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Subjective Rating of Working Memory is Associated with Frontal Lobe Volume in Schizophrenia

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Abstract

Background—Patients with schizophrenia commonly show deficits in working memory on objective neuropsychological measures, and brain imaging studies have documented neural abnormalities during performance of working memory tasks. It remains unclear to what extent such patients are able to accurately gauge the integrity of their working memory in their daily lives. **Aims:** We evaluated the relationship between subjective rating of working memory integrity in daily life and volumes of the frontal, temporal, and parietal lobes in patients with schizophrenia.

Methods—Participants included 29 patients with schizophrenia and 26 healthy comparison subjects. Participants completed a structural magnetic resonance imaging (MRI) scan, the Self Report form of the Behavioral Rating Scale of Executive Function – Adult version (BRIEF-A), and Digit Span Backwards as an objective measure of working memory. Lobar volumes were obtained using an automated processing package and adjusted for total intracranial volume.

Results—The patient group reported worse working memory in daily life, and performed worse on Digit Span Backwards, than the comparison group. Within the patient group, poorer working memory in daily life was associated with smaller left and right frontal lobe volumes. Shorter backwards digit span was associated with smaller left frontal and left and right temporal lobe volumes.

Conclusions—The significant relationship between frontal lobe volumes and subjective working memory in daily life provides some support for the validity of self report measures of cognitive

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Conflict of interest

RMR and JKI are authors of the Behavior Rating Inventory of Executive Function – Adult version and receive a royalty from the publisher. The authors declare no other conflict of interest related to the content of this article.

Contributors

All authors participated in the conceptualization and design of the study. MAG and RMR conducted literature searches, were involved with participant recruitment and evaluation, and undertook the statistical analyses. MAG processed the neuroimaging data. LAF and RMR conducted the diagnostic and symptom interviews. All authors contributed to and approved the final manuscript.

functioning in patients with schizophrenia, and provides further evidence for a contribution of frontal lobe abnormality to executive dysfunction in the illness.

Keywords

Working Memory; Subjective; Frontal Lobe; MRI; Schizophrenia

1. INTRODUCTION

Performance-based measures of cognitive functioning are commonly employed as outcome measures in pharmacological and cognitive remediation studies of schizophrenia (Flashman and Green, 2004; Keefe et al., 1999; Wexler and Bell, 2005). In contrast, the use and validity of subjective measures of cognitive functioning in schizophrenia have received limited empirical investigation. Such measures could potentially be of significant benefit in identifying patients in need of objective neuropsychological evaluation, gauging the effects of treatment, and examining the impact of patient's perceived cognitive functioning in relation to other variables such as quality of life and actual cognitive functioning.

Patients with schizophrenia tend to report more cognitive problems in general (Moritz et al., 2001), and with executive functions specifically (Kumbhani et al., in press), than do healthy comparison samples. Indeed, several studies have observed associations between subjective ratings of cognitive functioning, measured using the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS), and objective neuropsychological test performance in patients with schizophrenia (Prouteau et al., 2004; Stip et al., 2003). Patients' perception of their cognitive problems on the SSTICS was also found to be associated with clinician-rated severity of cognitive problems on a different measure (Lecardeur et al., 2009), as well as with self-esteem and mood (Lecardeur et al., 2009; Stip et al., 2003).

Other studies, however, have reported a lack of association between subjective functioning in specific cognitive domains and performance on objective tests of the same domain (Prouteau et al., 2004), as well as discrepancies between subjective ratings of cognitive functioning and objective test performance in general (Medalia and Lim, 2004; Medalia et al., 2008; Zanello and Huguelet, 2001). The heterogeneity of findings of subjective and objective cognitive measures in schizophrenia is also seen in studies involving other populations. These studies have generally reported either non-significant or at best low to modest correlations between subjective ratings of cognitive functioning and objective cognitive test performance (Marrie et al., 2005; Sawrie et al., 1999). Other research in non-schizophrenia samples has, however, reported better predictive power of subjective than objective measures for a number of outcome variables such as community integration, for example, following traumatic brain injury (Reid-Arndt et al., 2007). Furthermore, a recent study of typically developing children reported a significant relationship between parental ratings of working memory in daily life and frontal lobe volume (Mahone et al., 2009). These findings raise the possibility that subjective ratings of cognitive functioning in schizophrenia may be associated with salient variables other than objective cognitive test performance. Identifying such relationships would provide evidence for the validity of subjective ratings of cognitive functioning in these patients, affording a more solid basis for evaluating the usefulness of such ratings for treatment planning and for predicting outcome in cognitive remediation, pharmacological and other treatment studies.

In the present study, we investigated whether subjective ratings of working memory in daily life are associated with brain morphology measured via structural magnetic resonance imaging (MRI) in patients with schizophrenia. Patients with schizophrenia show deficits on objective tests of working memory (Brown et al., 2007; White et al., 2006), and functional neuroimaging studies involving schizophrenia have revealed abnormalities of distributed neural circuitry

during working memory tasks, most notably in the frontal lobes (Manoach et al., 2000; Schneider et al., 2007; Tan et al., 2006). Finally, reduced volume of the frontal lobes, as well as other brain regions, has been reported in schizophrenia (Shenton et al., 2001). We therefore predicted that greater subjective difficulty with working memory would be associated with smaller volume of the frontal lobes in a sample of patients with schizophrenia. As a secondary aim we also evaluated the extent to which an objective measure of working memory was associated with frontal lobe volume in these patients. In order to determine whether the present sample of patients have subjective and objective working memory difficulties a sample of healthy individuals was included for comparison.

2. METHODS

2.1 Sample

Participants included 29 patients with schizophrenia and 26 healthy comparison subjects. Diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) criteria using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002). Healthy comparison subjects were recruited through advertisements in local newspapers and were screened for any past or current psychiatric illness (First et al., 1998). Participants were excluded if they had a history of neurological disorder, mental retardation, cerebrovascular disease, significant systemic medical illness, or head injury with loss of consciousness longer than five minutes. Patients were also excluded if they met criteria for alcohol or substance use disorder (other than nicotine) in the six months prior to participation. All patients were receiving stable doses of antipsychotic medications at the time of the study. After complete description of the study, written informed consent was obtained following a protocol approved by the Dartmouth College Committee for the Protection of Human Subjects and this and subsequent research protocols were completed in accordance with the Helsinki Declaration (<http://www.wma.net/e/policy/b3.htm>).

2.2 Measures

All participants completed the self report form of the Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A). This measure is a 75 item questionnaire designed to assess executive functioning in daily life over the previous one month (Roth et al., 2005). The inventory yields nine scales (Inhibit, Shift, Emotional Control, Self Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials). T scores are based on comparison to the normative sample comprised of 1050 Self reports, with higher scores reflecting greater difficulty. The BRIEF-A has been shown to have good psychometric properties including reliability and validity (Rabin et al., 2006; Roth et al., 2005). Only the Working Memory T score was examined in the present study. A more detailed analysis of BRIEF-A scores, which included a subset of the participants from the present study, is presented in a separate report (Kumbhani et al., in press). The Beck Depression Inventory–II (BDI-II) was used to evaluate mood (Beck et al., 1996) in the 26 patients and 23 healthy subjects for whom scores were available.

Participants were administered the Digit Span subtest of the Wechsler Adult Intelligence Scale – III (Wechsler, 1997). The maximum number of digits that can be recalled in reverse order, Digit Span Backwards, is commonly employed as an objective measure of working memory (Ho et al., 2005).

2.3 MRI data acquisition

MRI scans were acquired with a GE Signa 1.5-T Horizon LX magnet with echo speed gradients using a standard RF head coil. A T1-weighted three-dimensional spoiled gradient echo (SPGR) coronal volume was acquired. Parameters were: TR = 25 ms, TE = 3 ms or minimum, flip angle

= 40 degrees, NEX = 1, and slice thickness = 1.5 mm, yielding 124 contiguous slices with a 24 cm field of view, and a 256×256 matrix with an 0.9375 mm in-plane resolution. Total intracranial volume (ICV) as well as left and right hemisphere frontal, temporal and parietal lobe volumes (in cubic centimeters, cm^3) were calculated using BRAINS, a standardized semiautomated software package developed at the University of Iowa; detailed methods, including boundary definitions, have been previously reported (Andreasen et al., 1996). Lobar volumes were adjusted for ICV using a regression model.

2.4 Statistical Analysis

Statistical analyses were carried out using SPSS 16.0 (www.spss.com). Group differences on subject characteristic data, Working Memory T score, Digit Span Backwards, total intracranial volume, and adjusted lobar volumes were evaluated using t-tests and analysis of covariance as appropriate. Correlations were calculated between adjusted lobar volumes and Working Memory T score and Digit Span Backwards. A significance level of $p < 0.05$ was employed.

3. RESULTS

Table 1 presents descriptive statistics for subject characteristics, Working Memory score, and Digit Span Backwards. The patient group was significantly older [$t(1) = 2.54, p = .01$], had lower mean parental education [$t(1) = -2.65, p = .01$], and was more depressed [$t(1) = 4.01, p = .001$] than the healthy comparison group. The groups were well matched for gender [$\chi^2(1) = 0.812, p = .42$] and handedness [$\chi^2(1) = 0.859, p = .61$]. In addition, the patient group reported poorer subjective working memory [$F(1, 45) = 9.29, p = .004$] and performed worse on Digit Span Backwards [$F(1, 45) = 5.57, p = 0.02$] than the comparison group, with age, parental education and depression score employed as covariates. Further analysis of our data revealed that both men [$F(1, 29) = 14.90, p = .001$] and women [$F(1, 22) = 13.52, p = .001$] with schizophrenia reported worse subjective working memory than their gender matched controls. The men and women with schizophrenia did not, however, differ from each other [$F(1, 27) = .007, p = .93$], and the group by gender interaction effect was not significant [$F(1, 51) = 0.24, p = .63$].

Table 2 presents MRI volume data for the patient and comparison groups. No group differences were observed with respect to adjusted lobar volumes or ICV. Findings remained non-significant even after statistically controlling for age, parental education, and depression score.

In the schizophrenia group, significant correlations were observed between Working Memory T score and depression score ($r = .50, p = .007$), but not age ($r = .31, p = .11$) or parental education ($r = -.06, p = .75$). Partial correlations, controlling for depression score, showed a negative correlation between subjective working memory and adjusted left ($r = -.44, p = .02$) and right ($r = -.38, p = .04$) frontal lobe volumes. No significant association was observed between subjective working memory and temporal (left: $r = -.17, p = .40$; right $r = -.23, p = .26$), parietal (left: $r = .23, p = .26$; right: $r = -.30, p = .13$), or total intracranial ($r = .17, p = .39$) volumes.

In the schizophrenia group, Digit Span Backwards was not associated with depression score ($r = -.17, p = .40$), age ($r = .07, p = .71$) or parental education ($r = .19, p = .34$). Digit Span Backwards was, however, correlated significantly with adjusted left frontal ($r = -.40, p = .03$) and left (left: $r = -.45, p = .01$) and right ($r = -.46, p = .01$) temporal volumes. No significant association was observed with adjusted right frontal ($r = -.28, p = .14$), adjusted parietal (left: $r = .17, p = .40$; right: $r = .03, p = .89$), or total intracranial ($r = .25, p = .19$) volumes. Digit Span Backwards was significantly correlated with subjective working memory ($r = .41, p = .03$), even after controlling for depression score ($r = .54, p = .003$). Statistically controlling for

medication dosage, available for only a subset of the patient sample, did not alter the pattern of findings.

Correlation analysis between lobar volumes and the subjective and objective working memory measures was also conducted for the comparison group. No significant relationships were observed, irrespective of whether any covariates were included or not.

4. DISCUSSION

The primary aim of this study was to evaluate the relationship between subjective, self report, working memory in daily life and ICV corrected volumes of the frontal, temporal and parietal lobes in patients with schizophrenia. Poorer subjective working memory was reported by the patient relative to the comparison group, which is in agreement with other research reporting greater subjective cognitive difficulty in schizophrenia (Kumbhani et al., in press; Moritz et al., 2001). Consistent with our hypothesis, poorer subjective working memory was associated with smaller adjusted left and right frontal lobe volumes in the patient sample, and this finding could not be accounted for by the higher level of depressed mood in the schizophrenia sample. This finding is consistent with the evidence of a prominent frontal lobe contribution to working memory (D'Esposito, 2007) and abnormalities in this region during working memory task performance in schizophrenia (Honey and Fletcher, 2006). Furthermore, the finding is consistent with the recent observation of a relationship between reduced gray matter volume in the dorsolateral prefrontal cortex bilaterally, but no other brain regions, and greater self reported executive dysfunction as measured using a different instrument than that employed in the present study (Kawada et al., 2009). It should be noted, however, that while the relationship between subjective working memory and non-frontal lobar volumes in our study was not significant, they were in the expected direction. It is possible that with a larger sample size some of the relationships observed would have been significant, and thus we cannot rule out at this time the possibility that subjective working memory is related to the integrity of these other brain regions.

As with subjective working memory, the schizophrenia group showed worse performance on an objective test of working memory, Digit Span Backwards. To our knowledge, there are no prior reports that examined the relationship between Digit Span Backwards specifically and brain anatomy in schizophrenia. In our sample, poorer ability to recall digits backwards was associated with smaller adjusted left frontal and left and right temporal lobe volumes. This finding indicates a somewhat different pattern of relationships between subjective and objective measures of working memory and regional lobar volumes, with only the left frontal lobe showing a relationship to both. This suggests that left frontal lobe functioning may play a common role in mediating working memory in daily life as well as performance during objective assessment.

Contrary to what might be expected, however, poorer subjective working memory was associated with better ability to recall digits backwards in our schizophrenia group. The nature of the working memory demands being assessed is quite disparate between the BRIEF-A and Digit Span Backwards. The BRIEF-A asks whether a person has problems with different behaviors reflecting working memory over the past month. In contrast, the Digit Span is a very specific measure of working memory, restricted to the brief maintenance and mental manipulation of digits. This important difference may have contributed to the observed discrepancy and emphasizes the disparate nature of objective and subjective measures of cognitive ability, which has been argued to impact the degree to which they correlate (Gioia and Isquith, 2004; Goldberg and Podell, 2000). It is also possible that the degree to which the patients had insight into their cognitive functioning impacted their subjective ratings, affecting the correlation with the objective measure. There is evidence that patients with schizophrenia

are variable with respect to insight into their cognitive functioning (Medalia et al., 2008). While we did not assess for insight, the finding of greater self reported working memory problems in the patient sample suggests to us that as a whole the sample had at least some degree of insight. Additionally, the differential deployment of cognitive strategies in patients with schizophrenia in everyday life versus the laboratory setting could also have potentially impact the degree to which subjective and objective measures correlated. Finally, we cannot rule out the possibility that the unexpected relationship is idiosyncratic to the present sample, and therefore further investigation is required to determine the reliability of the finding.

In contrast to the findings in our schizophrenia sample, both we and others (Premkumar et al., 2008) have observed that cognitive measures and brain volumes are unrelated in healthy adults. It is possible that the more restricted range of scores for the cognitive and volume measures in the healthy sample mitigated against finding a significant correlation. In addition, a relationship may be difficult to detect when cognitive or structural brain abnormality is not present, as would be expected in healthy participants screened for psychiatric, neurological and systemic illnesses.

The present findings must be interpreted within the context of the limitations of the study. The sample size was modest and therefore replication is required in a larger sample. Our study did not observe smaller adjusted lobar volumes in a group of patients with schizophrenia, which contrasts with a number of other studies (Shenton et al., 2001). This discrepancy may be due in part to heterogeneity with the patient population with respect to the extent of structural brain changes (Roth et al., 2004; Zakzanis and Heinrichs, 1999). The present investigation employed only gross volumetric measurements of entire lobes, and thus we cannot discount the possibility that subjective ratings would show significant correlations with the volume of temporal or parietal lobe subregions, given that such subregions have been implicated in working memory (Karlsgodt et al., 2005; Wager and Smith, 2003). Similarly, the present study did not address whether subjective ratings are associated with abnormality of specific subregions within the frontal lobes implicated in working memory. Separate examination of grey and white matter volumes would also be informative given evidence that these correlate differentially with parental ratings of working memory in typically developing children (Mahone et al., 2009). Additionally, only a single relatively simple objective measure of working memory was employed, thus studies using more demanding objective working memory measures would be helpful in elucidating the relationship between subjective and objective working memory in schizophrenia. Furthermore, data on age of illness onset in the patient sample was unavailable for the majority of participants and medication dosage was only available for a subset of participants. While it is therefore unknown whether duration of illness or medication dosage may have had an impact on the relationships observed, a recent study reported that neither the duration of illness nor medication accounted for the relationship between self report executive functioning and regional brain volume in schizophrenia (Kawada et al., 2009).

In conclusion, the present study provides some support for the validity of subjective rating of working memory in patients with schizophrenia. This information may prove helpful in guiding cognitive remediation or other interventions. It is important to recognize, however, that it is unlikely for subjective rating of cognitive functioning to be sufficiently sensitive and specific to implicate abnormality in highly circumscribed brain regions.

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Table 1

Subject Characteristic and Neuropsychological Data

Variable	Schizophrenia (N = 29)		Healthy (N = 26)	
	Mean	S.D.	Mean	S.D.
Age, years	38.2	11.3	30.5	11.3
Parental Education, years ^a	13.7	3.0	16.0	3.1
BDI-II ^b	14.8	12.2	4.1	5.2
BRIEF-A Working Memory T Score:	65.5	14.9	47.0	9.0
WAIS-III Digit Span Backwards	4.3	1.2	5.9	1.3
	N	%	N	%
Sex, male	18	62%	13	50%
Right Handed	26	90%	25	96%

^a N = 27 patients;

^b N = 23 Healthy comparison subjects

Note: BDI-II, Beck Depression Inventory-II; BRIEF-A, Behavior Rating Inventory of Executive Function – Adult version

Table 2

Neuroimaging Data

Variable	Schizophrenia (<i>N</i> = 29)		Healthy (<i>N</i> = 26)	
	Mean	S.D.	Mean	S.D.
Total Intracranial Volume, cm ³	1403	156	1383	145
Adjusted Lobar Volumes, cm ³				
Left Frontal	13.5	1.1	13.9	1.0
Right Frontal	14.4	1.3	14.9	1.1
Left Temporal	7.6	.66	7.7	.46
Right Temporal	7.7	.75	7.8	.50
Left Parietal	8.3	.71	8.4	.50
Right Parietal	8.5	.88	8.6	.49