Schizophrenia Research 169 (2015) 178–185

Contents lists available at ScienceDirect

Schizophrenia Research

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

Baseline putamen volume as a predictor of positive symptom reduction in patients at clinical high risk for psychosis: A preliminary study

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ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form 13 October 2015
Accepted 20 October 2015
Available online 31 October 2015

Keywords:
Clinical high risk
Psychosis
Positive symptom
Predictors
Putamen

ABSTRACT

Objectives: Illness course in individuals at clinical high risk (CHR) status for psychosis is heterogeneous, which limits effective treatment for all CHR subgroups. Baseline predictors of positive symptom trajectory in the CHR group will reduce such limitations. We singled out the putamen, thought to be involved in the generation of the key schizophrenia symptoms early in the course of disease, as a potential predictor of positive symptom trajectory in CHR patients.
Method: We recruited 45 CHR patients and 29 age- and gender-matched healthy controls (HC). The CHR group was divided into patients with positive symptom reduction (CHR-R) and patients without positive symptom reduction (CHR-NR) at 6 months. Comparisons were made between the baseline putamen volumes of CHR-R, CHR-NR and HC groups. The relationship between baseline putamen volumes and clinical measures was investigated.
Results: Left putamen volumes of CHR-R patients were significantly smaller than those of HCs ($p = 0.002$) and of CHR-NR patients ($p = 0.024$). CHR-R patients had significantly reduced leftward laterality compared to HCs ($p = 0.007$). In the CHR-R group, bilateral putamen volumes were correlated with positive symptom severity at baseline ($r = -0.552$, $p_{-} 0.001$) and at 6 months ($r = -0.360$, $p = 0.043$), and predicted positive symptom score change in 6 months at a trend level ($p = 0.092$).
Conclusion: Smaller left putamen volumes in CHR-R patients, and the correlation between positive symptom severity and putamen volumes suggest that putamen volume is a possible risk-stratifier and predictor of clinical course in the CHR population.

1. Introduction

The clinical high risk (CHR) state for psychosis is a heterogeneous population that is not only characterized by a heightened risk of transition to psychosis (Fusar-Poli et al., 2012a), but also by a range of comorbid psychiatric conditions (Fusar-Poli et al., 2014; Rietdijk et al., 2011; Rosen et al., 2006), as well as by cognitive (Fusar-Poli et al., 2012b), and functional deficits. Individuals who satisfy the criteria for the clinical high risk status have also been found to exhibit a number of structural (Meisenzahl et al., 2008; Nakamura et al., 2013; Peters et al., 2010; von Hohenberg et al., 2014) and functional brain changes (Dandash et al., 2014; Fornito et al., 2013; Lawrie et al., 2008), as reviewed previously (Fusar-Poli et al., 2011; Jung et al., 2012; Shim et al., 2010).

Recently, a trend of an increase in the proportion of CHR patients who never transition to psychosis has been observed (Simon and Umbricht, 2010; Simon et al., 2011). The majority of patients within the CHR cohort report a rapid improvement in their symptoms, and many undergo eventual remission (Lee et al., 2014) or report other residual psychiatric symptoms (Lin et al., 2015). Attempted early interventions include both nonpharmacological therapies such as intensive community care (Preti and Cella, 2010), cognitive behavioral therapy (de Koning et al., 2009), and pharmacological treatments such as antidepressants (Bowie et al., 2012; Fusar-Poli et al., 2014) and antipsychotics (Marshall and Rathbone, 2011; McGorry et al., 2009; Stafford et al., 2013). The heterogeneity in the CHR population and the low probability of transition, however, serve as deterrents in the development of optimal treatments for the entire spectrum of CHR patients. Stratification of the CHR population by identifying ways to predict the likely course that the symptoms of CHR patients will take will help uncover effective ways to treat even those help-seeking individuals who show persistent symptoms under current treatment regimens.

Presence and progression of positive symptoms, a hallmark in defining the onset of psychosis, are functionally (Agid et al., 2007a,b; Sorg et al., 2013) and structurally (Taylor et al., 2005) tied to abnormalities in the striatum. Increased presynaptic dopamine synthesis (Howes et al., 2009; Kegeles et al., 2010) and altered functional connectivity

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http://dx.doi.org/10.1016/j.schres.2015.10.029
0920-9964/

(Dandash et al., 2014; Roiser et al., 2013) also precede the onset of psychosis and have been related to various measures of positive symptom severity. The role of the striatum in coding salience and value helps explain how striatal malfunction (i.e. misattribution of value or salience to irrelevant stimuli) results in the emergence of key symptoms such as delusions and hallucinations (Heinz and Schlagenhauf, 2010; Kapur, 2003). The striatum is ideally situated within the cortico-striato-thalamic circuitry in a spatially organized manner that makes the alterations in morphology of the striatum particularly revealing in disease states (Looi and Walterfang, 2013). A further role of the striatum underlying cognitive function also suggests the possibility that striatal morphology may already be abnormal in CHR individuals (Simpson et al., 2010).

The putamen, the dorsal portion of the input nuclei making up the striatum, principally receives inputs from the sensorimotor and associative cortices (Utter and Basso, 2008). Previous findings have highlighted abnormal dopaminergic function in sensorimotor and associative striatum in early stages of schizophrenia (Kegeles et al., 2010; Mizrahi et al., 2012). Volume changes in the putamen are closely related to response to antipsychotic treatment (Taylor et al., 2005), and to symptoms and course of disease in schizophrenia (Brandt and Bonelli, 2008). Additionally, the size of the putamen has been linked to severity of positive symptoms (Gur et al., 1998), treatment response (Li et al., 2012; Taylor et al., 2005), and outcome (Mitelman et al., 2009). Abnormalities in putamen volume are already apparent in patients experiencing the first episode of psychosis (Glenthoj et al., 2007), and healthy relatives with high genetic risk for psychosis (Dougherty et al., 2012; Seidman et al., 1997), in whom the putamen volume is decreased when compared to controls.

Whereas the exact neurobiological phenomena contributing to such volume changes remain obscure, the above findings single out abnormality in the structural measures of the putamen as a plausible candidate to predict course of the key symptoms, especially positive symptoms, of schizophrenia (Smieskova et al., 2010) early in the course of disease.

In our study, we first compared manually traced baseline putamen volumes of CHR patients who showed reduced positive symptoms (CHR-R) at 6 months, CHR patients who showed no positive symptom reduction (CHR-NR) at 6 months, and healthy controls (HC). Next, we investigated the relationship between putamen volume and other clinical variables in the CHR group. We hypothesized that baseline putamen volumes of CHR-R patients will be different from those of CHR-NR patients and HCs.

2. Methods

2.1. Subjects

We recruited 45 help-seeking individuals who visited the Seoul Youth Clinic from November 2004 to September 2014, and who met the criteria for a prodromal psychosis syndrome. History of psychiatric illnesses was screened by the Structured Clinical Interview for DSM-IV Axis I (SCID-I). Subjects with a diagnosis of a psychotic illness, substance dependence, neurological disorder, a history of significant traumatic brain injury, or any other significant medical condition possibly manifesting as a psychiatric condition, and an IQ below 70 were excluded from the study.

Twenty-nine age- and gender-matched HCs were recruited from the community through advertisements. HCs were screened using the SCID-I, non-patient edition (SCID-NP). Exclusion criteria for HCs were the same as for CHRs with an additional criterion of no first or second degree relative with psychiatric illness.

All participants gave written informed consent after full explanation of the procedures, and approval by the institutional review board of SNUH was obtained (IRB approval number 1409–060-609).

2.2. Demographic data collection and clinical assessment

Handedness was assessed using Annett's questionnaire (Annett, 1967), and intelligence quotient was evaluated using the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) (Kim et al., 1994). Parental socioeconomic status was evaluated using the Hollingshead scale (Hollingshead, 1975). HC participants were screened for family history of psychotic disorders with the family interview for genetic studies (Gershon and Guroff, 1984).

CHR patients were assessed for psychiatric symptoms at enrollment into the cohort and at 6 months follow-up. The Structured Interview of Prodromal Symptoms (SIPS) (Miller et al., 2002) was used to assess for prodromal symptoms with the Scale of Prodromal Symptoms (SOPS), the Positive and Negative Symptom Scales (PANSS) to assess for positive, negative, and disorganized symptoms, and the Brief Psychiatric Rating Scale (BPRS) for general psychiatric symptoms. General function was assessed at both baseline and follow-up with the Global Assessment of Function (GAF). Additional assessments included the Hamilton Depression Rating Scale (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A). The cumulative chlorpromazine equivalent dose of antipsychotic drugs was calculated from prescription data during the six month period (Gardner et al., 2010).

Treatment was given in a naturalistic setting. All CHR patients received psychoeducation, case management, and crisis intervention from trained psychiatrists. Pharmacological interventions including psychotropic medication were given as needed.

2.3. Outcome measures at 6 months

Six months after enrollment into the CHR group, patients' positive symptoms were assessed with the SOPS positive symptom score. The criterion separating the CHR patients with positive symptom reduction (CHR-R) from CHR patients with no positive symptom reduction (CHR-NR) was any reduction of the SOPS positive symptom score equal to or greater than one point over the baseline at 6 months. Other clinical measurements at 6 months included the rest of the SOPS, BPRS, PANSS, HAM-D, HAM-A, and GAF.

2.4. Magnetic resonance imaging (MRI)

All MRI scans of CHR patients were acquired upon enrollment, or on a date close to enrollment, to the CHR group. For both HCs and CHRs, brain MRI images were acquired using a 3.0-T scanner (Siemens Magnetom Trio, Erlangen, Germany). Parameters for the scans were as follows: echo time/repetition time = 1.89 ms/1670 ms, flip angle = 9°, field of view = 250 mm, slice thickness = 1 mm, voxel dimensions = $0.82 \times 0.82 \times 0.82$ mm^3, 208 slices, matrix = 256×256.

2.4.1. Freesurfer segmentation

Processing of the MRI data from the CHR and HC participants was performed using the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu), which involved removal of non-brain tissue, registration to Talairach space, segmentation of subcortical gray and white matter, intensity normalization, identification of gray matter and white matter boundaries, topology correction, and registration to a spherical atlas. Only the estimated total intracranial volumes (eTIV) acquired with Freesurfer segmentation were used for analysis.

2.4.2. Manual tracing of the putamen

For manual tracing of the putamen of CHR participants, we employed 3D-Slicer (http://www.slicer.org). Trained raters who were blinded to subject group and treatment response traced bilateral putamen according to the guidelines from two neuroimaging laboratories (University of North Carolina, 2006; Westmoreland and Cretsinger, n.d.) (Fig. 1). Inter-rater reliability was assessed using the intra-class correlation coefficient (ICC).