Psychiatry Research: Neuroimaging 266 (2017) 10–18

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Brain neurodevelopmental markers related to the deficit subtype of schizophrenia

Tsutomu Takahashi[a,*], Yoichiro Takayanagi[a], Yumiko Nishikawa[a], Mihoko Nakamura[a], Yuko Komori[a], Atsushi Furuichi[a], Mikio Kido[a], Daiki Sasabayashi[a], Kyo Noguchi[b], Michio Suzuki[a]

[a] Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan
[b] Department of Radiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan

ARTICLE INFO

Keywords:
Deficit schizophrenia
Neurodevelopment
Adhesio interthalamica
Orbitofrontal cortex
Magnetic resonance imaging

ABSTRACT

Deficit schizophrenia is a homogeneous subtype characterized by a trait-like feature of primary and prominent negative symptoms, but the etiologic factors related to this specific subtype remain largely unknown. This magnetic resonance imaging study aimed to examine gross brain morphology that probably reflects early neurodevelopment in 38 patients with deficit schizophrenia, 37 patients with non-deficit schizophrenia, and 59 healthy controls. Potential brain neurodevelopmental markers investigated in this study were the adhesio interthalamica (AI), cavum septi pellucidi (CSP), and surface morphology (i.e., olfactory sulcus depth, sulcogyral pattern, and number of orbital sulci) of the orbitofrontal cortex (OFC). The subtype classification of schizophrenia patients was based on the score of Proxy for the Deficit Syndrome. The deficit schizophrenia group had a significantly shorter AI compared with the non-deficit group and controls. The deficit group, but not the non-deficit group, was also characterized by an altered distribution of the OFC sulcogyral pattern, as well as fewer posterior orbital sulcus compared with controls. Other neurodevelopmental markers did not differentiate the deficit and non-deficit subgroups. These results suggest that the deficit subtype of schizophrenia and its clinical manifestation may be at least partly related to prominent neurodevelopmental pathology.

1. Introduction

Detailed examination of specific schizophrenia subtypes is one possible approach to reduce heterogeneity, which could partly explain the discrepant neurobiological findings of the disorder (Keshavan et al., 2008; van Os and Kapur, 2009). Deficit schizophrenia is a clinical subtype characterized by primary and prominent negative symptoms that persist even during periods of relative remission (Carpenter et al., 1988). While etiologic factors related to this specific subtype remain elusive, the association of deficit schizophrenia with poor premorbid adjustment (Bucci et al., 2016; Kirkpatrick and Galderisi, 2008), neurological abnormalities (Peralta et al., 2014), and general cognitive impairments (reviewed by Mucci et al., in press) may support the hypothesis of its pervasive neurodevelopmental abnormalities (Galderisi et al., 2002; Peralta et al., 2014). Furthermore, a recent magnetic resonance imaging (MRI) study of network-level properties of cortical thickness demonstrated altered intracortical relationships, which may reflect reduced network differentiation during early neurodevelopment, in deficit schizophrenia (Wheeler et al., 2015). To our knowledge, however, no MRI studies have examined gross brain morphology closely associated with early neurodevelopment specifically in deficit schizophrenia.

Previous MRI studies of gross brain morphology in schizophrenia have implicated the role of aberrant neurodevelopmental processes in the pathophysiology of schizophrenia (Pantelis et al., 2005). A smaller adhesio interthalamica (AI), which is a narrow bridge connecting the medial surfaces of the thalami that develops during early gestation (O'Rahilly and Muller, 1990; Rosales et al., 1968), and increased prevalence of large (e.g., ≥6 mm in anterior-posterior length) cavum septi pellucidi (CSP) due to incomplete fusion of the septum pellucidum around birth (Rakic and Yakovlev, 1968) are thought to reflect early developmental characteristics in midline brain regions in schizophrenia (Landin-Romero et al., 2016; Trzesniak et al., 2011a, 2011b). However, a large number of MRI studies including our own study (Takahashi et al., 2007, 2013b) reported normal size of the CSP in schizophrenia (reviewed by Trzesniak et al., 2011b). The surface morphology of the

Abbreviations: AI, adhesio interthalamica; CSP, cavum septi pellucidi; IOS, intermediate orbital sulcus; LOS, lateral orbital sulcus; MOS, medial orbital sulcus; OFC, orbitofrontal cortex; PDS, Proxy for the Deficit Syndrome; POS, posterior orbital sulcus; TOS, transverse orbital sulcus

* Correspondence to: Department of Neuropsychiatry, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan.
E-mail address: tsutomu@med.u-toyama.ac.jp (T. Takahashi).

http://dx.doi.org/10.1016/j.pscychresns.2017.05.007
Received 17 February 2017; Received in revised form 29 March 2017; Accepted 19 May 2017
Available online 20 May 2017
0925-4927/

orbitofrontal cortex (OFC) is also a potential neurodevelopmental marker because it is largely established by birth (Armstrong et al., 1995; Chi et al., 1977); schizophrenia patients are generally characterized by a shallower olfactory sulcus (Nishikawa et al., 2016; Takahashi et al., 2013a, 2014), decreased Type I and increased Type III expression in the variation of the OFC 'H-shaped' sulcus [Type I, II, and III; defined by Chiavaras and Petrides (2000)] (Chakirova et al., 2010; Nakamura et al., 2007; Takayanagi et al., 2010), as well as a decreased number of intermediate and posterior orbital sulci (IOS/POS) (Bartholomeusz et al., 2013; Takahashi et al., 2016). We have previously demonstrated that AI length and number of POS are related to the severity of negative symptoms in schizophrenia (Takahashi et al., 2008a, 2016). Further, nucleus accumbens atrophy (De Rossi et al., 2016) as well as microstructural disruption of the forceps minor (Spalletta et al., 2015) in deficit schizophrenia may imply significant role of the OFC abnormalities in this clinical subtype, because both of these structures are functionally and structurally connected with the OFC (Catani and Thiebaut de Schotten, 2008; Diekhof et al., 2012). However, it remains largely unknown whether the deficit and non-deficit subtypes of schizophrenia have differences in the morphology of potential neurodevelopmental markers located in the midline and OFC regions.

This MRI study aimed to expand our previous studies of a range of neurodevelopmental markers [AI (Takahashi et al., 2008a, 2008b), CSP (Takahashi et al., 2007), olfactory sulcus (Nishikawa et al., 2016; Takahashi et al., 2013a), and OFC surface morphology (Nishikawa et al., 2016; Takahashi et al., 2016)] in schizophrenia by investigating the characteristics of these neurodevelopmental markers in well-defined deficit subtype schizophrenia in comparison with non-deficit subtype as well as healthy controls. On the basis of hypothesized pervasive neurodevelopmental abnormalities in deficit schizophrenia (Galderisi et al., 2002; Peralta et al., 2014), we predicted that the deficit patients would exhibit greater changes in brain neurodevelopmental markers compared with the non-deficit patients. We also investigated the association between brain neurodevelopmental markers and clinical variables in each schizophrenia subgroup. Given the role of gross brain morphology as a stable trait marker that mainly reflects early neurodevelopment, we predicted that it would not be related to the symptom severity (especially positive symptoms) at scanning and potential confounding factors after illness onset (e.g., medication, illness duration).

2. Methods

2.1. Subjects

Seventy-five patients with schizophrenia (38 deficit and 37 non-deficit subtypes) fulfilling the ICD-10 research criteria (World Health Organization, 1993), who were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry of Toyama University Hospital, were included in this study. The patients were diagnosed following a structured clinical interview by psychiatrists using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Clinical symptoms were rated by trained psychiatrists at the time of scanning using the Brief Psychiatric Rating Scale (BPRS; Rhoades and Overall, 1988), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b).

The subtype classification of schizophrenia patients was based on the score of Proxy for the Deficit Syndrome (PDS), which is a valid and stable case-identification tool to discriminate deficit and non-deficit subtypes of schizophrenia patients (Goetz et al., 2007; Kirkpatrick et al., 1993). The PDS score is defined as the sum of the scores of the anxiety, guilt feelings, depressive mood, and hostility items, subtracted from the score for blunted affect on the basis of the BPRS ratings (Kirkpatrick et al., 1993) in order to reflects 'primary' (i.e., not secondary to factors such as anxiety, suspiciousness and other psychotic symptoms, and depression) and enduring negative symptomatology in deficit syndrome (Carpenter et al., 1988). Because a cross-sectional assessment using the PDS may yield excessive false positives (Subotnik et al., 1998), we followed a categorization method of recent MRI study (Wheeler et al., 2015) in order to reduce the likelihood of false classification. Specifically, among the full schizophrenia sample whose MRI data and BPRS score are available in our dataset ($n = 135$), the patients with top (≥ -3) and bottom (≤ -8) quartiles of the PDS scores were defined as the deficit and non-deficit schizophrenia patients, respectively.

Fifty-nine control subjects were selected from our previous studies (e.g., Nishikawa et al., 2016; Takahashi et al., 2016) based on matching to the schizophrenia patients for age and gender. They were recruited from members of the local community, hospital staff, and university students, and were asked to complete a questionnaire consisting of 15 items concerning their personal (13 items; including a history of obstetric complications, substantial head injury, seizures, neurological or psychiatric disease, impaired thyroid function, hypertension, diabetes, and substance abuse) and family (2 items) histories of illness. Subjects with any personal or family history of psychiatric illness among their first-degree relatives were excluded.

All subjects were physically healthy at the time of the study and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse disorders. All participants were also screened for gross brain abnormalities (except a large CSP) by neuroradiologists. The control subjects and 51/75 schizophrenia patients in this study have been partly included in our previous studies of the CSP (Takahashi et al., 2007), AI (Takahashi et al., 2008a, 2008b), olfactory sulcus (Nishikawa et al., 2016; Takahashi et al., 2013a), and OFC surface morphology (Nishikawa et al., 2016; Takahashi et al., 2016). The Committee on Medical Ethics of Toyama University approved this study. Written informed consent was obtained from all subjects.

2.2. Magnetic resonance imaging procedures

MR images were obtained using a 1.5 T Magnetom Vision (Siemens Medical System, Inc., Erlangen, Germany) with a three-dimensional gradient-echo sequence FLASH (fast low-angle shots) yielding 160–180 contiguous T1-weighted slices of 1.0 mm thickness in the sagittal plane. The imaging parameters were as follows: repetition time = 24 ms; echo time = 5 ms; flip angle = 40°; field of view = 256 mm; and matrix size = 256 × 256 pixels. The voxel size was 1.0 × 1.0 × 1.0 mm. The intracranial volume (ICV) was measured to correct for differences in head size as described previously (Zhou et al., 2003); there were no significant group differences for ICV (Table 2).

2.3. Assessment of the neurodevelopmental markers

The images were processed on a Linux PC (Fujitsu Limited, Tokyo, Japan) using Dr. View software (Infocom, Tokyo, Japan). The brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure line. Assessment of the AI, CSP, and olfactory sulcus was performed by one rater (TT). A second rater (HH, KN, YN, or DS) measured these structures in randomly selected brains in order to confirm the measurement reliabilities. For the OFC surface morphology that has high inter-individual variabilities (Chiavaras and Petrides, 2000), two raters (TT and YN or MN) independently performed the sulcogyral pattern classification and sulcus count for all subjects. A consensus agreement was reached in all cases even when the initial classification/count differed between the raters. All of these raters were blind to the subjects' identity. High intra- and inter-rater reliabilities (> 0.8; Cronbach's α in nominal measures and intraclass correlation coefficient for continuous measures) have been established for all of these structures in the MR images ($n \geq 10$) scanned using the same scanner/parameters as in this study (Nishikawa