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Effect of Retrieval Effort and Switching Demand on fMRI Activation During Semantic Word Generation in Schizophrenia

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Abstract

Verbal fluency deficits in schizophrenia are difficult to interpret because the tasks are multi-factorial and groups differ in total words generated. We manipulated retrieval and switching demands by requiring alternation between over-learned sequences in which retrieval is relatively automatic (OS) and semantic categories requiring increased retrieval effort (SC). Controlled processing was also manipulated by including switching and non-switching conditions, and formal thought disorder (FTD) was assessed with the communication disorders index (CDI). The OS/SC semantic fluency paradigm was administered during fMRI to 13 patients with schizophrenia and 14 matched controls. Images were acquired on a 3 Tesla Siemens scanner using compressed image acquisition to allow for cued overt word production. Subjects alternated between OS, SC, OS-switch, SC-switch, and baseline blocks. Images were pre-processed in SPM-2, and a two-stage random effects analysis tested within and between group contrasts. There were no group performance differences. fMRI analysis did not reveal any group differences during the OS non-switching condition. Both groups produced expected activation in bilateral prefrontal and inferior parietal regions. However, during the SC condition patients had greater activation than controls in left prefrontal, right anterior cingulate, right superior temporal, bilateral thalamus, and left parietal regions. There was also evidence of patient over-activation in prefrontal, superior temporal, superior parietal, and visual association areas when a switching component was added. FTD was negatively correlated with BOLD response in the right anterior cingulate, cuneus and superior frontal gyrus during increased retrieval demand, and positively correlated with fMRI activation in the left lingual gyrus, right fusiform gyrus and left superior parietal lobule during increased switching demand. These results indicate that patients are able to successfully perform effortful semantic fluency tasks during non-speeded conditions. When retrieval is relatively automatic there does not appear to be an effect of schizophrenia on fMRI response. However, when retrieval and controlled processing demands increase, patients have greater activation than controls despite unimpaired task performance. This inefficient BOLD response may explain why patients are slower and less accurate on standard self-paced fluency tasks.

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Keywords

schizophrenia; verbal fluency; semantic memory; functional imaging; brain mapping

1. Introduction

Verbal fluency tasks demand rapid generation of words belonging to a specific category (e.g., “animals”), and successful performance necessitates intact lexical and semantic knowledge, well-organized semantic networks, and efficient word access and retrieval requiring varying degrees of cognitive control (Posner & DiGirolamo, 1998; Shallice, 1988). There is a general consensus that semantic knowledge in schizophrenia is intact (Elvevåg and Storms 2003), and that semantic impairments are due to deficits in processing speed (Vinogradov et al., 2002), organization of material retrieved from the semantic store (Moelter et al., 2005), dysfunctional word access and retrieval (Himelhoch et al., 1996), or a combination of these factors (Goldberg et al., 1998; Vinogradov et al., 2002; Zakzanis et al., 2000). The current study manipulated semantic retrieval and between-category switching demands to test the hypothesis that group differences in functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) response are secondary to the high level of cognitive control required by standard speeded verbal fluency paradigms. It is predicted that patients’ fMRI response will be unimpaired during generation of words to over-learned sequence categories (e.g., days of the week) when retrieval and switching demands are low.

Previous attempts to assess word retrieval during fluency tasks dissociated clustering from switching components (Troyer, Moscovitch, Winocur, 1997; Troyer et al., 1998; Robert et al., 1998). Clustering occurs when individuals generate exemplars within a specific sub-category such as “Farm Animal” (e.g., “horse, cow, pig”), and is thought to require minimal retrieval effort due to more automatic spread-of-activation (Collins & Loftus, 1975) between strongly associated nodes in the semantic network. Switching requires increased cognitive control to generate exemplars from a new sub-category (e.g., “Jungle Animal”) and inhibit responses to the previous sub-category once it has been exhausted. Investigators have found that individuals with schizophrenia have a reduced number of switches (Robert et al, 1998) and an increased switch latency (Elvevåg, Fisher, Gurd, Goldberg, 2002). Although some investigators have found that number of clusters and cluster size (Elvevåg et al., 2002) as well as associative strength within a cluster is intact (Moelter et al., 2001), others have found that cluster size and the proportion of clustered responses can be reduced (Bozikas et al., 2005; Moelter et al., 2001), suggesting that semantic organization might be disrupted even during less effortful retrieval conditions.

Functional imaging studies using word production tasks initially supported a fronto-temporal disconnection hypothesis in schizophrenia (Friston and Frith, 1995). In healthy subjects phonemic verbal fluency increased prefrontal and decreased superior temporal lobe activity (Frith et al., 1995). With one exception (Spence et al., 2000), patients had increased superior temporal gyrus (STG) activity relative to healthy comparison subjects (Frith et al., 1995; Liddle 1997; Yurgelun-Todd et al., 1996). However, results for the prefrontal cortex (PFC) were less consistent, with evidence of PFC reductions (Curtis et al., 1998; Schaufelberger et al., 2005; Yurgelun-Todd et al., 1996), unimpaired PFC function (Frith et al., 1995; Liddle 1997; Spence et al., 1998), and reduced PFC lateralization in schizophrenia (Weiss et al., 2004). Inconsistent PFC findings have been attributed to group differences in task performance (Fletcher et al., 1998). However, investigating task performance effects has been hindered due to use of covert word production tasks because of concerns about increased head motion. A recent study that equated groups on covert word production based on number of button presses (Boksman et al., 2005) found that patients demonstrated reduced activity in the PFC and anterior cingulate gyrus

(ACC), accompanied by reduced functional connectivity between the ACC and temporal cortex despite equivalent performance. Attenuated PFC and ACC activation was also seen in an overt phonemic fluency task where groups were matched on performance (Schaufelberger et al., 2005).

Variability in regional activation and semantic memory performance has also been attributed to different levels of formal thought disorder (FTD) within and between patient samples. FTD refers to the disordered speech of patients with schizophrenia (Andreasen, 1982) and has long been associated with semantic memory performance (Goldberg et al., 1998) and related prefrontal cortex (PFC) and superior temporal gyrus (STG) structure (Rajarethinam et al., 2000; Shenton et al., 1997; Vita et al., 1995) and function (Fu et al., 2005; Kircher et al., 2000, 2001). These studies have generally found an inverse relation between FTD and STG volume and function (Rajarethinam et al., 2000; Shenton et al., 1997; Vita et al., 1995; Kircher et al., 2001), and a positive relationship with PFC function (Kircher et al., 2000, 2001) although no relationship was found in a study of acutely ill patients (Fu et al., 2005). Investigation of severe FTD is complicated by the fact that acutely ill patients are often unable to provide consent or comply with task demands. Rather than study acutely ill patients with prominent FTD, the current study uses the communications disorder index (CDI; Docherty et al., 1996) to detect subtle communication failures indicative of disordered thinking, which has been shown to be more strongly correlated with measures of attention, memory and executive control than traditional clinical scales (Docherty et al., 2005).

A limitation of speeded fluency tasks is that dissociation of clustering from switching deficits can be confounded by group differences in total word production (Mayr 2002). This limitation was addressed by Elvevåg and colleagues (2002) who used total word output as a covariate and modified methods for scoring clusters and switches. However, an alternative approach is to control for total word production by using a cued retrieval task (Gurd et al., 2002). In the Gurd et al. paradigm (2002) retrieval demand is manipulated by alternating between less effortful over-learned sequences (OS; e.g., “days of the week”) and more effortful semantic categories (SC; e.g., “vegetables”). Switching is manipulated by including both single category and alternating category conditions (e.g., “vegetables” versus “vegetables/fruit”). In an fMRI study of healthy volunteers Gurd et al. (2002) found that greater retrieval demand (SC minus OS contrast) increased activity in bilateral prefrontal, anterior cingulate, and cerebellar areas, whereas increased switching demand (Switch minus No Switch contrast) led to greater activity in the bilateral superior parietal cortex. The current study will utilize an overt version of this paradigm to assess the impact of retrieval and between-category switching demands and FTD on regional brain activation in healthy volunteers and individuals with schizophrenia.

2. Experimental Materials and Methods

2.1. Participants

The final sample consisted of 13 patients with schizophrenia (7 female) and 14 healthy comparison subjects (6 female) from the Schizophrenia Center at the University of Pennsylvania. This sample did not include one comparison subject who later developed a psychiatric illness and one patient with excessive motion. Groups did not differ in age (comparison subjects: mean=34.3 years, SD=9.3; patients: mean=36.2 years, SD=6.9), education (comparison subjects: mean=13.6 years, SD=1.5; patients: mean=13.5 years, SD=2.6), or parental education (comparison subjects: mean=13.0 years, SD=2.9; patients: mean=14.3 years, SD=2.9). All comparison subjects and all but two patients were right-handed.

2.2. Clinical Evaluation

Research participants underwent standardized assessment, consisting of medical, neurological, psychiatric, and laboratory tests. The psychiatric evaluation for patients included clinical assessment, structured interview (First et al., 1996), history obtained from family, care providers, and records, and scales for measuring symptoms and functioning administered by investigators trained to a criterion reliability of 0.90, intra-class correlation. All patients had a DSM-IV (APA, 1994) diagnosis of schizophrenia or schizoaffective disorder - depressed type and no history of any other disorder or event that might affect brain function.

Patients were mildly to moderately ill according to the Scale for Assessment of Negative Symptoms (SANS; Andreasen et al., 1983; mean score=36.6, SD=31.8, range=0–124), Scale for Assessment of Positive Symptoms (SAPS; Andreasen et al., 1984; mean score=19.5, SD=14.2, range=2–46), and Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1980; mean score=33.8, SD=9.32, range=18.0–47.0). Patient speech samples were rated for FTD using the Communication Disorders Index (CDI; Docherty et al., 1996). After establishing inter-rater reliability (ICC=.85) two raters (MTB and STM) scored 10 minute speech transcripts for total communication failures, which were converted to frequency scores (per 100 words), and log transformed to normalize distributions. Patients had an average CDI score of 1.8 (SD=1.1, range 0.1–4.1), indicating mild to moderate communication failures. All patients were medicated (5 first generation, 8 second generation), with average daily dose of 415 mg/day in chlorpromazine equivalents (SD=261, range=200–1067) and 16.6 mg/day in olanzapine equivalents (SD=10.5, range=8.00–42.7). No patient was receiving anticholinergic or other psychotropic medication. Average age of onset of psychotic symptoms in the context of functional decline was 22.3 ± 7.51 (range 13–36), with illness duration of 10.6 ± 7.23 years.

Healthy participants underwent the same intake evaluation procedures and were administered the SCID non-patient version and the SCID-II (First et al., 1995, 1997). They had no history of illness affecting brain function or major psychiatric illness in first-degree relatives. After complete description of the study written informed consent was obtained.

2.3. Test Procedures

A modified version of the OS/SC word generation paradigm (Gurd et al., 2002) was administered as a block design during fMRI. Participants were asked to generate words during 4 conditions: over-learned sequence fluency (OS) – subjects produced words from single known ordered lists (days of the week, months of the year, numbers, letters of the alphabet); semantic category fluency (SC) – subjects produced words from a single semantic category (fruits, vehicles, furniture, vegetables); OS switching (OS Switch) – subjects alternated between two known lists (e.g., “one”, “Monday”, “two”, “Tuesday”); SC switching (SC Switch) – subjects alternated between two semantic categories (e.g., “chair”, “peach”, “table”, “apple”). Each condition was repeated twice in a pseudo-random order in blocks of 7 trials each, with a 4 sec. presentation rate and 2 sec. inter-stimulus-interval (ISI). A trial began with a visual cue (e.g., “Produce Fruit”) that remained on the screen during the 4 sec. verbal response window, and was replaced with a visual cross hair during the subsequent 2 sec. ISI. Participants were instructed to respond “Skip” if unable to generate a word on a given trial. There were also 8 baseline blocks (repeat the word “Rest”) between conditions.

Unlike the original covert version of the task, a compressed image acquisition sequence (Abrahams et al., 2003) was used to provide silent periods for generation of overt responses that were recorded by the task administrator. Each run lasted 11.2 min., and was repeated once, for a total task time of 23 minutes. Task administration was triggered by the scanner and coupled to image acquisition using the PowerLaboratory® platform (Chute & Westall, 1997). All

subjects correctly completed practice trials before imaging to ensure comprehension and familiarity with the response apparatus.

2.4. Image Acquisition

Data were acquired on a 3T Siemens Trio Scanner. A 5 minute magnetization-prepared, rapid acquisition gradient echo image (MPRAGE) was acquired for anatomic overlays of functional data and spatial normalization (Talairach & Tournoux, 1988). fMRI was acquired with blood oxygenation level dependent imaging (BOLD) (Bandettini et al., 1992) using a 36 slice whole-brain, single-shot gradient-echo (GE) echo-planar (EPI) sequence (TR/TE=6000/30 ms, FOV=240 mm, matrix= 64 X 64, slice thickness/gap=3/0.75 mm). A compressed pulse sequence (Abrahams et al., 2003) was used in which image acquisition occurred during the first 2 seconds of the TR, and overt word responses were generated during the subsequent 4 seconds when there was no sound from the MR gradients.

2.5. Data Analysis

Performance was indexed by measuring total number of words correctly generated (excluding “Skip” responses and non-responses). Repeated-measures multivariate analysis of variance (MANOVA) tested for effects of group (2 levels), condition (4 levels), fMRI run (2 levels), and higher order interactions. Significance threshold was set at $p < .05$ (two-tailed).

fMRI data were preprocessed in SPM2 (Wellcome Department of Cognitive Neurology, London, UK) using standard procedures. Images were slice-timed and motion-corrected to the median image using tri-linear interpolation. Despite overt word production, the amount of motion was small (less than 1.4 mm, and .03 degrees in all dimensions), and did not differ between groups for either translational [$F(1,25) = 0.32$, $p = .58$] or rotational parameters $F(1,25) = 0.28$, $p = .60$]. Structural images were co-registered to their median image, and spatial normalization parameters of the structural image to a standard T1 template were applied to all functional images. Resulting images were spatially smoothed (6mm FWHM, isotropic) and high-pass filtered (0.006 Hz).

Subject-level statistical analyses were performed using the general linear model in SPM2. Condition events were modeled using a modified boxcar haemodynamic response function. There were 4 event types: OS, SC, OS-switch, and SC-switch. Contrast maps were obtained through linear contrasts of event types. Random effects analyses were performed in SPM2 for within- and between-group comparisons. Within-group analyses were accomplished by entering whole brain contrasts for comparison subjects and patients separately into one-sample t-tests. Between-group analyses were accomplished by entering whole brain contrasts for each group into two-sample t-tests, with inclusive masks to restrict analysis to voxels with above-threshold activation obtained from within-group contrasts. A significance threshold of $p < .05$ corrected for multiple comparisons was calculated using a Monte Carlo simulation in AlphaSim (Ward, 2000) resulting in a height threshold of $p < 0.005$, requiring a minimum of 10 voxels in a cluster. Simple regression analyses were performed in SPM2 to examine correlations between task related activation and FTD in patients. Regressions utilized inclusive masks to restrict analyses to voxels with above-threshold task activation ($p < .05$, uncorrected), and were then corrected for multiple comparisons as previously described.

3. Results

3.1. Behavioral Data

All participants understood instructions and completed tasks with minimal errors. As illustrated in Table 1, there were no main effects of group [$F(1,25)=2.18$, $p=.15$], fMRI run [$F(1,25)=.05$, $p=.82$], or group by fMRI run interaction [$F(1,25)=.63$, $p=.43$]. There was an effect of task

condition [$F(1,25)=6.29$, $p<.05$], that did not interact with group [$F(1,25)=.47$, $p=.50$] or fMRI run [$F(1,25)=1.03$, $p=.32$]. Task effects reflected better performance during OS than SC [$t(26)=-5.48$, $p<.001$], during OS than OS-switch [$t(26)=2.30$, $p<.05$] and during OS-switch than SC-switch [$t(26)=-2.59$, $p<.05$]. The addition of a switching component did not affect SC performance [$t(26)=-.67$, $p<.51$].

3.2. fMRI Data

3.2.1. Effect of Retrieval Effort—Supporting our hypothesis, there were no between-group differences in fMRI activation during the OS condition (Table 2). Both groups showed bilateral activation in inferior frontal, middle frontal, and inferior parietal regions, with additional healthy control activation in the left cerebellum, and additional patient activation in the left postcentral gyrus and STG. As seen in Table 3, group differences were present for the SC minus baseline contrast. Comparison subjects had greater activation than patients in the right caudate. Patients had greater activation than comparison subjects in left prefrontal and motor cortex, right anterior cingulate gyrus, bilateral insula, right putamen, bilateral middle and STG, left inferior and superior parietal lobule, left lingual gyrus, left cuneus and precuneus, and cerebellum.

When the effect of increased retrieval demand was directly tested (SC minus OS contrast) both groups activated the left ventrolateral prefrontal cortex (VLPFC, BA 45, 47). This VLPFC activation was also seen in a previous positron emission tomography (PET) study of healthy volunteers (Gourovitch et al., 2000) that contrasted semantic fluency with a control task similar to the OS condition. Healthy subjects also activated the left anterior cingulate, left caudate and right putamen, and patients showed additional activation in bilateral middle frontal gyrus, left superior temporal gyrus, left parahippocampal gyrus and right caudate (Table 4). Between-group contrasts did not reveal any areas of greater comparison subject versus patient activation. However, the opposite contrast revealed that patients had increased activation relative to controls in the left STG, right middle temporal gyrus, right parahippocampal gyrus, and left cuneus (Figure 1).

3.2.2. Effect of Switching Demand—Adding a switching component differentially affected fMRI activation in the two groups. When retrieval demand was low (OS Switch minus OS No Switch contrast) comparison subjects did not show any areas of increased activation. However, patients increased activity in the right putamen, right lingual gyrus and left precuneus (Table 5), and their activation was greater than comparison subjects in the right middle frontal gyrus, anterior and posterior aspects of the left caudate, right thalamus, bilateral middle temporal gyrus, left STG, and right superior parietal lobule. When the retrieval demand was high (SC Switch minus SC No Switch contrast; Table 6), addition of a switching component increased right superior parietal activation in healthy comparison subjects, consistent with previous findings (Gurd et al., 2002). Patients also activated the right superior parietal lobule, and showed additional effects in the right precuneus. Between group contrasts did not reveal any areas of greater comparison subject activation. However, patients had greater activation than comparison subjects in the left medial frontal cortex.

3.2.3. Relationship with Thought Disorder—Regression analyses revealed inverse findings for FTD relationships with retrieval effort and switching demand (Table 7). There were no correlations for the OS minus baseline contrast. For the SC minus baseline contrast higher FTD was associated with lower activation in right anterior cingulate and cuneus. A negative relationship was also found between FTD and activity in the right superior frontal gyrus for the SC minus OS contrast. For the OS Switch minus No Switch contrast higher FTD was associated with greater activation in left lingual gyrus and right fusiform gyrus. There was

also a positive FTD correlation for the SC Switch minus No Switch contrast in the left superior parietal lobule.

4. Discussion

Under non-speeded task conditions patients with schizophrenia can successfully perform semantic word generation tasks even when word retrieval and switching demands are increased. This supports previous conclusions that reduced processing speed contributes to verbal fluency deficits in schizophrenia (Vinogradov, 2002). During fMRI patients had normal frontal and parietal lobe activation when generating words to over-learned sequences where retrieval demands were low. However, when generating words during more effortful SC conditions, patients had increased left STG activation relative to controls. This increase in patient versus control STG activation was characteristic of previous phonemic and semantic fluency studies (Frith et al., 1995; Liddle 1997; Yurgelun-Todd et al., 1996). Over-activation was also observed when a between-category switching demand was added. STG over-activation extended to PFC, middle temporal, parietal, and basal ganglia regions. Results suggest that during paced, over-learned conditions, neural mechanisms of lexical retrieval and word generation are relatively intact in schizophrenia, and that poorly modulated neural response during standard fluency tasks is secondary to well documented deficits (Braff, 1993; Liddle, 1993; Cohen & Servan-Schreiber, 1992) in cognitive control.

In the current study controlled processing demands increased at word selection and generation stages as subjects moved from OS to SC conditions. During the OS condition selection of category exemplars required minimal control because strong direct links between associated nodes in the network facilitated an automatic spread-of-activation (Collins & Loftus, 1975) between related exemplars (e.g., “Monday”, “Tuesday”). Post-retrieval monitoring demands were also low because words were generated in a fixed sequence. Previous lexical priming studies have shown that patients are relatively unimpaired in automatic aspects of lexical processing (Minzenberg, Ober & Vinogradov, 2002). In contrast, SC conditions increased selection demand as subjects had to choose semantic subcategories to guide search (e.g., household furniture), and switch to new subcategories (e.g., office furniture) once exemplars from the previous subcategory were exhausted. Increased post-retrieval monitoring was also required to avoid repetitions since exemplars were no longer generated in a fixed sequence. Addition of a between-category switching component added further post-retrieval monitoring and additional response inhibition demands.

Initial verbal fluency imaging studies (Frith et al., 1995; Liddle 1997; Yurgelun-Todd et al., 1996) found reduced PFC and increased STG activation in patients, consistent with a fronto-temporal disconnection model (Friston and Frith, 1995) that has received support from recent functional connectivity studies (Jennings et al., 1998; Meyer-Lindenberg, 2005; Wolf et al., 2007). However, we found patient increases rather than decreases in PFC activity, which does not fit the classic disconnection model. A possible explanation for the current pattern of greater patient than control increases in the PFC and other regions is the inverted-U physiological inefficiency model (Callicott et al., 2003), which postulates that patients have reduced levels of activation when poorly performing a task that exceeds their capacity and increased levels of activation when accurately performing a task that is at their capacity. The current task paradigm employed a slowly paced cued presentation initially developed for early dementia patients. It is likely that even when retrieval and switching demands were increased the task was non-demanding for healthy subjects, but challenging for patients - placing them in the over-activation portion of the inverted-U function. The absence of group performance differences in even the most demanding task conditions suggest that patients never exceeded their cognitive capacity and, therefore, never entered the downward going portion of the inverted-U function that would lead to reduced PFC response. Optimizing fMRI designs to

match groups on mental effort rather than simply on level of performance is receiving increased attention (Karlsborg et al., 2007) and is an important consideration for future studies.

Formal thought disorder has long been associated with executive dysfunction and semantic memory impairment (Kerns & Berenbaum, 2002; Spitzer, 1997), STG gray matter reductions (Rajarethinam et al., 2000), and disrupted frontal and temporal lobe function during semantic tasks (Kircher et al., 2001a,b; Shenton et al., 1997). The current study did not find any FTD relationship with STG, and found reciprocal correlations for anterior and posterior brain regions depending upon task contrast. At high levels of retrieval demand (SC minus baseline contrast) more severe FTD was associated with reduced activation in dorsal anterior cingulate gyrus (ACC) and cuneus. Previous studies have found both negative (McGuire et al., 1998) and positive (Assaf et al., 2005; Liddle et al., 1992) correlations between ACC activity and FTD. The dorsal ACC is associated with conflict detection and response monitoring (Barch et al., 2000), and it is possible that more severely thought disordered patients were less able to detect conflict resulting in attenuated ACC activity. A negative correlation with FTD was also found in the right superior frontal gyrus for the SC minus OS task comparison. This contrasts with the positive correlation found with FTD in this same region by Kircher and colleagues (2001b) who scanned subjects while they were describing Rorschach inkblots.

In contrast, positive correlations were found between posterior brain regions (lingual gyrus, fusiform gyrus and superior parietal lobule) and FTD when the effect of increased switching demand was examined (OSswitch-OS, and SCswitch-SC contrasts). The fusiform gyrus has previously shown positive associations with FTD during sentence completion (Kircher et al., 2001a) and speech production tasks (McGuire et al., 1998). This relationship was also recently observed in an fMRI semantic priming paradigm and attributed to an increased spread of activation in more thought disordered patients (Kuperberg et al., 2007). There is less of a literature on the role that the superior parietal cortex and lingual gyrus might play in FTD and semantic memory impairment. In discussing the superior parietal cortex in relation to the current task Gurd and colleagues (2002) emphasized that it plays a role in the control of attentional switching across spatial and non-spatial stimulus modes. The lingual gyrus has also been associated with top-down control of visuospatial selective attention (Hahn, Ross, and Stein, 2006). Increased activation of parietal and lingual gyrus regions in more thought disordered patients may, therefore, reflect greater need for attentional control in these subjects.

There were certain limitations that deserve mention. First, all of the patients were treated with antipsychotic medications and there is some evidence that this can increase metabolism and blood flow in the basal ganglia (Miller et al., 1998) and possibly in the prefrontal cortex (Honey et al., 1999). Medication may, therefore, have contributed to fMRI over-activation. The sample was somewhat small, which likely reduced statistical power, and included two left-handed patients, which might have influenced laterality effects. Although the slowly-paced cued word format of the current study insured that patients were able to perform the task and controlled for total word production, it did not allow us to do a more detailed analysis of task performance. An advantage of standard self-paced verbal fluency tasks is that they allow for differentiation of more automatic generation of words within a category (i.e., clustering) from the more controlled process of generating words from a new category (i.e., switching). Comparing these two processes can provide information on the organizational structure of semantic memory in healthy and clinical populations. Because clustering is a relatively automatic process, items that are clustered co-occur in much closer temporal proximity (Lockhead, Gruenewald, King, 1978) than did the responses in our current cued response format. Because of this built-in response delay, we were not comfortable interpreting the meaning of word sequences within each task and relied instead on OS and SC contrasts to make inferences about the level of automatic and controlled processing. A possible solution in future studies would be to combine

the current fMRI paradigm with a comprehensive neuropsychological assessment of semantic memory.

In summary, our data suggest that it is the controlled processing demands of word production tasks that lead to group differences in brain activation between patients with schizophrenia and healthy comparison subjects even when groups are matched on behavioral performance. When patients are not under speeded conditions and can rely on overlearned retrieval processes activation in frontal and parietal regions is unimpaired. Our study also joins others (Barch et al., 1999) in demonstrating the feasibility of administering overt word production tasks during functional imaging.

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Figure 1. Blood-Oxygen-Level-Dependent fMRI Signal Change During Semantic Category (SC) Minus Over-Learned Sequence (OS) Word Generation. Statistical parametric maps are surface-rendered on smoothed brain images to illustrate activation in patients (red color) and controls (green color). Overlapping activation is illustrated in yellow. Colored areas indicate a difference in signal change that exceeds a threshold corresponding to a corrected p-value of 0.05.

Table 1
Performance During No Switching and Switching Conditions of an Overlearned Sequence (OS) versus Semantic Category (SC) Word Generation Task in Patients with Schizophrenia and Healthy Comparison Subjects.

Task Condition	Patients (N=13)		Comparison Subjects (N=14)	
	M	SD	M	SD
No Switching				
Overlearned Sequence, run 1	13.92	0.28	14.00	0.00
Overlearned Sequence, run 2	13.92	0.28	14.00	0.00
Semantic Category, run 1	13.00	1.08	13.07	1.00
Semantic Category, run 2	12.69	1.55	13.00	0.96
Switching				
Overlearned Sequence, run 1	13.62	0.87	13.71	0.47
Overlearned Sequence, run 2	13.62	0.87	13.93	0.27
Semantic Category, run 1	12.69	1.38	13.43	0.94
Semantic Category, run 2	12.62	2.26	13.5	0.76

Local Cluster-Level Maxima of Blood-Oxygen-Level-Dependent fMRI Signal Change During Over-learned Sequence (OS) versus Baseline Word Generation in Healthy Comparison Subjects and Patients With Schizophrenia.

Group and Region	Estimated Brodmann's Area	z Score ¹	x	Coordinates ²		z
				y		
Comparison subjects (n=14)						
Left Inferior Frontal Gyrus	47	4.77	-27	35		2
Right Middle Frontal Gyrus	9	3.53	50	22		34
Right Middle Frontal Gyrus	8	3.07	33	17		41
Left Inferior Parietal Lobule	40	3.30	-53	-42		37
Right Inferior Parietal Lobule	40	3.51	53	-35		49
Right Superior Parietal Lobule	7	3.05	33	-62		51
Left Cerebellum	-	3.10	-15	-71		-25
Patients (n=13)						
Right Inferior Frontal Gyrus	9, 46	3.89	48	4		20
Left Middle Frontal Gyrus	9, 46	3.25	-50	24		23
Right Middle Frontal Gyrus	9	3.65	39	31		36
Right Middle Frontal Gyrus	6	3.77	36	6		55
Medial Frontal Gyrus	6	4.03	0	3		59
Right Medial Frontal Gyrus	6	3.46	3	17		44
Left Postcentral Gyrus	6, 43	3.76	-53	-11		21
Left Superior Temporal Gyrus	22	5.04	-59	-37		9
Left Superior Temporal Gyrus	22	4.61	-56	3		4
Left Inferior Parietal Lobule	40	4.43	-50	-33		47
Right Inferior Parietal Lobule	40	3.61	53	-35		49

¹ **Note:** Peak activation in a cluster of at least ten voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05;

² Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).

Table 3

Local Cluster-Level Maxima of Blood-Oxygen-Level-Dependent fMRI Signal Change During Semantic Category (SC) versus Baseline Word Generation in Healthy Comparison Subjects and Patients With Schizophrenia.

Group and Region	Estimated Brodmann's Area	z Score ^J	x	Coordinates ² y	z
<i>Comparison Subjects (n=14)</i>					
Left Middle Frontal Gyrus	10	3.8	-27	47	15
Right Middle Frontal Gyrus	9	3.26	42	34	30
Left Superior Frontal Gyrus	6, 32	5.35	-3	6	59
Right Precentral Gyrus	9	3.75	36	5	35
Left Insula	13, 47	4.71	-33	18	3
Right Insula	13	3.81	33	14	-4
Right Cerebellum	-	4.09	36	-48	-30
<i>Patients (n=13)</i>					
Left Superior Frontal Gyrus	6	4.83	-9	12	62
Right Medial Frontal Gyrus	6	4.81	3	14	44
Left Thalamus	-	3.57	-12	-14	14
Right Lentiform Nucleus	-	3.92	15	-6	0
Left Superior Temporal Gyrus	22, 39	4.63	-50	-52	10
Right Superior Temporal Gyrus	22	3.67	48	-35	5
Right Middle Temporal Gyrus	21	3.19	56	-41	-5
Left Inferior Parietal Lobule	40	4.11	-53	-41	47
Left Middle Occipital Gyrus	19	3.75	-50	-56	-7
Left Lingual Gyrus	17	4.46	-12	-90	-2
Right Lingual Gyrus	17	3.63	15	-84	4
Left Cerebellum	-	3.93	-33	-65	-22
Right Cerebellum	-	4.28	3	-74	-22
Right Cerebellum	-	3.92	45	-60	-26
<i>Comparison Subjects > Patients</i>					
Right Caudate	-	3.04	9	9	13
<i>Patients > Comparison Subjects</i>					
Left Middle Frontal Gyrus	9	3.75	-42	30	26
Left Middle Frontal Gyrus	6	3.06	-24	0	51
Left Precentral Gyrus	6, 9	3.61	-53	-4	31
Left Precentral Gyrus	4	3.23	-42	-3	52
Left Precentral Gyrus	44	3.39	-42	15	7
Right Cingulate Gyrus	32	2.94	3	16	34
Left Insula	13	3.62	-36	-39	26
Right Insula	13, 45	3.05	39	12	7
Right Lentiform Nucleus	-	3.38	24	6	0
Left Middle Temporal Gyrus	37	3.26	-45	-50	-7
Right Middle Temporal Gyrus	37	3.21	50	-7	-7
Right Middle Temporal Gyrus	21	3.43	50	-40	12
Left Superior Temporal Gyrus	22	3.28	-45	-21	-6
Left Superior Temporal Gyrus	39	4.73	-53	-52	10
Right Superior Temporal Gyrus	22	3.13	48	-35	5
Left Inferior Parietal Lobule	40	3.73	-53	-41	47
Left Superior Parietal Lobule	7	3.67	-12	-64	58
Left Lingual Gyrus	19	4.29	-15	-58	-4
Left Lingual Gyrus	18	3.74	-9	-73	4
Left Cuneus	17, 18	4.28	-15	-90	4
Left Precuneus	7	3.80	-6	-59	48
Cerebellum	-	3.20	0	-74	-22

¹ **Note:** Peak activation in a cluster of at least ten voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05;

² Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).

Local Cluster-Level Maxima of Blood-Oxygen-Level-Dependent fMRI Signal Change During Semantic Category (SC) versus Over-learned Sequence (OS) Conditions in Healthy Comparison Subjects and Patients With Schizophrenia.

Group and Region	Estimated Brodmann's Area	z Score ¹	Coordinates ²		
			x	y	z
Comparison subjects (n=14)					
Left Inferior Frontal Gyrus	47	4.62	-36	17	-8
Left Inferior Frontal Gyrus	45	3.77	-39	21	16
Left Anterior Cingulate Gyrus	32	5.15	-6	22	37
Left Caudate	-	4.32	-12	-11	21
Right Putamen	-	4.83	21	-2	20
Patients (n=13)					
Left Inferior Frontal Gyrus	45	4.16	-45	24	19
Left Medial Frontal Gyrus	6	3.70	0	11	44
Left Middle Frontal Gyrus	6	3.53	-24	2	45
Right Middle Frontal Gyrus	6	3.65	30	-13	38
Right Middle Frontal Gyrus	9	2.96	53	10	34
Left Superior Temporal Gyrus	38	3.43	-48	8	-10
Left Parahippocampal Gyrus	27	3.79	-6	-32	-5
Right Caudate	-	3.33	18	7	17
Patients > Comparison Subjects					
Left Superior Temporal Gyrus	22	3.06	-45	-21	-6
Right Middle Temporal Gyrus	21	3.54	50	-40	12
Right Parahippocampal Gyrus	36	3.80	24	-30	-14
Left Cuneus	17	3.41	-18	-90	4

¹ **Note:** Peak activation in a cluster of at least ten voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05;

² Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).

Local Cluster-Level Maxima of Blood-Oxygen-Level-Dependent fMRI Signal Change During Over-Learned Sequence Switch (OS Switch) versus Over-learned Sequence No Switch (OS No Switch) Conditions in Healthy Comparison Subjects and Patients With Schizophrenia.

Group and Region	Estimated Brodmann's Area	z Score ¹	Coordinates ²		
			x	y	z
<i>Patients (n=13)</i>					
Right Lenticular Nucleus	-	4.04	24	-20	1
Right Lingual Gyrus	18	3.98	15	-76	-15
Left Precuneus	7	2.99	-24	-59	34
<i>Patients > Comparison Subjects</i>					
Right Middle Frontal Gyrus	6	3.2	24	-6	52
Left Caudate	-	4.09	-15	-28	29
Left Caudate	-	3.21	-30	-32	2
Right Thalamus	-	3.99	18	-23	5
Left Middle Temporal Gyrus	19	3.69	-30	-52	16
Right Middle Temporal Gyrus	21	2.87	50	-41	-5
Left Superior Temporal Gyrus	41	3.49	-42	-40	9
Right Superior Parietal Lobule	7	3.02	30	-56	40

¹ **Note:** Peak activation in a cluster of at least ten voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05;

² Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).

Local Cluster-Level Maxima of Blood-Oxygen-Level-Dependent fMRI Signal Change During Semantic Category Switch (SC Switch) versus Semantic Category No Switch (SC No Switch) Conditions in Healthy Comparison Subjects and Patients With Schizophrenia.

Group and Region	Estimated Brodmann's Area	z Score ¹	Coordinates ²		
			x	y	z
Comparison subjects (n=14)					
Right Superior Parietal Lobule	7	3.87	3	-64	55
Patients (n=13)					
Right Superior Parietal Lobule	7	3.79	27	-53	44
Right Precuneus	7	3.3	24	-67	51
Patients > Comparison Subjects					
Left Medial Frontal Gyrus	6	4.15	-15	-12	59

¹ **Note:** Peak activation in a cluster of at least ten voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05;

² Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).

Local Cluster-Level Maxima of Significant Correlation Between Blood-Oxygen-Level-Dependent fMRI Signal Change and Formal Thought Disorder Ratings on the Communication Disorders Index (CDI) in Patients With Schizophrenia.

Contrast and Region	Estimated Brodmann's Area	z Score ¹	Coordinates ²			z
			x	y	z	
SC (negative)						
Right Anterior Cingulate	32	3.38	12	27		19
Right Cuneus	17	3.7	9	-90		4
SC-OS (negative)						
Right Superior Frontal Gyrus	6	2.7	3	32		54
OSSW-OS (positive)						
Left Lingual Gyrus	17	3.17	-15	-87		1
Right Fusiform Gyrus	19	3.1	21	-79		-15
SCSW-SC (positive)						
Left Superior Parietal Lobule	7	3.41	-30	-55		58

¹Note: Significant correlation in a cluster of at least ten voxels in which the difference in signal change exceeded an extent and threshold corrected p-value of 0.05;

²Coordinates from the stereotaxic atlas of Talairach and Tournoux (1988).