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Semantic Association fMRI Impairments Represent a Potential Schizophrenia Biomarker

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Abstract

Semantic association retrieval task (SORT) requires participants to indicate whether word pairs recall a third object, e.g. 'honey' and 'stings' activates 'bees'. We have previously shown that individuals with schizophrenia with more severe positive symptoms tend to report associations between unrelated word pairs than healthy controls; schizophrenia individuals with more severe negative symptoms tend to fail to report associations between related word pairs. This *over-retrieval* and *under-retrieval* on SORT correlates with functional magnetic resonance imaging (fMRI) activity in inferior parietal lobule (IPL). To examine the suitability of SORT as an endophenotype for schizophrenia, we examined SORT performance and activity across multiple stages of the illness: chronic, relapse, first episode. We also examine SORT performance and activity in unaffected relatives. SORT performance and fMRI activity in schizophrenia-first episode, schizophrenia-chronic and schizophrenia-relapse were significantly impaired relative to healthy controls and unaffected relatives. Schizophrenia-chronic and schizophrenia-relapse participants showing more severe PANSS-positive and -general symptoms showed larger SORT impairments. For schizophrenia-first episode more severe negative symptoms were related to lower IPL activation, consistent with previous results showing that negative symptoms are among the first to emerge in the schizophrenia prodrome and that more severe symptoms in the first episode predict worse future outcomes. Unaffected relatives showed no impairments on SORT

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Contributors

Authors Assaf and Pearlson designed the study and wrote the protocol. Author O'Neil assisted with data collection, management and preliminary analyses. Author Jamadar managed the literature searches, analyses and wrote the first draft of the manuscript. All authors have contributed to and approved to final manuscript.

Conflict of Interest

All authors report no conflict of interest

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performance or fMRI activity relative to healthy controls, which is incompatible with the concept of SORT as an endophenotype for schizophrenia, but is consistent with the concept of SORT as a potential schizophrenia biomarker.

Keywords

semantic association; biomarker; fMRI; formal thought disorder; positive and negative symptoms

1. Introduction

Bleuler (1911/1950) considered *loosening of associations* to be a fundamental impairment in schizophrenia (SZ), and subsequent researchers have labeled SZ a disorder of abnormal semantic associative processing (Ketteler & Ketteler, 2010; Kuperberg, 2010b).

Associational loosening is known to be involved or related to multiple symptoms across the psychotic symptom spectrum, including formal thought disorder (FTD; Kuperberg, 2010a; 2010b; Jamadar et al., in press), positive symptoms (Andreasen et al., 1995; Liddle, 1987; 1992; Jamadar et al., in press) and even negative symptoms (Jamadar et al. in press, Messinger et al., 2010).

The Semantic Object Retrieval Task (SORT) indexes non-compositional semantic association. Pairs of words are presented and participants are required to indicate whether the words do (*Retrieval* trials) or do not retrieve a third object (*No-Retrieval* trials). SORT activates a distributed circuit in healthy individuals (Assaf et al., 2006a; Kraut et al., 2002; 2003) that is consistent with definitions of the heteromodal association network (Jamadar et al., in press). SZ individuals show less activation in inferior parietal lobule (IPL) relative to healthy controls (HC) during Retrieval vs. No-Retrieval trials and this correlates with severity of positive and general symptoms (Assaf et al., 2006b; Jamadar et al., in press), consistent with loosening of associations in positive psychotic symptomatology. In addition, SZ individuals with more severe negative symptoms were more likely to fail to report associations between related words, consistent with poverty of speech symptoms in negative thought disorder. Together, these findings are compatible with the hypothesis that semantic association deficits represent a core feature of the illness (e.g. Bleuler 1911/1950; Kuperberg, 2010a; 2010b). Importantly, while individuals with bipolar disorder (BP) showed decrements in performance similar to but less severe than seen in SZ, SORT performance and fMRI activity did not correlate with symptom scores in BP. This was despite similar levels of symptom severity and variability in symptom scores. Thus, the relationship between SORT performance, fMRI activity and psychosis symptoms appears to be specific to SZ (Jamadar et al., in press).

It is well established that symptom severity in SZ changes across the illness course, with periods of stability and relapse of acute psychotic symptoms after the first psychotic break (Harvey & Davidson, 2002; Jablensky et al., 2002). Many semantic language abnormalities such as verbal fluency and semantic memory impairments are present during both chronic and relapse phases of the illness, in the prodromal and first episodes of the illness and also in unaffected first-degree relatives of patients (Kuperberg, 2010a; Levy et al., 2010). In addition, some symptoms such as FTD can also be observed in biological first-degree relatives of patients, albeit with reduced severity (e.g. Kendler et al., 1995). Since this pattern of findings suggests that semantic memory impairments (a) represent a *trait* rather than *state* index of abnormal language processing in schizophrenia, and (b) show some level of heritability; semantic language impairments may represent a potential candidate *endophenotype* (Gottesman & Gould, 2003) for SZ. In this study we examine the potential for SORT as a candidate endophenotype by examining changes in SORT performance,

fMRI activity and their relationship with symptom severity in schizophrenia patients in multiple stages of the illness. Individuals with first episode SZ (SZ-FE), chronic stable SZ (SZ-CH), chronic SZ with current symptomatic relapse (SZ-RE), and healthy controls (HC) completed SORT while undergoing fMRI scanning. We hypothesized that SORT performance and fMRI impairments would present in multiple stages of the illness, and be highest in the most symptomatic groups (SZ-FE and SZ-RE), followed by SZ-CH. In addition, we examined a cohort of first-degree unaffected relatives of schizophrenia individuals (UR) in Supplementary Analyses. However, these latter analyses must be considered preliminary, as there was a substantial sex difference between UR and SZ-groups.

2. Methods and Materials

2.1 Participants

Participants (n=219) with no prior exposure to SORT consented to IRB-approved research at the Olin Neuropsychiatry Research Center, Institute of Living. Participants were categorized as HC, SZ-FE, SZ-CH and SZ-RE. For the SZ-groups, ‘first episode’ was defined as within 1-year from first hospitalization with psychotic breakdown; ‘chronic’ was defined as at least 2-years from initial diagnosis and stable on medication without hospitalization in the 3-months prior to recruitment; and ‘relapse’ was defined as within 3-months from hospitalization/medication change due to symptoms worsening in a patient at least 2-years from initial diagnosis. SZ-RE participants showed significantly more severe current symptoms relative to SZ-CH, consistent with the recruitment strategy targeting individuals with a relapse of symptoms (Table 1). Note that the HC subjects are those that were presented in our previous report (Jamadar et al., in press), and SZ-CH and SZ-RE participants together constituted the SZ-group in that earlier report. All participants were assessed for DSM-IV-TR Axis-1 disorders using SCID-IV (First, 2002). Exclusion criteria included history of significant medical or neurological disorder, including significant head injury for all subjects, any present or past Axis-1 psychiatric disorder for HC, family history of psychiatric disorder for HC, metallic object in-body, claustrophobia or positive urine toxicology screen for abused drugs or pregnancy.

Demographic information is shown in Table 1. Current symptoms were assessed on the day of scanning with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) and thought disorder index (TDI; Solovay et al., 1986), yielding four scores: PANSS-positive (average score across positive symptom scores), PANSS-negative, PANSS-general and TDI (total scores). PANSS and TDI scores for each of the groups are shown in Table 1.

2.2 Stimuli and Tasks

Full details of the task have been reported previously (Jamadar et al., in press). Briefly, prior to scanning all participants completed out-of-scanner training on SORT to ensure that task instructions were understood. During scanning, task stimuli were visually presented lower-case word pairs presented one above the other as black letters and described object features (e.g. ‘honey’, ‘stings’). Participants pressed a response button with their dominant index finger if the two words evoked a third object (‘bee’) and their dominant middle finger if they did not (e.g., ‘honey’, ‘quacks’). Participants completed 92-trials: 46 *Retrieval* and 46 *No-Retrieval* trials. Immediately following fMRI scanning, participants completed out-of-scanner debriefing. Participants identified the object elicited by the stimuli for every word pair they identified as a positive retrieval.

2.3 fMRI Acquisition

Magnetic resonance images were acquired using a Siemens (Erlangen, Germany) Allegra 3T dedicated head scanner equipped with 40mT/m gradients and a standard quadrature head coil. T2*-weighted images were acquired using an echo planar imaging (EPI) sequence (ascending axial acquisition, 426volumes, TR=1.86s, TE=27ms, FOV=24cm, acquisition matrix=64×64, flip angle=70°, voxel size=3.75×3.75×4mm, gap=1mm, 36slices). The first 16 images were discarded to account for T1 saturation effects.

2.4 Data Analysis

For all analyses, we first ran ANCOVAs controlling for all variables where the groups significantly differed (Table 1). We then examined the results for any significant demographic × experimental factor interaction, and then re-ran the analysis controlling for only those demographics showing a significant interaction with experimental factor.

2.4.1 Behavioral Data—For each subject, trials were categorized as Hit Retrieval, Hit No-Retrieval, Missed Retrieval and Missed No-Retrieval. Reaction time (RT) was analyzed with a 2-accuracy (hit,miss) × 2-condition (Retrieval,No-Retrieval) × 4-group (HC,SZ-FE,SZ-CH,SZ-RE) mixed ANOVA. Accuracy was calculated as the number of correct trials for Retrieval or No-Retrieval trials divided by the total number of trials for each condition (46); thus a higher number indicates more correct responses, i.e. better performance. To account for the non-normal distribution (Shapiro-Wilk's $p < .001$ for Retrieval,No-Retrieval), accuracy was arcsine transformed to normalize the distribution. Accuracy was then analyzed with a 2-condition (Retrieval,No-Retrieval) × 4-group (HC,SZ-FE, SZ-CH,SZ-RE) mixed ANOVA. For both RT and accuracy, significant effects of group were further explored using Tukey's Honestly Significant Difference (HSD) tests. When controlling for demographic differences, for all factors except age there were no interactions with experimental factors for either RT or accuracy (all $p > .165$), hence we report the results of the ANOVAs controlling for age only.

In our previous study we demonstrated significant correlations between accuracy and PANSS-negative and TDI. We hypothesized that these relationships would be maintained in the current study. Spearman's rho correlation coefficients were used to account for the violation of the normality assumption in the symptom scores (all Shapiro-Wilk's p between .001-.062).

2.4.2 fMRI Data—fMRI data were analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Differences in EPI slice acquisition timing were corrected using the central slice as reference. Image time series were realigned to the first non-dummy image using INRI-align (Friere et al., 2002), spatially normalized to Montreal Neurological Institute (MNI) space and spatially smoothed with a 9×9×9mm Gaussian kernel.

Events for each participant were categorized as described above. The duration of each event was determined by in-scanner RT; duration for trials where no response was made was defined as the maximum response window (2.7sec). For first-level analysis, a canonical hemodynamic response function was fitted to the onset of each event. Realignment parameters were included in the model as covariates of no interest.

As in our previous study, we specifically focused on Hit Retrieval vs. Hit No-Retrieval, as both trials include visual, motor and semantic search processes, but only Hit Retrieval trials involve semantic object retrieval. For second-level analyses, contrast images for Hit Retrieval vs. Hit No-Retrieval were submitted to a 4 group (HC,SZ-FE,SZ-CH,SZ-RE) full-

factorial ANOVA. Results were thresholded at $p < .05$ (FWE corrected), $k = 20$ voxels. To determine the direction of the main effect of group, contrast values were extracted by creating ROIs defined as a sphere (radius 10mm) around the peak of activity using MarsBar (Brett et al., 2002). The resulting contrast values were subjected to a 4 group (HC, SZ-FE, SZ-CH, SZ-RE) ANOVA in SPSS for each ROI, and Tukey's HSD post-hoc tests were used to test differences between the groups. When controlling for demographic differences, age showed a significant interaction with group for the right but not left IPL (left: $p = .112$; right: $p = .039$). No other demographic $\times$ group interaction was significant (all $p > .141$), hence we report the results of the ANOVAs controlling for age only (for both left and right IPL, for consistency).

In our previous study we found that fMRI activity (contrast values extracted from ROIs) in IPL correlated with PANSS-positive and -general symptoms. We hypothesized that these relationships would be maintained in this study. For completeness, we also examined correlations between fMRI activity and PANSS-negative symptoms, even though we had no clear hypotheses on the basis of our previous study (Jamadar et al., in press). To control for false positives, alpha was divided by the number of groups ($\alpha = .05/3 = .017$).

3. Results

3.1 Behavioral Results

3.1.1 Accuracy—Accuracy results are summarized in Figure 1. The significant effect of group ($F(3,212) = 7.29, p < .001$) confirmed that accuracy was better for HC than SZ-FE ($p = .020$), SZ-CH ($p = .009$) and SZ-RE ($p = .009$) with no difference between the SZ patient groups (all $p > .774$). To explore the significant group $\times$ condition interaction ($F(3,212) = 3.28, p = .022$) we examined the effect of group for each condition separately. To control for multiple comparisons, these analyses were thresholded at $\alpha = .05/2 = .025$. For Retrieval trials, the effect of group was significant ($F(3,214) = 9.75, p < .001$): SZ-RE and SZ-CH groups were less accurate than HC (HC vs. SZ-CH $p < .001$; HC vs. SZ-RE $p = .003$), with SZ-FE marginally so (HC vs. SZ-FE $p = .044$), and no significant difference between SZ-groups (all $p > .999$). For No-Retrieval trials, the effect of group was only marginally significant ($F(3,214) = 2.46, p = .067$) reflected in non-significant post-hoc tests (all $p > .125$).

For SZ-RE, accuracy for Retrieval trials significantly negatively correlated with PANSS negative symptoms ($r = -.463, p = .009$). Accuracy did not correlate with symptom scores in any other group (all $p > .111$; see Supplementary Analysis 3).

3.1.2 Reaction Time—RT results are summarized in Figure 1. The significant effect of group ($F(3,189) = 13.02, p < .001$) indicated that RT was faster in HC than SZ-CH ($p = .015$) and SZ-RE ($p < .001$), with no significant difference between HC and SZ-FE ($p = .102$). RT was also significantly faster in SZ-CH vs. SZ-RE ($p = .016$). The effects of accuracy, condition and accuracy $\times$ condition interaction were not significant after controlling for age (all $p > .205$)^a.

3.2 fMRI Results

Hit Retrieval vs. Hit No-Retrieval activated a distributed fronto-parieto-temporal network (Figure 2A; Table 2) consistent with our previous studies (Assaf et al., 2006a; Jamadar et al.

^aIn our previous paper, we found significant effects of accuracy, condition and accuracy $\times$ condition; to confirm whether we also see this when not controlling for age, we re-ran the analysis and found highly significant effects of accuracy (Miss > Hit; $F(1,207) = 97.65, p < .001$); condition (No-Retrieval > Retrieval; $F(1,207) = 63.39, p < .001$) and accuracy $\times$ condition interaction (larger Hit vs. Miss RT difference in Retrieval than No-Retrieval; $F(1,207) = 5.47, p = .020$). This analysis confirms that we replicate our previously reported effects of task.

in press). The main effect of group (Figure 2B) showed significant activity in bilateral IPL (left: -51,-48,51, $F(3,215)=15.14, p<.05$ FWE corrected; right: 45,-60,54, $F(3,215)=14.38, p<.05$, FWE corrected). When controlling for age, the maximum F value was reduced but still highly significant in each region (left: $F(3,215)=8.95, p<.001$; right: $F(3,215)=6.56, p<.001$).

Tukey's HSD test confirmed that left-IPL activity was larger in HC vs. SZ-CH ($p=.017$) and SZ-RE ($p<.001$) and marginally larger in HC vs. SZ-FE ($p=.063$). There were no significant differences between the SZ-groups (all $p>.304$). Right-IPL showed a similar pattern: activity was larger in HC vs. SZ-CH ($p=.016$) and SZ-RE ($p=.002$), with no significant difference between HC and SZ-FE ($p=.299$). There were no significant differences between the SZ-groups (all $p>.699$).

For SZ-CH, Hit Retrieval vs. Hit No-Retrieval activity in left-IPL was positively correlated with PANSS-general ($r=.347, p=.014$) and activity in right-IPL was positively correlated with PANSS-positive ($r=.336, p=.017$). For SZ-RE, activity in right-IPL was positively correlated with PANSS-general ($r=.349, p=.040$). For SZ-FE, activity in right-IPL was marginally negatively correlated with PANSS-negative ($r=-.620, p=.021$).

4. Discussion

4.1 SORT Performance and fMRI Activity in Schizophrenia

We found that all SZ-groups (SZ-FE, SZ-CH, SZ-RE) were less accurate than HC and UR (Supplementary Analyses), consistent with previous results (Jamadar et al., in press). Accuracy did not differ between the SZ-groups, suggesting that the tendency to over- or under-retrieve did not differ depending on illness stage. Retrieval trial accuracy was negatively correlated with PANSS-negative for SZ-RE only. This is consistent with our previous study (Jamadar et al., in press) and adds a level of specificity, demonstrating that this relationship is obtained only in chronic relapsing individuals, not in chronic stable patients or patients experiencing their first psychotic episode.

RT was slower in SZ-CH and SZ-RE groups vs. HC, consistent with our previous studies (Assaf et al., 2006b; Jamadar et al., in press) and the generalized slowing of processing speed in SZ (Morrens et al., 2007). RT was also slower in the SZ-RE vs. SZ-CH groups, indicating larger impairment for the more symptomatic group. RT did not significantly differ between HC and SZ-FE, although there was a trend towards increased RT in SZ-FE relative to HC. This is compatible with evidence that deterioration of processing speed occurs at differing rates following the first psychotic break, and continues to deteriorate as individuals enter the chronic stage of the illness (Gonzalez-Blanch et al., 2010).

Consistent with previous studies, Retrieval vs. No-Retrieval trials activated a distributed network encompassing frontal, parietal, temporal and subcortical regions (Assaf et al., 2006a; 2006b; Jamadar et al., in press; Kraut et al., 2002; 2003); consistent with the heteromodal association network that coordinates and integrates information from multiple sensory and motor regions to perform complex cognitive processes (Pearlson et al., 1996). We found a strong effect of group in bilateral IPL (Assaf et al., 2006b; Jamadar et al., in press). IPL activity did not differ between SZ-groups, suggesting that it reflects a generalized impaired activation for Hit Retrieval vs. Hit No-Retrieval in schizophrenia. The IPL plays a central role in SORT (Jamadar et al., in press), the semantic system (Binder & Desai, 2011) and the heteromodal association network (Pearlson et al., 1996). It is intimately involved in the integration and evaluation of multiple sensory inputs across sensory regions (Torrey, 2007). IPL gray matter is reduced in SZ (Meda et al., 2008; Zhou et al., 2007) is linked to reading-disorder genes (Jamadar et al., 2011), and is likely to play an important role in loosening of associations in schizophrenia (Jamadar et al., in press; Torrey, 2007).

Jamadar et al. (in press) showed that activity in right-IPL positively correlated with PANSS-positive and PANSS-general in SZ. Here, right-IPL/PANSS-positive relationship was obtained in SZ-CH only, suggesting that this relationship is only relevant during stable chronic stage of SZ. In addition IPL activity positively correlated with PANSS-general in both SZ-CH and SZ-RE, however in SZ-CH the correlation was obtained in the left hemisphere whereas in SZ-RE it was obtained on the right. It is not clear why this correlation was obtained in different hemispheres in the different groups, however we speculate that it is related to changes in laterality that occur across multiple stages of the illness. For example, changes in functional activation laterality are related to symptoms during auditory stimulation (Oertel et al., 2010) and functional connectivity during resting state fMRI (Ke et al., 2010). Changes in laterality across multiple schizophrenia states are a relatively understudied phenomenon and represents an interesting future direction for research.

Unexpectedly, SZ-FE showed a strong negative correlation between right-IPL signal and PANSS-negative symptoms, i.e., SZ-FE with more severe negative symptoms showed right-IPL activity levels more similar to SZ-CH and SZ-RE. This is consistent with poverty of content of speech, stereotyped thinking and difficulty in abstract thinking that characterizes the negative symptom spectrum. This relationship was not obtained in any other group here or previously (Assaf et al., 2006b; Jamadar et al., in press). Negative symptoms are among the first to emerge in the prodromal phase and may predict subsequent outcome (Stahl & Buckley, 2007). This suggests SORT may show promise as a predictive measure of future outcome in SZ. Future longitudinal studies should explore this possibility.

4.2 SORT as a Schizophrenia Biomarker

Given the specificity of SORT performance and fMRI activation deficits and their relationship with psychosis symptoms to SZ vs. BP (Jamadar et al., in press) and that these measures are differentially obtained across multiple illness stages (current study), SORT may represent a candidate endophenotype for further study. However, the endophenotype definition requires that phenotypes should both be heritable and also be apparent in UR, since SZ and first-degree UR share about half their genes (Gottesman & Gould, 2003). This possibility was explored in Supplementary Analyses; given the substantial sex imbalance between UR and SZ-groups, these results should be considered preliminary. UR and HC did not differ in any SORT measure, which is incompatible with the endophenotype concept^b. However, the specificity of SORT-performance, fMRI impairments and symptom relationship in SZ are compatible with a potential *biomarker* for the illness. The relationships between SORT performance, fMRI activity and symptoms varies between phases of the illness, and are specific to SZ, indicating that SORT is a state-independent measure of semantic association impairment in SZ. There remains one important caveat: to date all investigations have studied SORT in medicated SZ (Assaf et al., 2006b; Jamadar et al., in press). To be useful for targeted treatment development, it should be demonstrated that the SORT performance and fMRI impairments and their relationship to symptoms is conserved in unmedicated SZ. This would offer strong evidence for SORT as a potential biomarker for SZ (Carter et al., 2011). Future studies should explore this possibility.

^bAnecdotally, we have previously seen that UR individuals often dissociate into two separate groups, one that is similar to SZ patients and the second that is most similar to HC. This suggests that the UR subjects showing highest similarity to SZ might show a significantly larger genetic risk relative to those showing the highest similarity to HC. If this was the case in our data, it would suggest that SORT could indeed be considered an endophenotype for SZ. To test this possibility we examined the spread of UR individuals on all SORT performance and fMRI measures in comparison to HC and SZ, and found that UR did not fall into two distinct groups, and as a whole overlapped with both HC and SZ groups. This is compatible with our interpretation of SORT as a potential biomarker, rather than endophenotype.

5. Conclusions

SORT performance and fMRI activity were differentially related to psychosis symptoms throughout different stages of SZ. SORT performance and fMRI activity in SZ-FE, SZ-CH and SZ-RE were significantly impaired relative to HC and UR. SZ-CH and SZ-RE participants showing more severe PANSS-positive and –general symptoms showed larger SORT impairments. For SZ-FE more severe negative symptoms were related to lower IPL activation, consistent with previous results showing that negative symptoms are among the first to emerge in the schizophrenia prodrome and that more severe symptoms in the first episode predict worse future outcomes. UR showed no impairments on SORT performance or fMRI activity relative to HC, which is incompatible with the concept of SORT as an endophenotype for SZ, but is consistent with the concept of SORT as a potential SZ biomarker.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M. Symptoms of schizophrenia: methods, meanings and mechanisms. *Archives of General Psychiatry*. 1995; 52:341–351. [PubMed: 7726714]
- Assaf M, Calhoun VD, Kuzu CH, Kraut MA, Rickin PR, Hart J Jr, Pearlson GD. Neural correlates of the object-recall process in semantic memory. *Psychiatry Research*. 2006a; 147:115–126. [PubMed: 16938439]
- Assaf M, Rivkin PR, Kuzu CH, Calhoun VD, Kraut MA, Groth KM, et al. Abnormal object recall and anterior cingulate overactivation correlate with formal thought disorder in schizophrenia. *Biological Psychiatry*. 2006b; 59:452–459. [PubMed: 16199012]
- Binder JR, Desai RH. The neurobiology of semantic memory. *Trends in Cognitive Science*. 2011; 15:527–536.
- Bleuler, E. The basic symptoms of schizophrenia. In: Rapaport, D., editor. *Organisation and pathology of thought: selected sources*. New York, NY: Columbia University Press; 1919/1951.
- Brett, M.; Anton, J.L.; Valabregue, R.; Poline, J-B. Region of interest analysis using the MarsBar toolbox for SPM99. Presented at the 8th International Congress on Functional Mapping of the Human Brain; June 2-6 2002; Sendai Japan. 2002.
- Carter CS, Barch DM, Bullmore E, Beiling J, Buchanan RW, Butler P, et al. Cognitive neuroscience treatment research to improve cognition in schizophrenia II: developing imaging biomarkers to enhance treatment development for schizophrenia and related disorders. *Biological Psychiatry*. 2011; 70:7–12. [PubMed: 21529781]
- First MB. The DSM series and experience with DSM-IV. *Psychopathology*. 2002; 35:67–71. [PubMed: 12145486]
- Freire L, Roche A, Magin JF. What is the best similarity measure for motion correction in fMRI time series? *IEEE Transaction in Medical Imaging*. 2002; 21:470–484.
- Gonzalez-Blanch C, Rodriguez-Sanchez JM, Perez-Iglesias R, Pardo-Garcia G, Martinez-Garcia O, Vazquez-Barquero KL, Crespo-Facorro B. First episode schizophrenia patients

- neurpsychologically within the normal limits: evidence of deterioration in speed of processing. *Schizophrenia Research*. 2010; 119:18–26. [PubMed: 20335007]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Harvey, PD.; Davidson, M. Schizophrenia: course over the lifetime. In: Davis, KL.; Charney, D.; Coyle, JT.; Nemeroff, C., editors. *Neuropsychopharmacology: The Fifth Generation of Progress*. Lippincott, Williams & Wilkins; Philadelphia, PA: 2002.
- Higashima M, Takeda T, Kikuchi M, Nagasawa T, Hirao N, Oka T, Nakamura M, Koshino Y. State-dependent changes in intrahemispheric EEG coherence for patients with acute exacerbation of schizophrenia. *Psychiatry Research*. 2007; 149:41–47. [PubMed: 17140670]
- Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organisation ten-country study. *Psychological Medicine*. 1992; 20:1–97.
- Jamadar S, O'Neil K, Pearlson GD, Ansari M, Gill A, Jagannathan K, Assaf M. Impairments in semantic retrieval is associated with symptoms in schizophrenia but not bipolar disorder. *Biological Psychiatry*. in press.
- Jamadar S, Powers NR, Meda SA, Gelernter J, Gruen JR, Pearlson GD. Genetic influences of cortical gray matter in language-related regions in healthy controls and schizophrenia. *Schizophrenia Research*. 2011; 129:141–148. [PubMed: 21507613]
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS). *Schizophrenia Bulletin*. 1987; 12:483–496.
- Ke M, Zou R, Shen H, Huang X, Zhou Z, Liu Z, Xue Z, Hu D. Bilateral functional asymmetry disparity in positive and negative schizophrenia revealed by resting state fMRI. *Psychiatry Research: Neuroimaging*. 2010; 182:30–39.
- Kendler KS, McGue M, Gruenberg AM, Walsh D. Schizotypal symptoms and signs in the Roscommon Family Study. Their factor structure and familial relationship with psychotic and affective disorders. *Archives of General Psychiatry*. 1995; 52:296–303. [PubMed: 7702446]
- Ketteler D, Ketteler S. Is schizophrenia “the price Homo sapiens pays for language”? Subcortical language processing as the missing link between evolution and language disorder in psychosis – A neurolinguistic approach. *Journal of Neurolinguistics*. 2010; 23:342–353.
- Kraut MA, Calhoun V, Pitcock JA, Cusick C, Hart J Jr. Neural hybrid model of semantic object memory: implication from event-related timing using fMRI. *Journal of International Neuropsychology Society*. 2003; 9:1031–1040.
- Kraut MA, Kremen S, Segal JB, Calhoun VD, Moo LR, Hart J Jr. Object activation from features in the semantic system. *Journal of Cognitive Neuroscience*. 2002; 14:24–36. [PubMed: 11798384]
- Kuperberg GR. Language in schizophrenia. Part 1: An introduction. *Language and Linguistics Compass*. 2010a; 4:576–589. [PubMed: 20936080]
- Kuperberg GR. Language in schizophrenia Part 2: What can psycholinguistics bring to the study of schizophrenia... and vice versa? *Language and Linguistics Compass*. 2010b; 4:590–604. [PubMed: 20824153]
- Levy DL, Coleman MJ, Sing S, Ji F, Matthyse S, Mendell NR, Titone D. The genetic basis of thought disorder and language and communication disturbances in schizophrenia. *Journal of Neurolinguistics*. 2010; 23:176–192. [PubMed: 20161689]
- Liddle PF. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. *The British Journal of Psychiatry*. 1987; 151:145–151. [PubMed: 3690102]
- Liddle PF. Syndromes of schizophrenia on factor analysis. *The British Journal of Psychiatry*. 1992; 161:861. [PubMed: 1483180]
- Meda S, Guillian NR, Calhoun VD, Jagannathan K, Schretlen DJ, Pulver A, et al. A large scale (N=400) investigation of gray matter differences in schizophrenia using optimized voxel-based morphometry. *Schizophrenia Research*. 2008; 101:95–105. [PubMed: 18378428]
- Messinger JW, Tremeau D, Antonius D, Mendelsohn E, Prudent V, Stanford AD, Malaspina D. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. *Clinical Psychology Review*. 2011; 31:161–168. [PubMed: 20889248]

- Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophrenia Bulletin*. 2007; 33:1038–1053. [PubMed: 17093141]
- Oertel V, Knochel C, Rotarska-Jagiela A, Schonmeyer R, Lindner M, et al. Reduced laterality as a trait marker of schizophrenia – evidence from structural and functional neuroimaging. *The Journal of Neuroscience*. 2010; 30:2289–2299. [PubMed: 20147555]
- Pearlson GD, Petty RG, Ross CA, Tien AY. Schizophrenia: a disease of heteromodal association cortex? *Neuropsychopharmacology*. 1996; 14:1–17. [PubMed: 8719025]
- Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. *Annual Review of Neuroscience*. 1995; 18:555–586.
- Solovay MR, Shenton ME, Gasperetti C, Coleman M, Kestnbaum E, Carpenter JT, Holzman PS. Scoring manual for the thought disorder index. *Schizophrenia Bulletin*. 1986; 12:483–496. [PubMed: 3764364]
- Stahl SM, Buckley PF. Negative symptoms of schizophrenia: a problem that will not go away. *Acta Psychiatrica Scandinavica*. 2007; 115:4–11.
- Torrey EF. Schizophrenia and the inferior parietal lobule. *Schizophrenia Research*. 2007; 97:215–225. [PubMed: 17851044]
- Zhou SY, Suzuki M, Takahashi T, Hagino H, Kawasaki Y, Matsui M, et al. Parietal lobe volume deficits in schizophrenia spectrum disorders. *Schizophrenia Research*. 2007; 89:35–48. [PubMed: 17064881]

Figure 1.

Behavioural Results. A Main effect of group for (i) arcsine accuracy and (ii) reaction time (ms). B Behaviour-symptom relationships for SZ-RE group (i) retrieval accuracy and PANSS negative symptoms, (ii) reaction time and PANSS positive symptoms, and (iii) Hit No-Retrieval reaction time and PANSS general symptoms. Abbreviations: HC, healthy control; SZ-FE, schizophrenia-first episode; SZ-CH, schizophrenia-chronic, SZ-RE, schizophrenia-relapse; PANSS, positive and negative syndrome scale

Figure 2. fMRI results for Hit Retrieval > Hit No-Retrieval contrast. A. Main effect of condition. B. Main effect of group. Contrast values for left and right inferior parietal lobule for the four groups separately. C. fMRI-symptom relationships: top left: left IPL activity and PANSS general symptoms for SZ-CH; top right: right IPL activity and PANSS positive symptoms for SZ-CH; bottom left: right IPL activity and PANSS general symptoms for SZ-RE; bottom right: right IPL activity and PANSS negative symptoms for SZ-FE. Abbreviations: HC, healthy control; SZ-FE, schizophrenia-first episode; SZ-CH, schizophrenia-chronic; SZ-RE, schizophrenia-relapse; PANSS, positive and negative syndrome scale; L, left; R, right; IPL, inferior parietal lobule.

Table 1

Demographic information for the four groups

Demographic (# available)	HC	SZ-FE	SZ-CH	SZ-RE	Statistic
n	133	13	46	27	
Age (246)¹	32.48 (1.05)	22.38 (1.68)	35.24 (1.79)	37.88 (2.29)	F(3,215)=5.63, p=.001 HC vs. SZ-FE p<.001; SZ-FE vs. SZ-CH p<.001 ⁴
Sex (246) M/F	68/65	8/5	38/8	20/7	$\chi^2=17.31$, p<.001
Handedness (239) R/L/A	127/5/1	23/4/0	40/3/1	23/4/0	p=.331
Race (246)					$\chi^2=32.35$, p=.006
White	96	8	25	16	
Black	16	3	13	9	
Hispanic	8	0	1	0	
Asian	5	0	2	0	
Other	8	2	5	2	
HART (186)					
n	99	10	37	22	
VIQ	106.66 (0.80)	100.10 (3.69)	102.10 (1.91)	94.29 (1.88)	F(3,164)=11.73, p<.001 HC vs. SZ-RE p<.001 SZ-CH vs. SZ-RE p=.031 ⁴
FSIQ	108.50 (0.71)	102.78 (3.23)	104.48 (1.67)	97.31 (1.68)	F(3,164)=12.28, p<.001 HC vs. SZ-RE p<.001 SZ-CH vs. SZ-RE p=.023 ⁴
TDI (75)					p=.183
n	0	8	26	23	
Score		22.24 (4.20)	37.89 (4.72)	39.47 (5.16)	
PANSS (79)					
n	0	11	40	26	
Positive		1.80 (0.21)	2.35 (0.13)	2.52 (0.15)	F(2,74)=3.33, p=.041 SZ-FE vs. SZ-CH p=.043; SZ-FE vs. SZ-RE p=.012 ⁵

Demographic (# available)	HC	SZ-FE	SZ-CH	SZ-RE	Statistic
Negative					
General		2.35 (0.29)	1.96 (0.10)	2.44 (0.18)	$F(2,74)=3.10, p=.051$; SZ-CH vs. SZ-RE $p=.021$ ⁵
		1.98 (0.13)	1.82 (0.06)	2.18 (0.10)	$F(2,74)=5.02, p=.009$; SZ-CH vs. SZ-RE $p=.002$ ⁵
Medication ²					
None	129	3	22	9	
Atypical Antipsychotic	0	10	14	14	
Typical Antipsychotic	0	1	8	8	
Lithium	0	0	2	1	
Anticonvulsant	2	1	6	5	
Antidepressant	0	6	13	6	
Benzodiazepine	0	1	3	2	
Anticholinergic	0	1	4	7	
Analeptic	1	0	0	0	

Notes:

¹ Mean (standard error).

² Many participants were on more than 1 type of medication.

³ Two subjects' scores reached criteria for outliers (greater than 3SDs from the mean), when these were removed, TDI mean (SE) = 26.42 (2.65).

⁴ Dunnett's T3 post-hoc test.

⁵ Fishers' s LSD test

Abbreviations: M: male, F: female, R: right, L: left, A: ambidextrous; HART: Hopkins Adult Reading Test; VIQ: verbal IQ, FSIQ: full-scale IQ

Table 2

MNI coordinates, Brodmann area labels and T values for regions activated by Hit Retrieval > Hit No-Retrieval main effect of condition

Region	MNI Coordinate	T Value
<i>Cluster 1, 1591 voxels</i>		
L Middle Temporal Gyrus (BA 21)	-60 -45 -9	86.71
L Inferior Parietal Lobule (BA 40)	-54 -51 42	85.52
L Superior Parietal Lobule (BA 7)	-33 -63 48	72.60
L Precuneus (BA 7)	-33 -69 39	67.08
L Inferior Temporal Gyrus (BA 20)	-54 -48 -15	41.36
L Middle Occipital Gyrus (BA 19)	-50 -58 -10	33.27
L Superior Temporal Gyrus (BA 22)	-54 -57 21	28.49
<i>Cluster 2, 2928 voxels</i>		
R Caudate	12 9 0	67.45
L Insula	-33 21 -6	65.64
L Globus Pallidus	-12 6 3	62.98
R Globus Pallidus	12 6 3	60.19
L Caudate	-12 6 9	59.83
L Middle Frontal Gyrus (BA 10)	-39 51 0	59.12
L Inferior Frontal Gyrus (BA 47)	-39 21 -6	57.86
L Putamen	-15 6 3	56.44
L Middle Frontal Gyrus (BA 9)	-42 18 39	53.37
L Superior Medial Frontal Gyrus (BA 9)	-6 36 36	53.25
R Putamen	15 6 3	51.20
L Supplementary Motor Area (BA 8)	-3 24 51	34.60
L Precentral Gyrus	-45 6 36	34.04
L Thalamus	-6 -6 6	33.17
L Anterior Cingulate (BA 32)	-3 36 27	32.34
R Thalamus	9 -3 6	30.73
<i>Cluster 3, 539 voxels</i>		
L Mid Cingulate (BA 31)	-3 -33 36	60.38
R Mid Cingulate (BA 31)	3 -33 36	46.62
L Precuneus (BA 7)	-3 -66 39	40.12
<i>Cluster 4, 406 voxels</i>		
R Inferior Parietal Lobule (BA 40)	36 -63 39	46.70
R Precuneus (BA 7)	36 -69 36	38.64
R Superior Parietal Lobule (BA 7)	36 -60 51	36.69
<i>Cluster 5, 115 voxels</i>		
R Middle Temporal Gyrus (BA 21)	63 -45 -2	37.95
R Inferior Temporal Gyrus (BA 20)	60 -48 -15	34.21

Region	MNI Coordinate	T Value
<i>Cluster 6, 120 voxels</i>		
Cerebellar Tuber	33 -63 -36	36.36
<i>Cluster 7, 63 voxels</i>		
R Inferior Frontal Gyrus (BA 47)	36 21 -9	29.75

Abbreviations: L, left; R, right; BA, Brodmann area