Psychiatry Research: Neuroimaging 222 (2014) 10–16

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

A multi-scanner study of subcortical brain volume abnormalities in schizophrenia

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ARTICLE INFO

Article history:
Received 16 August 2013
Received in revised form
13 January 2014
Accepted 21 February 2014
Available online 28 February 2014

Keywords:
Psychosis
Magnetic resonance imaging (MRI)
Effect size
Imaging

ABSTRACT

Schizophrenia patients show significant subcortical brain abnormalities. We examined these abnormalities using automated image analysis software and provide effect size estimates for prospective multi-scanner schizophrenia studies. Subcortical and intracranial volumes were obtained using FreeSurfer 5.0.0 from high-resolution structural imaging scans from 186 schizophrenia patients (mean age ± S.D. = 38.9 ± 11.6, 78% males) and 176 demographically similar controls (mean age ± S.D. = 37.5 ± 11.2, 72% males). Scans were acquired from seven 3-Tesla scanners. Univariate mixed model regression analyses compared between-group volume differences. Weighted mean effect sizes (and number of subjects needed for 80% power at $\alpha = 0.05$) were computed based on the individual single site studies as well as on the overall multi-site study. Schizophrenia patients have significantly smaller intracranial, amygdala, and hippocampus volumes and larger lateral ventricle, putamen and pallidum volumes compared with healthy volunteers. Weighted mean effect sizes based on single site studies were generally larger than effect sizes computed based on analysis of the overall multi-site sample. Prospectively collected structural imaging data can be combined across sites to increase statistical power for meaningful group comparisons. Even when using similar scan protocols at each scanner, some between-site variance remains. The multi-scanner effect sizes provided by this study should help in the design of future multi-scanner schizophrenia imaging studies.

1. Introduction

Schizophrenia patients show significant structural brain abnormalities when studied with magnetic resonance imaging (MRI). In vivo study of these abnormalities may aid in our understanding of etiology, pathogenesis, and treatment effects. In this study we examine whether subcortical volume alterations can be observed in prospective multi-center imaging studies despite

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http://dx.doi.org/10.1016/j.pscychresns.2014.02.011
0925-4927

additional between-scanner variance. We provide effect size estimates for single center (based on meta-analysis of single site effects) versus multi-center (based on mega-analysis correcting for site effects) structural imaging studies in schizophrenia.

Effect size estimates for structural brain alterations in schizophrenia are predominantly based on single center studies (Haijma et al., 2013; Shepherd et al., 2012); but for a simulation of multi-center study effect sizes, see Suckling et al. (2010). The increase in multi-scanner imaging studies, as well as increased efforts towards data sharing, emphasizes the need for effect-size estimates for multi-scanner data acquisitions. The ability to detect statistically significant differences between conditions depends on the effect size, sample size, α-level, and power of the test (Cohen, 1992). In power analyses, the researcher sets the desired α-level and power of the test. The effect size is preferably gleaned from the literature or otherwise estimated, and the sample size that will be required to observe a statistically significant effect is estimated.

The effect size for mean comparisons can be computed as the mean difference between two conditions divided by the pooled standard deviation of the measurements (Cohen, 1992) and thus depends on measurement variability. In single scanner studies, such variability depends on subject variability, between-acquisition scanner variability, and measurement-method reliability. In multi-scanner studies it also depends on between-scanner and other between-site (e.g., sample demographics) variance. Subject variability depends on the relative homogeneity or heterogeneity of the sample(s). Between-acquisition scanner variability depends on the stability over time of the MRI scanner. Brain-measurement reliabilities are estimated from multiple measurements on the same cases and include inter- and intra-scanner reliability (Jovicich et al., 2009), rater reliability (van Erp et al., 2004), and measurement-method reliability (Dewey et al., 2010; Tae et al., 2008; Wonderlick et al., 2009).

Measurements should not only be reliable but also valid. A measure is considered valid when the inferences made from it are appropriate, meaningful, and useful. The calculation of inter-method reliability in which a new method is compared to a GOLD standard, or a method that has been shown to produce valid measurements, provides one way to validate a measurement method. The more similar the measurements are (the higher the intra-class correlation), the more valid the measurements based on the new method. Nevertheless, validation should also be established by confirming that meaningful variability can be observed with the measurements.

Given between-scanner variability, the question remains as to how many additional data sets need to be collected in multi-scanner versus single scanner studies to observe differences between schizophrenia patients and controls? In this study, we compare subcortical volumes between chronic schizophrenia patients and healthy volunteers, and we report the weighted mean effect sizes as well as multi-center-based ($n=7$) effect sizes for subcortical volumes. Based on the effect sizes reported in meta-analyses (Haijma et al., 2013; Shepherd et al., 2012) (see Table 4), we hypothesized that we would find smaller amygdala, hippocampus, and intracranial volume and larger lateral ventricle and pallidum volumes in patients with schizophrenia compared with healthy volunteers.

2. Methods

2.1. Participants

The participants comprised 186 schizophrenia patients (mean age ± S.D.= 38.9 ± 11.6, 145 males) and 176 healthy volunteers (mean age ± S.D.=37.5 ± 11.2, 126 males) with similar mean age, sex, handedness, and race distributions from seven sites (Table 1; see Supplement 1, Tables 1S, for demographic data by site). Patient inclusion criteria were schizophrenia diagnosis based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002b). All patients were clinically stable outpatients whose antipsychotic medications and doses had not changed within the last 2 months. Current neuroleptic medication data were available for 171 of the 186 patients (antipsychotics: 136 atypical, 20 typical, 10 both; mood stabilizers: 2, and anxiolytics: 3). Chlorpromazine-equivalent dosages could be computed for 151 patients (www.scottwilliamwoods.com/files/Equivtext.doc). Schizophrenia patients and healthy volunteers with a history of major medical illness, drug dependence in the last 5 years, current substance abuse disorder, MRI contraindications, or eyesight not correctable to normal acuity with MRI-compatible lenses were excluded. Patients with significant extrapyramidal symptoms and healthy volunteers with a current or past history of major neurological or psychiatric illness (First et al., 2002a) or with a first degree relative with an Axis-I psychotic disorder diagnosis were also excluded. Patient's clinical assessments included the Positive and Negative Symptoms Scale (Kay et al., 1989). All participants were assessed for socioeconomic status (Hollingstead, 1975), handedness (Oldfield, 1971), basic demographics, and premorbid IQ (Uttl, 2002). The sample includes 137 paranoid, 7 disorganized, 30 undifferentiated, and 12 residual patients. Before data collection, experienced clinicians were jointly trained on the

Table 1
Sample demographics.

	Schizophrenia patients ($n=186$)	Healthy volunteers ($n=176$)	Statistic	p-value
Mean age (S.D.)	38.9 (11.6)	37.5 (11.2)	$t_{360}=1.12$	0.26
Subject education[b] (S.D.)	3.4 (0.9)	2.3 (0.9)	$t_{360}=11.47$	<0.0001
Parental education[b] (S.D.)	2.4 (1.8)	2.1 (1.5)	$t_{360}=1.49$	0.14
NAART	29.4 (12.4)	39.7 (11.4)	$t_{357}=-8.22$	<0.0001
Age at onset	21.8 (7.6)			
Duration of illness	17.1 (11.5)			
PANSS positive	15.5 (5.1)			
PANSS negative	14.5 (5.6)			
PANSS general	28.6 (7.5)			
PANSS composite	0.9 (6.3)			
Gender (M/F)	145/41	126/50	$\chi^2_1=0.83$	0.36
Handedness[a] (bilateral/left/right)	4/12/170	2/7/167	FET	0.46
Race			FET	0.10
American Indian or Alaskan Native	4	3		
Asian	22	16		
Black or African American	38	20		
Native Hawaiian or Pacific Islander	2	2		
White	120	135		

FET=Fisher's exact test.
NAART=North American adult reading test (Uttl, 2002).
PANSS=Positive and Negative Symptoms Scale (Kay et al., 1989).

[a] Based on Edinburgh Handedness Inventory (Oldfield, 1971).
[b] Based on the Hollingstead Socioeconomic Status Scale (Hollingstead, 1975).