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Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse

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ABSTRACT

Childhood trauma is associated with smaller gray matter volume, similar to the pattern seen in psychotic disorders. We explored the relationship between childhood abuse, psychosis, and brain volume in a group of 60 individuals with a psychotic disorder and 26 healthy control subjects. We used voxel-based morphometry (VBM) to quantify gray and white matter volume and the Childhood Trauma Questionnaire (CTQ) to measure childhood abuse. Within the psychotic disorder group, total gray matter volume was inversely correlated with the severity of childhood sexual abuse ($r = -.34$, $p = .008$), but not the other types of abuse. When the 24 patients with sexual abuse were compared with demographically matched samples of 23 patients without sexual abuse and 26 control subjects, only patients with a history of sexual abuse had reduced total gray matter volume ($t(48) = 2.3$, $p = .03$; Cohen's $d = .63$). Voxel-based analysis revealed a cluster in the prefrontal cortex where volume was negatively correlated with sexual abuse severity. Voxel based comparison of the three matched groups revealed a similar pattern of results, with widespread reductions in psychosis patients with sexual abuse relative to controls that were not found in psychosis patients without sexual abuse. These findings indicate that some of the variance of gray matter volume in psychotic disorders can be explained by a history of sexual abuse.

1. Introduction

Reduced gray matter volume across multiple brain regions is a consistent finding in studies of schizophrenia and bipolar disorder (Hirayasu et al., 2001; Glahn et al., 2008; Ellison-Wright and Bullmore, 2010; Smieskova et al., 2010; Shepherd et al., 2012). Global gray matter loss is found in both chronic (Zipursky et al., 1992; Lim et al., 1996) and neuroleptic-naïve patients (Gur et al., 1999), with volume loss ranging from 2 to 6%. Despite the strong evidence for reduced gray matter volume in psychotic disorders, the etiology and time course of this process remain unclear.

The diathesis-stress model of mental illness suggests that a major life stressor such as childhood trauma could have a serious impact on the trajectory of brain development and contribute to the onset of a psychiatric disorder (Rosenthal, 1970; Mirsky and Duncan, 1986; Cicchetti and Lynch, 1995). Consistent with this notion, multiple studies have found a higher prevalence of psychotic disorders in individuals who have experienced childhood abuse (Mullen et al., 1993; Spauwen et al., 2006; Cutajar et al., 2010). While abuse early in life is a major risk factor for mental illness, childhood trauma is known to impact brain structure, even in individuals without a psychiatric diagnosis (Twardosz and Lutzker, 2010). Specifically, childhood trauma has been linked to reduced total brain volume (De Bellis et al., 1999), and selective gray matter volume loss in the hippocampus (Vythilingam et al., 2002), prefrontal cortex (De Bellis et al., 2002), amygdala (Aas et al., 2012), and visual cortex (Tomoda et al., 2009). Interestingly, many of the brain abnormalities seen in abused individuals, in particular gray matter volume loss, are similar to those found in psychotic disorder patients (Honea et al., 2005; Hart and Rubia, 2012). This overlap led us to explore the relationship between gray matter volume, childhood trauma, and the diagnosis of a psychotic disorder.

We used voxel-based morphometry (VBM) to quantify gray and white matter volume and the Childhood Trauma Questionnaire (CTQ) to measure childhood abuse in a group of patients with a primary psychotic disorder and healthy control subjects with no history of mental illness. With this data we tested the following hypotheses: 1) psychotic disorder patients experience more childhood trauma than healthy control subjects, 2) severity of childhood abuse is negatively correlated with gray matter volume and 3) gray matter volume loss is most pronounced in psychotic disorder patients with a history of childhood abuse.

2. Methods

2.1. Subjects

Participants included 60 psychotic disorder patients (26 schizophrenia, 17 schizoaffective disorder, 17 bipolar disorder type I with psychotic features) and 26 healthy control subjects. Psychotic

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disorder patients were recruited from the inpatient and outpatient clinic of the Vanderbilt Psychiatric Hospital, and healthy controls were recruited via advertisements within the community. All participants completed written informed consent after approval of the study protocol by the Vanderbilt University Institutional Review Board, Nashville, Tennessee. All participants were administered the Structured Clinical Interview of the DSM-IV-TR (SCID) to confirm diagnoses in patients and rule out current or past psychiatric illness in healthy controls. An estimate of pre-morbid IQ was collected from all participants using the Wechsler Test of Adult Reading (Weschler, 2001). In addition, we assessed all patients with the Hamilton Rating Scale for Depression (HAMD), Young Mania Rating Scale (YMRS) and Positive and Negative Syndrome Scale (PANSS) (Hamilton, 1960; Young et al., 1978; Kay et al., 1987). Exclusion criteria included age less than 16 or greater than 65, estimated pre-morbid IQ of less than 70, presence of a systemic medical illness (e.g. diabetes, cardiovascular disease) or central nervous system disorder (e.g. multiple sclerosis, epilepsy) that would affect study results, reported pregnancy or lactation, history of significant head trauma, psychotropic drug use (healthy subjects only), substance abuse within the last three months (patients) or lifetime history of substance abuse/dependence (healthy subjects), and MRI contra-indicators (e.g. metal implants, claustrophobia) (for subject demographics, see Table 1).

2.2. Measures

2.2.1. Childhood Trauma Questionnaire (CTQ)

All participants completed the short version of the Childhood Trauma Questionnaire (CTQ, (Bernstein et al., 1997)), a self-report questionnaire that measures the experience and severity of five different types of childhood trauma: physical abuse, sexual abuse, emotional abuse, emotional neglect, and physical neglect (Bernstein et al., 2003). Each category of trauma is assessed with five questions (e.g. someone tried to touch me in a sexual way or tried to make me touch them) for which the subject had to select a level of frequency: never true, rarely true, sometimes true, often true, or very often true. These responses were then coded on a 5-point Likert scale. Total CTQ scores range from 25 to 125, with each individual abuse sub-scale ranging from 5 to 25 and higher scores indicating more severe abuse. The validity and reliability of the CTQ have been verified in independent studies (Scher et al., 2001; Wright et al., 2001; Paivio and Cramer, 2004). Additionally, the CTQ has been previously used to assess childhood trauma in psychotic disorder patients (Holowka et al., 2003; Compton et al., 2004; Schafer et al., 2006) and prior research has demonstrated the validity of self-report measures in individuals with serious mental illness (Meyer et al., 1996; Goldberg et al., 2002; Niv et al., 2007) and of retrospective reports of abuse in patients with psychosis (Dill et al., 1991; Fisher et al., 2011). Individuals were defined as "abused" for each abuse sub-type if their score corresponded with the lowest threshold for "moderate–severe abuse" as defined by the CTQ manual (for rates of abuse in both groups, see Table 2).

2.2.2. MRI acquisition

Imaging data for all participants was collected on a 3 T Philips Intera Achieva scanner located at the Vanderbilt University Institute of Imaging Science (VUIIS). We acquired a high-resolution T1-weighted fast field echo (FFE) structural scan (170 sagittal slices, matrix = 256 × 256, 1.0 mm isovoxel resolution, TR/TE = 8.0/3.7 ms) on each subject. Foam padding was used to stabilize the head, and earplugs and headphones were provided for each subject to minimize scanner noise. Each subjects' anatomical T1-weighted image was visually inspected and images with obvious artifact related to movement (i.e. ringing) or significant signal inhomogeneity were not included in the analysis.

2.2.3. Voxel-based morphometry

T1-weighted structural brain images were pre-processed and quantitatively analyzed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/download/) for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Following bias-correction, the T1-weighted images were segmented and affine (i.e. linear) normalized to MNI space. Following linear normalization, tissue class images were non-linearly normalized using the high-dimensional DARTEL algorithm to predefined templates provided with the VBM8 toolbox. The gray matter tissue class images were then modulated using the non-linear components derived from the high-dimensional DARTEL normalization step, thereby preserving the absolute amount of tissue after correcting for variation in individual brain sizes. The non-linear modulated DARTEL normalized gray matter images were smoothed with an 8 mm kernel and used in the subsequent voxel-based statistical analyses described below. In addition to the non-linear modulated gray matter images derived through the high-dimensional DARTEL normalization procedure, the native space tissue class images were also output from the VBM8 toolbox from which total gray, white, CSF, and intracranial volume (i.e. GM + WM + CSF) was calculated.

2.3. Statistical analysis

2.3.1. Childhood trauma and brain volume: global effects

The relationship between childhood trauma and brain volumes was analyzed with a partial correlation controlling for age and gender, testing the hypothesis that severity of childhood abuse is correlated with total gray matter volume. A repeated measures analysis of variance (ANOVA) was then used to compare the average brain volume between three demographically-similar groups of subjects: psychotic disorder patients who were sexually abused (n = 24; sexual abuse score ≥ 8), psychotic disorder patients who were not sexually abused (n = 23; sexual abuse score ≤ 7), and healthy control subjects (n = 26). Main

Table 1
Demographic and clinical characteristics of participants.

	Healthy control subjects (n = 26)	All patients (n = 60)	Sub-group: patients with sexual abuse (n = 24)	Sub-group: patients without sexual abuse (n = 23)
Sex (male/female)	13/13	32/28	8/16	11/12
Race (White/Black/Other)	13/12/1	40/18/2	18/5/1	12/10/1
Age	38.2 (10.8)	35.5 (13.3)	41.7 (11.9)	36.3 (13.5)
Participant's education, years[a]	15.3 (2.0)	13.0 (2.4)	12.8 (2.3)	12.6 (2.5)
Parental education, years	13.4 (1.9)	13.5 (2.6)	13.1 (2.6)	13.1 (2.7)
Pre-morbid IQ, WTAR[b]	103.7 (13.6)	98.1 (16.9)	94.7 (16.7)	95.8 (17.5)
HAM-D	–	13.4 (10.7)	16.4 (9.9)	12.3 (12.6)
YMRS	–	9.0 (8.0)	8.6 (8.1)	9.2 (8.9)
PANSS total	–	63.4 (15.4)	60.7 (13.9)	66.5 (17.5)

HAM-D, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; WTAR, Wechsler Test of Adult Reading; YMRS, Young Mania Rating Scale. Mean (SD) values are reported unless indicated otherwise.

[a] Significantly different between healthy controls and all psychotic disorder patients, $p < .001$.

[b] Significantly different between healthy controls and psychosis patients with sexual abuse, $p < .05$.