in achieving functional recovery (Jaaskelainen et al. 2013) and from various physical health problems (DE Hert et al. 2011). Many attempts have been made for the purpose of delaying or preventing frank psychosis in individuals with an at-risk mental state (ARMS) for psychotic disorders (Stafford et al. 2013). The establishment of surrogate makers to reliably predict a future onset of overt psychosis in ARMS individuals is crucial since the majority (>60%) of this population do not eventually develop psychosis (Fusar-Poli et al. 2012). Neurophysiological tests (Higuchi et al. 2014; Bodatsch et al. 2015), structural magnetic resonance imaging (sMRI) (Bois et al. 2015; Takahashi and Suzuki 2018), and functional magnetic resonance imaging (Allen et al. 2015) have been used to identify biological changes predating the transition to psychosis in ARMS. For instance, previous sMRI studies have shown gray matter (GM) reduction or cortical thinning of the anterior cingulate cortex (ACC) (Borgwardt et al. 2007; Fornito et al. 2008; Takayanagi et al. 2017), superior temporal gyrus (Borgwardt et al. 2007), and insular (Borgwardt et al. 2007; Takahashi et al. 2009) and parahippocampal gyrus (Mechelli et al. 2011) in ARMS subjects who later developed frank psychosis (ARMS-P).

Cognitive impairment in ARMS subjects has become well established in the past decade, as shown in two recent meta-analyses (Bora et al. 2014; Hauser et al. 2017) that also indicated that ARMS-P subjects performed lower in many neuropsychological domains, including attention and working memory, than those who did not develop psychosis (ARMS-NP), or healthy subjects. Likewise, a large-scale multisite study conducted in North America demonstrated attention and working memory deficits in ARMS-P group compared with ARMS-NP subjects (Seidman et al. 2016).

The dorsal lateral prefrontal cortex (DLPFC, Brodmann areas 46 and 9) is located in the midanterior part of the middle frontal gyrus (MFG) and is thought to be involved in various cognitive processes, particularly attention (Vossel et al. 2012; Bidet-Caulet et al. 2015) and working memory (Barbey et al. 2013; Weinberger et al. 1986), both of which are shown to be impaired in ARMS-P subjects as noted above. Although many sMRI studies have reported reduced GM volume or cortical thickness of the MFG in patients with schizophrenia, compared with healthy subjects (Kuperberg et al. 2003; Suzuki et al. 2005; Kasparek et al. 2007; Nesvag et al. 2008; Schultz et al. 2010; Takayanagi et al. 2011; Takayanagi et al. 2019), relatively few studies exclusively examined the DLPFC morphology in schizophrenia or ARMS subjects (Kikinis et al. 2010).

Whole-brain analytic methods, such as voxel-based morphometry (VBM) and surface-based analysis (SBM), have widely been used for cortical morphometry in psychiatric disorders, such as schizophrenia (Kuperberg et al. 2003; Kasparek et al. 2007; Nesvag et al. 2008; Schultz et al. 2010; Takayanagi et al. 2011; Takayanagi et al. 2019). However, no research found the morphological abnormalities of MFG in ARMS-P subjects prior to the onset of frank psychosis by using VBM or SBM (Pantelis et al. 2003; Borgwardt et al. 2007; Koutsouleris et al. 2009; Mechelli et al. 2011; Tognin et al. 2014; Cannon et al. 2015). Labeled cortical distance mapping (LCDM) is a neuroimaging analytical tool that calculates the distances between labeled GM voxels and the GM/white matter (WM) cortical surface. LCDM can reliably characterize the morphometry of the laminar cortical mantle of cortical structures, such as cortical thickness and GM volume (Ceyhan et al. 2011). Although the boundary between WM and cerebrospinal fluid (CSF) is oftentimes obscure, LCDM can partly resolve this challenge since it treats the region of interest (ROI) as a laminar structure consisting of GM voxels and a local surface co-ordinate system based on an anatomically defined GM/WM cortical surface. Thus, this method is less susceptible to signal intensity inhomogeneity than whole-brain analyses. Using LCDM, we previously reported a reduced thickness of ACC in ARMS subjects who later develop full-blown psychosis when compared with healthy subjects (Takayanagi et al. 2017).

In this study, we examined DLPFC morphology based on our hypothesis that DLPFC structural anomalies may predate the onset of psychosis and underlie cognitive impairments (e.g., attention and working memory deficits) in ARMS subjects. We used ROI-based technique, namely LCDM, considering its advantage over whole-brain analyses (i.e., better tissue segmentation). We also assessed cognitive function in some of the ARMS participants by using the Japanese version of the brief assessment of cognition in schizophrenia (BACS-J) (Kaneda et al. 2007) to examine the relationship between the DLPFC morphology and cognitive performance.

Materials and Methods

Participants

Seventy-three ARMS subjects were recruited at three sites (Toho University Hospital, Tohoku University Hospital, and Toyama University Hospital), where specialized clinical services for ARMS are offered (Mizuno et al. 2009). The Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al. 2005) (University of Toyama and Tohoku University) or the Structured Interview for Prodromal Syndrome/the Scale of Prodromal Symptoms (SIPS/SOPS) (Miller, McGlashan, et al. 2003) (Toho University) were used for the diagnosis of ARMS. ARMS subjects were clinically monitored for at least 2 years after magnetic resonance imaging (MRI) scanning to see if they developed overt psychosis. Transition to psychosis was determined based on the CAARM or the SIPS criteria as detailed in our previous study (Takayanagi et al. 2017). Eighteen of 73 ARMS subjects developed frank psychosis (i.e., ARMS-P subjects) after MRI scanning. Based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (American Psychiatric Association 1994) criteria, the diagnoses of ARMS-P subjects comprised 12 schizophrenia cases, 1 delusional disorder case, 1 schizophreniform disorder case, and 4 cases with psychotic disorder not otherwise specified (NOS).

Seventy-four healthy controls (HC) were recruited from the community, hospital staff, and students at each site. HC were matched for age and gender with the ARMS subjects.

All subjects were physically healthy at the time of MRI scanning. Subjects were excluded if they 1) had a lifetime history of serious head injury, neurological illness, or other serious physical disease; 2) fulfilled the criteria for substance abuse/dependence; or 3) had previous psychotic episodes which met the criteria of DSM-IV. Most of the participants of this study (98.6%) overlap with those of our previous study (Takayanagi et al. 2017). All subjects provided written informed consent. If the participants were minors, written informed consent was provided by their parents. This study was approved by the Committee on Medical Ethics at each site.

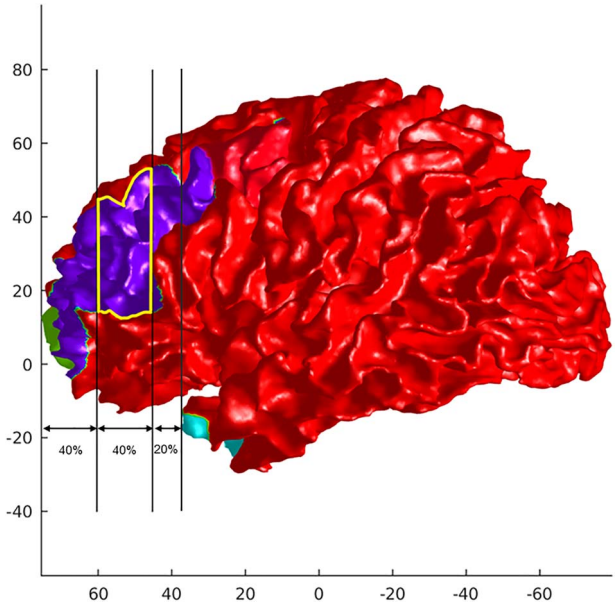

Figure 1. An example of DLPFC (yellow line) cut from the MFG (blue) on the left hemisphere.

MRI Data Acquisition

The MRI scanners and data acquisition parameters used at each site are detailed in the supplementary material. All three sites used scanners with field strength of 1.5 T.

FreeSurfer-Initialized Labeled Cortical Distance Mapping

First, all images were preprocessed by FreeSurfer software suite (version 5.3) working on a Macintosh workstation (MAC OS 10.7). The FreeSurfer pipeline is publicly available (https://surfer.nmr.mgh.harvard.edu/). FreeSurfer's standard preprocessing steps consist of tissue intensity inhomogeneity normalization, nonbrain tissue removal, transformation to Talairach-like space, and segmentation of GM/WM tissue (Fischl 2012). The preprocessed images were carefully inspected, and errors were manually corrected by one trained researcher (D.S.) who was blinded to the subject's identity. FreeSurfer extracts the surfaces of GM/WM and automatically parcellates 68 cortical ROIs using the Desikan-Killiany Atlas (Desikan et al. 2006), including the MFG.

The DLPFC surface was then cut from the MFG surface using an established automatic protocol (Al-Hakim et al. 2006; Kikinis et al. 2010): 1) The distance between the most anterior point of the frontal pole and most anterior point of the temporal pole was measured. 2) Cuts were made at 40% of the distance and 80% of the distance measured from the tip of the frontal pole. These anatomical rules to locate the DLPFC were established based on cytoarchitectonic data of BA46 from five human brains (Rajkowska and Goldman-Rakic 1995; Al-Hakim et al. 2006). For this automatic DLPFC cutting, we used own MATLAB (the MathWorks Inc.) script. Figure 1 shows an example of the extracted DLPFC on the left hemisphere.

Next, the cropped MRI was segmented into WM, GM, and CSF using a mixture model averaging method with alternating kernel mixture (AKM) (Lee et al. 2008; Wentz 2012). Compared with other segmentation methods using traditional Bayesian segmentation, AKM yields smaller errors, indicating the robustness and wide applicability of AKM across different structures (Lee et al. 2008). The GM/WM threshold from the segmentation was used to generate triangulated isosurfaces representing the 2D cortical surface. The previously developed method for generating LCDMs (Miller et al. 2000; Miller, Hosakere, et al. 2003; Ratnanather et al. 2004) was applied. To generate a distance map for the GM, the distance between each GM voxel and the closest GM/WM surface vertex was calculated at a $1 \times 1 \times 1$ mm resolution. GM voxels associated with a vertex in the DLPFC surface were labeled DLPFC. Voxels in the range of -2 to 8 mm were used for the analysis. The result of LCDM is a probability distribution function of the GM distance from the DLPFC GM/WM surface. Finally, three DLPFC measures (i.e., cortical thickness, GM volume, and surface area) were estimated. Cortical thickness was determined using the distance at the 95th percentile of the distance distribution. Due to outlier voxels at distances >6 mm, the volume of voxels with distance $\leq$95th percentile was taken as the volume of the DLPFC. The area of the GM/WM boundary surface was calculated from the triangulated surface. By using LCDM, challenges stemming from the obscureness of the boundary between WM and CSF can partly be clarified. The algorithm for LCDM has been published several times (Miller et al. 2000; Miller, Hosakere, et al. 2003; Ratnanather et al. 2004) and is readily coded with the R statistical software package (https://www.r-project.org).

Neurocognitive Assessment

After the FreeSurfer-initialized labeled cortical distance mapping (FSLCDM) analyses, the availability of BACS-J (Kaneda et al. 2007) scores at baseline was retrospectively checked. Thirty-six ARMS subjects (49%) had undergone BACS-J assessment by trained psychiatrists or psychologists at baseline.

Statistical Analysis

One-way analysis of variance, independent two-sample *t*-tests, or a chi-squared test were used for the comparison of clinical measures across the diagnostic groups. DLPFC measures (i.e., cortical thickness, volume, and surface area) were compared among the groups (i.e., controls, ARMS-NP, and ARMS-P) by using repeated measures analysis of covariance (ANCOVA), with diagnosis as the between-subject factor; hemisphere as the within-subject factor; and age, sex, intracranial volume (ICV), antipsychotic use, and scanning sites as nuisance covariates. Sex, antipsychotic use, and each scanning site were entered as binary variables. For the post hoc pairwise comparison, we used Bonferroni's correction. Furthermore, for the purpose of better management of intersite variance, we performed a meta-analytic calculation of overall effect sizes for a random effect model (Han and Eskin 2011) by using Review Manager version 5.4. (the Nordic Cochrane Centre, Cochrane Collaboration) based on previous studies (van Erp et al. 2016; Sasabayashi et al. 2020). The associations between DLPFC measures and neurocognitive functions (i.e., BACS scores) in ARMS subjects were evaluated by calculating partial correlation coefficients adjusted for age, sex, ICV, antipsychotic use, and scanning sites. Bonferroni's correction was again adopted for these correlational analyses. When a significant DLPFC structural change was found between ARMS-P and ARMS-NP/healthy subjects, the correlation of the DLPFC measure with the duration (weeks) between MRI scanning and the onset of psychosis in ARMS-P subjects was evaluated by calculating partial correlation coefficients controlling only for sites, considering the small sample size of this group ($n = 18$). All statistical analyses were conducted using SPSS (ver.18) (IBM Corp.). The significance level was set at $P < 0.05$ (two-tailed).

Results

Clinical Characteristics

Table 1 summarizes the clinical characteristics of the diagnostic groups. HC, ARMS-NP, and ARMS-P groups were similar in terms of age, gender distribution, and parental educational level. Thirty of 73 ARMS subjects (41%) were taking antipsychotics at baseline. Self-reported educational attainment was significantly higher in HC than in ARMS-NP ($P < 0.001$) and ARMS-P ($P < 0.001$) groups. The BACS subscores did not differ among ARMS-NP and ARMS-P groups.

DLPFC Measures

Repeated measures ANCOVA adjusted for age, gender, ICV, antipsychotic use, and scanning site demonstrated a significant hemisphere × diagnosis interaction for the volume of the DLPFC ($F_{2,138} = 3.799$, $P = 0.025$). Post hoc testing showed that the volume of the right DLPFC was smaller in the ARMS-P group relative to the ARMS-NP ($P_{corrected} = 0.042$) and HC ($P_{corrected} = 0.028$) groups (Fig. 2, Table 2). The GM volume reduction of the right DLPFC in ARMS-P subjects compared with ARMS-NP was replicated in the meta-analysis (Cohen's $d = -0.66$, $P = 0.02$) (Supplementary Fig. S1), while the difference between ARMS-P group and HCs did not reach the statistically significant level ($P = 0.24$) (Supplementary Fig. S2). In HC, a rightward laterality was confirmed ($P_{corrected} = 0.003$), while such asymmetry was not detected in ARMS-NP ($P_{corrected} = 0.28$) and ARMS-P groups ($P_{corrected} = 0.09$) (Table 2). We found a significant positive correlation of right DLPFC volume with weeks between MRI scanning and onset of psychosis in the ARMS-P group ($r = 0.58$, $P = 0.018$) (Fig. 3). There was a trend-level positive association between the left DLPFC thickness and BACS symbol coding score ($r = 0.541$, $0.05/36 = 0.0014 < P = 0.0017 < 0.1/36 = 0.0028$) in the 36 ARMS subjects who underwent BACS.

Discussion

We found a GM reduction of the right DLPFC in ARMS individuals who later developed frank psychosis as compared with those who did not using LCDM. We also found a positive relationship between the right DLPFC volume and the duration prior to the onset of frank psychosis (i.e., a smaller DLPFC volume at baseline was associated with earlier onset of subsequent psychosis). Taken together, our findings may suggest that the DLPFC volume change might be useful as a prognostic marker of future psychosis in individuals with ARMS. Our finding of altered DLPFC morphology preceding the onset of psychosis collaborates with previous studies that demonstrated GM volume or cortical thickness reductions in the ACC (Fornito et al. 2008; Takayanagi et al. 2017), parahippocampal gyrus (Mechelli et al. 2011), superior temporal gyrus (Borgwardt et al. 2007), and insula (Borgwardt et al. 2007; Takahashi et al. 2009) among ARMS-P subjects.

Previous studies using whole-brain analyses, such as VBM or SBM, did not detect cortical changes in the middle frontal regions among ARMS-P subjects prior to the onset of overt psychosis (Pantelis et al. 2003; Borgwardt et al. 2007; Koutsouleris et al. 2009; Mechelli et al. 2011; Tognin et al. 2014; Cannon et al. 2015), and thus our finding is not consistent with these works. The discrepancy may be due to differences in the methodology (e.g., ROI analysis vs. whole-brain analysis or the difference in the tissue segmentation method) and the sample size between studies.

GM reductions and cortical thinning of the MFG in schizophrenia patients relative to HC have been demonstrated in a number of MRI studies (Kuperberg et al. 2003; Suzuki et al. 2005; Kasparek et al. 2007; Nesvag et al. 2008; Kikinis et al. 2010; Schultz et al. 2010; Takayanagi et al. 2011; Takayanagi et al. 2019). Taken together with our data, the GM reduction in MFG, or more specifically the DLPFC, may exist prior to the onset of frank psychosis.

Our data showed that a smaller volume of the right DLPFC at baseline was associated with earlier onset of frank psychosis. This positive relationship may suggest that DLPFC volume could be useful for identifying ARMS individuals at an imminent risk for psychosis. On the other hand, we are unable to determine whether such DLPFC volume change in ARMS-P subjects is progressive or static since we lack follow-up MRI scanning.

We demonstrated a rightward asymmetry of DLPFC volume in healthy subjects but not in ARMS subjects. GM volume reduction of the left DLPFC in established schizophrenia patients has been shown by the VBM meta-analysis (Bora et al. 2012). The previous study which used the same DLPFC cutting method (Kikinis et al. 2010) demonstrated 1) the rightward laterality both in schizophrenia patients and HCs and 2) the left dominancy of MFG volume reduction. Take together with our results, the lack of rightward asymmetry of DLPFC volume in both ARMS-NP and ARMS-P subjects might be associated with the vulnerability to psychosis. Previously reported volume reduction of the left MFG/DLPFC in schizophrenia may occur during/after the manifestation of psychotic symptoms, while the alteration on the right hemisphere may predate the onset of psychosis.

Table 1 Demographic and clinical characteristics

Variables	Group				
	HC	ARMS-NP	ARMS-P	Statistics	P
Total number of subjects	74	55	18		
Site					
Toyama	52	11	5		
Toho	5	19	4		
Tohoku	17	25	9		
Age (mean ± SD)	22.6 ± 4.3	22.3 ± 6.5	20.1 ± 4.3	$F = 1.7$	0.19
Sex (male/female)	37/37	21/34	5/13	$X^2 = 3.7$	0.16
Handedness[a] (right/both/left)	58/0/0	34/8/2	10/2/2		
Education years[b] (mean ± SD)	14.8 ± 1.9	12.2 ± 2.6	12.3 ± 2.3	$F = 23.8$	<0.001
Parental education years[c] (mean ± SD)	12.9 ± 2.2	13.5 ± 2.0	13.4 ± 1.6	$F = 0.86$	0.43
Weeks between scanning and onset of psychosis (mean ± SD)			40.1 ± 32.6		
On antipsychotics (*n*, %)		21, 38%	9, 50%	$X^2 = 0.64$	0.78
Antipsychotics dose (mean mg ± SD, chlorpromazine equivalent)[d]		145 ± 102	196 ± 130	$t = 1.1$	0.26
BACS-J subscores[e]					
Verbal memory (mean ± SD)		46.4 ± 10.1	50.7 ± 12.6	$t = 1.0$	0.32
Digit sequencing task (mean ± SD)		18.3 ± 5.0	21.0 ± 5.4	$t = 1.4$	0.18
Token motor task (mean ± SD)		70.9 ± 14.1	70.0 ± 8.1	$t = 0.18$	0.86
Category/letter fluency (mean ± SD)		40.2 ± 12.8	44.3 ± 10.2	$t = 0.87$	0.39
Symbol coding (mean ± SD)		63.3 ± 12.9	64.9 ± 19.2	$t = 0.28$	0.78
Tower of London (mean ± SD)		17.8 ± 2.5	18.1 ± 2.4	$t = 0.28$	0.73

NP, did not develop psychosis; P, developed psychosis.
[a]Data missing for 30 subjects.
[b]Data missing for 7 subjects.
[c]Data missing for 38 subjects.
[d]Calculated in all ARMS subjects
[e]36 ARMS subjects (27 ARMS-NP and 9 ARMS-P subjects) underwent BACS-J.

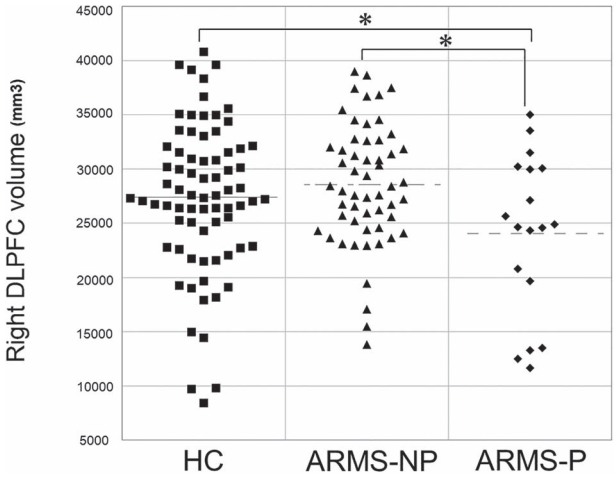

Figure 2. Comparisons of volume of the right DLPFC among HC, ARMS-NP, and ARMS-P patients. $*P < 0.05$.

We used 1.5-T scans which may not be state of the art. With lower resolution, there is the potential for a larger standard deviation (SD) in thickness measures, and thus larger sample size may be required for showing group differences. In addition, there is also potential for deep folds (with only a thin layer of WM or CSF) to be mischaracterized as GM, which can lead to overestimates of thickness. On this point, we performed quality control of segmentations and reperformed segmentation with AKM in failed cases. AKM has been shown to have greater accuracy (Lee et al. 2008). For 1.5-T images, LCDMs have been shown to be robust to different cortical regions, such as cingulate gyrus and ventromedial prefrontal cortex (Miller et al. 2000).

The later versions of FreeSurfer (e.g., version 6.0) can be applied for the FSLCDM pipeline, though we use version 5.3. FreeSurfer 6.0 updated the mappings for subcortical structures, added features to handle more error cases in registration (e.g., when ventricles are very large), and introduced some speed-ups. We believe these changes do not significantly affect the FSLCDM pipeline.

Table 2 Comparisons of DLPFC measures among diagnostic groups

	HC ($n = 74$)		ARMS-NP ($n = 55$)		ARMS-P ($n = 18$)		ANCOVA[a]					
							Diagnosis		Hemisphere		Hemisphere × diagnosis	
Measures	Mean	SD	Mean	SD	Mean	SD	*F*	*P*	*F*	*P*	*F*	*P*
Left DLPFC thickness (mm)	3.50	0.72	3.14	0.62	3.42	0.64	2.133	0.122	0.010	0.921	1.557	0.214
Right DLPFC thickness (mm)	3.65	0.69	3.35	0.65	3.30	0.79						
Left DLPFC volume (mm^3)	25 479	6231	27 500	5311	26 119	6782	1.983	0.142	0.774	0.380	**3.799***,**	**0.025**
Right DLPFC volume (mm^3)	27 383	6905	28 546	5605	24 048	7400						
Left DLPFC area (mm^2)	3167	1008	2994	929	3026	1032	2.137	0.122	0.089	0.766	0.337	0.715
Right DLPFC area (mm^2)	2979	1197	3177	944	2804	996						

DLPFC, dorsolateral prefrontal cortex. [a]Age, gender, ICV, use of antipsychotics, and scanning site were entered as covariates.
*Post hoc tests showed that volume was reduced on the right hemisphere in ARMS-P subjects compared with ARMS-NP ($P = 0.042$) and HC ($P = 0.028$) groups.
**A rightward laterality (left < right) was seen only in HC ($P = 0.003$).

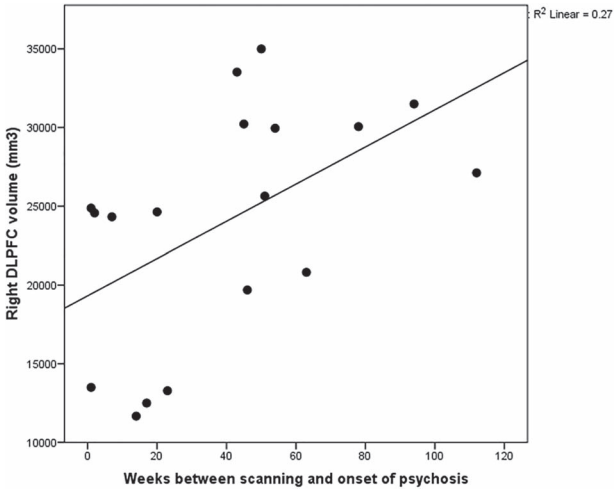

Figure 3. Correlation of the right DLPFC volume with weeks between scanning and onset of psychosis in ARMS-P subjects.

For vertex-wise analyses, cortical thickness might be more sensitive for detecting focal GM changes when compared with volume or surface area (Pereira et al. 2012). We, however, used the ROI approach with LCDM. Our previous studies using the ROI-based LCDM analyses yielded various results, such as thickness/volume reductions of ACC in deficit-schizophrenia patients (Takayanagi et al. 2013), thickness reduction of ACC in ARMS-P group (Takayanagi et al. 2017), and no significant changes of planum temporale in ARMS-P/ARMS-NP subjects (Takayanagi et al. 2020). Thus, the imaging methods used in our study and the regional specificity may have affected our results (i.e., volume was more meaningful than thickness/area).

We failed to replicate previous works that have shown attention or working memory deficits in ARMS-P groups (Bora et al. 2014; Hauser et al. 2017). Although it might be difficult to speculate the reasons for the negative finding regarding attention/-working memory function among ARMS cases in our study, the small number of ARMS subjects who underwent BACS may have influenced this result.

Our finding might have been confounded by the mixed use of different criteria for ARMS (i.e., SIPS/SOPS or CAARMS) among sites. As the CAARMS criteria is less restrictive than that of SIPS though they largely overlap (Miller, McGlashan, et al. 2003; Yung et al. 2005), some subjects may not meet the criteria of one of these instruments. Fusar-Poli et al. (2016) demonstrated a high CAARMS-versus-SIPS agreement in the identification of ARMS subjects (overall agreement = 86%; kappa = 0.781). Therefore, we believe most of the ARMS subjects meet the criteria of both CAARMS and SIPS.

We should consider several limitations. First, MRI scanners and acquisition parameters were different among sites. In addition, the disproportion of comprising controls and ARMS subjects across research sites may have confounded the results. Particularly, the number of the HC recruited at the Toho site ($n = 5$) was significantly smaller than those of other sites. However, we believe that our finding was not merely a consequence of these site differences because our statistical models accounted for site differences. Furthermore, there were no diagnosis × site or hemisphere × diagnosis × site interactions. Second, some ARMS subjects took antipsychotics; the effects of antipsychotic medications on brain morphology cannot be excluded (Vita et al. 2015), although we treated usage of antipsychotics as a nuisance covariate in each statistical model. Third, the sample size of

ARMS-P group ($n = 18$) was relatively small. Likewise, only about half of the ARMS subjects underwent BACS measurement as noted above. Thus, the statistical power of some comparison/-correlation analyses may not be sufficient. Fourth, we were unable to consider handedness in the statistical models due to missing data ($n = 30$). Finally, due to the cross-sectional design of this study, we were unable to see whether the DLPFC alteration (i.e., GM reduction) is static or progressive. Longitudinal analyses are warranted in future studies.

In summary, this multisite study using LCDM suggested that GM alteration of the DLPFC predates the onset of frank psychosis in individuals with ARMS. On the other hand, previously reported attention or working memory deficits before the onset of psychosis were not detected. The DLPFC morphological change might be useful as an objective marker for the prediction of future transition to psychosis in the clinical high-risk population.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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Notes

Conflict of Interest: None declared.

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