Psychiatry Research: Neuroimaging 201 (2012) 40–47

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Neural markers of early remission in first-episode schizophrenia: A volumetric neuroimaging study of the parahippocampus

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ARTICLE INFO

Article history:
Received 26 January 2011
Received in revised form 22 April 2011
Accepted 11 July 2011

Keywords:
First-episode schizophrenia
Remission
Clinical outcome
Parahippocampus
Structural neuroimaging

ABSTRACT

Using voxel-based morphometry (VBM), our laboratory recently identified significantly lower grey matter concentration in the parahippocampal gyrus bilaterally in non-remitted patients with a first episode of psychosis (FEP) compared with remitted FEP patients. These results identified a localized difference but did not reveal which cortex (entorhinal, perirhinal, or parahippocampal), if any, was predominantly affected. So, the parahippocampal gyrus was manually segmented and grey matter volumes from the three cortices were compared between 42 non-remitted and 17 remitted patients with a first episode of schizophrenia (FES). Remission was defined as mild or less on eight key symptoms and maintained for 6 consecutive months following the 2005 consensus definition. The non-remitted patients displayed smaller volumes in the parahippocampal cortex – trend-level difference on the left [mm^3, mean (S.D.): non-remitted = 2486 (413); remitted = 2775 (593)] and significant difference on the right [mm^3, mean (S.D.): non-remitted = 2546 (463); remitted = 2926 (525)]. No notable differences were found in the entorhinal or perirhinal cortices. This result supported our VBM finding of reduced parahippocampal grey matter bilaterally in non-remitted patients and further suggested differences may be selectively limited to the parahippocampal cortex. A smaller parahippocampal cortex may represent a neural marker in FES patients who do not achieve remission after 1 year of treatment.

1. Introduction

One of the great challenges of research in schizophrenia is to better understand the heterogeneity in clinical outcome following a first episode of psychosis. With markers of outcome considered synonymous with risk and resilience factors (Emsley et al., 2008), the identification of neuroanatomical makers of remission could lead to a better understanding of the heterogeneity of outcome and ultimately the disorder itself. Our laboratory recently attempted to identify structural neuroimaging differences between non-remitted and remitted patients with a first episode of psychosis using an exploratory, whole-brain analysis (voxel-based morphometry, VBM). Results from this analysis revealed significantly lower grey matter concentration in the parahippocampal gyrus in non-remitted patients compared to remitted patients (Bodnar et al., 2011). Although a grey matter difference was identified within the parahippocampal gyrus, the finding was localized to a specific cluster of voxels and did not reveal which cortex (entorhinal, perirhinal, or parahippocampal), if any, was predominately affected.

The VBM finding is of interest, but the identification of a specific structure would allow future studies to replicate and expand upon our finding with more certainty. In fact, there are several advantages to using VBM: (1) no variance between raters, (2) easy and quick to analyze, and (3) not dependent on a particular hypothesis (Ashburner and Friston, 2001; Pletson, 2007). As such, VBM represents a heuristic exploratory approach which can lead to the generation of specific regions of interest – as with the current analysis examining the parahippocampal gyrus. However, a VBM analysis can fail to detect very small grey matter differences due to (1) the changes in the shape or displacement of structures during spatial normalization (Bookstein, 2001; Davatzikos, 2004; Pletson, 2007; Thacker, 2008) or (2) the variability of gyrification (Park et al., 2004) that has been shown to be present in schizophrenia (Kulynych et al., 1997; Harris et al., 2004; Wheeler and Harper, 2007; Schultz et al., 2010). Therefore, VBM findings require validation through manual tracing methodology (Pletson, 2007).

The current analysis set out to investigate grey matter volumetric differences in the three cortices of the parahippocampal gyrus between remitted and non-remitted patients with a first episode of

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doi:10.1016/j.pscychresns.2011.07.012

schizophrenia. As it was the first study to investigate parahippocampal volume with respect to remission in schizophrenia, no hypothesis was put forward as to which cortex, if any, would show a significant between-group difference.

2. Materials and methods

2.1. Participants and treatment setting

Individuals admitted and treated at the Prevention and Early Intervention Program for Psychoses (PEPP) aged 18 to 30 years with no previous history of neurological disease or head trauma causing loss of consciousness were eligible for the neuroimaging study. The PEPP is a specialized service offered at the Douglas Mental Health University Institute in Montreal, Canada. Persons aged 14 to 30 years from a local catchment area suffering from either affective or non-affective psychosis who had not taken antipsychotic medication for more than 1 month and who had an IQ higher than 70 were consecutively admitted as either in- or out-patients. For complete program details see Malla et al. (2003) or visit http://www.douglas.qc.ca/pages/view?section_id=165). The patient sample for this analysis was a subset of the sample from our previous VBM analysis that was limited to first-episode patients diagnosed with schizophrenia or a related spectrum disorder since remission in schizophrenia was the focus.

In all, 59 first-episode schizophrenia (FES) patients agreed to take part in the neuroimaging study subsequently separated into two groups: non-remitted ($n=42$, 71.2%) and remitted ($n=17$, 28.8%). Remission was defined as 3 (mild) or less on eight symptoms of the Positive and Negative Syndrome Scale (PANSS) [delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), blunted affect (N1), passive or apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), mannerisms and posturing (G5), and unusual thought content (G9)] and maintained for 6 consecutive months (from month 6 to 12, in our case) in accordance with the Remission in Schizophrenia Working Group consensus definition (Andreasen et al., 2005). All patients met DSM-IV criteria for schizophrenia (remitted = 13; non-remitted = 33), schizoaffective (remitted = 3; non-remitted = 9), or schizophreniform (remitted = 1) diagnoses according to the Structured Clinical Interview for DSM-IV (First et al., 1998); diagnoses were confirmed between two senior research psychiatrists (A.M. and R.J.).

After a comprehensive description of the study, written informed consent was obtained from all participants. Research protocols were approved by the McGill University Faculty of Medicine review board.

2.2. Data collection

2.2.1. Demographic, cognitive, and clinical data

As per the PEPP protocol, the following data were obtained at each interview session conducted at first assessment and at months 1, 2, 3, 6, 9, and 12 following first assessment; first assessment took place within 1 month after admission (days; median = 23.8, mean = 25.4, range = 4.8–51.0). Positive and negative symptoms were assessed using the (PANSS) (Kay et al., 1987); PEPP evaluators have established an ICC of 0.75 on this scale. The type and dosage of antipsychotic taken were recorded and subsequently converted into chlorpromazine equivalents (Woods, 2003; Jensen and Regier, 2010). Medication adherence, based on a 5-point scale ranging from 0 (never) to 4 (fully), was obtained from patients or, when possible, from family members (Malla et al., 2006). At first assessment, parental socio-economic status (SES) during upbringing was measured with the Hollingshead two-factor index (Hollingshead, 1965) and handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). Duration of illness was defined as the period beginning with the first onset of any psychiatric symptoms to the time of scan. In dating the onset of first psychiatric symptoms, childhood disorders such as developmental disorders (e.g. autism) or attention deficit disorders were not included. Psychiatric symptoms refer to symptoms indicating behavioural change such as anxiety, depression, suicidal ideation, or social withdrawal.

A standard neuropsychological battery was also administered to all patients. Testing took place within several months after admission (months; median = 2.3, mean = 2.7, range = 0.7–13.5); the two groups did not differ with respect to when testing took place [months, mean (S.D.): non-remitted = 2.9 (2.4); remitted = 2.4 (1.3); $t_{57}=0.84$, $P=0.402$]. From these data, six cognitive domains were created: *verbal learning and memory* from the Logical Memory subtests of the Wechsler Memory Scale – Third Edition (WMS-III) (Wechsler, 1997b); *visual learning and memory* from the Visual Reproduction subtests of the WMS-III; *working memory* from the Spatial Span subtests of the WMS-III and the Digit Span subtests of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997a); *speed of processing* from the Trail Making Test A (completion time) (Reitan, 1992) and the Digit Symbol subtest of the WAIS-III; *reasoning and problem solving* from the Trail Making Test B (completion time) and the Block Design subtest of the WAIS-III; and *attention* from the d2 Test of Attention (concentration performance score) (Brinkenkamp and Zillmer, 1998). Once these data were verified to be normally distributed, test scores were transformed into standard equivalents (z-scores) using the mean and standard deviation of a healthy control group ($n=49$) that were part of our longitudinal study [previously analyzed and described elsewhere (Bodnar et al., 2008; Bodnar et al., 2011)]. Cognitive domains were then calculated by averaging the z-scores of the pertinent tests and then normalized using the mean and standard deviation of the healthy control group. We also investigated Full-scale IQ as per the WAIS-III (Wechsler, 1997a).

2.2.2. Scanning procedure and MRI data acquisition

Scanning was carried out at the Montreal Neurological Institute on a 1.5 T Siemens whole body MRI system. Structural T1 volumes were acquired for each participant using a three-dimensional (3D) gradient echo pulse sequence with sagittal volume excitation (repetition time = 22 ms, echo time = 9.2 ms, flip angle = 30º, 180 1- mm contiguous sagittal slices). The rectangular field-of-view for the images was 256 mm (SI) × 204 mm (AP). Scanning took place only when patients were stable enough to tolerate the scanning session with suitability to participate reassessed on a weekly basis until our clinical and research team agreed that acute symptoms would not interfere with the protocol (e.g., being able to stay still for more than 1 h). Scanning took place within several months after admission (months; median = 4.6, mean = 4.6, range = 1.7–8.5); the two groups did not differ with respect to when scanning took place [months, mean (S.D.): non-remitted = 4.4 (1.9); remitted = 5.1 (2.0); $t_{57}=-1.23$, $P=0.225$]. Total intracranial volume was estimated for each participant using the VBM8 toolbox created by C. Gaser (http://dbm.neuro.uni-jena.de/vbm/download/).

2.2.3. Automated MRI data preprocessing

All T1 images were transferred to a Macintosh workstation. A combination of different algorithms was used to prepare the raw MRI volumes for manual segmentation. This process corrected for image intensity non-uniformities (Sled et al., 1998), linear stereotaxic transformation (Collins et al., 1994) into MNI coordinates based on the Talairach atlas (Talairach and Tournoux, 1988) and resampling onto a 1- mm voxel grid prior to image segmentation using a linear interpolation kernel. It has been shown that the automatic stereotaxic transformation is as accurate as the manual procedure, but shows higher stability (Collins et al., 1994). Also, the correction for image intensity has been shown to recover most of the artifacts present in raw MRI data (Sled et al., 1998). Finally, signal-intensity normalization was performed across all subjects in the study to adjust individual signal range and render the contrast between subjects comparable.