Published in final edited form as:

Biol Psychiatry. 2013 March 15; 73(6): 555–564. doi:10.1016/j.biopsych.2012.07.027.

Impairment in Semantic Retrieval is Associated with Symptoms in Schizophrenia but not Bipolar Disorder

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Abstract

Background—The Semantic Object Retrieval Task (SORT) requires participants to indicate whether word pairs recall a third object. Schizophrenia individuals (SZ) tend to report associations between non-associated word pairs; this *over-retrieval* is related to formal thought disorder (FTD). Since semantic memory impairments and psychosis are not specific to SZ but are also found in bipolar disorder (BP), we examined whether SORT impairments and their relationship to symptoms is also present in BP.

Methods—Participants (n=239; healthy controls (HC)=133; BP=32; SZ=74) completed SORT while undergoing fMRI scanning.

Results—Retrieval accuracy negatively correlated with negative symptoms and No-Retrieval accuracy negatively correlated with FTD severity in SZ but not BP. Retrieval vs. No-Retrieval trials activated a distributed fronto-parieto-temporal network; bilateral inferior parietal lobule (IPL) activity was larger in HC vs. SZ and HC vs. BP, with no difference in SZ vs. BP. Right IPL activity positively correlated with positive and general psychosis symptoms in SZ but not BP.

Conclusions—SZ reported more associations between unrelated word pairs than HC; this over-retrieval increased with FTD severity. SZ were also more likely to fail to find associations between related word pairs; this *under-retrieval* increased with negative symptom severity. fMRI-symptom correlations in IPL in SZ are consistent with arguments that IPL abnormality relates to loosening of associations in SZ. By comparison, BP showed intermediate impairments on SORT, uncorrelated with symptoms, suggesting that the relationship between SORT performance, fMRI activity and psychotic symptoms is schizophrenia-specific.

Keywords

semantic association retrieval task; schizophrenia; bipolar disorder; formal thought disorder; positive symptoms; fMRI

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Financial Disclosure All authors report no biomedical financial interests or potential conflicts of interest

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Introduction

Language disturbance is an important clinical manifestation of psychosis (1). Schizophrenia (SZ) patients show a broad range of language dysfunction, in part reflecting underlying semantic memory-related impairments (2). Such impairments are linked particularly to formal thought disorder (FTD), and are associated with impaired semantic priming (3-6), categorization (7,8) and association (9,10). Language dysfunction and semantic memory in bipolar disorder (BP) is less studied. BP is often associated with general language and specific semantic memory abnormalities including FTD, although these are typically less severe than in SZ (11-15). Since the disorders share common genetic mechanisms (16-19), clinical and neurocognitive impairments (20-22), impaired semantic memory processing seen in SZ may also be present in BP.

Semantic association allows prediction of related concepts and facilitates memory retrieval during communication (23). Two forms of semantic association are defined: compositional and non-compositional (24). Two types of non-compositional association are also defined (24): (i) where the third item is present lexically in the presented features (e.g. 'computer-virus'); and (ii) where two words fuse semantically to evoke a third un-presented word from semantic memory, e.g. 'honey', 'stings' activates 'bee'. The Semantic Object Retrieval Task (SORT) indexes this specific form of non-compositional semantic association.

In SORT, participants indicate whether word-pairs retrieve a third object (*Retrieval* trials^a) or do not (*No-Retrieval* trials). SORT requires activation of multiple feature representations corresponding to each word and entails searching multiple relationships between feature-pairs until convergence on the appropriate object from semantic memory (25). Engaging and framing the object search is mediated by the dorsal anterior cingulate (ACC), pre-supplementary motor area (pre-SMA), and thalamus (24-26).

Assaf et al.(9) reported that SZ showed reduced accuracy for No-Retrieval trials (reporting associations between non-related pairs; *over-retrieval*) than healthy controls (HC). The number of over-retrieved trials correlated positively with FTD severity. SZ showed more activation in task-relevant areas including pre-SMA, ACC and lateral/medial temporal regions versus HC during Retrieval vs. No-Retrieval trials. ACC activity also correlated positively with FTD severity, consistent with associational loosening in SZ/FTD and with arguments that SZ manifests impaired connections between/within semantic representational memory system.

Here, we seek to replicate and extend our previous findings using SORT in larger samples of HC and SZ, and to substantially increase trial numbers per condition (Retrieval, No-Retrieval). We also investigate SORT in BP to determine specificity of semantic association impairment to SZ. Given previous findings, we hypothesize SZ will show reduced accuracy for No-Retrieval trials and over-recruit regions typically engaged by SORT (36), proportional to FTD severity. We further hypothesize BP will show similar, less severe decrements in SORT performance and brain activity than SZ. If SORT impairment relates to FTD in both disorders, this suggests that impaired semantic association is specific to FTD independent of diagnosis.

^aPrevious studies have referred to Retrieval and No-Retrieval trials as Recall and No-Recall trials, respectively. However these labels could be misleading in that subjects do not *recall* any object that was previously presented, rather they activate an object that is *associated* with the presented items. We have therefore used the terms Retrieval and No-Retrieval to more accurately label these processes.

Methods and Materials

Participants

We assessed 239 individuals with no prior SORT exposure who consented to IRB-approved (Yale, Hartford Hospital) research at Olin Neuropsychiatry Research Center, Institute of Living. Participants were categorized as HC, SZ or BP (Table1) and assessed for DSM-IV-TR Axis-1 disorders using SCID-IV (27). Exclusion criteria included history of significant neurological disorder including head injury for all subjects, present/past/family history of Axis-1 psychiatric disorder for HC, positive urine toxicologic screen for abused drugs or pregnancy in women. Current symptoms were assessed on scanning day with the Positive and Negative Symptom Scale (PANSS (28)) and Thought Disorder Index (TDI (29)), yielding four scores: PANSS positive (positive scale average score), negative, and general symptoms and TDI total scores.

Stimuli and Tasks

Prior to scanning, participants completed out-of-scanner SORT training to ensure task instructions were understood. Stimuli, conceptually similar but different to those used in-scanner, were presented on a computer screen and examiner feedback provided.

In-scanner, participants completed SORT (25,31), programmed in E-Prime (Psychology Software Tools, Pittsburgh). Stimuli were visually-presented lower-case word-pairs arrayed one above the other as black letters on white background on a screen positioned 1-2 inches from participant's eyes. Word pairs described object features (e.g. 'honey', 'stings'). Following stimuli presentation, participants pressed one response button with their dominant index finger if the two words evoked a third object (e.g. 'bee') and another with their dominant middle finger if they did not. Participants completed 46 Retrieval and 46 No-Retrieval trials. To minimize stimulus-specific effects of the words themselves, word pairs in the No-Retrieval trials were permutations of the words used in the Retrieval trials (i.e. the same word stimuli were used in each condition in different pairings). Stimuli were presented for 2.7sec and replaced with a fixation cross for a 5.5sec inter-stimulus interval (ISI). Although the ISI is fixed, Retrieval and No-Retrieval events were presented in non-fixed intervals (e.g. R/R/NR/R/NR/NR/NR/R...), so the actual ISI between events in each condition is a multiple of 8.2sec, thus jittering the ISI (32).

Immediately following scanning, participants completed out-of-scanner debriefing. Word pairs were presented on a computer monitor in the same order as in-scanner; participants read the words aloud and replicated their prior responses. Participants identified the object elicited by the stimuli for every word pair they identified as a positive retrieval. Trials where in- and out-of-scanner responses differed were categorized as errors and removed from analysis.

fMRI Acquisition

Magnetic resonance images were acquired using a Siemens (Erlangen, Germany) Allegra 3T dedicated head scanner equipped with 40mT/m gradients and standard quadrature head coil. T2*-weighted images were acquired using an echo planar imaging (EPI) sequence (ascending sequential 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). Task instructions were shown during the first 10 images, these images were discarded, along with the subsequent 6 images discarded to account for T1 saturation effects

Data Analysis

Behavioral Data—For each subject, trials were categorized as Correct Retrieval, Correct No-Retrieval, Incorrect Retrieval and Incorrect No-Retrieval. Reaction time (RT) was analyzed with a 2-accuracy (correct, incorrect) $\times$ 2-condition (Retrieval, No-Retrieval) $\times$ 3-group (HC, BP, SZ) 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 higher numbers indicate better performance. To account for the non-normal distribution (Shapiro-Wilk's $p < .001$ for Retrieval and No-Retrieval), accuracy was arcsine-transformed to normalize distribution then analyzed with a 2-condition (Retrieval, No-Retrieval) $\times$ 3-group (HC, BP, SZ) mixed-ANOVA. For both RT and accuracy^b, significant group effects were further explored with *post-hoc* tests using Tukey's Honestly Significant Difference (HSD) test.

fMRI Data—fMRI data were analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London). EPI slice acquisition timing differences were corrected using the central slice as reference. Image time series were realigned to the first non-dummy image using INRI-align (33), spatially normalized to Montreal Neurological Institute (MNI) space using the SPM5 template, and spatially smoothed with a 9mm³ Gaussian kernel to ameliorate differences in inter-subject localization. Quality of registration was checked for each individual using CheckReg (SPM5).

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.

In this study, we specifically focused on Correct Retrieval vs. Correct No-Retrieval, as both trials include visual, motor and semantic search processes, but only Correct Retrieval trials involve semantic object retrieval^c. So, for second-level analyses contrast images for Correct Retrieval vs. Correct No-Retrieval were submitted to a 3-group [(HC, BP, SZ) unequal variances assumed] full factorial random effects analysis. Results were estimated using classical restricted maximum likelihood estimation and thresholded at $p < .05$ (FWE corrected), minimum cluster size $k = 5$ voxels. To determine the direction of the main effect of group, contrast values were extracted by creating ROIs defined as spheres (radius 10mm) around peaks of activity using MarsBar (34). These were subjected to 3-group (HC, BP, SZ) one-way ANOVA in SPSS for each ROI; Tukey's HSD *post-hoc* tests were used to test differences between groups.

We examined relationship between SORT performance accuracy, fMRI contrast values, and PANSS and TDI scores in BP and SZ. Correlations between accuracy, TDI and PANSS positive symptoms and fMRI and TDI scores were planned analyses based on our previous results (9), so multiple comparisons correction was not applied. We additionally performed exploratory correlations between PANSS negative/general symptoms and accuracy, and PANSS positive/negative/general scores and fMRI, thus multiple comparisons correction was applied by dividing alpha by the number of additional analyses ($\alpha = .05/5 = .01$). To

^bSince groups differed in gender, race and HART FSIQ, and these were considered potentially important confounds, we first ran behavioral analyses controlling for these factors. However there were no interactions between these factors and accuracy or Retrieval for either RT or accuracy (all $p > 0.10$), hence we report effects from the ANOVA without covariates only.

^cNote that we also examined fMRI results for Correct Association vs. Incorrect Association (comparison of correct and incorrect Retrieval trials) and Correct Retrieval vs. Incorrect No-Retrieval (comparison of Retrieval and 'over-retrieval trials'; see Assaf et al., 2006), however these analyses yielded no significant results above threshold, and thus are not presented.

account for the violation of the assumption of normality in the symptom scores (all Shapiro-Wilk's $p < .021$), Spearman's rho correlation coefficients were used. To statistically compare correlations between groups, the confidence interval method (35) was used.

Results

Sample Characteristics

Demographic information is shown in Table 1. Groups did not differ in handedness, but differed in age, sex, ethnicity, years of education, Hopkin's Adult Reading Test (HART) Verbal IQ (VIQ) and Full Scale IQ (FSIQ). Patient groups did not differ in PANSS positive or general symptoms, or in TDI total score, but did differ in PANSS negative symptoms (greater in SZ). Given the significant demographic differences between groups, we ran an additional matched-samples analysis (see Supplementary Materials); these results were compatible with results obtained in the larger sample.

Behavioral Results

Accuracy—Figure 1 summarizes accuracy results. Accuracy for No-Retrieval trials was significantly better than for Retrieval trials ($F(1,236)=24.31, p < .001$). The main effect of group was significant ($F(1,236)=18.41, p < .001$): SZ were less accurate than BP (Tukey's HSD $p=.040$) and HC ($p < .001$); with no difference between HC and BP ($p=.160$). Although the condition $\times$ group interaction was not significant ($F(2,236)=2.03, p=.134$), to test our hypothesis that SZ would show over-retrieval of No-Retrieval trials relative to HC, we performed planned analyses comparing groups for Retrieval and No-Retrieval trials separately using 3-group (HC,BP,SZ) ANOVAs. For Retrieval trials the effect of group was significant ($F(2,236)=18.67, p < .001$); accuracy for SZ was significantly lower than HC (Tukey's HSD $p < .001$) and BP ($p=.005$), with no difference between HC and BP ($p=.522$). For No-Retrieval trials the effect of group was significant ($F(2,236)=4.99, p=.008$); accuracy for SZ was significantly lower than HC ($p=.007$) but did not differ from BP ($p=.794$), and BP and HC did not differ ($p=.266$).

For SZ, accuracy for Retrieval trials was marginally negatively correlated with PANSS negative symptoms ($r=-.306, p=.029$) and accuracy for No-Retrieval trials was significantly negatively correlated with TDI scores ($r=-.309, p=.035$). Accuracy did not correlate with symptoms in BP (all $p > .150$). The relationship between Retrieval accuracy and PANSS negative scores was stronger in SZ than BP ($Z=5.11, p < .0001$); the difference in correlation strength between groups for No-Retrieval accuracy and TDI scores was not significant ($p=.496$).

Reaction Time—Figure 2 summarizes RT results. RT for Correct trials were significantly^d faster than Incorrect trials ($F(1,210)=138.93, p < .001$), and Retrieval trials were performed faster than No-Retrieval trials ($F(1,210)=95.98, p < .001$). The accuracy $\times$ condition interaction ($F(1,210)=12.86, p < .001$) confirmed that the increase in RT for Incorrect vs. Correct trials was larger for Retrieval than No-Retrieval trials. The significant main effect of group ($F(2,210)=29.09, p < .001$) was further explored using Tukey's HSD post-hoc tests. HC was faster than SZ ($p < .001$) and BP ($p=.002$), with no difference between SZ and BP ($p=.160$). There was no significant 2-way or 3-way interaction between group/accuracy/condition (all $F < 2.07$).

^dNote that the degrees of freedom reflect the fact that some subjects showed perfect accuracy for either Retrieval or No-Retrieval trials, or both.

fMRI Results

Correct Retrieval vs. Correct No-Retrieval trials activated a distributed fronto-parieto-temporal network (Figure 3A; Table 2), broadly compatible with our previous study (26, see also Supplementary Material). The main effect of group (Figure 3B, Table 3) showed significant activity in bilateral inferior parietal lobule (IPL). Tukey's HSD confirmed (Figure 3C, Table 3) that activity was larger in HC vs. SZ and in HC vs. BP, with no difference between SZ and BP.

Correlations were conducted between PANSS and TDI symptoms and fMRI contrast values in left and right IPL for SZ and BP. For BP, PANSS and TDI showed no significant correlation with fMRI activity in either region (both $p > .10$). PANSS positive and general symptoms in SZ correlated positively with right IPL activity (Figure 3E). The relationship between PANSS positive symptoms and right IPL activity was significantly stronger for SZ than BP ($Z = 5.26, p < .0001$); as was the relationship between PANSS general scores and right IPL activity ($Z = 3.56, p < .0001$).

Discussion

Performance and fMRI Activity During SORT Across Groups

Consistent with previous studies, participants were faster and made more errors for Retrieval than No-Retrieval trials (26). Across groups, correct Retrieval trials activated a distributed bilateral fronto-subcortical-temporal-parietal network relative to correct No-Retrieval trials. These results are specifically related to semantic association processing, since both Retrieval and No-Retrieval trials include visual, motor and semantic search processes, but only Retrieval trials involve recall from semantic memory (see Supplementary Material). This activation pattern overlaps almost entirely with the heteromodal association network (36,37), which coordinates and integrates information from multiple sensory and motor regions to perform complex cognitive processes. Given Retrieval vs. No-Retrieval trials involve integration of information from multiple components of semantic memory, it is perhaps unsurprising that SORT activates this network.

The activation extent during SORT we obtained is more widespread than reported previously (24-26,9). Our paradigm differed from previous ones in two important ways: (a) 46 trials of Retrieval and No-Retrieval conditions each; previous studies used 16 word pairs (24,46,31,9; but see 25); (b) Our N was substantially larger than any prior fMRI SORT study: previous studies had between $n = 9-18$ (24,46,31,9; but see 25). Our large N allowed us to examine more comprehensively the neural correlates of SORT while implementing strong correction for multiple comparisons. It is thus likely that early studies that developed the task and sought to establish the fMRI correlates of SORT suffered from power issues and may have included a number of false positives.

Changes in SORT Performance and fMRI Activity in Schizophrenia and Bipolar Disorder

Both SZ and BP showed impaired performance and fMRI activity relative to HC during SORT; on all measures SZ were most impaired, with BP showing intermediate deficits between HC and SZ.

Relative to HC, SZ were slower and less accurate overall. Slowed RT in SZ is consistent with our previous study (9) and with the well-established generalized slowing of RT in SZ (38). Consistent with our hypotheses, SZ showed reduced accuracy for No-Retrieval trials relative to HC, tending to over-retrieve or report associations between unrelated word pairs. Accuracy for No-Retrieval trials correlated negatively with TDI: individuals with more severe FTD were more likely to report associations between unrelated word pairs, consistent

with our previous result (9) and compatible with loosening of associations in FTD (39,40). Interestingly, SZ also showed reduced accuracy for Retrieval trials relative to HC, tending to under-retrieve or failing to report associations between related pairs. In this case, accuracy for Retrieval trials was negatively correlated with PANSS negative symptoms: individuals with more severe negative symptoms were more likely to miss associations between related words. This is consistent with poverty of speech found in individuals manifesting negative symptoms^e(41).

By comparison, BP showed intermediate impairments on SORT: similar but lesser RT impairment than SZ, consistent with reports of slowed processing in BP (42). Accuracy was better in BP than SZ, with no significant difference from HC for both Retrieval and No-Retrieval^f trials. Although slower, BP did not over- or under-retrieve associations like SZ. Furthermore, BP SORT performance was not related to positive, negative, general or FTD symptoms, which is not due to reduced symptom scores or performance variability in BP, since patient groups showed similar score variances (Table 1; Figures 1&2). This suggests that SORT performance impairments and their relationship with negative and FTD symptoms are SZ-specific and do not extend to BP.

In fMRI data, a strong main effect of group was obtained in bilateral IPL, with HC showing strongest activation, followed by BP with SZ showing least activation. This is compatible with our previous study where SZ showed reduced bilateral IPL activation for Retrieval trials relative to HC (9); our results extend this finding, showing similar activation decrements also occur in BP. Similar to performance data, IPL activation correlated with symptom scores in SZ only: right IPL activity positively correlated with positive and general symptoms, confirming our conclusion that the relationship between clinical symptoms and semantic association impairments does not cross diagnostic borders.

Relationship with Semantic System Models and Psycholinguistic Impairment in Schizophrenia

When concepts become activated in semantic memory, activation spreads to other nearby concepts until passive decay or active inhibition occurs (43). Automatic spread of activation probably occurs faster and spreads more widely in SZ, activating loosely associated, possibly irrelevant concepts (43-45). Semantic network over-activation is particularly implicated in FTD (43,45,46), consistent with our findings that SZ with more FTD were more likely to associate unrelated word pairs. In contrast, individuals with predominantly negative symptoms, particularly poverty of speech, show intact spreading of activation of the semantic network but have difficulty in controlled retrieval of information from this network (46), consistent with our observation that SZ with more severe negative symptoms fail to report associations between related words.

IPL plays a central role in both the semantic system (47,48) and the heteromodal association network (37,49), serving as a 'supramodal convergence zone', binding representations from

^eInterestingly, it is also compatible with Bleuler's original argument that the primary pathological process in SZ is loosening of associations, and that this primary pathology underlies all deficits in SZ, including negative symptoms. While linking positive symptoms and formal thought disorder to impairments in semantic association makes intuitive sense, linking loosening of association with negative symptoms seems a little counter-intuitive. Bleuler (1919) argued "[In schizophrenia] the associations lose their connections. As a result...there may be a paucity of ideas to the point of mono-ideism..." p.584 "In some cases all threads of the train of thought are torn asunder; if no new associative pathways are chosen, the result is stupor or blocking." p. 593. "... the boundary between blocking and negativism is vague, both theoretically and symptomatically. The two phenomena may shade into each other, and passive negativism may even be explained by a combination of blockings. The blocking of one patient was very similar to negativism: she gave slow, halting and faint answers, and would even lose her voice... In some cases it is impossible to determine whether one deals with blocking or negativism..." pp. 618-619.

^fNote that accuracy for No-Retrieval trials for BP was not significantly different from SZ as well. So it is possible that there is a trend for BP to over-retrieve associations for No-Retrieval trials. Future studies should examine this possibility.

multiple sensory/motor/affective zones to allow efficient, rapid processing of the current context. It is involved in integration and evaluation of information from multiple sensory regions (48, 50). Compared to other regions, IPL is relatively understudied in SZ and BP. IPL volume is reduced in SZ bilaterally (51-53) or left (54,55) or right-lateralized (56-58). Reduced IPL gray matter has also been reported in BP (59-62). Torrey (63) noted impaired IPL function underlies loosening of associations; our finding that regional SORT activity is related to positive and general symptoms in SZ is compatible with this position. IPL activation level may reflect the amount of semantic information retrievable on the basis of a given input (48); in this way it mediates the spread of activation within the semantic system. This may explain one finding that is initially counter-intuitive: increased IPL activity was associated with greater PANSS positive/general symptoms – i.e. the more ‘normal’ the activity, the worse symptoms were. Increased IPL activation should result in more co-activated concepts in semantic memory (48); our results suggest that this also holds in SZ, where the ‘starting’ level of activity during semantic tasks in the IPL is lower than in HC. This argument is admittedly speculative and should be examined further. However in sum, the finding that IPL is specifically implicated in impaired SORT processing in SZ and BP is consistent with the known function of the region and its impairment in the disorders.

Strengths and Limitations of the Current Study and Directions for Future Research

Our large sample size was a significant strength, allowing us to examine fMRI activity with a conservative FWE correction and to make explicit links between SORT activity and heteromodal association networks. Despite replicating and extending our previous performance and IPL fMRI results (9), we did not replicate the finding that SZ over-recruit SORT regions relative to HC. As mentioned earlier, that study was preliminary, with fewer trials, less conservative fMRI threshold and substantially smaller N. It is therefore likely that our earlier finding was a false positive. Indeed, exploratory analyses directly contrasting SZ and HC (ignoring BP) for Retrieval>No-Retrieval trials showed no activation in our sample, even at the threshold used in our previous manuscript ($p_{\text{uncorr}} < .05$), confirming this conjecture[§]. A second strength was we examined semantic association in both SZ and BP; reports directly comparing these groups on the same task are surprisingly uncommon, at least for the semantic system. One limitation of the current study is we did not distinguish between diagnostic subtypes: both BP and SZ are diagnostically heterogeneous, with subtypes showing variable neurocognitive impairment (64). A second limitation is that we did not record in-scanner vocalizations, but relied on debriefing to score performance, due to technical issues with voice recording in-scanner; our future studies will endeavor to record in-scanner responses. Third, our original sample was unmatched for demographics, however Supplementary Analyses on a subset of matched participants confirmed our findings from the larger sample. Fourth, we did not control for possible medication effects on performance or fMRI activity. Future studies should examine if SORT performance, fMRI activity and relationships with clinical symptoms differ between diagnostic subtypes, or medication type/exposure/dosage. Lastly, both the current study and (9) examined relationships between global TDI scores and SORT performance/activity. An interesting future direction is to examine whether the relationship between these factors differs between TDI sub-types.

[§]One major finding of our previous study was that activation in left ACC was positively correlated with TDI scores in SZ. Although we saw no group differences in ACC activity in this study, we wanted to specifically test whether a similar effect was also obtained here. TDI scores correlated positively with fMRI activity in left ACC in SZ ($r=.316, p=.030$) but not BP ($p=.203$). So while we did not replicate the whole-brain results of our previous study, our finding that fMRI activity in left ACC during SORT is related to FTD in SZ is replicated.

Conclusions

We examined SORT performance and fMRI activity in the largest sample to date. BP and SZ are impaired in SORT performance and fMRI activity, with SZ showing most impairment in performance and fMRI activity, and BP showing intermediate impairment levels largely in fMRI activity, despite comparable FTD severity. SZ with FTD were more likely to associate unrelated word pairs and those with negative symptoms were more likely to miss associations between related word pairs. Similarly, right IPL fMRI activity (an important heteromodal region impaired in SZ) was related to positive and general symptoms in SZ. The relationship between psychotic symptoms and SORT performance and fMRI activity was restricted to SZ, suggesting that the relationship between clinical symptoms and semantic association impairments does not cross diagnostic borders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was partially supported by The Patrick and Catherine Weldon Donaghue Medical Research Foundation (PI: M. Assaf), NIMH grants: R37 MH43775 (MERIT) and R01 MH74797 (PI: G.D. Pearlson).

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Figure 1.

Accuracy for (a) main effects of group and condition, (b) for each group separately, and (c) correlation between arcsine accuracy for (left) Retrieval trials and PANSS negative symptoms for the schizophrenia group; (right) No-Retrieval trials and TDI scores for the schizophrenia group. A higher score corresponds to more accurate performance.

Figure 2. Reaction time (ms) for (a) main effects of group, accuracy and condition and (b) for each group separately

Correct Retrieval > Correct No-Retrieval

A. Main Effect of Condition

B. Main Effect of Group

C. Main Effect of Group

D. Relationship with Symptoms - SZ

Figure 3.

fMRI results for Hit Retrieval > Hit No-Retrieval, thresholded at $p < .05$ FWE corrected, $k = 5$ voxels. (A) Main effect of condition; (B) main effect of group; (C) contrast values and standard errors for the main effect of group in the left and right IPL; (D) contrast values and standard errors for Hit Retrieval > Baseline and Hit No-Retrieval > Baseline for the three groups in left and right IPL; (E) relationship between PANSS positive (left) and general (right) scores and Hit Retrieval > Hit No-Retrieval activity in the right IPL in schizophrenia. Abbreviations: L: left; R: right; IPL: inferior parietal lobule; HC: healthy controls; BP: bipolar disorder; SZ: schizophrenia; PANSS: positive and negative symptom scale.

Table 1

Demographic information for the three groups.

Demographic (# available)	Healthy Control (HC)	Bipolar (BP) ³	Schizophrenia (SZ)	Statistic
n	133	32	74	
		27 Bipolar-I	57 Paranoid type	
		5 Bipolar-Not Otherwise Specified	17 Undifferentiated type	
Age (239)¹	32.48 (1.05)	36.66 (2.1)	36.35 (1.40)	F(2,238)=31.14,p=.045
Gender (239) M/F	68/65	15/16	59/14	$\chi^2=19.28,p<.001$
Handedness (226)	133	27	72	$\chi^2=5.29,p=.259$
R/L/Ambidextrous	127/5/1	24/3/0	63/8/1	
Race (239)	133	32	74	$\chi^2=23.08,p=.003$
White	96	23	42	
Black	16	1	22	
Hispanic	8	4	1	
Asian	5	0	2	
Other/unknown	8	4	7	
Years of Education (195)¹	13.99 (0.26)	12.04 (0.60)	11.47 (0.43)	F(2,194)=15.66,p<.001
HART (182)¹	99	23	60	
VIQ	106.42 (0.84)	103.32 (2.27)	98.87 (1.47)	F(2,181)=11.91,p<.001
FSIQ	108.29 (0.74)	105.38 (0.68)	101.54 (1.30)	F(2,181)=12.29,p<.001
TDI (70)	0	23	47	
Total score	-	14.15 (2.58)	18.77 (2.56)	t(68)=1.13,p=.262
PANSS (76)	0	25	51	
Positive	-	2.12 (.17)	2.41 (0.11)	t(75)=1.45,p=.136
Negative	-	1.46 (0.08)	2.16 (0.11)	t(74)=5.33,p<.001 ⁴
General	-	1.77 (0.10)	1.89 (0.07)	t(75)=.979,p=.333

Demographic (# available)	Healthy Control (HC)	Bipolar (BP) ³	Schizophrenia (SZ)	Statistic
Medication²				
None	129	11	30	
Atypical Antipsychotic	0	17	31	
Typical Antipsychotic	0	2	16	
Lithium	0	9	2	
Anticonvulsant	2	7	12	
Antidepressant	0	12	18	
Benzodiazepine	0	4	4	
Benzotropine	0	3	10	
Zolpidem	1	1	2	
Antimuscarinic	0	1	0	
Modafinil	1	0	0	
Donepezil	0	0	0	
Anxiolytic	0	0	1	

Notes:

¹ Mean (standard error).

² Note many participants were on more than one type of medication.

³ All participants in BP met criteria for psychotic BP on the basis of the presence of hallucinations/delusions during at least one episode in their illness (30). Each BP participant was additionally assessed for current psychosis on the day of testing on the basis of scores 3 in one or more of the following PANSS positive symptom scales: delusions, conceptual disorganization, hallucinations and suspicious/persecutory delusions. On the basis of these criteria, 63% of BP participants had current psychosis.

⁴ Corrected for unequal variances

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

Table 2

MNI coordinates of regions activated in Correct Retrieval > Correct No-Retrieval: main effect of condition. Contrast thresholded at $p < .05$ FWE corrected, $k=5$ voxels. Anatomical locations including Brodmann areas were determined using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as implemented in xjview (<http://www.alivelearn.net/xjview>) and verified using the atlas of Mai et al. (2008).

Region (BA)	Left Hemisphere		Right Hemisphere	
	MNI	F	MNI	F
Superior/Middle Frontal Orbitalis (10)	-39 48 -6	129.86	18 54 -3	22.50
Superior Frontal (9/6/10)	-18 39 39	70.04	12 24 42	33.85
Middle Frontal (9/46)	-42 27 36	85.28	39 15 42	36.68
Inferior Frontal Orbitalis (10/47)	-45 39 -6	92.26	36 27 -12	29.19
Inferior Frontal Triangularis (46/45)	-42 27 24	72.21	54 24 24	28.48
Inferior Frontal Operculum (44)	-51 12 12	68.92	51 15 30	30.50
Insula	-33 18 -6	84.75	30 15 -18	29.69
Precentral (6)	-45 6 42	99.89	48 6 36	29.99
Supplementary Motor Area (8)	-21 24 57	99.41	6 18 48	26.41
Anterior Cingulate (32)	-6 36 21	71.30	6 36 15	40.72
Mid Cingulate (23/31)	-3 -30 36	124.50	6 -27 36	83.74
Posterior Cingulate (31)	-6 -39 30	93.78	6 -45 24	41.55
Thalamus	-12 -9 3	67.59	9 -12 0	49.82
Caudate	-6 12 3	33.52	12 15 3	65.34
Putamen	-18 12 0	57.50	21 12 -3	25.23
Superior Parietal (7)	-34 -66 50	173.96	21 -69 51	34016
Precuneus (7)	-6 -69 42	99.47	9 -60 42	48.66
Inferior Parietal (40)	-48 -57 48	234.15	36 -63 42	134.62
Parahippocampal	-24 -12 -30	35.56	27 -36 -6	26.81
Hippocampus	-15 -6 -15	43.05	18 -4 -12	36.38
Superior Temporal (22)	-57 -45 15	35.46		
Middle Temporal (21/22)	-54 -39 -6	127.91	54 -42 -3	56.51
Inferior Temporal (20)	-51 -51 -9	56.45	60 -45 -12	85.54
Temporal Pole (38)	-39 18 -36	32.57	34 12 -32	23.66
Fusiform (37)	-40 -54 -18	32.23	27 -36 -18	27.52

Region (BA)	Left Hemisphere		Right Hemisphere	
	MNI	F	MNI	F
Superior Occipital (19)	-22 -70 34	34.91	27 -69 42	52.57
Cuneus (19)	-12 -66 24	32.81	18 -66 33	23.16
Middle Occipital (19/39)	-33 -69 33	114.81	36 -72 36	72.41
Cerebellum 4/5	-6 -51 -15	27.84	27 -39 -27	27.54
Cerebellar Vermis 4/5	0 -54 -5	22.08	6 -56 -18	24.27
Cerebellum 6	-27 -60 -30	34.30	30 -60 -27	30.69

MNI coordinates of regions showing a significant effect of group in Correct Retrieval > Correct No-Retrieval. Tukey's HSD was used to determine the direction of the main effect. Contrast thresholded at $p < .05$ FWE corrected, $k = 5$ voxels. Anatomical locations including Brodmann areas were determined using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) as implemented in xjview (<http://www.alivelearn.net/xjview>) and verified using the atlas of Mai et al. (2008).

Table 3

Region (BA)	MNI	F	F ANCOVA ¹	Tukey's HSD		
				HC vs. SZ	HC vs. BP	SZ vs. BP
Left Inferior Parietal Lobule (40)	-54 -45 48	20.94	15.00	$p < .001$	$p = .010$	$p > .05$
Right Inferior Parietal Lobule (40)	39 -57 48	20.36	17.99	$p < .001$	$p = .018$	$p > .05$

Notes:

¹ Since groups differed in age, sex and FSIQ, we re-ran the Correct Retrieval > Correct No-Retrieval contrast controlling for these three variables. Missing FSIQ values were replaced with the mean within that subject's group. Activity in both regions remained significant, however the maximum F value was reduced in each region, suggesting that these group differences do not account for the effect of group.