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

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**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 nonassociated word pairs; this overretrieval is related to formal thought disorder (FTD). Since semantic memory impairments and psychosis are also found in bipolar disorder (BP), we examined whether SORT impairments and their relationship to symptoms are also present in BP.

**Methods:** Participants ($n$ = 239; healthy control subjects [HC] = 133; BP = 32; SZ = 74) completed SORT while undergoing functional magnetic resonance imaging (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 versus no-retrieval trials activated a distributed fronto-parieto-temporal network; bilateral inferior parietal lobule (IPL) activity was larger in HC versus SZ and HC versus BP, with no difference in SZ versus 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 overretrieval increased with FTD severity. Schizophrenia individuals were also more likely to fail to find associations between related word pairs; this underretrieval 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.

**Key Words:** Bipolar disorder, fMRI, formal thought disorder, positive symptoms, schizophrenia, semantic association retrieval task

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) are less studied. Bipolar disorder 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 noncompositional (24). Two types of noncompositional association are also defined (24): where the third item is present lexically in the presented features (e.g., computer-virus); and where two words fuse semantically to evoke a third unpresented word from semantic memory (e.g., honey, stings activates bee). The Semantic Object Retrieval Task (SORT) indexes this specific form of noncompositional semantic association.

In SORT, participants indicate whether word pairs retrieve a third object (retrieval trials[1]) 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 cortex (ACC), pre-supplementary motor area, and thalamus (24–26).

Assaf *et al.* (9) reported that SZ showed reduced accuracy for no-retrieval trials (reporting associations between nonrelated pairs; overretrieval) than healthy control subjects (HC). The number of overretrieved trials correlated positively with FTD severity. Schizophrenia individuals showed more activation in task-relevant areas, including pre-supplementary motor area, ACC, and lateral/medial temporal regions versus HC during retrieval versus 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 overrecruit regions typically engaged by SORT (9), 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

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Received Dec 14, 2011; revised Jul 4, 2012; accepted Jul 5, 2012.

[1]Previous 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.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.07.027

impaired semantic association is specific to FTD independent of diagnosis.

## Methods and Materials

### Participants

We assessed 239 individuals with no prior SORT exposure who consented to Institutional Review Board approved (Yale, Hartford Hospital) research at Olin Neuropsychiatry Research Center, Institute of Living. Participants were categorized as HC, SZ, or BP (Table 1) and assessed for DSM-IV Axis I disorders using Structured Clinical Interview for DSM-IV (27). Exclusion criteria included history of significant neurological disorder including head injury for all subjects, present/past/family history of Axis I 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 Syndrome 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

Before scanning, participants completed SORT training outside the scanner to ensure task instructions were understood. Stimuli, conceptually similar but different to those used inside the scanner, were presented on a computer screen and examiner feedback provided.

Inside the scanner, participants completed SORT (25,30), programmed in E-Prime (Psychology Software Tools, Pittsburgh, Pennsylvania). Stimuli were visually presented lowercase word pairs arrayed one above the other as black letters on white background on a screen positioned 1 to 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 2.7 seconds and replaced with a fixation cross for a 5.5-second interstimulus interval (ISI). Although the ISI was fixed, retrieval and no-retrieval events were presented in nonfixed intervals (e.g., R/R/NR/R/NR/NR/NR/R...), so the actual ISI between events in each condition was a multiple of 8.2 seconds, thus jittering the ISI (31).

Immediately following scanning, participants completed debriefing outside the scanner. Word pairs were presented on a computer monitor in the same order as inside the 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 responses inside and outside of the scanner differed were categorized as errors and removed from analysis.

### Functional Magnetic Resonance Imaging Acquisition

Magnetic resonance images were acquired using a Siemens (Erlangen, Germany) Allegra 3T dedicated head scanner equipped with 40 mT/m gradients and standard quadrature head coil. T2*-weighted images were acquired using an echo planar imaging sequence (ascending sequential axial acquisition, 426 volumes, repetition time = 1.86 sec, echo time = 27 msec, field of view = 24 cm, acquisition matrix = 64 × 64, flip angle = 70°, voxel size = 3.75 × 3.75 × 4 mm, gap = 1 mm, 36 slices). 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) × 2-condition (retrieval, no-retrieval) × 3-group (HC, BP, SZ) mixed analysis of variance (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 nonnormal distribution (Shapiro-Wilks $p < .001$ for retrieval and no-retrieval), accuracy was arcsine-transformed to normalize distribution, then analyzed with a 2-condition (retrieval, no-retrieval) × 3-group (HC, BP, SZ) mixed ANOVA. For both RT and accuracy,[2] significant group effects were further explored with post hoc tests using Tukey's Honestly Significant Difference (HSD) test.

**Functional Magnetic Resonance Imaging Data.** Functional magnetic resonance imaging (fMRI) data were analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London, United Kingdom). Echo planar imaging slice acquisition timing differences were corrected using the central slice as reference. Image time series were realigned to the first nondummy image using INRI-align (32), spatially normalized to Montreal Neurological Institute space using the SPM5 template, and spatially smoothed with a 9 $mm^3$ Gaussian kernel to ameliorate differences in intersubject 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 RT inside the scanner; duration for trials where no response was made was defined as the maximum response window (2.7 sec). 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 versus correct no-retrieval, as both trials included visual, motor, and semantic search processes, but only correct retrieval trials involved semantic object retrieval.[3] So, for second-level analyses, contrast images for correct retrieval versus 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 $p < .05$ (family-wise error corrected), minimum cluster size $k = 5$ voxels. To determine the direction of the main effect of group, contrast values were extracted by creating regions of interest defined as spheres (radius 10 mm) around peaks of activity using MarsBar (33). These were subjected to 3-group (HC, BP, SZ) one-way

[2]Since groups differed in gender, race, and Hopkins Adult Reading Test full-scale IQ, 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 $p > .10$); hence, we report effects from the ANOVA without covariates only.

[3]Note that we also examined fMRI results for correct association versus incorrect association (comparison of correct and incorrect retrieval trials) and correct retrieval versus incorrect no-retrieval (comparison of retrieval and overretrieval trials; see [9]); however, these analyses yielded no significant results above threshold and thus are not presented.