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# Associative Memory Processes in Schizophrenia

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# ASSOCIATIVE MEMORY PROCESSES IN SCHIZOPHRENIA

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Abstract

Individuals with schizophrenia demonstrate cognitive deficits in a number of domains, including episodic memory (EM). Memory for both individual items and associations between items is impaired in schizophrenia, with some indication of a more severe deficit in associative memory. Furthermore, such memory impairments have been consistently linked with abnormalities in brain activation during both encoding and retrieval. However, certain experimental manipulations at the encoding and retrieval stages of EM significantly benefit memory performance in schizophrenia, suggesting that a strategic processing deficit may underlie memory impairment in schizophrenia. Additionally, the provision of beneficial encoding strategies increases encoding-related brain activity in key memory processing regions in schizophrenia participants, although such manipulations have not yet been tested in participants with schizophrenia during retrieval. The goal of the current study was to examine the impact of encoding and retrieval strategies on associative memory function and brain activity in schizophrenia. Behavioral and functional neuroimaging data were collected from 23 DSM-IV diagnosed participants with schizophrenia and 24 demographically equivalent comparison subjects while performing associative memory encoding and recall tasks in the fMRI scanner. Two factors of interest were manipulated and studied: 1) orientation to the semantic relatedness of associative pairs; and 2) provision of memory cues at subsequent recall. Behaviorally, schizophrenia participants (like controls) demonstrated significant memory benefits from both the provision of support for effective encoding (orientation to semantic relatedness) and retrieval strategies (provision of memory cues). In addition, support for the use of an effective encoding strategy was also associated with increased

brain activity in a variety of brain areas in schizophrenia participants, whereas the manipulation of retrieval strategies did not serve to increase retrieval-related brain activity among individuals with schizophrenia. Lastly, both groups showed significant associations between inherent semantic processing ability and episodic memory performance. Schizophrenia participants also demonstrated significant associations between semantic processing ability and semantic encoding-related brain activity in prefrontal cortex, whereas controls did not show any such relationships. Overall, these findings suggest that memory performance in schizophrenia can be improved via manipulations at the encoding and retrieval stages, and that brain activity enhancements are observed under supportive encoding conditions as well. These data also provide evidence that individual differences in cognitive abilities among individuals with schizophrenia can significantly affect behavioral and neurobiological responses to strategic memory interventions. Finally, the current findings suggest that individuals with schizophrenia and healthy individuals rely on partially overlapping networks of brain regions to support EM processes under supportive conditions. Although certain deficits in memory performance and brain activation persist, it is clear that orientation to advantageous memory strategies can partially ameliorate EM function among individuals with schizophrenia.

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## Chapter 1: Introduction and Overview

Schizophrenia is a neuropsychiatric disease that is characterized by profound impairments in a number of cognitive abilities. Among these, deficits in *episodic memory* (EM) function are some of the most salient. Episodic memory is a past-oriented memory system, likely unique to humans, which allows for mental time travel and supports memory for unique events (Tulving, 2002). As such, EM encompasses both *item memory* (memory for individual items) and *associative memory* (memory for associations between items). Individuals with schizophrenia demonstrate deficits in both forms of memory. For example, significantly lower recognition and recall rates of individual items have been found for participants with schizophrenia, as compared to healthy control participants (Barch *et al.*, 2002; J. M. Gold *et al.*, 1992; Hazlett *et al.*, 2000; Jessen *et al.*, 2003). Others have reported impaired performance on associative memory tasks in participants with schizophrenia, relative to controls (Bazin & Perruchet, 1996; Danion *et al.*, 1999; Elvevag *et al.*, 2000; Waters *et al.*, 2004).

EM deficits found in schizophrenia may be related, at least in part, to memory strategy deficits at the encoding and retrieval stages. For example, individuals with schizophrenia fail to encode stimuli as deeply as controls and are less likely to generate effective strategies to learn new information (Brebion *et al.*, 1997; Iddon *et al.*, 1998). Individuals with schizophrenia also fail to benefit from commonalities among to-be-learned material (such as semantic relatedness) in order to facilitate learning (Hazlett et al., 2000; Nohara *et al.*, 2000). Thus, there is convincing evidence that strategy deficits and memory impairments are linked to some degree in schizophrenia.

Importantly, however, studies that have constrained encoding strategy use or provided advantageous schemas at encoding have shown that participants with schizophrenia show memory benefits from such interventions. For example, studies that have utilized the levels-of-processing paradigm (Craik & Lockhart, 1972) in schizophrenia have shown that members of this group recognize words that have been processed "deeply" significantly better than those they have processed in a "shallow" manner (Bonner-Jackson *et al.*, 2005; Kubicki *et al.*, 2003; Paul *et al.*, 2005; Ragland *et al.*, 2005; Ragland *et al.*, 2003). Such evidence indicates that memory dysfunction in schizophrenia may be related to an underlying impairment in strategic memory processing, rather than being a permanent fixture of the disease. Of note, however, is the finding that although such encoding manipulations benefit individuals with schizophrenia, they do not fully "normalize" memory performance. This may be attributable to the fact that participants with schizophrenia are not typically provided with an effective strategy or framework with which to retrieve information. Therefore, supportive conditions at both the encoding and retrieval stages may be required in order for memory performance in individuals with schizophrenia to be equivalent to that of control participants. Indeed, the presence of support or cues at retrieval has been shown to profoundly influence retrieval success in schizophrenia (Sengel & Lovallo, 1983). Thus, it may be possible to equate memory performance in control and schizophrenia subjects using beneficial techniques at both of these crucial processing stages.

In addition to numerous behavioral studies that have identified EM deficits in schizophrenia, functional neuroimaging studies of memory processing in schizophrenia have consistently identified abnormal activation patterns in a number of cortical and

subcortical regions (Barch et al., 2002; Heckers *et al.*, 1998; Hofer *et al.*, 2003a; Ragland *et al.*, 2004), including prefrontal cortex (PFC), which is thought to govern the generation and application of memory strategies, and parts of medial temporal lobe (MTL), which is also crucial for EM function. The deficits observed in frontal cortex function may be related to the strategic impairments that have been found in participants with schizophrenia. Neuroimaging studies in participants with schizophrenia have consistently identified cortical activation impairments in PFC during verbal item encoding (Hofer *et al.*, 2003b; Kubicki et al., 2003; Ragland *et al.*, 2001; Rubin, 1998). Furthermore, even when beneficial strategies are provided at encoding, participants with schizophrenia show dysregulation of activity in PFC and hippocampal regions during verbal item retrieval, with greater than normal PFC activity combined with underactivation of hippocampus (Heckers et al., 1998; A. P. Weiss *et al.*, 2003). Given that strategic deficits likely underlie some of the activation deficits observed in schizophrenia, it is possible that the provision of beneficial memory strategies during both the encoding and retrieval stages would promote brain activity in prefrontal and hippocampal structures closely resembling that of control participants.

Although there have been numerous functional neuroimaging studies of item memory in schizophrenia, few imaging studies investigating associative memory in schizophrenia exist. However, results of certain behavioral studies may allow us to draw preliminary conclusions regarding brain function in individuals with schizophrenia during associative memory paradigms. For example, a key component of associative memory organization, called *transitive inference*, is impaired in individuals with schizophrenia (Titone *et al.*, 2004) and is associated with activity in medial temporal lobe

(Heckers & Titone, 2005). Furthermore, individuals with schizophrenia are impaired on other tasks that strongly rely on the integrity of medial temporal lobe regions, including tests of binding and memory for context (Waters et al., 2004). Because successful associative encoding is hypothesized to require modulation of both hippocampal and prefrontal cortex structures, impaired item and associative memory task performance in schizophrenia may be related to dysfunction in these critical brain structures.

While most neuroimaging research of memory in schizophrenia has found impaired memory function in combination with abnormal patterns of brain activation, experimental interventions at the encoding stage can improve task performance and normalize brain activity (Bonner-Jackson et al., 2005; Ragland et al., 2005). Furthermore, constraining encoding processes during associative memory tasks may have similar effects on behavior and brain activity. Although such interventions have been carried out in studies of item memory, to our knowledge there have been no such studies of brain activity during associative memory encoding in schizophrenia. The current study examined encoding of paired associates (words and scenes) using functional magnetic resonance imaging. The factors under study were the effects of orientation to semantic relatedness of word-scene pairs and the presence of retrieval cues on associative memory success and associative memory-related brain activity in schizophrenia. One goal of the proposed research was to test the hypothesis that associative memory function in individuals with schizophrenia can be improved both by the provision of effective encoding strategies and by the support of effective retrieval strategies. However, it was hypothesized that memory performance of schizophrenia participants would only be equivalent to that of controls when both types of support were provided. A second goal of

the proposed research was to test the hypothesis that individuals with schizophrenia would show brain activity equivalent to that of controls during associative encoding and retrieval of word-scene pairs when beneficial encoding strategies and retrieval cues were provided.

## Chapter 2: General Review of the Literature:

## Episodic Memory, Memory Strategy Use, and Functional Neuroimaging Studies

I will review the published literature in the areas relevant to this research: episodic memory, effect of memory strategies, and functional neuroimaging studies of episodic memory. This review will include empirical studies in these research domains related to participants with schizophrenia as well as healthy control populations. I will divide the review into research covering two domains – 1) episodic memory deficits in individuals with schizophrenia; and 2) findings from functional neuroimaging studies of individuals with schizophrenia. Within each section, I will examine findings related to episodic memory encoding, storage, and retrieval, including patterns of memory performance and brain activity impairment typically observed in schizophrenia, as well as factors that contribute to improvements in behavior or more "normalized" patterns of brain activity.

### Episodic Memory Deficits in Schizophrenia

As described above, *episodic memory* (EM) is a past-oriented memory system, likely unique to humans, which allows for mental time travel and supports memory for unique events (Tulving, 2002). EM has typically been categorized as one element of the declarative memory system and is posited to represent a memory system distinct from that of *semantic memory*, which refers to knowledge of facts or concepts. Episodic

memory has typically been divided into three separable stages: encoding, storage, and retrieval. *Encoding* refers to the initial learning stage of memory, in which information or knowledge is acquired. *Storage* refers to the maintenance of information over time. *Retrieval* refers to the process of accessing stored information. Empirical research on EM has utilized a wide variety of memory measures (e.g., recognition, free recall, cued recall) and stimuli in a number of different domains (e.g., words, faces, sounds, complex scenes).

*General evidence for the presence of EM deficits in schizophrenia.* Individuals with schizophrenia perform poorly on tests of EM function (Aleman *et al.*, 1999; Fioravanti *et al.*, 2005; Heinrichs & Zakzanis, 1998). Although there is some degree of variability between studies, the majority of research suggests at least a moderate EM impairment in individuals with schizophrenia. For example, a meta-analysis of 70 memory studies conducted by Aleman and colleagues detected a large effect size for verbal recall (d = 1.20) and a moderate effect size (d = 0.61) for verbal recognition performance in schizophrenia participants, as compared to healthy controls (Aleman *et al.*, 1999). Another meta-analysis of 113 studies by Fioravanti and co-workers found a standard mean difference (SMD) of 1.18 between control and schizophrenia participants on measures of memory (Fioravanti *et al.*, 2005). Finally, Heinrichs and Zakzanis (1998) reviewed 204 studies that compared individuals with schizophrenia to healthy control participants on a wide range of cognitive variables. The authors reported that global verbal memory performance represented the largest difference (as measured by effect size) between control and schizophrenia participants among all the variables studied (Heinrichs & Zakzanis, 1998). Large-scale meta-analyses and reviews such as these

suggest that memory deficits are a pervasive feature of the schizophrenia cognitive profile.

In addition to meta-analyses suggesting that EM function is consistently impaired in individuals with schizophrenia, there is also evidence that such deficits (particularly for verbal material) exceed the impairments observed in other cognitive domains. For example, a review of 110 studies by Cirillo and Seidman (2003) cited "overwhelming evidence" of a verbal declarative memory deficit in schizophrenia, and they suggested that deficits in verbal memory represent one of the most impaired functions in this disease (Cirillo & Seidman, 2003). Saykin and colleagues also found evidence for a selective deficit in verbal learning and memory compared to other cognitive functions among a sample of schizophrenia participants (Saykin *et al.*, 1991). Others have reported substantial memory deficits in individuals with schizophrenia that were determined to be disproportionate to intellectual functioning (Egeland *et al.*, 2003; McKenna *et al.*, 1990; Tamlyn *et al.*, 1992).

Research designs utilizing unaffected relatives of individuals with schizophrenia have also provided evidence of a specific verbal memory deficit in this disease (Sponheim *et al.*, 2004; Toulopoulou *et al.*, 2003a; Toulopoulou *et al.*, 2003b). For example, Toulopoulou and colleagues compared schizophrenia participants with their healthy relatives and control participants on a battery of cognitive measures. They found that individuals with schizophrenia were most impaired on measures of immediate verbal recall and visual learning and memory. The authors also identified difficulties with verbal memory and strategy formation in the relatives of schizophrenia participants and

suggested that a selective deficit in verbal memory may represent a significant risk factor for the development of schizophrenia (Toulopoulou et al., 2003a).

Despite strong evidence to support the notion of a selective deficit in verbal EM in schizophrenia (relative to deficits observed in other cognitive domains), the literature in this area is not entirely consistent. Specifically, in contrast to those studies outlined above that have identified selective deficits in verbal learning and memory in schizophrenia, others have reported more generalized memory impairments (Clare *et al.*, 1993; Rushe *et al.*, 1999). For example, Clare and co-workers (1993) compared individuals with schizophrenia and healthy comparison subjects on a number of long-term memory measures using a variety of paradigms. They reported that the schizophrenia group showed significant deficits on recall of prose material, as well as forced choice recognition of both words and faces (Clare et al., 1993). Rushe and colleagues (1999) also reported equivalent deficits on measures of verbal and non-verbal long term memory, as well as verbal and non-verbal paired associate learning, among a group of chronic schizophrenia participants (Rushe et al., 1999). Thus, there is not currently a consensus regarding the relative severity of verbal memory impairment and whether it is selectively impaired relative to other cognitive functions.

Multiple theories exist as to why deficits in verbal EM processing exist in schizophrenia. Below, I present evidence to support three prominent hypotheses regarding the underlying causes of these deficits: impairments at the encoding stage, impairments at the retrieval stage, and impairments in binding and associative memory processes.

*Evidence for encoding deficits in schizophrenia.* One line of evidence regarding verbal EM deficits in schizophrenia has suggested that such deficits are due to impairments at the encoding, or initial learning, stage of episodic memory. Before reviewing empirical work in this area, it is important to note that behavioral studies of EM encoding cannot solely implicate faulty encoding operations in the EM deficits that are typically seen among individuals with schizophrenia. It is possible that deficits at other stages (e.g., EM retrieval) contribute to EM dysfunction, and these studies are unable to dissociate these factors. Therefore, this fact should be considered in reviewing the following research that is putatively focused on the encoding stage of EM.

Some empirical studies have addressed verbal encoding processes in schizophrenia via word list learning paradigms, in which lists of words that vary in semantic relatedness are presented to participants. Encoding strategy is inferred based on the degree to which participants use this semantic relatedness to improve recall (Brebion *et al.*, 1997; Brebion *et al.*, 2004; Iddon *et al.*, 1998; Kareken *et al.*, 1996; Koh, 1978; Traupmann, 1980). For example, using word lists varying in semantic relatedness and typicality of exemplars, Brebion and colleagues (2004) found evidence for reduced semantic organization at recall in individuals with schizophrenia, which was hypothesized to reflect a decreased tendency to use inherent semantic relationship among to-be-learned items to improve encoding success. The authors also stated that such reduced organization makes a significant contribution to verbal memory deficits often observed in schizophrenia and may be linked to DLPFC pathology in this group (Brebion et al., 2004). Work by Iddon and co-workers (1998) found that individuals with schizophrenia were significantly impaired in their ability to spontaneously generate

memory strategies for both visuospatial and verbal memory tasks, with evidence for a disproportionate impairment on the verbal strategy task. As a result, verbal memory scores in the schizophrenia participants were significantly lower than in the control group (Iddon et al., 1998). A series of studies conducted by Koh (1978) determined that individuals with schizophrenia have difficulty in remembering various types of verbal material, including unrelated word lists and affective word lists, which could be partially attributed to the inefficiency of mnemonic organization on the part of individuals with schizophrenia (Koh, 1978). Russell and colleagues (1975) found that individuals with schizophrenia were unable to use inherent stimulus characteristics to increase performance. In their study, schizophrenia participants, unlike controls, did not show memory benefits for high-association word pairs, relative to low-association pairs. The authors concluded that a failure to effectively organize information at the encoding stage contributed to these findings (Russell *et al.*, 1975). Taken together, this group of studies provides ample evidence to support the notion of semantic organization and encoding strategy deficits during verbal learning paradigms in schizophrenia.

Other studies of encoding strategy and semantic organization in schizophrenia have relied on card sorting tasks, in which participants are given note cards with words printed on them and are asked to sort them into subjectively-defined categories (Larsen & Fromholt, 1976; Russell & Beekhuis, 1976). Russell and Beekhuis (1976) reported results of a study in which participants with schizophrenia and healthy controls were asked to sort cards into self-defined categories, followed by a free recall test. The authors found that the schizophrenia group showed significantly worse free recall performance than controls following the sorting task. Clustered recall, as measured by both objective

category group membership and subjective sorting, was also substantially impaired in schizophrenia participants (Russell & Beekhuis, 1976). Thus, deficits in semantic organization at the time of encoding are tied to recall deficits in schizophrenia.

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Encoding deficits among individuals with schizophrenia have also been linked to deficits in *binding*, or *associative memory*, which is thought to involve the integration of various components of an event into a cohesive whole. Many aspects of memory function rely on efficient binding of elements together during encoding and the ability to successfully retrieve those elements at a later time.

Binding in schizophrenia has been assessed in a variety of ways. A common practice is to utilize tests that measure *transitive inference* (TI), which refers to the ability to learn and infer relationships among items. Individuals with schizophrenia typically demonstrate significant difficulties in correctly inferring relations between novel pairings of previously-seen items, often with normal or near normal memory for previously-presented pairs (Hanlon *et al.*, 2005; Heckers & Titone, 2005; Ongur *et al.*, 2005; Titone *et al.*, 2004), although others have found deficits in recognition of previously-seen paired associates as well (Ragland *et al.*, 1998). In one study of TI in schizophrenia, Titone and colleagues (2004) trained control and schizophrenia participants on a series of hierarchically organized discriminations (A > B, B > C, etc.), using abstract shapes as stimuli, and then tested subjects on previously seen training pairs and novel inference pairs. While participants with schizophrenia correctly responded to the training pairs and the novel pairs not requiring inference, they were significantly poorer in responding to novel relational pairs requiring inferential reasoning, implicating relational memory organization processes (Titone et al., 2004).

Deficits in the use of contextual information to successfully bind information together have also been suggested to play a role in EM impairments in schizophrenia (Waters *et al.*, 2004). In these studies, individuals with schizophrenia have shown impairments in identifying the source and temporal context in which events took place. Others have reported intact use of contextual information in schizophrenia participants, and have instead attributed associative memory deficits to faulty encoding and retrieval processes (Bazin & Perruchet, 1996). Previous work has also examined interference effects on associative memory in individuals with schizophrenia (Elvevag *et al.*, 2000; Lepage *et al.*, 2005; O'Carroll, 1995). Elvevag and co-workers, for example, found that schizophrenia participants were not significantly more susceptible to interference effects from previously-learned information than control participants, potentially because of poorer memory for previously-learned information (Elvevag et al., 2000). Lepage and colleagues (2005) reported similar findings, attributing non-significant interference effects among schizophrenia participants to impairments in associative memory functioning (Lepage et al., 2005). Further investigation has attributed associative memory difficulties in schizophrenia to patterns of "non-selective learning," referring to the inability of individuals with schizophrenia in learning to utilize contextual cues and other variables effectively in order to improve memory (Kopp & Reischies, 2000).

Finally, there are indications that impairments in associative memory exceed those observed on tests of item memory. For example, a meta-analysis of 23 studies of recognition memory conducted by Achim and Lepage concluded that associative recognition was significantly impaired in schizophrenia relative to item recognition. The authors hypothesized that, while item recognition can be performed on the basis of

familiarity, associative recognition requires conscious recollection, which is impaired in schizophrenia (Achim & Lepage, 2003). A study by the same group (Lepage *et al.*, 2006) confirmed these results, reporting no difference in item recognition between controls and schizophrenia participants but significantly lower associative recognition performance in the schizophrenia group. One potential confound of such a contrast relates to the differences in task difficulty and discriminating power of each type of memory test. Certain psychological measures are thought to be more sensitive to cognitive impairment than other measures, making comparisons between the two types of measures risky (Chapman & Chapman, 1978). Thus, this set of findings must be interpreted with caution.

Given the numerous reports of encoding strategy and semantic organization deficits and their effects on memory performance in schizophrenia, there has been some effort to explain why such impairments are present. Difficulties in applying mnemonic strategies are often hypothesized to underlie memory deficits in schizophrenia. Following an extensive battery of cognitive tests given to schizophrenia participants and controls, Hutton and co-workers (1998) found that the schizophrenia group consistently showed deficits in organization, planning, and strategy use (Hutton *et al.*, 1998). Kay (1982) has hypothesized that individuals with schizophrenia may be more oriented to the *salience* of to-be-remembered words, rather than to their semantic properties, rendering them less likely to use the inherent relationships among words to boost recall performance (Kay, 1982). Other work (Stone *et al.*, 1998) has reported that decreased working memory capacity is related to deficits observed in long term strategic memory performance in individuals with schizophrenia, whereas Brebion et al. (2000) have suggested that deficits in deep encoding ability and semantic organization in schizophrenia are related to

processing speed impairments (Brebion *et al.*, 2000). Thus, there are likely multiple mechanisms related to encoding strategy impairments and memory dysfunction in schizophrenia.

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Although there is evidence for verbal memory impairments in schizophrenia, such impairments may be somewhat alleviated through improved encoding conditions (Chan *et al.*, 2000; J. M. Gold *et al.*, 1992; McClain, 1983), further supporting the hypothesis of faulty encoding strategies in schizophrenia. For example, Gold and co-workers (1992) tested schizophrenia participants and healthy comparison subjects on recall and recognition memory following the presentation of word lists that varied in semantic relatedness and organization (i.e., blocked vs. non-blocked). They found that individuals with schizophrenia showed a lower probability of recall during a free recall test, although they did show significant memory benefits following the blocked presentation of words, suggesting the ability to benefit from supportive encoding conditions (J. M. Gold et al., 1992). A similar finding was reported by McClain (1983), who found that under unsupported memory conditions (no encoding or retrieval cues), schizophrenia participants showed significantly worse word recall than controls. Following encoding cues (blocking), recall in the schizophrenia group showed improvement, suggesting that although individuals with schizophrenia typically do not spontaneously adopt encoding strategies, they can benefit from them when they are provided (McClain, 1983). Taken together, these results suggest that memory deficits in schizophrenia are not immutable and can be modified under advantageous encoding conditions.

As the above research suggests, helpful encoding manipulations (such as blocked stimulus presentation) have proven useful in boosting subsequent memory performance

among individuals with schizophrenia. More recent work has investigated the effects of other types of encoding manipulations on schizophrenia participants. One influential theory of episodic memory states that in general, information that is processed more "deeply" or meaningfully at the time of initial learning is more likely to be retrieved than information processed in a "shallow" or superficial manner (Craik & Lockhart, 1972). This phenomenon is known as the *levels-of-processing (LOP) effect* and posits that the operations carried out at the time of initial learning are the key factor that determines retention and subsequent retrieval, rather than simply the intention to learn (Craik & Tulving, 1975). This effect has been demonstrated in numerous studies of healthy subjects using a variety of orienting tasks (Eysenck, 1974; Hyde & Jenkins, 1969, 1973; Tulving & Madigan, 1970). For example, manipulations that promote semantic or "deep" processing of verbal stimuli include judgments of "living" (whether word represents a living or non-living thing), judgments of concreteness (whether word represents an abstract or concrete entity), and judgments of pleasantness (whether word is pleasant or unpleasant). In contrast, other orienting tasks emphasize "shallow" or superficial processing of words, including alphabetizing decisions (whether first or last letter of the word comes earlier in the alphabet), case decisions (whether word is written in uppercase or lowercase), and syllable decisions (how many syllables does the word have). It should be noted, however, that although semantic encoding tends to be associated with better subsequent memory than other types of encoding, studies of transfer appropriate processing have demonstrated that subsequent memory success is also dependent on the retrieval context and tasks utilized at retrieval (Morris *et al.*, 1977). Therefore, one must interpret studies of encoding manipulations cautiously and with this caveat in mind.

A number of investigators have utilized the LOP paradigm in individuals with schizophrenia to address questions regarding encoding strategy use in this population (Bonner-Jackson *et al.*, 2005; Heckers *et al.*, 1998; Koh & Peterson, 1978; Kubicki *et al.*, 2003; Paul *et al.*, 2005; Ragland *et al.*, 2006; Ragland *et al.*, 2003; A. P. Weiss *et al.*, 2003). Participants in a study by Koh & Peterson (1978) were constrained to encode words under four different orienting tasks (letter processing, rhyme processing, category processing, sentence processing), and subsequent free recall and recognition tests were administered, which were either expected or unexpected by the participants. Individuals with schizophrenia responded to the LOP manipulation in similar manner as controls and showed equivalent recognition rates for more deeply encoded words (category and sentence processing). However, free recall performance remained significantly lower in participants with schizophrenia, and being forewarned about a later memory test did not significantly increase recall performance (Koh & Peterson, 1978). Thus, these findings indicate that: 1) individuals with schizophrenia show behavioral benefits from advantageous memory strategies implemented at the encoding stage; 2) in the absence of retrieval cues free recall performance in schizophrenia participants will remain impaired, despite the presence of encoding support; and 3) knowledge of a later memory test does not improve subsequent memory performance in individuals with schizophrenia.

Participants with schizophrenia also show significant recognition benefits from deep encoding, relative to shallow encoding. A study conducted by Heckers and colleagues (1998) investigated memory performance in individuals with schizophrenia and healthy comparison subjects following processing of words under “low recall” (count the number of T-junctions) and “high recall” (count the number of meanings) encoding

conditions. Results indicated that like controls, participants with schizophrenia showed substantially improved memory for words encoded under "high recall" conditions, as compared to "low recall," although "high recall" performance in the schizophrenia group remained lower than "high recall" performance in the control group (Heckers et al., 1998). It is important to note that, although schizophrenia participants respond positively to memory manipulations, their memory performance (even for deeply-encoded words) is generally not reported to be equivalent with that of controls. This may indicate that retrieval cues, in addition to encoding support, are necessary in order for memory performance in individuals with schizophrenia to equal that of their healthy control peers. Taken together, these studies demonstrate that individuals with schizophrenia can benefit to a similar degree as controls from advantageous encoding conditions, although such benefits may be limited to certain tests of memory function (i.e., recognition).

Studies such as those described above raise the question as to whether the demonstration of intact LOP effects in individuals with schizophrenia represents a novel or unexpected finding. One could argue that deep encoding manipulations will result in better subsequent memory in any group of participants, regardless of psychiatric diagnosis or compromised memory capacity. In this sense, individuals with amnesia are the most logical group against which to compare individuals with schizophrenia, as both groups demonstrate significant deficits in the ability to learn and recall new information. However, in contrast to research on schizophrenia, studies examining LOP effects in amnestic patients have reported reduced benefits and poorer subsequent memory in this group (relative to controls) following encoding manipulations (Cermak *et al.*, 1995; Hamann & Squire, 1996; Keane *et al.*, 1997). For example, Keane and colleagues (1997)

reported impaired explicit memory performance in a group of amnestic patients (relative to control group) following a levels-of-processing manipulation despite normal priming in the amnestic group. Others have found that controls show larger LOP effects and benefit more from a LOP manipulation than amnestic patients (Hamann & Squire, 1996)

Another group against which to compare individuals with schizophrenia in memory performance following encoding manipulations is patients with frontal lobe damage. In contrast to studies of amnestic patients, research on patients with frontal lesions has demonstrated significant memory benefits following orientation to beneficial encoding strategies (Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Incisa della Rocchetta & Milner, 1993). For example, Gershberg and Shimamura (1995) reported that patients with frontal lobe damage showed significant memory benefits from strategic instruction and category cues at both study (encoding) and test (retrieval) phases. Based on their findings, the authors suggested that the free recall deficits observed in individuals with frontal lesions are due at least in part to deficits in organizational strategies (Gershberg & Shimamura, 1995). Other researchers have shown that patients with frontal lobe damage perform normally on memory tests when encoding and retrieval strategies are provided (Incisa della Rocchetta & Milner, 1993). Unlike patients with amnesia, therefore, individuals with damage to the frontal lobes show a pattern of memory deficits that appear to be modifiable through strategic instruction at encoding and retrieval. This pattern appears to be more consistent with data from studies of individuals with schizophrenia, who are known to have memory impairments as well as deficits in frontal lobe function.

Thus, individuals with schizophrenia have impairments in initial learning and encoding of information. Furthermore, such deficits are attributable, at least partially, to difficulty in generating and applying mnemonic strategies. However, it appears that provision of such strategies under experimental conditions can alleviate memory deficits in schizophrenia to some degree, a finding which has been demonstrated in some clinical populations (e.g., patients with frontal lobe lesions) but not others (e.g., patients with amnesia).

*Evidence for storage deficits in schizophrenia.* Based on the above review, individuals with schizophrenia demonstrate clear impairments in EM encoding, which is likely one source of EM dysfunction in this group. However, it is possible that deficits in EM function among individuals with schizophrenia may also be attributable to failures in memory storage or increased rates of forgetting. It is not possible to examine memory storage *per se* using only behavioral measures. Rather, storage can only be assessed indirectly, and it is impossible to disentangle deficits that may arise at the storage stage from those at either the encoding or retrieval stages. Thus, the majority of work focusing on this question in schizophrenia has examined rates of forgetting. Some researchers have assessed forgetting rates in individuals with schizophrenia by comparing the percentage of information recalled at immediate recall that can be successfully recalled after a delay. Nuyen et al (2005), for example, found evidence of verbal storage deficits among first-episode schizophrenia patients (Nuyen *et al.*, 2005), as did Tracy and colleagues (Tracy *et al.*, 2001). Others (Cirillo & Seidman, 2003) have reported increased rates of forgetting among schizophrenia participants, although such deficits were mild relative to more pronounced difficulties in other EM domains (e.g., encoding or retrieval). Forgetting

rates among schizophrenia participants have also been classified as “mild” relative to other neuropsychiatric disorders with memory impairments (Seidman *et al.*, 1998).

Overall, however, individuals with schizophrenia do not demonstrate increased rates of forgetting (Lee *et al.*, 2006; Lewis & Kopelman, 1998) or storage deficits (Brebion et al., 1997; Brebion *et al.*, 2007; Landro *et al.*, 2001) in EM tasks, despite showing marked deficits in encoding, retrieval, or memory strategy. Furthermore, it is conceivable that previous reports of storage deficits in schizophrenia are largely attributable to more pronounced deficits at the encoding stage. For example, a study by Gold et al. (2000) found that control and schizophrenia participants matched on initial recall performance had nearly identical delayed recall scores. This suggests that individuals with schizophrenia have deficits in initial learning and information acquisition, rather than storage deficits or abnormally accelerated forgetting rates (J.M. Gold *et al.*, 2000).

In summary, individuals with schizophrenia demonstrate impairments in EM storage and mildly increased rates of forgetting, relative to control samples. However, such findings are often in the context of more severe deficits observed in encoding or retrieval. On the whole, the EM deficits that are consistently found in individuals with schizophrenia cannot be attributed to impairments in the storage of information.

*Evidence for retrieval deficits in schizophrenia.* In addition to encoding deficits in schizophrenia, deficits in EM retrieval also contribute to memory impairments in this group. As mentioned above, encoding and retrieval processes cannot be fully dissociated using behavioral paradigms, and one cannot assess EM retrieval independent of encoding. However, researchers have often examined retrieval processes in schizophrenia

by manipulating aspects of the retrieval environment, while holding the encoding context stable. In this way, the cognitive operations occurring at retrieval can be more effectively isolated.

One approach to assessing retrieval deficits in schizophrenia has been to compare schizophrenia participants to controls on tests of free recall, in which previously-presented information must be retrieved without any external support (Koh & Kayton, 1974; Sattler & Nordmark, 1971). For example, Koh and Kayton observed significant free recall impairments in a group of schizophrenia participants, which were attributed to a number of factors, including vulnerability to intrusion and inefficient organization strategies (Koh & Kayton, 1974). Although these and other studies provide evidence of impairment in the ability to reliably retrieve information in schizophrenia, they are unable to conclusively implicate retrieval operations *per se*, as opposed to other cognitive operations involved in EM functioning. For example, encoding or storage deficits could potentially underlie the inability to remember information as well, rather than difficulties with memory retrieval, and such studies are unable to dissociate these factors.

An additional method for assessing the integrity of retrieval operations in schizophrenia is to compare memory accuracy during free recall to accuracy during recognition, usually within the same group of participants. Although factors related to encoding are also involved, individuals who manifest a disproportionate memory benefit during recognition testing, relative to free recall, are typically characterized as having a *retrieval deficit*. The underlying assumption of this method is that the to-be-recalled information was available in memory, but was not able to be accessed during free recall due to faulty retrieval operations, whereas in the presence of a salient retrieval cue during

recognition testing (i.e., the original stimulus) the information can be retrieved. However, a potential confound arises in directly comparing recall and recognition, as recall is substantially more difficult and has more discriminating power than recognition. Additionally, comparisons between the two memory tasks are risky because the task demands are so dissimilar. While successful recall depends on *conscious recollection* of previously presented material, it has been suggested that recognition tasks can be completed based only on *familiarity* with the items. Thus, the two tasks are tapping two putatively distinct cognitive processes supported by potentially dissociable memory traces. Such comparisons must, therefore, be interpreted carefully.

Although comparison of free recall to recognition accuracy has been used widely in studies of EM in schizophrenia, the literature is mixed concerning the nature of such deficits. Specifically, discrepancies exist regarding the relative benefit that is conferred to schizophrenia participants during recognition relative to free recall tasks. One line of research indicates that although recognition performance is less impaired than free recall performance in individuals with schizophrenia, it is nonetheless still significantly lower than recognition in controls (Aleman et al., 1999; Calev, 1984; Clare et al., 1993; Goldberg *et al.*, 1989; Lee et al., 2006; Paulsen *et al.*, 1995; Perry *et al.*, 2000). For example, a meta-analysis by Aleman et al. (1999) reported recognition performance in schizophrenia that was less severely disturbed than performance in free recall, but was still substantially lower than in control subjects. Goldberg and colleagues (1989) detected a larger discrepancy between recall and recognition performance in schizophrenia participants than in control participants, suggesting disproportionate difficulties in EM retrieval. As in previous studies, recognition performance in the schizophrenia group

remained significantly impaired relative to controls (Goldberg et al., 1989). Thus, this collection of studies indicates that recognition performance in schizophrenia is superior to that of recall performance, but nevertheless remains inferior to that of controls. However, the role of task difficulty and differences in discriminability between the two task types (recall and recognition) must be considered. As mentioned above, recall and recognition tasks differ in discriminating power and may, therefore, differ in the reliability of their estimates of memory performance in schizophrenia.

In contrast, another line of research has reported recognition rates in individuals with schizophrenia that do *not* differ significantly from those of control participants, even when free recall in the schizophrenia group is significantly impaired (Bauman, 1971; Bauman & Murray, 1968; Beatty *et al.*, 1993; Koh *et al.*, 1973; Nachmani & Cohen, 1989). For example, Nachmani and Cohen (1989) reported significantly fewer words recalled and significantly more intrusion errors by participants with schizophrenia than by controls, but found no between-group differences in recognition ability (Nachmani & Cohen, 1989). Others have reported similar results within a sample of schizophrenia participants, although there was not a comparison group used (Tracy et al., 2001).

Additional evidence to suggest the presence of retrieval impairments in schizophrenia comes from studies utilizing retrieval cues. As mentioned above, recognition paradigms provide participants with one type of retrieval cue (i.e., the original stimulus), which have been shown to foster varying degrees of improvement in memory performance. Other work has demonstrated the benefits of category cueing on recall in schizophrenia (Culver *et al.*, 1986; McClain, 1983; Sengel & Lovallo, 1983; Tompkins *et al.*, 1995). Sengel and Lovallo found that participants with schizophrenia

and control participants benefited equally from the provision of category cues at recall (Sengel & Lovallo, 1983). Individuals with schizophrenia also show equivalent recall performance to that of controls, but only when both encoding and retrieval cues are available (McClain, 1983). Culver and colleagues also found the same pattern of recall for control and schizophrenia participants when encoding and retrieval cues were present, although recall deficits in the schizophrenia group were not entirely eliminated (Culver et al., 1986). Taken together, this group of studies indicates that the use of recognition and category cues improves memory performance in schizophrenia, further suggesting that memory deficits are at least partially attributable to faulty retrieval operations.

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A final line of evidence posits that individuals with schizophrenia have difficulty in *conscious recollection* of information, while the sense of *familiarity* of information appears to remain intact. This theory has been advanced based on various pieces of evidence. One piece is related to the recall vs. recognition dissociation described above. Free recall, it is argued, can only be successfully completed via conscious recollection of to-be-remembered information, whereas recognition requires the participant only to be familiar with the particular item. Additional evidence for the recollection/familiarity dichotomy is found in studies utilizing the Remember/Know paradigm (Tulving, 1985): during a recognition task, participants are instructed to label previously-seen items as "Remember" if the item is accompanied by a conscious recollection of having previously seen the item, and "Know" if the item is accompanied only by a feeling of familiarity of the item without conscious recollection of having seen it before.

Across a variety of studies, individuals with schizophrenia have demonstrated markedly lower rates of Remember judgments, with intact rates of Know judgments in

nearly all cases (Danion *et al.*, 1999; Huron *et al.*, 1995; Sonntag *et al.*, 2003; Tendolkar *et al.*, 2002; Thoma *et al.*, 2006). This phenomenon has been attributed to a number of causes, including a failure to elaborately process information (Huron et al., 1995) and an inability to link separate aspects of events into cohesive memories (Danion et al., 1999). Electrophysiological research has also identified abnormal event-related potentials (ERPs) in various brain regions during both Remember and Know judgments in individuals with schizophrenia (Tendolkar et al., 2002). Thus, a recollection deficit in individuals with schizophrenia likely contributes to impairments in EM retrieval.

Overall, reports of deficits in EM retrieval among individuals with schizophrenia are common. Among the most impaired functions is free recall, while mixed evidence exists regarding the degree of memory impairment seen for recognition. However, individuals with schizophrenia demonstrate memory benefits when given cues to aid retrieval, suggesting that impairments in retrieval strategy or semantic organization at retrieval may significantly contribute to these deficits.

*Summary of Episodic Memory Deficits in Schizophrenia.* Episodic memory represents a significant cognitive deficit in the schizophrenia syndrome. Deficits in EM have been attributed to ineffective processing of information at encoding, as well as deficits in mnemonic processes at retrieval. Relatedly, individuals with schizophrenia are impaired in the ability to bind together information within a particular context, another factor that renders memory formation more difficult. Importantly, however, supportive conditions at the encoding and retrieval stages improve memory performance in schizophrenia, suggesting that the mechanisms underlying cognitive deficits in schizophrenia may be pliable and receptive to beneficial manipulations.

## Functional Neuroimaging Studies of Episodic Memory in Schizophrenia

Supplementing the behavioral research on EM in schizophrenia, recent work has utilized functional neuroimaging techniques (such as fMRI, PET, and EEG) to investigate the neural substrates of memory processes in individuals with this disease. I will briefly review some of the major neuroimaging findings in healthy controls before discussing functional neuroimaging studies of EM in schizophrenia.

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Functional neuroimaging studies of EM encoding in healthy control participants have revealed distinctive patterns of cortical activity associated with performance of these tasks. Among the areas most crucial for successful EM encoding is left prefrontal cortex (PFC). Left PFC is activated during successful verbal encoding (Baker *et al.*, 2001; Buckner *et al.*, 2001; Fletcher et al., 2003; L. J. Otten et al., 2001; A. D. Wagner *et al.*, 1998) and is posited to be involved in semantic elaboration (Demb et al., 1995; Kapur et al., 1994). Additionally, left prefrontal cortex (and particularly left inferior frontal gyrus) responds robustly during supportive encoding conditions (Savage *et al.*, 2001), under conditions in which one needs to impose organizational structure on to-be-learned material (Fletcher *et al.*, 1998), and following implementation of organizational strategic training (Miotto *et al.*, 2005). Medial temporal lobe regions (particularly hippocampus) have also been implicated in successful encoding of individual words (Fletcher et al., 2003; L.J. Otten & Rugg, 2001; A. D. Wagner et al., 1998), as well as associative binding (Dolan & Fletcher, 1997; Jackson & Schacter, 2004). Thus, the neural substrates supporting item and associative memory are overlapping and rely on some of the same structures.

Just as successful EM encoding has been linked to activity in left prefrontal cortex and left medial temporal lobe structures, brain activity associated with successful EM retrieval has also been identified in these regions. Item retrieval engages bilateral PFC, with indications that right PFC is particularly crucial (Buckner *et al.*, 1998; Henson *et al.*, 1999; Jernigan *et al.*, 1998). ERP work has also demonstrated a role for bilateral PFC under elevated retrieval demands (Ranganath & Paller, 2000). Others have reported that areas of the bilateral medial temporal lobe (MTL) support retrieval processes (Cabeza *et al.*, 1997; Lepage *et al.*, 1998). Cabeza and colleagues (2003) found evidence for both bilateral MTL and right PFC involvement in EM retrieval, which they postulated to be linked to attentional processes (Cabeza *et al.*, 2003). There is also empirical support for the role of the parietal lobes in EM retrieval (A.D. Wagner *et al.*, 2005), which seem to be crucial in identifying old vs. new items, and are also more active during conscious recollection of old items (as compared to items that simply evoke a sense of familiarity).

Similarly, retrieval of associative or relational information has been associated with activity in both left posterior hippocampus and left dorsolateral prefrontal cortex (Prince *et al.*, 2005). Hippocampal structures have also been shown to be involved in the retrieval of associate pairs (M. W. Brown & Aggleton, 2001; Giovanello *et al.*, 2004; Ongur et al., 2005), demonstrating a critical role for this structure in memory function. Left hippocampus, in particular, appears to be preferentially activated during context-dependent verbal memory processing (Burgess *et al.*, 2002). Regions of prefrontal cortex and medial temporal lobe, therefore, represent key components of the EM system in healthy individuals.

More recently, advances in functional neuroimaging techniques have allowed for more detailed study of the functional neuroanatomy of EM in schizophrenia. One of the most common findings among functional neuroimaging studies of EM in schizophrenia is abnormal brain activity patterns in combination with poorer memory task performance relative to healthy controls. Furthermore, many such studies have found these abnormal activation patterns in prefrontal cortex and medial temporal lobe, among other regions. For example, a 2005 meta-analysis by Achim and Lepage found that the left inferior prefrontal cortex was the primary region that distinguished between control and schizophrenia participants during both EM encoding and retrieval. They also found consistent evidence for reduction in right hippocampal activation during encoding among individuals with schizophrenia (Achim & Lepage, 2005b).

Below, I will review functional neuroimaging evidence related to two cognitive domains hypothesized to underlie EM impairments in schizophrenia: encoding and retrieval. Unlike the review of the behavioral episodic memory literature, I will not include a section on storage, as there are no existing functional neuroimaging studies that have convincingly isolated episodic memory storage available at this time.

*Functional neuroimaging studies of encoding in schizophrenia.* Empirical research examining EM in individuals with schizophrenia has repeatedly found evidence of abnormal encoding-related brain activation patterns in this group. Specifically, individuals with schizophrenia often show underactivation during encoding in a number of brain regions thought to be crucial for EM function, particularly areas of PFC (Barch *et al.*, 2002; Hofer *et al.*, 2003a; Kubicki et al., 2003; Ragland *et al.*, 2001), which are hypothesized to be associated with the generation and application of memory strategies.

Reduced activity in PFC has also been linked to inefficient strategy use and poorer memory performance in schizophrenia (Hazlett *et al.*, 2000; Nohara *et al.*, 2000). Furthermore, individuals with schizophrenia demonstrate PFC dysfunction even when memory performance is equivalent to that of control subjects (Hofer et al., 2003a; Hofer *et al.*, 2003b), suggesting a fundamental disruption of encoding processes in schizophrenia. Thus, deficits in frontal cortex function may be related to the strategic impairment often seen in schizophrenia and likely contribute in some manner to the faulty memory function that is often observed in this group.

Another region commonly implicated in encoding deficits among individuals with schizophrenia is the medial temporal lobe, particularly the hippocampus. Deficits have been consistently identified in the recruitment of medial temporal lobe areas during both verbal (Barch et al., 2002; Jessen *et al.*, 2003) and non-verbal encoding tasks (Leube *et al.*, 2003). Such deficits are typically found in medial temporal lobe in combination with poorer subsequent memory performance, although even encoding of subsequently remembered items has also been associated with reduced hippocampal activity (Heinze *et al.*, 2006). In addition, computational models have suggested that reduced connectivity between the parahippocampal gyrus, another medial temporal lobe region, and other areas (such as entorhinal cortex) contributes to encoding deficits in schizophrenia (Talamini *et al.*, 2005).

Despite the overwhelming evidence of brain activation deficits during encoding, however, individuals with schizophrenia can engage typical encoding-related brain regions when provided with beneficial encoding strategies. Similar to the findings of behavioral studies described above, functional neuroimaging studies in schizophrenia

have shown that experimental interventions at the encoding stage can improve task performance and "normalize" brain activity (Bonner-Jackson et al., 2005; Ragland *et al.*, 2005). For example, Ragland and colleagues (2005) found that individuals with schizophrenia showed normal levels-of-processing effects in left PFC when oriented to process words using deep encoding strategies, suggesting that individuals with schizophrenia can benefit from such interventions and activation deficits in PFC may be related to strategic impairments in this group (Ragland et al., 2005). However, areas of significant under- or over-activation often persist in these studies, even under beneficial encoding conditions. Schizophrenia participants in the Ragland study, for example, overactivated areas of the hippocampus, thalamus, and lingual gyrus relative to controls during deep (semantic) encoding. Therefore, encoding manipulations do not represent a sufficient mechanism in normalizing brain activity in schizophrenia.

In addition to the functional neuroimaging studies of item encoding described above, other work has examined the neural underpinnings of associative memory function in schizophrenia. Although such studies are rarer than those examining encoding of individual items, existing studies may provide insights into the deficits seen in schizophrenia. As mentioned previously, transitive inference (a key component of relational memory organization) is impaired in individuals with schizophrenia (Titone et al., 2004), and this behavioral deficit is associated with reduced medial temporal lobe activity among schizophrenia participants, relative to healthy controls (Heckers & Titone, 2005). These findings are consistent with those of Ongur and co-workers (2006), who reported deficits on a relational memory task among individuals with schizophrenia, which was associated with decreases in right parietal and left hippocampal activation

(Ongur et al 2006). Hanlon et al (2005), using magnetoencephalography (MEG), found evidence for abnormal lateralization of hippocampal activation in schizophrenia participants and reduced performance on a transverse patterning associative memory task (Hanlon et al 2005). Collectively, these studies link associative memory impairments and hippocampal activation deficits in individuals with schizophrenia.

Although medial temporal lobe structures are frequently implicated in binding deficits in schizophrenia, functional neuroimaging studies have also found evidence of impairments in prefrontal cortex during completion of these tasks (Lepage et al 2006; Ragland et al 1998). For example, Lepage and colleagues (2006) found deficits in PFC activation among schizophrenia participants during both associative encoding and recognition, relative to encoding and recognition of individual items. These findings indicate that deficits in the recruitment of prefrontal areas partially underlie the impaired abilities in relational memory observed in schizophrenia.

*Functional neuroimaging studies of retrieval in schizophrenia.* Similar to the findings from functional neuroimaging studies of encoding, research on retrieval-related brain activity in schizophrenia has consistently found evidence of dysfunction in key neural systems thought to underlie successful mnemonic function. Although such deficits have been found in a number of cortical and subcortical areas in schizophrenia participants, the regions hypothesized to be most crucial in EM retrieval include bilateral PFC and medial temporal lobe.

Areas of the medial temporal lobe, and the hippocampus in particular, which are hypothesized to be engaged during conscious retrieval of information, show under-activation among individuals with schizophrenia during EM retrieval tasks (Heckers *et*

*al.*, 1999; Jessen et al., 2003; A. P. Weiss *et al.*, 2004). A study by Jessen et al (2003), for example, found deficits in the recruitment of hippocampus bilaterally in schizophrenia participants, relative to controls, in combination with poorer performance on an EM recognition task. Weiss and co-workers (2004) reported that individuals with schizophrenia, unlike control subjects, failed to activate right hippocampus during the evaluation of novel items at retrieval, in addition to showing poorer subsequent memory performance.

Paralleling the findings from the encoding literature, individuals with schizophrenia also demonstrate impairments in recruitment of prefrontal cortex regions during retrieval tasks. Ragland and colleagues (2004) reported impairments in left DLPFC activation among individuals with schizophrenia, and found that retrieval success was associated with increased right PFC activity only in controls, not in schizophrenia participants, suggesting an abnormal relationship between brain activity and task performance in schizophrenia (Ragland *et al.*, 2004).

Although PFC deficits are typically observed in the context of poorer memory performance by schizophrenia participants, prefrontal activation deficits during retrieval persist even when memory performance among schizophrenia participants is equivalent to that of comparison subjects (Andreasen *et al.*, 1996; Crespo-Facorro *et al.*, 1999; Hofer et al., 2003a; Hofer et al., 2003b). Weiss et al. (2006) also found equivalent performance between control and schizophrenia participants on a verbal memory task, but the groups recruited different networks to achieve the same level of performance (A.P. Weiss *et al.*, 2006). Notably, the highest-performing comparison subjects in their study showed significant modulation of hippocampal activity, while the highest-

performing schizophrenia participants did not. This study provides another instance in which individuals with schizophrenia do not show the same relationship between brain activation and memory performance as control participants.

Furthermore, even when beneficial strategies are provided at encoding, participants with schizophrenia show dysregulation of activity in PFC and hippocampal regions during retrieval. The Heckers group conducted two studies (Heckers et al., 1998; A. P. Weiss et al., 2003) in which participants were oriented to encode words either deeply or shallowly. During retrieval, participants completed three-letter word stems of previously studied items. In both studies, participants with schizophrenia demonstrated greater than normal DLPFC activity combined with underactivation of hippocampus during EM retrieval. The authors suggested that individuals with schizophrenia must recruit prefrontal regions to compensate for impaired medial temporal regions during retrieval. Similarly, Ragland and co-workers found overactivation of left PFC, as well as under-recruitment of right PFC, among individuals with schizophrenia following a levels-of-processing encoding manipulation (Ragland et al., 2005). These studies indicate that constraining individuals with schizophrenia to encode words deeply is not sufficient to induce normal retrieval processes. It is possible, however, that the provision of beneficial memory strategies at both encoding and retrieval would produce “normalized” activity in both prefrontal and hippocampal structures.

*Summary of Functional Neuroimaging Studies of Episodic Memory in Schizophrenia.* Functional neuroimaging studies of EM in schizophrenia demonstrate impaired recruitment of brain regions that are crucial for memory function in healthy populations. Areas of prefrontal cortex and medial temporal lobe, among other regions,

show abnormal patterns of activation and dysregulation during EM encoding and retrieval, which has been linked in some instances to improper strategy use. Notably, however, experimental manipulations that promote beneficial memory strategy use can both improve episodic memory function and "normalize" brain activation in individuals with schizophrenia.

## Chapter 3: Purpose, Research Design, and Hypotheses of Dissertation

### *Purpose*

Deficits in memory function are a well-established feature of schizophrenia and represent real challenges to the autonomy and daily functioning of those who suffer from them. Remembering to take one's medication, go to a doctor's appointment, or attend a job interview all depend heavily on the integrity of memory. It is not surprising, therefore, that memory ability (particularly verbal memory) is highly associated with functional outcome among individuals with schizophrenia (Green, 1996). Thus, it is of great importance to address such issues, as they have a significant impact on the quality of life experienced by individuals with schizophrenia and can dramatically affect the likelihood of improvement and recovery.

Although memory impairments and deficits in memory-related brain activity have long been considered a stable aspect of the schizophrenia cognitive profile, more recent empirical evidence from behavioral and neurobiological studies suggests that such deficits are not immutable. Rather, certain experimental manipulations at the initial learning stage have dramatic effects on subsequent memory success and are associated with increased activation in brain areas known to support memory function in healthy individuals. Despite these advances in our understanding, however, many of the

underlying mechanisms related to memory deficits in schizophrenia have yet to be characterized.

Further investigation into the underlying behavioral causes of memory deficits (i.e., inefficient encoding, deficits in retrieval processes) may aid in cognitive rehabilitation and treatment interventions. Likewise, functional neuroimaging findings in this regard may provide information about the neural substrates of these impairments and can help guide future drug targets for alleviation of certain cognitive deficits. Taken together, the information provided by such a line of research could prove invaluable in impacting the lives of individuals with schizophrenia.

*Research Question*

The current project was designed to examine the extent to which behavioral measures of episodic memory and brain activity among individuals with schizophrenia can be improved – potentially to the point where they are similar to healthy controls – through the implementation of beneficial strategies provided during both encoding and retrieval.

*Research Design*

The current study was executed in two separate data collection sessions. The first session lasted approximately 1.5 to 2 hours and consisted of a structured clinical interview, collection of demographic information, a series of symptom rating scales, and brief neuropsychological testing. The neuropsychological measures assessed vocabulary, abstract reasoning, and semantic processing ability. The second data collection session took place on a separate day and lasted 2.5 to 3 hours. In this session, structural and functional neuroimaging data was collected from participants using a 3-Tesla magnetic

resonance imaging scanner at the Mallinckrodt Institute of Radiology (Washington University School of Medicine). While in the scanner, participants performed an episodic memory cognitive activation task consisting of separate encoding and retrieval phases. During half of the encoding runs, participants made semantic judgments about word-scene pairs, while during the other half they made non-semantic (location) judgments about a different set of word-scene pairs. During the retrieval scans, participants were shown scenes, most of which had been previously presented and some of which were new (never presented). For each scene, participants were asked to recall the word that was originally paired with the scene. Half of the scenes were accompanied by one-letter cues and half were uncued. Thus, the current study is a 2 x 2 x 2 mixed factorial design with two within-subjects variables (Encoding Orientation, Cueing) and one between-subjects variable (Group). Each of the within-subjects variables has two levels: Encoding Orientation – Semantic vs. Non-Semantic; Cueing – Cued vs. Uncued. The between-subjects variable also has two levels: Group – Control vs. Schizophrenia. Behavioral data associated with performance of the episodic memory task was also collected and analyzed concurrently with the neuroimaging data.

*Hypotheses*

The present study contained four sets of hypotheses, with each set related to a different area of focus. The four sets of hypotheses include predictions regarding the following aspects of this study: 1) Behavioral performance; 2) Encoding-related brain activity; 3) Retrieval-related brain activity; and 4) Individual difference measures. Below, I outline the hypotheses associated with each area of focus individually.

## Behavioral Performance: Predictions

The first set of hypotheses outlined below concerns behavioral performance on the episodic memory tasks. Specifically, the focus of the following predictions relates to the effects of encoding task and cueing on subsequent memory performance in each group, as well as the interactive effects of these variables. The specific questions used to address this area of interest are as follows:

1. Schizophrenia participants (as well as controls) would recall significantly more words seen during Semantic encoding than Non-Semantic encoding, and more words that were Cued than Uncued. I also predicted that the recall difference between groups would be smaller following Semantic encoding, relative to Non-Semantic encoding (Group x Encoding Task interaction).
2. The provision of retrieval cues would improve recall in schizophrenia participants (and controls), and this improvement would be significantly higher for the schizophrenia group (Group x Retrieval Cue interaction). Furthermore, the schizophrenia group would show a significantly greater recall benefit than control participants when oriented to the semantic encoding strategy and when provided with retrieval cues (Group x Encoding Task x Retrieval Cue interaction).
3. Schizophrenia participants would perform more poorly on the Semantic encoding task than the Non-Semantic encoding task. Additionally, schizophrenia participants would perform more poorly than control participants on the Semantic encoding task, while the groups would perform equally well on the Non-Semantic encoding task.

## Encoding-Related Brain Activation: Predictions

The second set of hypotheses outlined below concerns brain activity during encoding. Specifically, the focus of the following predictions relates to the effect of Encoding Orientation (Semantic vs. Non-Semantic) on encoding-related brain activity in participants with schizophrenia and healthy controls, as well as interactions between Encoding Condition and Group. Additionally, the following set of hypotheses addresses questions regarding subsequent memory effects in brain activity. Specifically, I will present predictions regarding brain areas that are more active during encoding of subsequently-recalled items, as well as the effect of Encoding Orientation on these findings. The specific questions used to address this area of interest are as follows:

1. Within group analyses among schizophrenia participants would reveal significant deficits in encoding-related brain activation during Non-Semantic (relative to Semantic) encoding, particularly in left inferior frontal gyrus (BA 45/47), left middle frontal gyrus (BA 6/44), and hippocampus, among other regions.
2. Furthermore, I predicted significant between-group differences (control > schizophrenia) in encoding-related brain activity during non-semantic encoding in the areas described above (left inferior frontal gyrus, left middle frontal gyrus, hippocampus).
3. In contrast, I predicted that during Semantic (relative to Non-Semantic) encoding, schizophrenia participants would show significant activation in typical semantic processing regions, such as left inferior frontal gyrus (BA 45/47), left middle frontal gyrus (BA 6/44), and hippocampus.

4. Furthermore, between-group differences (control > schizophrenia) in these regions (left inferior frontal gyrus, left middle frontal gyrus, hippocampus) would be dramatically reduced or absent during Semantic (relative to Non-Semantic) encoding.
5. I predicted a significant overlap in subsequent memory activity between groups in posterior/parietal regions. In contrast, subsequent memory activity among schizophrenia participants would be associated with significant underactivation (relative to controls) in anterior/frontal brain regions.

**Retrieval-Related Brain Activation: Predictions**

The third set of hypotheses outlined below concerns brain activity during retrieval. Specifically, the focus of the following predictions relates to the effect of both Encoding Orientation (Semantic vs. Non-Semantic) and Cueing (Cued vs. Uncued) on retrieval-related brain activity in participants with schizophrenia and healthy controls. Furthermore, this set of hypotheses examines the interactive effects of Encoding Orientation, Cueing, and Group on brain activity during retrieval. The specific questions used to address this area of interest are as follows:

1. I predicted that during retrieval of Uncued words (compared to retrieval of Cued words), schizophrenia participants would show the typical pattern of fronto-temporal dysregulation found in previous studies, including overactivation of frontal regions and underactivation of hippocampus.
2. Furthermore, I predicted significant between-group differences (Control > Schizophrenia) in retrieval-related brain activity during retrieval of Uncued words.

3. In contrast, during retrieval of Cued words, schizophrenia participants would activate a more typical network of retrieval-related brain regions.
4. I also predicted that Cued (relative to Uncued) retrieval would be associated with fewer between-group differences in retrieval-related brain activity.
5. Consistent with previous work, schizophrenia participants would demonstrate significant deficits in retrieval-related brain activation during retrieval of words encoded Non-Semantically.
6. Furthermore, retrieval of items encoded Non-Semantically would be associated with significant between-group differences (control > schizophrenia) in retrieval-related brain activity.
7. In contrast, schizophrenia participants would show more typical retrieval-related brain activity patterns during recall of items encoded Semantically.
8. Furthermore, retrieval of items encoded Semantically would be associated with fewer between group differences (control > schizophrenia) in brain activity.

**Individual Difference Measures: Predictions**

The fourth set of hypotheses outlined below concerns the effect of individual differences on behavior and brain activity. Specifically, the focus of the following predictions relates to the influence of inherent semantic processing ability on episodic memory and task-related brain activity in individuals with schizophrenia and healthy controls. The specific questions used to address this area of interest are as follows:

1. I predicted that participants from both groups who scored higher on measures of semantic processing ability would show greater subsequent memory benefits for

semantically-encoded items (relative to items encoded non-semantically) than participants who scored lower on semantic processing measures.

2. Participants from both groups who scored higher on measures of semantic processing ability would show greater activation enhancements (Semantic encoding > Non-Semantic encoding) in brain regions typically associated with semantic encoding, including left inferior frontal gyrus (BA 45/47).

## Chapter 4: Method

### Participants

***Human Subjects Involvement and Characteristics:*** Participants were 24 individuals DSM-IV diagnosed with schizophrenia and 24 comparison participants. The comparison participants were members of the surrounding community and were matched with members of the schizophrenia group on age, gender, race, handedness, and parental education level. In order to be eligible, all participants were required to be without current or past DSM-IV diagnosis of substance abuse or dependence, any neurological disorder, and documented history of concussion or head injury. Additionally, all potential participants were required to be 18-50 years of age; able to give informed consent to participate in research; must not be pregnant, claustrophobic, or have any non-removable metallic objects in their body; and could not meet criteria for mental retardation. Participants with schizophrenia were required to meet DSM-IV criteria for schizophrenia or schizoaffective disorder and could not be in an acute or unstable phase of the illness. Comparison participants could not have any lifetime history or family history of psychotic disorders.

***Recruitment and Informed Consent:*** Recruitment of individuals with schizophrenia occurred through four sources: 1) individuals who have participated in the Conte Center studies of Dr. Barch and Dr. Csernansky (a collaborator of Dr. Barch); 2) individuals who have completed studies as a part of the Treatment Units Research Network (TURNS), in which Drs. Barch and Csernansky are actively involved; 3) recruitment from local outpatient treatment facilities; and 4) advertisements placed in local community newspapers. Like participants with schizophrenia, control participants who completed studies as a part of the Conte Center or TURNS were invited to participate in the proposed research. Additional control participants were recruited through local advertisements and flyers. Control participants were recruited from the same areas and neighborhoods as the participants with schizophrenia. Informed consent was obtained by a member of the research personnel for every participant prior to their participation in the study. Consent forms were explained in detail and all aspects of the study, including both potential risks and benefits to the participant, were covered during the consenting process. A copy of each consent form, signed by both the participant and by the research staff member who has obtained consent, was retained.

***Diagnosis and Clinical Assessment:*** To determine each participant's diagnosis, a structured clinical interview was administered by a trained interviewer, using the Structured Clinical Interview for DSM-IV (SCID-IV). The SCID-IV interviewer had access to all present and past data sources, including hospital records and charts and corroborative sources (family members) in order to make a decision. Both participants with schizophrenia and control participants underwent identical diagnostic processes. Additionally, participants with schizophrenia were administered the Scale for the

Assessment of Positive Symptoms (SAPS; (Andreasen, 1983b) and the Scale for the Assessment of Negative Symptoms (SANS; (Andreasen, 1983a). I took an active role in the clinical assessment and diagnosis process and was been trained by Dr. Barch and the Conte Center staff to conduct the interviews.

***Medications:*** In compliance with Missouri state law, all participants with schizophrenia were medicated at the time of study. Most recent research on cognition in schizophrenia has studied individuals with this illness while medicated. More specifically, studies of item and associative memory in schizophrenia have found that deficits in these areas persist even when participants are taking medication (Jessen et al., 2003; Ragland et al., 2004; Waters et al., 2004). Detailed records of current medications and dosage levels were kept for each participant with schizophrenia in order to determine whether any of these factors significantly altered our results.

Procedure

In the present study, participants underwent testing in two separate sessions: a session consisting of a diagnostic clinical interview, clinical ratings, and brief neuropsychological testing; and a 1.5-hour functional neuroimaging session. During the neuroimaging session, participants underwent structural and functional neuroimaging and performed an associative memory task while in the scanner. I used the behavioral and functional neuroimaging data derived from these sessions in the current study.

Measures

*Associative Memory Task:* The associative memory task that participants performed while in the scanner was modeled after the paired associates paradigm described by Naveh-Benjamin and colleagues (Naveh-Benjamin *et al.*, 2002). In this

paradigm, participants learn associations between complex visual scenes and words, and the effects of supportive techniques during encoding and retrieval are assessed. In the current study, participants underwent functional neuroimaging scans while encoding and subsequently retrieving information about word-scene pairs. The encoding phase was accomplished over 6 functional imaging runs (3 runs for the Semantic encoding task, 3 runs for the Non-Semantic encoding task), while the retrieval phase took place over 3 runs. During the *encoding phase,* participants were shown a visual scene and a word simultaneously on the screen and were asked to study each word-scene pair for a memory test to be administered later. During half of the encoding runs ("Semantic Orientation" condition), participants were instructed to indicate whether the current word-scene pair was strongly or weakly associated by pressing one of two buttons. During the other half of the encoding runs ("Location" condition), participants were asked to indicate whether the word in the current word-scene pair was above or below the scene by pressing one of two buttons. Additionally, half of the to-be-encoded words were "strongly" related to their associated scene and half were "weakly" related to the scene, as determined by normative data collected from pilot subjects (see below). All participants were instructed to try to learn the relationship between visual scenes and words for a later memory test. Thus, in both conditions participants knew that they must learn the word-scene relationships for a later memory test and must make a judgment and execute a motor response at the time of encoding. However, only during the "Semantic Orientation" condition were participants explicitly oriented to process the semantic relationship between the scene and the word. Task order was counterbalanced across participants within each group, such that half of the participants performed the Semantic encoding

task prior to the Non-Semantic encoding task, and half performed the Non-Semantic encoding task prior to the Semantic encoding task. Additionally, the order of each of the three Semantic encoding runs and the three Non-Semantic encoding runs was counterbalanced in a pseudo-random fashion, such that the encoding stimuli were always presented in a different order for each participant.

Over the course of the encoding scans, each of the 120 word-scene pairs were shown 4 times (2 times with the word above the scene, 2 times with the word below the scene), in order to improve subsequent recall performance and avoid potential floor effects (particularly among the schizophrenia participants). Each stimulus was encoded in only one manner (i.e., Semantic or Non-Semantic) across all four presentations. Stimuli were presented every 2.5 seconds in a rapid event-related design, with fixation trials intermixed pseudo-randomly. During the *retrieval phase*, participants were presented with each of the 120 previously-viewed scenes once, as well as 30 new (not previously-viewed) scenes in order to discourage guessing. Scenes were presented one at a time, and participants were instructed to recall and vocally produce the word that was originally paired with the scene, or to say "New" if they believe the scene was never previously presented. Additionally, in order to examine the effect of retrieval cues on recall performance, half of the to-be-retrieved words were cued with a first letter followed by a blank line below the scene, while the other half only had a blank line. One-letter retrieval cues were counterbalanced across participants within each group, such that half of the participants received cues for half of the pictures, while the other half of the participants were cued for the other half of the pictures. Although the use of vocal responses in the scanner introduces potential problems (e.g., increased head movement, decreased signal-

to-noise ratios), previous work in our lab and in other research groups has utilized techniques that allow for vocal responses in the scanner (Palmer *et al.*, 2001; Racine, 2005). Furthermore, I calculated movement parameters and signal-to-noise (SNR) ratios for each BOLD run for each participant, in order to verify that all included data met minimum quality requirements before being included in analyses.

I completed data collection from 30 participants for a pilot study to generate valid associate words to be paired with the scenes. Participants in the pilot study were shown complex scenes on a computer screen, one at a time, and were asked to generate a word or phrase that they believe is associated with, but not physically in, the current scene. The word that was most frequently generated for a scene was used for the "strongly" associated word-scene pairs. "Weakly" associated words consisted of exemplars that were produced by pilot subjects but were not the most commonly produced. Word-scene pairs were designated to the "strongly" or "weakly" associated group on a random basis.

*Neuropsychological Measures.* All participants underwent a brief neuropsychological assessment battery, which included the Vocabulary, Similarities, and Matrix Reasoning subtests from the Wechsler Adult Intelligence Scale (WAIS-III; (Wechsler, 1997), as well as the Pyramids and Palm Trees Test (Howard & Patterson, 1992), which measures semantic access and semantic processing ability. I created a composite semantic processing variable to use as a variable of interest in the analysis of the behavioral and neuroimaging data. To do this, I converted scores for each participant on the WAIS-Vocabulary, WAIS-Similarities, and the Pyramids and Palm Trees Test to standardized z-scores and summed them.

*Symptom Measures.* As mentioned above, participants were administered the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) during the clinical interview. In order to assess the relationship between symptomotology and other factors of interest (i.e., task performance, semantic processing ability), I created symptom summary scores for three symptom clusters (positive, negative, and disorganized) by summing global rating scores for each domain from the SAPS and SANS. The positive cluster consisted of the sum of global hallucinations and global delusions ratings. The negative cluster consisted of the sum of global affective flattening, alogia, apathy, and anhedonia ratings. The disorganized cluster consisted of the sum of global bizarre behavior, positive formal thought disorder, and attention ratings. I then performed correlations between the symptoms summary measures and recall performance, as well as between the symptom summary measures and the semantic processing composite variable, given the established relationship between symptomotology and cognition in schizophrenia.

*fMRI Scanning Methods:* All structural and functional neuroimaging data collection was performed on the 3 Tesla Siemens Trio system at the Research Imaging Center of the Mallinckrodt Institute of Radiology at the Washington University School of Medicine. The functional images were acquired in a series of 9 runs using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygen level-dependent (BOLD) contrast (T2*; TR = 2500 msec, TE = 27 msec, FOV = 256 mm, slice thickness = 4mm). Encoding runs consisted of 168 frames (i.e., whole brain volume acquisitions). This included 80 task trials and 80 fixation trials intermixed pseudo-randomly, as well as 4 frames of fixation at the beginning of each run to allow the scanner to reach steady state

and 4 frames at the end of each run in order for the hemodynamic response to return to baseline. Retrieval runs consisted of 163 frames, 50 task trials and 55 fixation trials, as well as 4 frames of fixation at the beginning and end of each run. During structural imaging, 176 4-mm thick slices were acquired using a coronal MPRAGE 3D T1-weighted sequence (TR = 2400 msec, TE = 3.13 msec, FOV = 256 mm, voxel size = 1 x 1 x 1.2mm) and were used for between subject registration and anatomic localization.

Preprocessing of fMRI data included a number of steps, including the following: 1) compensation for slice-dependent time shifts; 2) elimination of odd/even slice intensity differences due to interpolated acquisition; 3) realignment of all data acquired in each subject within and across runs to compensate for rigid body motion; 4) intensity normalization to a whole brain mode value of 1000; and 5) spatial smoothing with an 8-mm FWHM Gaussian kernel. The functional neuroimaging data was transformed into the stereotaxic atlas space of Talairach and Tournoux (Talairach & Tournoux, 1988) by computing a sequence of affine transformations (first frame EPI to T2-weighted TSE to MPRAGE to atlas representative target) composed by matrix multiplication. The first four frames of each scanning run were fixation trials. These were discarded in the analysis of the functional neuroimaging data, in order to allow the MR signal to reach steady state. The last four frames of each functional neuroimaging run were also fixation trials. Following the standard pre-processing stream, all functional neuroimaging data was inspected for quality and integrity. Signal-to-noise ratios (SNR) were calculated for each scanning run for each participant, and participants with low average SNR values across all nine scanning runs (mean SNR < 150) were excluded from the neuroimaging analyses. Three participants were excluded from neuroimaging analyses for this reason.

Participants with head movement that exceeded 4 mm in any direction (X, Y, or Z) were also discarded and were not included in subsequent analyses. Based on mean head movement, the same three participants were identified for exclusion as had been identified based on mean SNR values. No additional participants were excluded from analyses based on these parameters.

To analyze the fMRI data from the encoding and retrieval conditions, I created estimates of encoding- and retrieval-related activity in each voxel for each participant separately, using a general linear model (GLM) convolved with a canonical Boynton hemodynamic response function, which was estimated over 7 scanning frames (17.5 seconds) following each stimulus presentation. In this manner, I created separate estimates for each encoding and retrieval task type. For the encoding data, I created two sets of GLM contrasts for each participant. In the first set (used in analyses of encoding-related activity), I coded 2 trial types: 1) Semantic encoding (semantic relatedness decisions); and 2) Non-Semantic encoding (word location decisions). In the second set (used in analyses of subsequent memory effects), I coded each stimulus event within each encoding run as one the following categories, based on encoding condition and subsequent memory performance: 1) correct-Semantic (correct recall for words seen during Semantic encoding); 2) correct-non-Semantic (correct recall for words seen during Non-Semantic encoding); 3) incorrect-Semantic (words seen during Semantic encoding that were not correctly recalled); and 4) incorrect-non-Semantic (words seen during non-Semantic encoding that were not correctly recalled).

For the retrieval data, I created 2 sets of GLM contrasts for each participant. In the first set, I coded 4 trial types: 1) Semantic-Cued (cued retrieval of words seen during

Semantic encoding); 2) Non-Semantic-Cued (cued retrieval of words seen during Non-Semantic encoding); 3) Semantic-Uncued (uncued retrieval of words seen during Semantic encoding); and 4) Non-Semantic-Uncued (uncued retrieval of words seen during Non-Semantic encoding). In the second set, I coded 8 trial types: 1) Semantic-Uncued-Correct (correct uncued retrieval of words seen during Semantic encoding); 2) Non-Semantic-Uncued-Correct (correct uncued retrieval of words seen during Non-Semantic encoding); 3) Semantic-Cued-Correct (correct cued retrieval of words seen during Semantic encoding); 4) Non-Semantic-Cued-Correct (correct cued retrieval of words seen during Non-Semantic encoding); 5) Semantic-Uncued-Incorrect (words seen during Semantic encoding that were uncued and not correctly retrieved); 6) Non-Semantic-Uncued-Incorrect (words seen during non-Semantic encoding that were uncued and not correctly retrieved); 7) Semantic-Cued-Incorrect (words seen during Semantic encoding that were cued and not correctly retrieved); and 8) Non-Semantic-Cued-Incorrect (words seen during non-Semantic encoding that were cued and not correctly retrieved). These estimates were used in the ANOVAs and t-tests. All analyses were appropriately corrected for multiple comparisons using cluster size algorithms to ensure whole-brain false positive rates of $p < .05$.

## Chapter 5: Results

Of the 67 participants who consented to participate in the study, 20 were excluded (7 control participants, 13 participants with schizophrenia) due to a variety of factors related to the quality of the behavioral and/or neuroimaging data [very low memory performance (N = 4), poor signal-to-noise ratio or excessive movement while in scanner (N = 3), incomplete scanning sessions (N = 7), failure to attend scan session (N = 6)].

The groups with usable neuroimaging and behavioral data consisted of 24 control participants and 23 participants with schizophrenia, and all analyses of neuroimaging data are based on these participants, unless otherwise specified. In order to maximize power, an additional 5 participants (1 control, 4 schizophrenia) with usable behavioral data (and unusable neuroimaging data) were included in analyses of behavioral data only, resulting in groups consisting of 25 control participants and 27 participants with schizophrenia for the behavioral analyses. Demographic and clinical data for included participants from both neuroimaging and behavioral analyses are presented in Table 1, and neuropsychological data are included in Table 2.

With regard to demographic variables, the control and schizophrenia groups did not differ in terms of gender distribution, age, parental education, or handedness. As a group, controls had significantly more years of education than schizophrenia participants ($p < .005$). Regarding performance on neuropsychological measures (Table 2), control participants performed significantly better than schizophrenia participants on the WAIS Vocabulary ($p < .005$), WAIS Matrix Reasoning ($p < .005$), and Pyramids and Palm Trees ($p < .005$) measures. The groups did not differ in their performance on the WAIS Similarities subtest.

***Table 1: Demographic and Clinical Data***

| | Mean Imaging* *(Mean Behavioral)** | | SD Imaging* *(SD Behavioral)** | | |
|---|---|---|---|---|---|
| *Characteristic* | Control Participants | Participants with Schizophrenia | Control Participants | Participants with Schizophrenia | p-value for statistical test |
| Age (years) | 37.4 *(37.0)* | 36.3 *(36.6)* | 7.9 *(8.0)* | 8.1 *(8.4)* | .64 *(.87)* |
| Sex (% male) | 75.0 *(76.0)* | 82.6 *(81.4)* | | | .52 *(.63)* |
| Participant Education (years) | 15.6 *(15.6)* | 13.4 *(13.2)* | 2.8 *(2.8)* | 2.1 *(2.1)* | **.001 *(< .005)*** |
| Parental education (years) | 13.9 *(13.9)* | 14.1 *(13.9)* | 2.0 *(2.0)* | 3.4 *(3.2)* | .95 *(.95)* |
| Handedness (1=left, 5=right) | 4.6 *(4.7)* | 4.3 *(4.3)* | 0.75 *(.75)* | 0.85 *(.80)* | .11 *(.11)* |
| Negative symptoms | 1.6 *(1.6)* | 6.4 *(6.5)* | 1.9 *(1.9)* | 3.4 *(3.2)* | **< .001 *(< .001)*** |
| Disorganization symptoms | 1.2 *(1.2)* | 1.8 *(2.0)* | 1.5 *(1.5)* | 1.7 *(1.7)* | .17 *(.08)* |
| Positive symptoms | 0.1 *(0.1)* | 3.0 *(2.9)* | 0.3 *(0.3)* | 2.1 *(2.2)* | **< .001 *(< .001)*** |
| Atypical medications only (%) | - | 82.6 *(80.7)* | | | |
| Typical medications only (%) | - | 17.3 *(19.2)* | | | |
| Anti-cholinergic medication (%) | - | 13.0 *(15.4)* | | | |

*Data are presented separately for participants with usable behavioral data and participants with both usable behavioral and neuroimaging data.

**Data regarding participant education, parental education, handedness, symptom ratings, and medication information not available for 2 participants in behavioral group (1 control, 1 schizophrenia).

***Table 2: Neuropsychological Data***

| | Mean Imaging Group *(Mean Behavioral Group)* | | SD Imaging Group *(SD Behavioral Group)* | | |
|---|---|---|---|---|---|
| *Measure* | Control Participants | Participants with Schizophrenia | Control Participants | Participants with Schizophrenia | p-value for statistical test |
| WAIS Vocabulary (scaled) | 11.3 *(11.3)* | 8.6 *(8.4)* | 2.7 *(2.7)* | 3.3 *(3.2)* | **< .005 *(< .005)*** |
| WAIS Similarities (scaled) | 10.1 *(10.1)* | 9.2 *(8.9)* | 2.9 *(2.9)* | 3.8 *(3.7)* | .38 *(.21)* |
| WAIS Matrix Reasoning (scaled) | 13.1 *(13.1)* | 10.5 *(10.2)* | 2.4 *(2.4)* | 3.4 *(3.4)* | **< .005 *(< .005)*** |
| Pyramids and Palm Trees | 49.6 *(49.6)* | 47.3 *(47.0)* | 2.0 *(2.0)* | 2.5 *(2.8)* | **< .005 *(< .001)*** |
| Semantic Processing Composite | 1.02 *(1.14)* | -0.99 *(-1.05)* | 2.1 *(2.1)* | 2.9 *(2.9)* | **< .01 *(< .005)*** |

*Neuropsychological data not available for 2 participants in behavioral group (1 control, 1 schizophrenia)

Below, I will address the findings for each of the specific hypotheses outlined above in each of the four domains: 1) Behavioral performance; 2) Encoding-related brain activity; 3) Retrieval-related brain activity; and 4) Individual difference measures.

## Behavioral Performance: Results

The first set of results outlined below concerns behavioral performance on the episodic memory tasks. Specifically, the focus of the following predictions relates to the effects of encoding task and cueing on subsequent memory performance in each group, as well as the interactive effects of these variables. The specific questions used to address this area of interest are as follows:

*1. Schizophrenia participants (as well as controls) would recall significantly more words seen during Semantic encoding than Non-Semantic encoding. I also predicted that the recall difference between groups would be smaller following Semantic encoding, relative to Non-Semantic encoding (Group x Encoding Task interaction).*

In order to address this hypothesis, I conducted within-group paired samples t-tests for recall in each group following each encoding condition (Semantic vs. Non-Semantic). Consistent with my stated hypothesis, participants with schizophrenia [$t(26) = 13.89$, $p < .001$], as well as controls [$t(24) = 6.22$, $p < .001$], demonstrated significant recall benefits for words encoded Semantically, relative to Non-Semantically (Table 3).

***Table 3. Behavioral Data: Encoding & Recall Task Performance***

Mean (SD)

| Task | Measure | Control Participants | Participants with Schizophrenia |
|---|---|---|---|
| *Encoding: Non-Semantic* | Accuracy | 0.93 (0.15)[2] | 0.93 (0.08)[2] |
| | Reaction Time (ms)[1] | 943 (192) | 968 (189) |
| *Encoding: Semantic* | Accuracy | 0.60 (0.16) | 0.57 (0.13) |
| | Reaction Time (ms)[1] | 1218 (206)[3] | 1226 (159)[3] |
| *Recall: Overall* | Accuracy | 0.79 (0.15)[4] | 0.70 (0.12) |
| *Recall: Old Items only* | Accuracy | 0.75 (0.18) | 0.67 (0.14) |
| *Recall: New Items only* | % Correct Rejections | 0.92 (0.11)[5] | 0.84 (0.16) |
| *Recall: Non-Semantic* | Accuracy | 0.63 (0.25) | 0.50 (0.19) |
| *Recall: Semantic* | Accuracy | 0.88 (0.12)[6] | 0.84 (0.12)[6] |
| *Recall: Uncued* | Accuracy | 0.72 (0.20) | 0.64 (0.15) |
| *Recall: Cued* | Accuracy | 0.80 (0.16)[7] | 0.72 (0.14)[7] |
| *Recall: Non-Semantic Uncued* | Accuracy | 0.57 (0.30) | 0.43 (0.20) |
| *Recall: Non-Semantic Cued* | Accuracy | 0.68 (0.25)[8] | 0.56 (0.20)[8] |
| *Recall: Semantic Uncued* | Accuracy | 0.86 (0.14) | 0.82 (0.12) |
| *Recall: Semantic Cued* | Accuracy | 0.91 (0.10) | 0.87 (0.11) |

*Encoding task performance data not available for six participants (3 control, 3 schizophrenia)

[1]RT presented for correct encoding trials only
[2]Main effect of Encoding Task ($p < .001$)
[3]Main effect of Encoding Task ($p < .001$)
[4]Control > Schizophrenia, % Overall Recall ($p < .05$)
[5]Control > Schizophrenia, % Correct Rejections ($p < .05$)
[6]Main effect of Encoding Task ($p < .001$)
[7]Main effect of Cueing ($p < .001$)
[8]Encoding Task x Cueing interaction ($p < .005$)

Next, I conducted a repeated measures ANOVA, with Group (Control, Schizophrenia) as the between subjects variable, and Encoding Task (Semantic, Non-Semantic) and Cueing (Cued or Uncued at retrieval) as the within subjects variables. Results of the analysis revealed main effects of Encoding Task [$F(1, 50) = 148.70$, $p < .001$] and Cueing [$F(1, 50) = 87.56$, $p < .001$]. Post-hoc comparisons showed that participants demonstrated better subsequent recall for words encoded Semantically relative to Non-Semantically, as well as better recall of words that were Cued relative to those that were Uncued. Furthermore, the analysis revealed a significant Encoding Task x Cueing interaction [$F(1, 50) = 9.05$, $p < .005$], such that the recall benefit conferred by Cueing was greater for words encoded Non-Semantically relative to words encoded Semantically (Table 3). Consistent with my prediction, the between-group effect size (Control > Schizophrenia) for Semantic recall ($d = 0.34$) was substantially smaller than that for Non-Semantic recall ($d = 0.61$), although the Encoding Task x Group interaction reached only trend-level significance ($p = .08$).

*2. The provision of retrieval cues would improve recall in schizophrenia participants (and controls), and this improvement would be significantly higher for the schizophrenia group than the control group (Group x Retrieval Cue interaction). Furthermore, the schizophrenia group would show a significantly greater recall benefit than control participants when oriented to the semantic encoding strategy and when provided with retrieval cues (Group x Encoding Task x Retrieval Cue interaction).*

In order to address this hypothesis, I conducted within-group paired samples t-tests comparing Cued recall to Uncued recall within each group separately. Consistent with my predictions, both participants with schizophrenia [$t(26) = 7.61$, $p < .001$], as

well as control participants [t (24) = 5.47, p < .001], recalled more words that were Cued at recall than Uncued (Table 3).

Next, I conducted the ANOVA described above, in order to address the potential interactive effects of Encoding Task, Cueing, and Group on subsequent recall. As described above, the analysis revealed a main effect of Cueing [F (1, 50) = 87.56, p < .001], such that Cued words were more successfully recalled than Uncued words. The analysis also revealed a significant Encoding Task x Cueing interaction [F (1, 50) = 9.05, p < .005], such that the recall benefit conferred by Cueing was greater for words encoded Non-Semantically relative to words encoded Semantically (Table 3). Contrary to my hypotheses, however, the Group x Cueing (p > .60) and Group x Encoding Task x Cueing (p > .66) interactions were non-significant, although calculation of between-group effect sizes suggest that the predictions were somewhat fulfilled. Effect sizes reflecting between-group differences in recall success suggest that the schizophrenia group demonstrated the greatest recall benefit for Semantic Uncued words ($d$ = 0.29), whereas the largest difference between groups was observed for Non-Semantic Uncued words ($d$ = 0.55).

*3. Schizophrenia participants would perform more poorly on the Semantic encoding task than the Non-Semantic encoding task. Additionally, schizophrenia participants would perform more poorly than control participants on the Semantic encoding task, while the groups would perform equally well on the Non-Semantic encoding task.*

Although this hypothesis was not of central interest to the present study, it was included to serve as a manipulation check to verify that participants were properly engaging in the encoding tasks. In order to address this hypothesis, I conducted a

repeated measures ANOVA on the accuracy data (see Table 3), with Group (Control, Schizophrenia) as the between subjects variable, and Encoding Task (Semantic, Non-Semantic) as the within subjects variable. Results of the analysis revealed a main effect of Encoding Task [$F(1, 48) = 420.37$, $p < .001$], while the effect of Group ($p > .67$) and the Group x Encoding Task interaction ($p > .49$) were both non-significant. Post-hoc comparisons revealed that, consistent with my hypothesis, participants with schizophrenia (as well as control participants) performed significantly worse on the Semantic encoding task than the Non-Semantic encoding task. However, contrary to my predictions, the individuals with schizophrenia did not perform significantly worse than controls on the Semantic encoding task. Finally, consistent with my hypothesis, the groups performed equally well on the Non-Semantic encoding task.

Additionally, reaction time (RT) data during encoding tasks was calculated (for correct encoding trials only), although no initial predictions were made regarding these data. RT data from 6 participants (3 control participants, 3 participants with schizophrenia) was unusable and excluded due to equipment failure. In order to assess potential RT differences between encoding tasks or groups, I conducted a repeated measures ANOVA, with Group (Control, Schizophrenia) as the between subjects variable, and Encoding Task (Semantic, Non-Semantic) as the within subjects variable. Results of the analysis revealed a main effect of Encoding Task [$F(1, 44) = 118.72$, $p < .001$], while the effect of Group ($p > .73$) and the Encoding Task x Group interaction ($p > .72$) were both non-significant. Post-hoc comparisons revealed significantly longer RTs for both groups during correct Semantic than correct Non-Semantic encoding trials (Table 3).

*Behavioral Performance: Summary*

Similar to the control group, individuals with schizophrenia recalled more words that were encoded Semantically than Non-Semantically and more words that were Cued than Uncued at recall. Both findings are consistent with the literature in this area and suggest that individuals with schizophrenia show memory benefits from encoding and retrieval support. Importantly, the magnitude of between-group differences across conditions was also supportive of my initial hypotheses. The smallest differences between groups were observed for items encoded Semanticaly and items that were Cued at retrieval, suggesting that such manipulations were effective in equating memory performance of schizophrenia participants with that of controls. Additionally, the analyses revealed that for both groups, Cueing during retrieval was significantly more beneficial for words encoded Non-Semantically than Semantically. Although unexpected, this finding reinforces the notion that cues are often most helpful for remembering poorly-encoded items, and that individuals with schizophrenia respond in a similar fashion as controls to beneficial memory cues.

## Encoding-Related Brain Activation: Results

The second set of results outlined below concerns brain activity during encoding. Specifically, the focus of the following predictions relates to the effect of Encoding Orientation (Semantic vs. Non-Semantic) on encoding-related brain activity in participants with schizophrenia and healthy controls, as well as interactions between Encoding Condition and Group. The specific questions used to address this area of interest are as follows:

*1. I predicted that during Semantic (relative to Non-Semantic) encoding, schizophrenia participants would show significant activation in typical semantic processing regions, such as left inferior frontal gyrus (BA 45/47), left middle frontal gyrus (BA 6/44), and hippocampus.*

More specifically, regarding "typical semantic processing regions," I am referring to significant areas of activity with a centroid in left inferior (BA 45/47) or left middle frontal gyrus (BA 6/44). In order to address this hypothesis, I conducted a within-group t-test in schizophrenia participants comparing encoding-related brain activity in the Semantic and Non-Semantic encoding conditions. Consistent with my predictions, compared to Non-Semantic encoding, Semantic encoding among schizophrenia participants was associated with significant increases in brain activity in a number of brain regions typically recruited during episodic memory encoding and semantic processing (see Table 4), including left middle frontal gyrus (BA 6). I did not detect significant activation during Semantic > Non-Semantic encoding among schizophrenia participants in hippocampus proper, although the contrast did reveal significant activity in right parahippocampal gyrus (BA 36). The analysis also failed to reveal Semantic > Non-

***Table 4. Regions of significant encoding-related activity: Schizophrenia participants***

| Region of Interest | Brodmann Area(s) | X | Y | Z |
|---|---|---|---|---|
| ***Semantic > Non-Semantic*** | | | | |
| Left medial frontal gyrus | 8 | -3 | 18 | 44 |
| Left middle frontal gyrus | 6 | -34 | 6 | 56 |
| Left middle frontal gyrus | 9 | -47 | 24 | 35 |
| Left middle frontal gyrus | 46 | -50 | 34 | 15 |
| Left superior frontal gyrus | 6 | -8 | 8 | 61 |
| Left superior frontal gyrus | 10 | -36 | 50 | 17 |
| Left superior frontal gyrus | 8 | -22 | 33 | 52 |
| Left precentral gyrus | 6 | -41 | 0 | 29 |
| Left insula | | -33 | 19 | 1 |
| Left thalamus | | -7 | -15 | 13 |
| Left cingulate gyrus | 31 | -3 | -41 | 35 |
| Left posterior cingulate gyrus | 30 | -10 | -53 | 8 |
| Left inferior parietal lobule | 40 | -41 | -54 | 42 |
| Left precuneus | 31 | -9 | -67 | 23 |
| Left precuneus | 19 | -26 | -72 | 41 |
| Left fusiform gyrus | 19 | -32 | -76 | -11 |
| Left middle occipital gyrus | 19 | -32 | -86 | 19 |
| Left lingual gyrus | 18 | -21 | -96 | -6 |
| Left cerebellum | | -27 | -39 | -16 |
| Left cerebellum | | -42 | -59 | -18 |
| Right medial frontal gyrus | 9 | 11 | 31 | 30 |
| Right middle frontal gyrus | 9 | 46 | 31 | 28 |
| Right middle frontal gyrus | 8 | 30 | 9 | 45 |
| Right superior frontal gyrus | 10 | 16 | 59 | 17 |
| Right insula | 13 | 37 | 20 | 4 |
| Cingulate gyrus | 24 | 1 | -12 | 37 |
| Right parahippocampal gyrus | 36 | 34 | -24 | -26 |
| Right middle temporal gyrus | 19 | 37 | -73 | 21 |
| Right fusiform gyrus | 37 | 45 | -41 | -18 |
| Right fusiform gyrus | 37 | 41 | -63 | -12 |
| Right cuneus | 17 | 17 | -95 | -1 |
| Right precuneus | 7 | 17 | -75 | 37 |
| Right precuneus | 7 | 19 | -55 | 46 |
| Right inferior occipital gyrus | 18 | 33 | -83 | -5 |
| Right cerebellum | | 19 | -41 | -10 |
| Right cerebellum | | 33 | -64 | -31 |
| Right cerebellum | | 7 | -78 | -31 |
| ***Non-Semantic > Semantic*** | | | | |
| Left superior temporal gyrus | 22 | -52 | -4 | 4 |
| Left insula | | -56 | -32 | 18 |

Semantic encoding activity in left (or right) inferior frontal gyrus (BA 45/47). Inspection of the separate maps for Semantic and Non-Semantic encoding suggested that activity in this region was quite similar across contrasts and any differences between conditions were likely not robust enough to reach significance. However, as described above a number of other regions in left and right frontal cortex were significantly more activated in semantic compared to non-semantic encoding.

*2. I also predicted significant between-group differences (Control > Schizophrenia) in encoding-related brain activity during Non-Semantic encoding, particularly in left inferior frontal gyrus (BA 45/47), left middle frontal gyrus (BA 6/44), and hippocampus, among other regions.*

In order to address this hypothesis, I conducted a between-group t-test comparing encoding-related brain activity during the Non-Semantic encoding condition in control and schizophrenia participants. In support of my hypotheses, I detected a significant between-group difference (Control > Schizophrenia) in left middle frontal gyrus (BA 6). However, contrary to my predictions none of the remaining between-group differences observed in this contrast were in the predicted frontal or hippocampal regions (see Table 5, Figure 1). The opposite contrast (Schizophrenia > Control) revealed that schizophrenia participants activated certain areas to a significantly greater degree than controls, including bilateral superior temporal gyrus (BA 22), left inferior (BA 40) and superior (BA 7) parietal lobule, and left precentral gyrus (BA 4). Results are displayed in Table 5 and Figure 1.

*3. In contrast, between-group differences (Control > Schizophrenia) in the regions described above (left inferior frontal gyrus, left middle frontal gyrus, hippocampus)*

*would be dramatically reduced or absent during Semantic (relative to Non-Semantic) encoding.*

In order to address this hypothesis, I first conducted a between-group t-test comparing encoding-related brain activity during the Semantic encoding condition in control and schizophrenia participants. Consistent with my hypothesis, between-group differences in which controls showed greater activity than participants with schizophrenia were dramatically reduced during the Semantic encoding condition (see Table 6, Figure 1). Only 2 regions of significant group differences in brain activity were detected, both in left cerebellum. In fact, nearly all regions of between-group differences during Semantic encoding were in the opposite direction (Schizophrenia > Control). Altogether, schizophrenia participants activated 19 regions in frontal, temporal, and parietal cortices to a significantly greater degree than control participants. These regions included left inferior frontal gyrus (BA 44), left superior frontal gyrus (BA 6), bilateral inferior parietal lobule (BA 40), bilateral superior parietal lobule (BA 7), and anterior cingulate gyrus (BA 24). All regions are displayed in Table 6 and Figure 1.

***Table 5. Regions of significant between-group differences: Non-Semantic Encoding***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Z-value for Region of Interest |
|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | |
| Left middle frontal gyrus | 6 | -33 | 21 | 54 | 2.68 |
| Left medial globus pallidus | | -17 | -5 | 0 | 3.10 |
| Left thalamus | | -24 | -26 | 6 | 2.22 |
| Left parahippocampal gyrus | 35 | -23 | -23 | -15 | 2.02 |
| Left middle temporal gyrus | 19 | -29 | -62 | 20 | 2.59 |
| Left fusiform gyrus | 36 | -42 | -31 | -18 | 3.32 |
| Left cerebellum | | -6 | -42 | -12 | 2.40 |
| | | | | | |
| Right putamen | | 20 | 2 | 11 | 2.73 |
| Right thalamus | | 12 | -17 | 9 | 2.88 |
| Right pons | | 13 | -28 | -21 | 2.75 |
| Right posterior cingulate gyrus | 30 | 6 | -55 | 20 | 2.34 |
| Right fusiform gyrus | 37 | 42 | -29 | -15 | 2.86 |
| | | | | | |
| ***Schizophrenia > Control*** | | | | | |
| Left precentral gyrus | 4 | -25 | -14 | 65 | 3.58 |
| Left superior temporal gyrus | 22 | -59 | -35 | 18 | 4.91 |
| Left inferior parietal lobule | 40 | -43 | -36 | 46 | 3.97 |
| Left superior parietal lobule | 7 | -29 | -55 | 56 | 4.84 |
| | | | | | |
| Right postcentral gyrus | 2 | 48 | -27 | 45 | 3.71 |
| Right superior temporal gyrus | 22 | 66 | -25 | 16 | 3.91 |

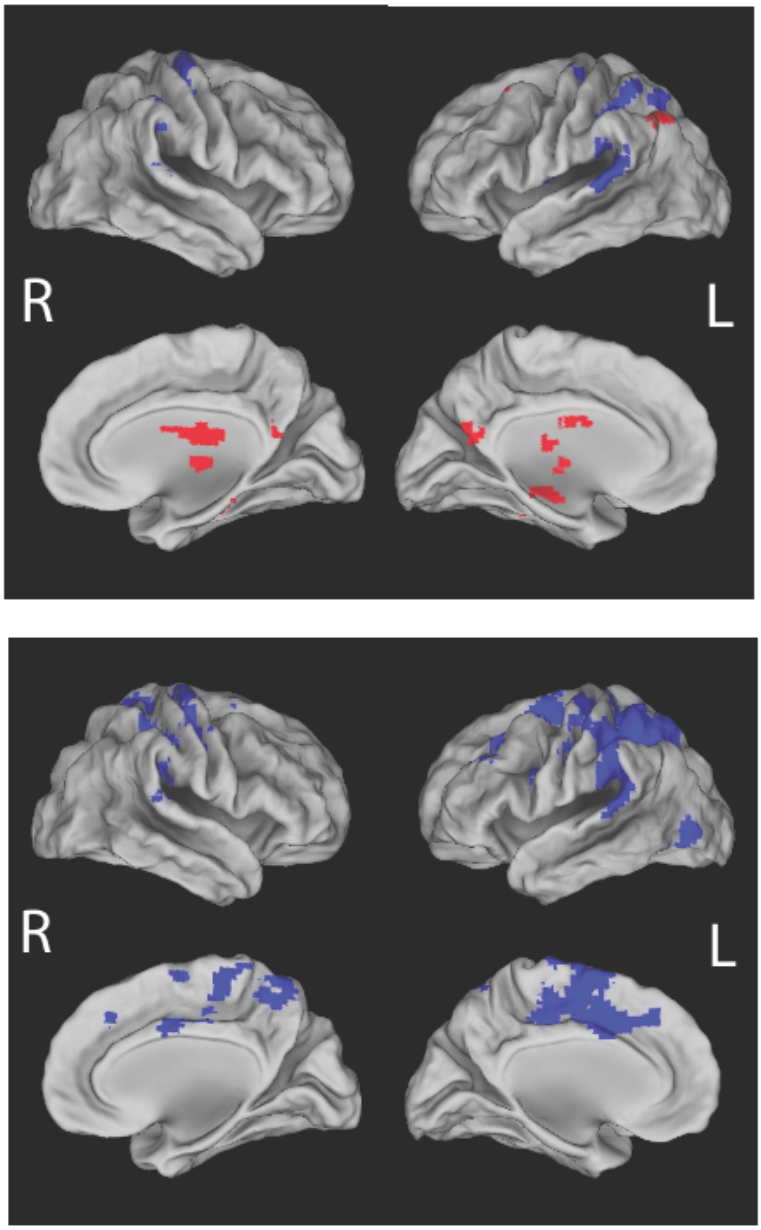
The enhanced pattern of activation observed in the participants with schizophrenia relative to the control group could be attributable to one of at least two possible mechanisms. First, if the additional activation served a compensatory role, one would expect that those schizophrenia participants who performed the best (i.e., recalled the most items) would show the most enhanced brain activity during encoding. Alternatively, the pattern of over-activation could also be interpreted as a sign of underlying pathology and inefficient cognitive processing. In this scenario, one would predict that pathology and cognitive inefficiency would be associated with worse subsequent recall performance. Thus, we would expect those schizophrenia participants with poorer memory performance to show the most enhanced encoding-related brain activity, relative to higher performing schizophrenia participants. To address this issue, I divided the schizophrenia participants into two groups based on subsequent recall of semantically-encoded items: a high-performing group (N = 12, recall = 94%) and a low-performing group (N = 11, recall = 77%). When high- and low-performing schizophrenia participants were directly compared on brain activity during Semantic encoding, I found a pattern of more robust and enhanced activation in the low-performing group. Specifically, low-performing schizophrenia participants activated a number of regions, including areas of bilateral prefrontal cortex, during Semantic encoding to a greater degree than high performers. In contrast, the high-performing group activated few regions more than the low-performing group. Furthermore, comparisons of high- and low-performing schizophrenia participants to the controls revealed many regions of significant differences between the low-performing group and the control group. In particular, differences were observed in regions of left prefrontal cortex and parietal lobe (low performing

schizophrenia > control). In contrast, direct comparison of the high-performing schizophrenia participants and controls revealed few areas of significant differences. Taken together, these results suggest that the pattern of over-activation observed in the participants with schizophrenia relative to controls was associated with poorer subsequent memory performance, whereas schizophrenia participants with better memory accuracy demonstrated encoding-related brain activity that was more like that of controls. Therefore, it is conceivable that activation enhancements, at least in this sample, were a marker of underlying pathology and cognitive inefficiency, rather than serving a compensatory role. This conclusion is based on post-hoc analyses, however, and must be interpreted cautiously.

***Table 6. Regions of significant between-group differences: Semantic Encoding***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Z-value for Region of Interest |
|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | |
| Left cerebellum | | -21 | -66 | -38 | 2.41 |
| Left cerebellum | | -38 | -54 | -37 | 2.31 |
| | | | | | |
| ***Schizophrenia > Control*** | | | | | |
| Left inferior frontal gyrus | 44 | -45 | 3 | 23 | 2.94 |
| Left middle frontal gyrus | 9 | -32 | 30 | 37 | 2.55 |
| Left medial frontal gyrus | 8 | -1 | 30 | 37 | 2.23 |
| Left superior frontal gyrus | 6 | -16 | -1 | 65 | 3.65 |
| Left anterior cingulate gyrus | 24 | -1 | 5 | 36 | 3.30 |
| Left precentral gyrus | 4 | -47 | -12 | 44 | 2.77 |
| Left precentral gyrus | 4 | -25 | -25 | 60 | 3.19 |
| Left superior temporal gyrus | 22 | -62 | -34 | 20 | 4.81 |
| Left inferior parietal lobule | 40 | -44 | -37 | 48 | 3.61 |
| Left superior parietal lobule | 7 | -23 | -65 | 54 | 3.54 |
| Left middle occipital gyrus | 19 | -46 | -73 | -6 | 2.37 |
| | | | | | |
| Right medial frontal gyrus | 6 | 11 | 2 | 62 | 2.95 |
| Right precentral gyrus | 6 | 43 | -7 | 34 | 2.77 |
| Right precentral gyrus | 4 | 31 | -15 | 64 | 3.25 |
| Right paracentral lobule | | 4 | -28 | 67 | 3.50 |
| Right paracentral lobule | | 1 | -17 | 46 | 3.05 |
| Right insula | | 55 | -30 | 19 | 3.23 |
| Right inferior parietal lobule | 40 | 47 | -31 | 41 | 3.36 |
| Right superior parietal lobe | 7 | 18 | -46 | 58 | 3.33 |

***Figure 1.***




Upper panel: Task-related brain activation during Non-Semantic encoding. Regions representing control > schizophrenia are shown in red. Regions representing schizophrenia > control are shown in blue.
Lower panel: Task-related brain activation during Semantic encoding. Regions representing control > schizophrenia are shown in red. Regions representing schizophrenia > control are shown in blue.

I then examined the effects of Group and Encoding Condition on encoding-related brain activity using a voxel-wise repeated measures ANOVA, with Group (Control, Schizophrenia) as the between subjects variable and Encoding Task (Semantic, Non-Semantic) as the within subjects variable. Consistent with my hypothesis, I detected a significant main effect of Encoding Condition (Semantic > Non-Semantic) on task-related brain activity in a canonical network of episodic memory encoding regions, including left inferior frontal gyrus (BA 44, 47), bilateral middle frontal gyrus (BA 6), and bilateral parahippocampal gyrus (BA 36), Results are displayed in Table 7 and Figure 2.

I also found significant Group x Encoding Condition interactions in bilateral prefrontal and parietal lobe regions, including left middle frontal gyrus (BA 8) and bilateral inferior parietal lobule (BA 40). Results are displayed in Table 8. Notably, and consistent with my predictions, post-hoc comparisons revealed that task-related activation differences between Semantic and Non-Semantic encoding were greater for schizophrenia participants than controls in a variety of regions, including left middle frontal gyrus (BA 8) and left inferior parietal lobule (BA 40). Furthermore, the nature of the interaction in nearly all regions was such that schizophrenia participants showed greater activity during Semantic (relative to Non-Semantic) encoding, whereas controls showed either no difference between Semantic and Non-Semantic encoding or greater activity during Non-Semantic encoding (relative to Semantic encoding; see Table 8). The groups were then directly compared in the regions showing Group x Encoding Condition interactions. The analyses for Semantic encoding revealed four regions in which schizophrenia participants activated more than controls (including left precentral gyrus

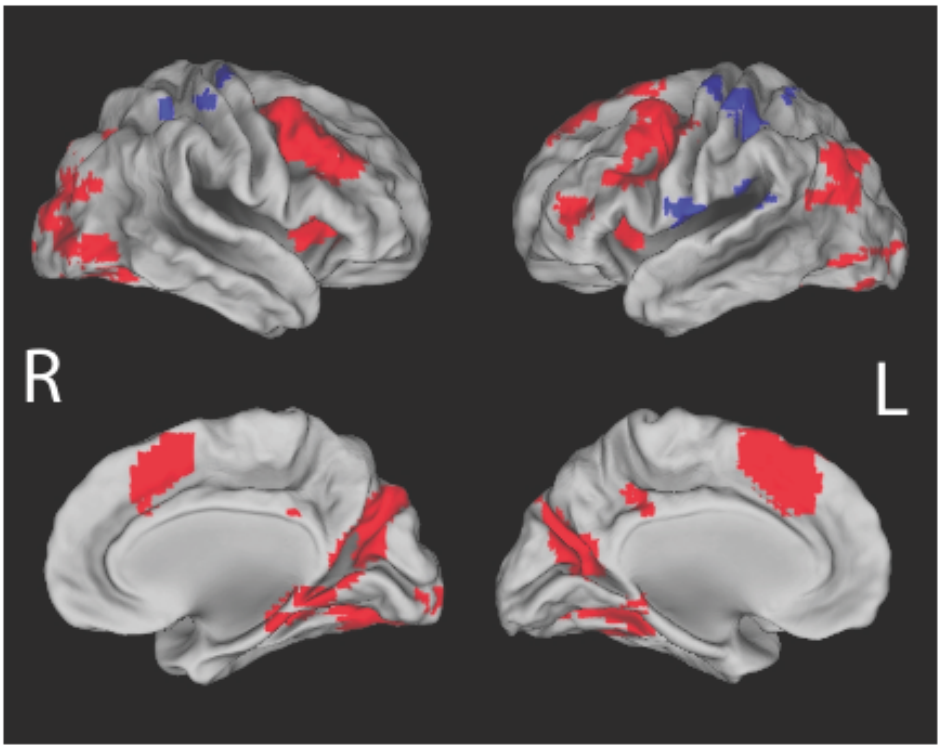
and left inferior parietal lobule), whereas the Non-Semantic encoding analyses revealed that controls activated three regions to a greater degree than schizophrenia participants. Brain activity in all other regions was equivalent across groups in each encoding condition.

***Table 7. Regions demonstrating a significant main effect of Encoding Task***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Direction |
|---|---|---|---|---|---|
| Left inferior frontal gyrus | 46 | -47 | 40 | 8 | Sem > Non-Sem |
| Left inferior frontal gyrus | 47 | -39 | 20 | -5 | Sem > Non-Sem |
| Left inferior frontal gyrus | 44 | -41 | 3 | 29 | Sem > Non-Sem |
| Left middle frontal gyrus | 6 | -28 | 15 | 57 | Sem > Non-Sem |
| Left middle frontal gyrus | 6 | -45 | 2 | 49 | Sem > Non-Sem |
| Left middle frontal gyrus | 9 | -48 | 24 | 30 | Sem > Non-Sem |
| Left medial frontal gyrus | 6 | -1 | 19 | 46 | Sem > Non-Sem |
| Left parahippocampal gyrus | 36 | -36 | -31 | -18 | Sem > Non-Sem |
| Left posterior cingulate gyrus | 31 | -2 | -38 | 35 | Sem > Non-Sem |
| Left precuneus | 19 | -28 | -73 | 42 | Sem > Non-Sem |
| Left precuneus | 31 | -14 | -65 | 18 | Sem > Non-Sem |
| Left cerebellum | | -33 | -60 | -17 | Sem > Non-Sem |
| Left lingual gyrus | 18 | -21 | -93 | -4 | Sem > Non-Sem |
| Left orbital gyrus | 19 | -38 | -84 | 25 | Sem > Non-Sem |
| Left cerebellum | | -33 | -81 | -17 | Sem > Non-Sem |
| | | | | | |
| Left precentral gyrus | 4 | -35 | -18 | 66 | Non-Sem > Sem |
| Left superior temporal gyrus | 42 | -56 | -5 | 9 | Non-Sem > Sem |
| Left inferior parietal lobule | 40 | -54 | -32 | 22 | Non-Sem > Sem |
| Left inferior parietal lobule | 40 | -45 | -32 | 49 | Non-Sem > Sem |
| | | | | | |
| Right middle frontal gyrus | 46 | 49 | 30 | 25 | Sem > Non-Sem |
| Right middle frontal gyrus | 6 | 38 | 8 | 49 | Sem > Non-Sem |
| Right medial frontal gyrus | 9 | 8 | 30 | 31 | Sem > Non-Sem |
| Right parahippocampal gyrus | 36 | 26 | -37 | -12 | Sem > Non-Sem |
| Right posterior cingulate | 31 | 12 | -62 | 16 | Sem > Non-Sem |
| Right precuneus | 19 | 20 | -71 | 36 | Sem > Non-Sem |
| Right middle occipital gyrus | 19 | 39 | -68 | -9 | Sem > Non-Sem |
| Right middle occipital gyrus | 19 | 34 | -82 | 18 | Sem > Non-Sem |
| Right lingual gyrus | 18 | 18 | -94 | -3 | Sem > Non-Sem |
| Right cerebellum | | 33 | -63 | -31 | Sem > Non-Sem |
| Right cerebellum | | 13 | -80 | -32 | Sem > Non-Sem |
| | | | | | |
| Right inferior parietal lobule | 40 | 43 | -35 | 54 | Non-Sem > Sem |
| Right precentral gyrus | 6 | 33 | -15 | 65 | Non-Sem > Sem |

-Sem = Semantic; Non-Sem = Non-Semantic

***Figure 2.***




Brain regions showing a main effect of Encoding Condition. Regions representing Semantic > Non-Semantic encoding activity are displayed in Red. Regions representing Non-Semantic > Semantic encoding activity are displayed in Blue.

***Table 8. Regions demonstrating a significant Group x Encoding Condition interaction***

| Region of Interest | Brodmann Area(s) | X | Y | Z | CON | SCZ | Z-value for ROI |
|---|---|---|---|---|---|---|---|
| Left middle frontal gyrus | 8 | -30 | 29 | 43 | S = N-S | S > N-S** | 2.93 |
| Left precentral gyrus | 4 | -20 | -31 | 59 | N-S > S* | S = N-S | 2.78 |
| Left posterior cingulate gyrus | 23 | -10 | -58 | 16 | S = N-S | S > N-S**** | 3.16 |
| Left inferior parietal lobule | 40 | -35 | -49 | 39 | S = N-S | S > N-S* | 3.23 |
| Left fusiform gyrus | 19 | -39 | -66 | -13 | S = N-S | S > N-S**** | 3.27 |
| Left inferior occipital gyrus | 18 | -17 | -97 | -4 | S = N-S | S > N-S*** | 3.12 |
| Left cerebellum | | -19 | -32 | -17 | S = N-S | S > N-S*** | 3.31 |
| | | | | | | | |
| Right cingulate gyrus | 24 | 17 | 4 | 44 | S = N-S | S > N-S** | 2.97 |
| Right anterior cingulate gyrus | 24 | 1 | -14 | 40 | S = N-S | S > N-S*** | 3.29 |
| Right inferior parietal lobule | 40 | 28 | -46 | 41 | N-S > S** | S > N-S* | 3.15 |
| Right fusiform gyrus | 20 | 32 | -25 | -25 | S = N-S | S > N-S*** | 3.33 |
| Right fusiform gyrus | 18 | 40 | -75 | -13 | S = N-S | S > N-S**** | 3.34 |
| Right precuneus | 19 | 27 | -68 | 37 | S = N-S | S > N-S**** | 3.25 |
| Right lingual gyrus | 17 | 13 | -91 | -4 | S = N-S | S > N-S**** | 2.94 |

CON = Control; SCZ = Schizophrenia
S = Semantic encoding; N-S = Non-Semantic encoding
ROI = Region of interest
*p < .05
**p < .01
***p < .005
****p < .001

*5. I predicted a significant overlap in subsequent memory activity between groups in posterior/parietal regions. In contrast, subsequent memory activity among schizophrenia participants would be associated with significant underactivation (relative to controls) in anterior/frontal brain regions.*

Four participants (3 controls, 1 participants with schizophrenia) were excluded from the subsequent memory analyses for Semantically-encoded items because of missing trial types (i.e., no subsequently missed items that were seen during Semantic encoding).

To address this hypothesis, I conducted a 2 x 2 repeated measures ANOVA, with Group (Control, Schizophrenia) as the between-subjects variable and Subsequent Memory (Remembered, Missed) as the within-subjects variable, separately for Semantically-encoded and Non-Semantically encoded items. For both encoding types, I predicted a main effect of Encoding Task, such that both groups would show significantly greater activity during encoding of subsequently recalled words than during encoding of subsequently missed words. I hypothesized that this effect would be observed in posterior brain regions, such as bilateral inferior parietal lobe (BA 40). In contrast, I predicted that neither group would show significantly greater activation during encoding of subsequently missed words, relative to encoding of subsequently remembered words.

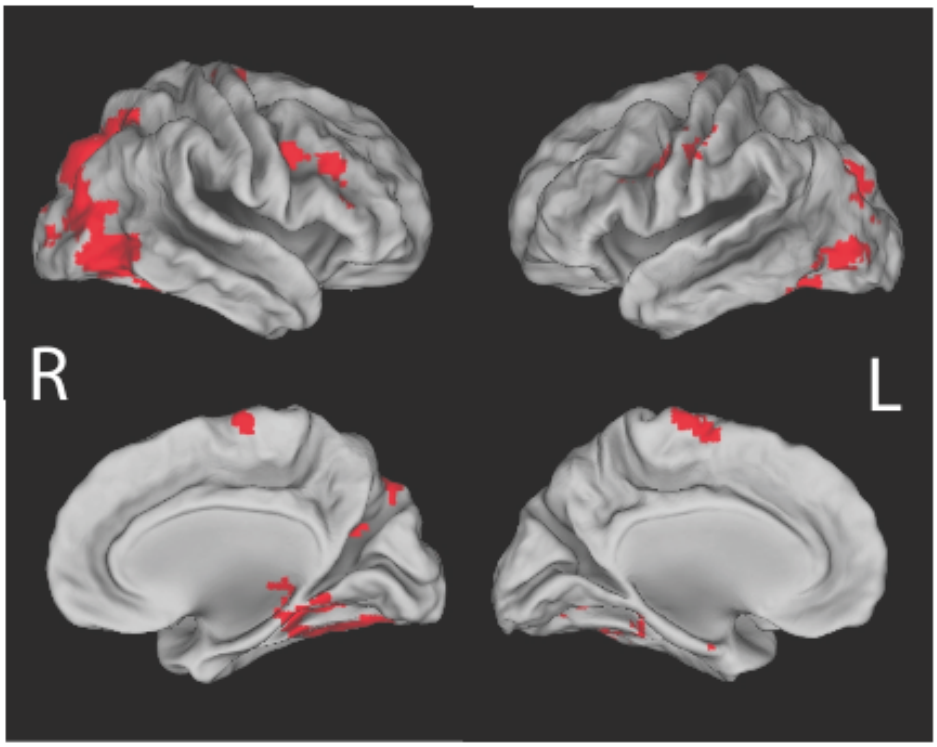
The ANOVA for Non-Semantically encoded items demonstrated that, contrary to my hypothesis, control and schizophrenia participants showed significant overlap in subsequent memory activity (Remember > Miss) in a number of areas of frontal cortex, including left and right inferior frontal gyrus (BA 44), left precentral gyrus (BA 6), and right middle frontal gyrus (BA 46). Consistent with my hypothesis, however, the groups

also demonstrated considerable overlap in subsequent memory activity (Remember > Miss) in posterior brain regions, including right superior parietal lobule (BA 7) and bilateral fusiform gyrus (BA 37; see Table 9, Figure 3). One region was identified which showed greater activity during Non-Semantic encoding for Missed than Remembered items (left superior temporal gyrus, BA 39). Finally, contrary to my hypothesis the analysis for Semantic encoding did not reveal any regions showing a significant main effect of Subsequent Memory (Table 9, Figure 3).

***Table 9. Regions demonstrating a significant main effect of Subsequent Memory***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Direction |
|---|---|---|---|---|---|
| ***Non-Semantic encoding*** | | | | | |
| Left inferior frontal gyrus | 44 | -50 | 22 | 26 | Remember > Miss |
| Left precentral gyrus | 6 | -44 | 2 | 35 | Remember > Miss |
| Left postcentral gyrus | 3 | -57 | -11 | 43 | Remember > Miss |
| Left fusiform gyrus | 37 | -40 | -48 | -13 | Remember > Miss |
| Left inferior occipital gyrus | 18 | -40 | -80 | -2 | Remember > Miss |
| Left middle occipital gyrus | 18 | -34 | -90 | 12 | Remember > Miss |
| Left middle occipital gyrus | 19 | -40 | -64 | -10 | Remember > Miss |
| Left precuneus | 19 | -25 | -79 | 36 | Remember > Miss |
| Left cerebellum | | -31 | -40 | -23 | Remember > Miss |
| Left cerebellum | | -1 | -45 | -17 | Remember > Miss |
| Left cerebellum | | -48 | -51 | -28 | Remember > Miss |
| Left cerebellum | | -16 | -39 | -15 | Remember > Miss |
| | | | | | |
| Right inferior frontal gyrus | 44 | 43 | 9 | 31 | Remember > Miss |
| Right inferior frontal gyrus | 46 | 53 | 38 | 11 | Remember > Miss |
| Right middle frontal gyrus | 46 | 47 | 30 | 23 | Remember > Miss |
| Right inferior temporal gyrus | 37 | 52 | -55 | -6 | Remember > Miss |
| Right fusiform gyrus | 20 | 29 | -35 | -16 | Remember > Miss |
| Right fusiform gyrus | 37 | 39 | -50 | -16 | Remember > Miss |
| Right superior parietal lobule | 7 | 28 | -64 | 47 | Remember > Miss |
| Right middle occipital gyrus | 19 | 37 | -68 | -10 | Remember > Miss |
| Right middle occipital gyrus | 19 | 41 | -83 | 10 | Remember > Miss |
| Right orbital gyrus | 19 | 34 | -74 | 27 | Remember > Miss |
| Right cerebellum | | 17 | -48 | -8 | Remember > Miss |
| | | | | | |
| Left superior temporal gyrus | 39 | -59 | -61 | 29 | Miss > Remember |
| ***Semantic encoding*** | | | | | |
| *no regions of significant activity* | | | | | |

***Figure 3.***




Brain regions showing a main effect of Subsequent Memory. Regions representing encoding activity for Remembered > Missed items are displayed in Red. Regions representing encoding activity for Missed > Remembered items are displayed in Blue.

I also predicted a significant Group x Subsequent Memory interaction, such that controls would show greater subsequent memory activity than schizophrenia participants for Non-Semantically-encoded items. Specifically, I hypothesized that for Non-Semantically encoded items, controls would show greater subsequent memory-related activity (remember > miss) than schizophrenia participants in left inferior frontal gyrus (BA 45/47), inferior parietal lobe (BA 40), and hippocampus. However, I predicted that between-group differences in subsequent memory activity would be reduced or eliminated for Semantically encoded items.

The ANOVAs revealed 3 regions that demonstrated a significant Group x Subsequent Memory interaction for Semantic encoding, as well as 17 regions demonstrating a significant Group x Subsequent Memory interaction for Non-Semantic encoding (Table 10, Figure 4).

Contrary to my predictions, post-hoc comparisons for the Semantic encoding regions revealed that controls showed significantly greater activity for Missed items than Remembered items in two of the three areas, while schizophrenia participants showed greater activity for Remembered than Missed items in one area (right inferior parietal lobule, BA 40). Contrary to my predictions, post-hoc comparisons for the Non-Semantic encoding regions revealed that in 14 of the 17 regions, schizophrenia participants demonstrated significantly greater encoding-related activity during items that were subsequently remembered (relative to subsequently missed). Notably, some of these regions have been previously identified in studies of subsequent memory in healthy controls (e.g., left superior frontal gyrus, left fusiform gyrus, left superior parietal lobule, left cerebellum), although others have not. In contrast, controls showed greater encoding

activity during items that were subsequently missed (relative to subsequently remembered) in 8 of the 17 regions (see Table 10, Figure 4). Surprisingly, a subset of the regions showing Miss > Remember activity among controls have also been identified as subsequent memory regions in previous studies (e.g., left medial frontal gyrus, left middle frontal gyrus, left cerebellum).

***Table 10. Regions demonstrating significant Group x Subsequent Memory interactions***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Control | Schizophrenia | Z-value for ROI |
|---|---|---|---|---|---|---|---|
| ***Semantic encoding*** | | | | | | | |
| Left middle frontal gyrus | 46 | -46 | 30 | 24 | **M > R**** | R = M | 2.95 |
| Right superior temporal gyrus | 22 | 49 | -29 | 0 | **M > R*** | R = M | 2.76 |
| Right inferior parietal lobule | 40 | 42 | -50 | 39 | R = M | **R > M**** | 3.13 |
| ***Non-Semantic encoding*** | | | | | | | |
| Left medial frontal gyrus | 9 | -3 | 38 | 29 | **M > R**** | R = M | 2.89 |
| Left superior frontal gyrus | 10 | -17 | 53 | -5 | **M > R***** | R = M | 3.22 |
| Left superior frontal gyrus | 8 | -22 | 49 | 39 | R = M | **R > M**** | 3.11 |
| Left superior parietal lobule | 7 | -29 | -70 | 44 | R = M | **R > M***** | 2.72 |
| Left fusiform gyrus | 19 | -29 | -47 | -12 | R = M | **R > M****** | 2.87 |
| Left cuneus | 19 | -26 | -86 | 22 | R = M | **R > M****** | 3.13 |
| Left cuneus | 18 | -21 | -99 | -1 | **M > R*** | **R > M**** | 3.50 |
| Left cerebellum | | -11 | -45 | -2 | R = M | **R > M***** | 2.94 |
| Left cerebellum | | -23 | -82 | -24 | **M > R***** | **R > M**** | 3.87 |
| Left cerebellum | | -46 | -60 | -35 | **M > R***** | **R > M**** | 4.08 |
| | | | | | | | |
| Right inferior frontal gyrus | 47 | 47 | 23 | -8 | **M > R*** | **R > M***** | 3.66 |
| Right superior frontal gyrus | 6 | 9 | 10 | 66 | **M > R**** | R = M | 3.07 |
| Right cuneus | 17 | 13 | -95 | 2 | **M > R*** | **R > M*** | 2.96 |
| Right cerebellum | | 26 | -55 | -13 | R = M | **R > M****** | 2.89 |
| Right cerebellum | | 36 | -71 | -26 | R = M | **R > M****** | 3.03 |
| Right cerebellum | | 9 | -80 | -33 | R = M | **R > M**** | 3.07 |
| Right cerebellum | | 20 | -79 | -15 | R = M | **R > M**** | 2.96 |

R = Remember; M = Miss; ROI = Region of interest

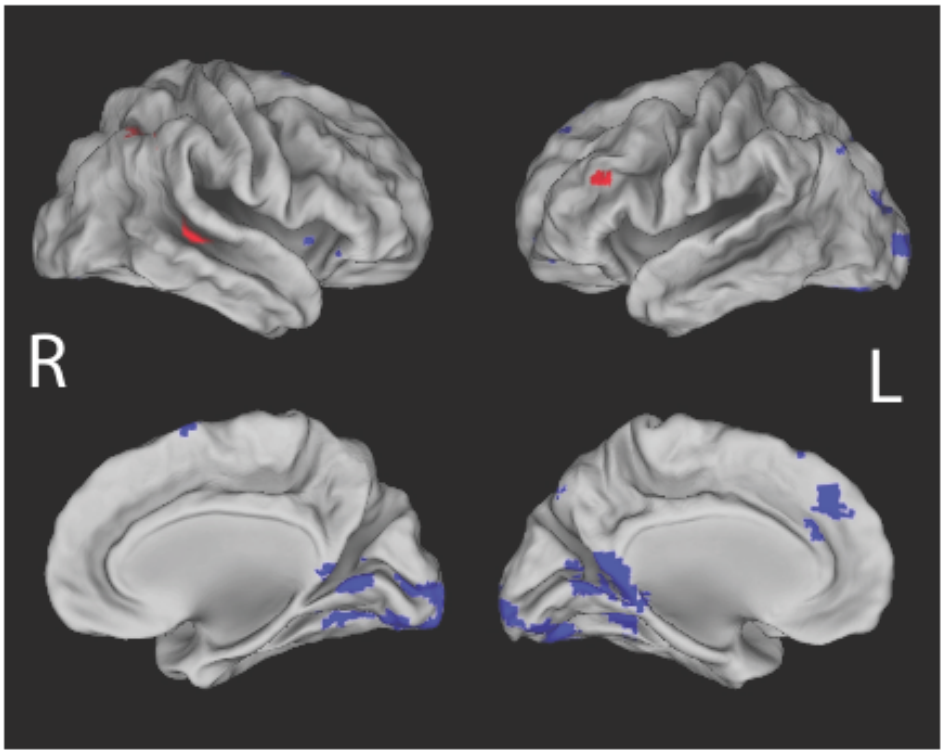
*p < .05

**p < .01

***p < .005

****p < .001

***Figure 4.***




Brain regions demonstrating significant Group (control, schizophrenia) x Subsequent Memory (Remember, Miss) interactions. Areas demonstrating interactions for Semantically encoded items are displayed in red. Areas demonstrating interactions for Non-Semantically-encoded items are displayed in blue.

*Encoding-Related Brain Activity: Summary*

The analyses in this section examined encoding-related and subsequent memory-related brain activity in both groups. Regarding encoding-related brain activity, a number of predictions were upheld. Most notably, individuals with schizophrenia demonstrated robust brain activity differences between encoding conditions (Semantic > Non-Semantic), whereas controls largely showed no differences or differences in the opposite direction. There was also evidence that Semantic encoding was associated with significant increases in task-related activation among schizophrenia participants relative to controls, in regions that included left inferior frontal (BA 44) and middle frontal gyrus (BA 9) and bilateral inferior parietal lobule (BA 40). Both findings further support the notion that individuals with schizophrenia show enhanced brain activity during supportive encoding conditions in episodic memory paradigms, although post-hoc analyses suggested that the additional activity in the schizophrenia group was pathological rather than compensatory in nature. In contrast to my hypotheses, I did not find the predicted significant activity in left inferior frontal gyrus during Semantic > Non-Semantic encoding among schizophrenia participants. Furthermore, I did not find any significant between-group differences (control > schizophrenia) in the predicted frontal or hippocampal regions.

Regarding the subsequent memory data, I identified a number of brain regions in which subsequent memory effects were found in both controls and individuals with schizophrenia, as well as additional regions in which subsequent memory effects were found exclusively in schizophrenia participants. As predicted, the analyses revealed a significant degree of overlap in subsequent memory activity between the control and

schizophrenia participants in posterior brain areas (e.g., right superior parietal lobule, left precuneus). This finding contributes to a small but growing literature suggesting that subsequent memory activity in schizophrenia is similar to that of controls in areas of parietal cortex. Contrary to my predictions, however, controls and schizophrenia participants also showed overlapping patterns of subsequent memory activation in regions of bilateral frontal cortex (among other areas). Furthermore, schizophrenia participants showed significant activation differences between remembered and missed items (Remember > Miss) in additional regions of frontal cortex, whereas controls largely showed either no differences between remembered and missed items or greater activity for missed than remembered items in those areas. To my knowledge, this is a novel finding and suggests that subsequent memory effects in schizophrenia participants can also be identified in frontal regions and overlap to some degree with subsequent memory activity found in healthy controls.

## Retrieval-Related Brain Activity: Results

The third set of results outlined below concerns brain activity during retrieval. Specifically, the focus of the following predictions relates to the effect of both Encoding Orientation (Semantic vs. Non-Semantic) and Cueing (Cued vs. Uncued) on retrieval-related brain activity in participants with schizophrenia and healthy controls. Furthermore, this set of hypotheses examines the interactive effects of Encoding Orientation, Cueing, and Group on brain activity during retrieval. The specific questions used to address this area of interest are as follows:

*Effects of Cueing on Retrieval-Related Brain Activity*

*1. I predicted that during retrieval of Uncued words (relative to Cued retrieval), schizophrenia participants would show the typical pattern of fronto-temporal dysregulation found in previous studies, including overactivation of frontal regions and underactivation of hippocampus.*

In order to address this hypothesis, I directly compared the control and schizophrenia groups on Uncued retrieval-related activity, using a between groups t-test. I predicted significant between-group differences (control > schizophrenia) in retrieval-related brain activity during retrieval of Uncued words. Specifically, schizophrenia participants will show significant reductions in hippocampal activity, in combination with significantly greater activity in frontal cortex regions, such as inferior frontal gyrus (BA 45/47), bilateral middle frontal gyrus (BA 6/44) and anterior prefrontal cortex (BA 10/46).

Contrary to my predictions, results of the analysis revealed that controls activated frontal regions (among others) to a significantly greater extent than schizophrenia participants. Regions of significant between group differences included left (BA 47) and right (BA 45) inferior frontal gyrus, bilateral middle frontal gyrus (BA 10), and left superior frontal gyrus (BA 8). However, also contrary to my predictions, I did not detect any significant between-group differences in hippocampus. All regions are displayed in Table 11.

***Table 11. Regions of significant between-group differences: Uncued retrieval***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Z-value for ROI |
|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | |
| Left inferior frontal gyrus* | 47 | -43 | 21 | -5 | 3.64 |
| Left middle frontal gyrus* | 10 | -37 | 42 | 12 | 3.07 |
| Left middle frontal gyrus* | 9 | -37 | 15 | 33 | 3.52 |
| Left middle frontal gyrus | 9 | -27 | 38 | 36 | 3.02 |
| Left superior frontal gyrus | 8 | -27 | 14 | 52 | 2.66 |
| Left caudate* | | -13 | 5 | 11 | 3.75 |
| Left putamen | | -26 | -11 | 7 | 2.69 |
| Left middle temporal gyrus* | 39 | -51 | -75 | 25 | 3.66 |
| Left superior temporal gyrus | 22 | -60 | -1 | 9 | 3.17 |
| Left inferior parietal lobule* | 40 | -42 | -68 | 45 | 3.96 |
| Left inferior parietal lobule* | 40 | -54 | -49 | 45 | 3.42 |
| Posterior cingulate gyrus | 23 | -1 | -28 | 33 | 3.08 |
| Posterior cingulate gyrus* | 31 | -1 | -61 | 28 | 3.37 |
| Left middle occipital gyrus | 19 | -31 | -78 | 20 | 3.09 |
| Left lingual gyrus* | 18 | -6 | -89 | -1 | 3.14 |
| | | | | | |
| Right inferior frontal gyrus* | 44 | 39 | 36 | 2 | 3.31 |
| Right inferior frontal gyrus* | 45 | 55 | 21 | 5 | 3.43 |
| Right middle frontal gyrus | 10 | 32 | 43 | 21 | 3.01 |
| Right middle frontal gyrus | 9 | 44 | 32 | 34 | 2.95 |
| Right superior frontal gyrus* | 8 | 9 | 30 | 48 | 3.42 |
| Right precentral gyrus | 6 | 51 | 2 | 17 | 3.13 |
| Right anterior cingulate gyrus | 32 | 6 | 31 | 22 | 2.98 |
| Right insula | | 37 | -16 | 10 | 2.81 |
| Right thalamus | | 1 | -23 | 10 | 3.09 |
| Right middle temporal gyrus* | 21 | 55 | -39 | -3 | 3.04 |
| Right middle temporal gyrus | 39 | 48 | -62 | 11 | 3.20 |
| Right middle temporal gyrus | 21 | 49 | -12 | -12 | 2.82 |
| Right posterior cingulate* | 30 | 20 | -57 | 12 | 3.22 |
| Right inferior parietal lobule* | 40 | 34 | -52 | 45 | 3.69 |
| Right angular gyrus* | 39 | 50 | -66 | 33 | 3.21 |
| Right orbital gyrus* | 19 | 33 | -82 | 27 | 3.13 |
| Right inferior occipital gyrus* | 18 | 27 | -85 | -5 | 3.60 |
| Right cerebellum* | | 55 | -48 | -26 | 3.38 |
| | | | | | |
| ***Schizophrenia > Control*** | | | | | |
| *no regions of significant activity* | | | | | |

*Denotes regions that continued to show significant between-group differences when signal-to-noise ratio was equated between groups.

*2. I also predicted that Cued (relative to Uncued) retrieval would be associated with fewer between-group differences in retrieval-related brain activity.*

In order to address this hypothesis, I compared control and schizophrenia participants on retrieval-related brain activity during Cued retrieval using a between groups t-test. I predicted that schizophrenia participants would show markedly reduced activation differences in hippocampus (control > schizophrenia), as well as inferior frontal (BA 45/47), middle frontal (BA 6/44), and anterior prefrontal (BA 10/46) cortices (schizophrenia > control), although such differences would persist despite the presence of retrieval cues.

Contrary to my hypothesis, Cued retrieval was not associated with noticeably fewer between-group differences in retrieval-related brain activity. Similar to the Uncued retrieval condition, control participants continued to show greater retrieval-related activity than schizophrenia participants in a wide variety of fronto-temporal regions, as well as posterior areas (see Table 12). Unlike Uncued retrieval, however, schizophrenia participants showed greater activity than controls in one brain region (left cerebellum).

Next, in order to assess the effects of Cueing and Group on retrieval-related brain activity, I conducted a voxel-wise repeated measures ANOVA, with Group (control, schizophrenia) as the between-subjects variable and Cueing (Cued, Uncued) as the within-subjects variable. I predicted a significant main effect of Cueing, such that both groups would show significantly greater hippocampal activity (particularly in left hemisphere) for Cued (relative to Uncued) recall.

***Table 12. Regions of significant between-group differences: Cued retrieval***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Z-value for ROI |
|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | |
| Left inferior frontal gyrus* | 47 | -42 | 24 | -8 | 3.71 |
| Left middle frontal gyrus* | 10 | -43 | 46 | 11 | 3.17 |
| Left middle frontal gyrus* | 9 | -41 | 13 | 39 | 3.43 |
| Left superior frontal gyrus | 9 | -22 | 42 | 33 | 3.06 |
| Left superior frontal gyrus* | 8 | -4 | 32 | 53 | 3.00 |
| Left putamen | | -19 | 9 | 9 | 3.20 |
| Left middle temporal gyrus* | 21 | -57 | -50 | 2 | 3.54 |
| Left superior temporal gyrus | 22 | -57 | 8 | 0 | 3.40 |
| Left posterior cingulate gyrus | 31 | -1 | -28 | 35 | 2.94 |
| Left inferior parietal lobule* | 40 | -51 | -42 | 43 | 3.25 |
| Left precuneus* | 18 | -3 | -67 | 27 | 3.26 |
| Left middle occipital gyrus | 19 | -31 | -79 | 19 | 3.49 |
| | | | | | |
| Right inferior frontal gyrus | 44 | 41 | 18 | 12 | 3.30 |
| Right inferior frontal gyrus | 44 | 56 | 3 | 19 | 3.38 |
| Right middle frontal gyrus | 10 | 35 | 37 | -3 | 3.35 |
| Right medial frontal gyrus | 8 | 7 | 46 | 37 | 3.33 |
| Right superior frontal gyrus* | 8 | 16 | 33 | 50 | 3.59 |
| Right superior frontal gyrus* | 8 | 33 | 11 | 48 | 3.58 |
| Right superior frontal gyrus | 9 | 31 | 43 | 26 | 3.42 |
| Right middle temporal gyrus* | 39 | 51 | -64 | 24 | 3.33 |
| Right middle temporal gyrus* | 21 | 59 | -49 | -6 | 3.54 |
| Right middle temporal gyrus | 21 | 50 | -13 | -11 | 2.91 |
| Right insula | | 46 | -24 | 17 | 2.84 |
| Right caudate | | 22 | -32 | 15 | 2.56 |
| Right caudate* | | 9 | 2 | 10 | 3.35 |
| Right anterior cingulate gyrus | 24 | 15 | 8 | 35 | 2.81 |
| Right superior parietal lobule* | 7 | 39 | -55 | 49 | 3.87 |
| Right fusiform gyrus* | 18 | 29 | -84 | -14 | 3.22 |
| Right superior occipital gyrus* | 19 | 33 | -82 | 28 | 2.89 |
| | | | | | |
| ***Schizophrenia > Control*** | | | | | |
| Left cerebellum* | | -13 | -40 | -40 | 2.88 |

*Denotes regions that continued to show significant between-group differences when signal-to-noise ratio was equated between groups.

My hypothesis regarding the main effect of Cueing was largely unsupported. The analysis revealed only one region demonstrating a significant main effect of Cueing (left lingual gyrus, BA 18). Post-hoc comparisons revealed that both groups activated this region more during Cued than Uncued retrieval. However, I did not detect any main effects in the predicted regions (i.e., hippocampus).

Furthermore, I predicted a significant Cueing x Group interaction, such that participants with schizophrenia would show more enhanced hippocampal activity (relative to controls) during Cued than Uncued recall. Specifically, I predicted that the provision of recall cues will be associated with a robust pattern of brain activity in hippocampus, in combination with reduced activity in bilateral prefrontal cortex (BA 45/47, 10/46), in the schizophrenia group.

Contrary to my hypothesis, schizophrenia participants did not show significant activation enhancements in hippocampus relative to controls during Cued recall (as compared to Uncued recall). In fact, a Group by Cueing interaction was detected in only one region, an area in left frontal cortex closest to BA 6 (-26, 1, 32). Post-hoc comparisons revealed that the between-group difference (control > schizophrenia) during Cued retrieval was smaller than during Uncued retrieval.

*Effects of Cueing: Summary*

My predictions with regard to the effects of Cueing on retrieval-related brain activity were unsupported. During both Cued and Uncued retrieval, controls activated a network of frontal, temporal, and posterior regions to a significantly greater degree than schizophrenia participants. Thus, despite the behavioral benefits conferred by the

retrieval cues, schizophrenia participants did not demonstrate the expected modulations in brain activity when these cues were present.

*Effects of Encoding Orientation on Retrieval-Related Brain Activity*

*3. Consistent with previous work, schizophrenia participants would demonstrate significant deficits in retrieval-related brain activation during retrieval of words encoded Non-Semantically.*

To address this hypothesis, I conducted a between-groups t-test directly comparing retrieval-related activity between groups for retrieval of words encoded in the Non-Semantic encoding condition. I predicted that retrieval of items encoded Non-Semantically would be associated with significant between-group differences (control > schizophrenia) in retrieval-related brain activity. More specifically, controls would show significantly greater retrieval-related activity than schizophrenia participants in hippocampus, while schizophrenia participants would show significantly greater activation than controls in bilateral frontal regions (BA 45/47, BA 10/46).

My predictions regarding this hypothesis were somewhat supported. The analysis revealed significant between-group differences (control > schizophrenia) in retrieval-related brain activity in variety of regions, including those that are typically associated with episodic memory retrieval (e.g., left middle frontal gyrus, left inferior parietal lobule). However, between-group differences were not detected in hippocampus (see Table 13 for all regions).

***Table 13. Regions of significant between-group differences: Non-Semantic retrieval***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Z-value for ROI |
|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | |
| Left inferior frontal gyrus* | 47 | -39 | 20 | -8 | 3.90 |
| Left middle frontal gyrus | 6 | -21 | 19 | 52 | 2.78 |
| Left middle frontal gyrus* | 10 | -39 | 44 | 14 | 3.21 |
| Left middle frontal gyrus | 9 | -25 | 42 | 34 | 2.98 |
| Left middle frontal gyrus* | 9 | -42 | 14 | 38 | 3.43 |
| Left superior frontal gyrus | 8 | -3 | 42 | 44 | 3.43 |
| Left middle temporal gyrus | 21 | -55 | -29 | -6 | 2.89 |
| Left middle temporal gyrus* | 37 | -56 | -53 | -2 | 3.16 |
| Left superior temporal gyrus* | 22 | -57 | 5 | 1 | 3.62 |
| Left putamen* | | -22 | 5 | 9 | 3.56 |
| Left inferior parietal lobule* | 40 | -54 | -44 | 44 | 3.51 |
| Left precuneus* | 31 | -6 | -61 | 26 | 3.59 |
| Left middle occipital gyrus* | 19 | -31 | -79 | 19 | 3.54 |
| | | | | | |
| Right inferior frontal gyrus* | 45 | 54 | 22 | 2 | 3.72 |
| Right inferior frontal gyrus | 44 | 36 | 39 | 1 | 3.22 |
| Right middle frontal gyrus | 9 | 35 | 42 | 27 | 3.41 |
| Right superior frontal gyrus* | 8 | 14 | 32 | 48 | 3.50 |
| Right superior frontal gyrus* | 8 | 33 | 13 | 49 | 3.49 |
| Right precentral gyrus | 6 | 57 | 3 | 14 | 3.42 |
| Right insula | 13 | 39 | 10 | -4 | 3.06 |
| Right insula | 13 | 37 | 4 | 17 | 2.97 |
| Right insula | 13 | 46 | -19 | 14 | 2.80 |
| Right anterior cingulate gyrus | 24 | 8 | 30 | 16 | 3.01 |
| Right anterior cingulate gyrus | 24 | 14 | 8 | 37 | 2.76 |
| Right thalamus | | 22 | -27 | 6 | 2.79 |
| Right middle temporal gyrus | 21 | 56 | -38 | -3 | 3.20 |
| Right middle temporal gyrus | 21 | 55 | -17 | -18 | 3.01 |
| Right middle temporal gyrus* | 39 | 51 | -64 | 28 | 3.08 |
| Right superior parietal lobule* | 7 | 39 | -58 | 52 | 3.64 |
| Right inferior occipital gyrus* | 18 | 27 | -87 | -14 | 3.26 |
| Right lingual gyrus* | 17 | 3 | -91 | -4 | 3.29 |
| | | | | | |
| ***Schizophrenia > Control*** | | | | | |
| *no regions of significant activity* | | | | | |

*Denotes regions that continued to show significant between-group differences when signal-to-noise ratio was equated between groups.

*4. In contrast, schizophrenia participants would show more typical retrieval-related brain activity patterns during recall of items encoded Semantically.*

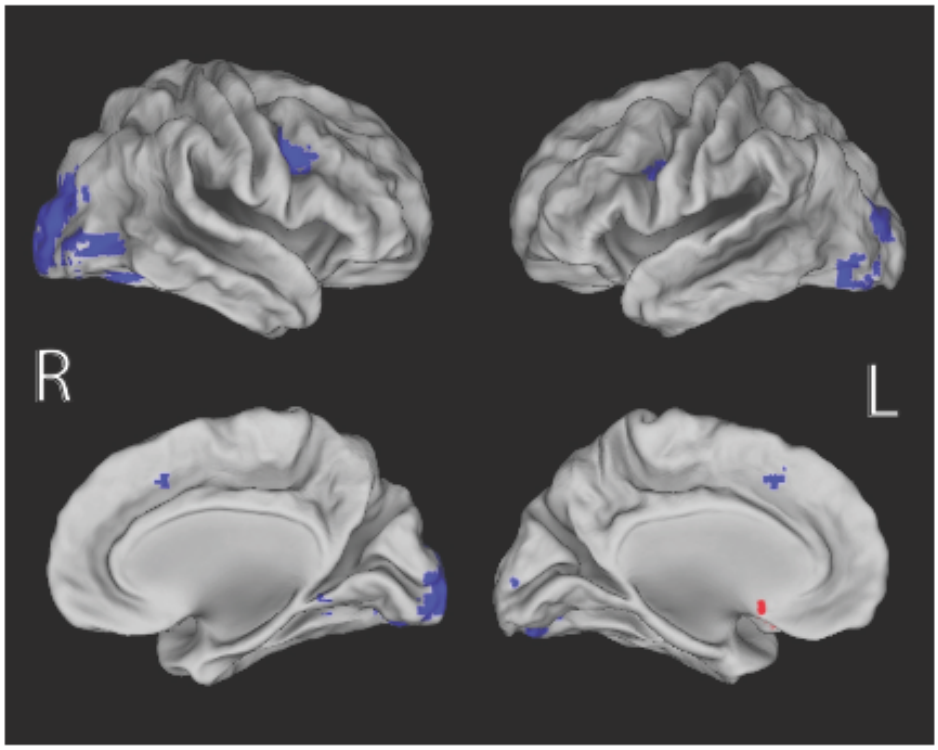
In order to address this hypothesis, I conducted a within-group t-test comparing retrieval-related brain activity for items encoded Semantically vs. Non-Semantically among schizophrenia participants. I predicted that during retrieval of items that were encoded Semantically (as compared to Non-Semantically), schizophrenia participants would show enhanced activity in left inferior frontal gyrus (BA 45/47), anterior prefrontal cortex (BA 10/46), inferior parietal lobe (BA 40), and hippocampus (among other regions).

Contrary to my hypothesis, retrieval of items encoded Semantically (relative to Non-Semantically) among schizophrenia participants was associated with significant activity in only one region (left subcallosal gyrus, BA 25). The opposite contrast (Non-Semantic retrieval > Semantic retrieval), however, revealed significant activity in 12 regions, with some indication of more right-lateralized than left-lateralized activity. Full results are displayed in Table 14 and Figure 5.

***Table 14. Regions of significant retrieval-related activity for items encoded Semantically vs. Non-Semantically: Schizophrenia participants***

| Region of Interest | Brodmann Area(s) | X | Y | Z |
|---|---|---|---|---|
| ***Semantic > Non-Semantic*** | | | | |
| Left subcallosal gyrus | 25 | -10 | 21 | -13 |
| | | | | |
| ***Non-Semantic > Semantic*** | | | | |
| Left inferior frontal gyrus | 44 | -42 | 7 | 26 |
| Left fusiform gyrus | 18 | -33 | -78 | -13 |
| Left middle occipital gyrus | 18 | -23 | -98 | 11 |
| | | | | |
| Right inferior frontal gyrus | 45 | 31 | 26 | 6 |
| Right middle frontal gyrus | 9 | 41 | 11 | 32 |
| Right anterior cingulate gyrus | 32 | 1 | 21 | 40 |
| Right parahippocampal gyrus | 37 | 23 | -45 | -8 |
| Right fusiform gyrus | 37 | 44 | -62 | -9 |
| Right fusiform gyrus | 19 | 27 | -80 | -11 |
| Right cuneus | 17 | 18 | -95 | -2 |
| Right middle occipital gyrus | 19 | 29 | -83 | 21 |
| Right cerebellum | | 4 | -74 | -31 |

***Figure 5.***




Brain regions in participants with schizophrenia demonstrating significant differences in brain activity for retrieval of Semantically-encoded vs. Non-Semantically-encoded items. The Semantic > Non-Semantic retrieval contrast is displayed in red. The Non-Semantic > Semantic retrieval contrast is displayed in blue.

*5. Furthermore, retrieval of items encoded Semantically would be associated with fewer between-group differences (control > schizophrenia) in brain activity.*

In order to address this hypothesis, I conducted a between groups t-test, in order to directly compare retrieval-related activity between groups for retrieval of words encoded Semantically. Based on previous findings in this area, I predicted that during retrieval of Semantically encoded items, controls would again show more activity than schizophrenia participants in hippocampus, while schizophrenia participants would show greater activity in bilateral inferior frontal gyrus (BA 45/47) and middle frontal gyrus (BA 6/44).

Contrary to my predictions, controls did not show significant enhancements in hippocampal activity relative to schizophrenia participants during retrieval of Semantically encoded items, although they demonstrated greater activity than schizophrenia participants in numerous other regions (see Table 15). These included bilateral inferior frontal (BA 44, 47) and middle frontal gyrus (BA 6, 9), anterior cingulate (BA 24), and right superior parietal lobule (BA 7). Also contrary to my hypothesis, schizophrenia participants failed to activate any brain regions to a greater degree than controls during retrieval of Semantically encoded items.

***Table 15. Regions of significant between-group differences: Semantic retrieval***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Z-value for ROI |
|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | |
| Left inferior frontal gyrus* | 47 | -41 | 23 | -8 | 3.34 |
| Left middle frontal gyrus* | 10 | -47 | 48 | -5 | 2.72 |
| Left middle frontal gyrus | 9 | -21 | 38 | 36 | 2.97 |
| Left middle frontal gyrus | 46 | -35 | 41 | 15 | 3.08 |
| Left middle frontal gyrus* | 9 | -44 | 24 | 31 | 3.19 |
| Left middle frontal gyrus* | 9 | -30 | 11 | 38 | 3.14 |
| Left cingulate gyrus | 23 | -1 | -28 | 33 | 3.15 |
| Left angular gyrus* | 39 | -53 | -61 | 36 | 3.95 |
| Left precuneus* | 31 | 0 | -62 | 26 | 3.22 |
| Left middle occipital gyrus | 19 | -31 | -79 | 19 | 3.32 |
| Left lingual gyrus | 18 | -13 | -84 | 4 | 2.82 |
| | | | | | |
| Right inferior frontal gyrus* | 44 | 55 | 16 | 15 | 3.14 |
| Right middle frontal gyrus | 46 | 37 | 35 | 26 | 3.13 |
| Right middle frontal gyrus* | 6 | 34 | 9 | 44 | 3.17 |
| Right medial frontal gyrus | 8 | 3 | 46 | 38 | 3.08 |
| Right superior frontal gyrus* | 8 | 11 | 26 | 50 | 3.39 |
| Right anterior cingulate gyrus | 24 | 10 | 30 | 17 | 2.89 |
| Right anterior cingulate gyrus | 24 | 13 | 5 | 34 | 2.84 |
| Right caudate* | | 9 | 2 | 12 | 3.35 |
| Right caudate | | 20 | -32 | 14 | 2.72 |
| Right middle temporal gyrus* | 37 | 53 | -66 | 9 | 3.34 |
| Right middle temporal gyrus* | 37 | 59 | -50 | -7 | 3.53 |
| Right transverse temporal gyrus | 41 | 47 | -20 | 13 | 2.91 |
| Right superior parietal lobule* | 7 | 38 | -56 | 50 | 4.00 |
| Right posterior cingulate gyrus | 30 | 25 | -68 | 7 | 3.09 |
| Right angular gyrus* | 39 | 54 | -68 | 30 | 3.41 |
| Right orbital gyrus* | 19 | 32 | -82 | 25 | 3.12 |
| Right fusiform gyrus* | 19 | 30 | -83 | -14 | 3.40 |
| Right precuneus | 19 | 9 | -80 | 40 | 2.84 |
| Right lingual gyrus | 18 | 6 | -91 | -1 | 3.00 |
| | | | | | |
| ***Schizophrenia > Control*** | | | | | |
| *no regions of significant activity* | | | | | |

*Denotes regions that continued to show significant between-group differences when signal-to-noise ratio was equated between groups.

Next, in order to further examine the effects of Group and Encoding Orientation on retrieval-related brain activity, I conducted a voxel-wise repeated measures ANOVA with Group (Control, Schizophrenia) as the between subjects variable and Encoding Orientation (Semantic, Non-Semantic) as the within-subjects variable. I first predicted a significant main effect of Orientation, such that both groups would show more left inferior frontal cortex (BA 45/47), anterior prefrontal cortex (BA 10/46), and hippocampal activity during retrieval of Semantically encoded words.

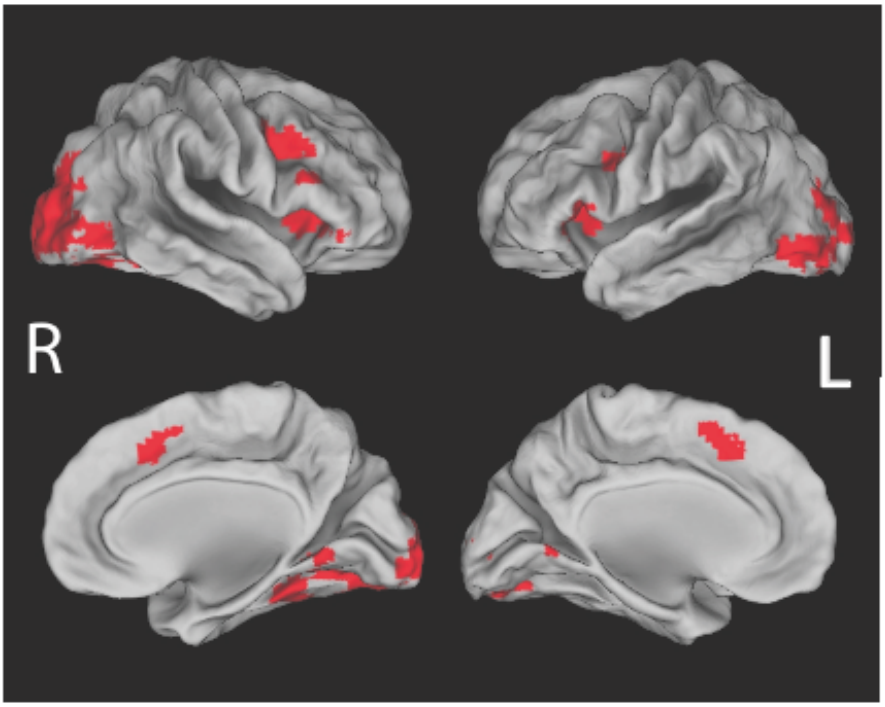
The ANOVA identified 16 regions that showed significant main effects of Encoding Orientation. Contrary to my predictions, however, the differences in all regions were in the direction of greater brain activity during retrieval of Non-Semantically encoded items (relative to Semantically-encoded items). The analysis revealed that both groups activated bilateral inferior frontal gyrus (BA 47), right middle frontal gyrus (BA 9), and right fusiform gyrus (BA 37) to a greater degree during retrieval of Non-Semantically encoded items. All regions are displayed in Table 16 and Figure 6.

***Table 16. Regions demonstrating a significant main effect of Encoding Condition for Retrieval-related brain activity***

| Region of Interest | Brodmann Area(s) | X | Y | Z | Direction |
|---|---|---|---|---|---|
| Left inferior frontal gyrus | 47 | -37 | 23 | 1 | Non-Sem > Sem |
| Left inferior frontal gyrus | 44 | -41 | 8 | 27 | Non-Sem > Sem |
| Left medial frontal gyrus | 8 | -1 | 19 | 45 | Non-Sem > Sem |
| Left middle occipital gyrus | 18 | -29 | -79 | -10 | Non-Sem > Sem |
| Left middle occipital gyrus | 18 | -25 | -91 | 7 | Non-Sem > Sem |
| Left cerebellum | | -5 | -76 | -30 | Non-Sem > Sem |
| | | | | | |
| Right inferior frontal gyrus | 47 | 36 | 24 | -1 | Non-Sem > Sem |
| Right inferior frontal gyrus | 47 | 50 | 39 | -11 | Non-Sem > Sem |
| Right middle frontal gyrus | 9 | 46 | 8 | 38 | Non-Sem > Sem |
| Right middle frontal gyrus | 46 | 52 | 24 | 24 | Non-Sem > Sem |
| Right fusiform gyrus | 37 | 42 | -60 | -17 | Non-Sem > Sem |
| Right inferior occipital gyrus | 18 | 32 | -79 | -6 | Non-Sem > Sem |
| Right middle occipital gyrus | 19 | 31 | -85 | 15 | Non-Sem > Sem |
| Right cuneus | 18 | 17 | -99 | 3 | Non-Sem > Sem |
| Right cerebellum | | 28 | -41 | -16 | Non-Sem > Sem |
| Right cerebellum | | 3 | -57 | 0 | Non-Sem > Sem |

*all p’s < .001

***Figure 6.***




Brain regions demonstrating a significant main effect of Encoding Condition for retrieval-related brain activity. In all regions (shown in red), retrieval of Non-Semantically-encoded items was associated with significantly greater brain activity than retrieval of Semantically encoded items

I also predicted a Group x Encoding Orientation interaction, such that participants with schizophrenia would show significantly greater retrieval-related brain activity *differences* in left inferior frontal gyrus (BA 45/47), anterior prefrontal cortex (BA 10/46), and hippocampus for retrieval of Semantically-encoded items (relative to Non-Semantically encoded items), compared to controls.

Contrary to my hypothesis, the analysis revealed only two regions that demonstrated a significant Group by Encoding Orientation interaction: right inferior temporal gyrus (BA 20; 58, -21, -17) and left caudate (-18, -24, 28). Post-hoc comparisons revealed that in both regions, between-group differences (control > schizophrenia) were greater during retrieval of Non-Semantically encoded items, compared to retrieval of Semantically encoded items.

*Effects of Encoding Orientation on Retrieval-Related Activity: Summary*

Nearly all of my hypotheses regarding encoding orientation effects on retrieval-related brain activity were unsupported. Between-group differences in retrieval activity (control > schizophrenia) following Non-Semantic encoding were not reduced or eliminated for retrieval of Semantically encoded items as I had predicted. Furthermore, schizophrenia participants activated numerous regions to a greater degree when retrieving Non-Semantically encoded items (relative to Semantically-encoded items). Although not predicted, this finding is notable and may suggest that more cognitive effort was exerted by schizophrenia participants in order to retrieve poorly encoded items.

*Interaction between Cueing and Encoding Orientation*

*6. Finally, I predicted that schizophrenia participants would show retrieval-related activity that was most similar to that of controls during Cued retrieval of Semantically encoded words.*

In order to address this hypothesis, I conducted a voxel-wise repeated measures ANOVA with Group (Control, Schizophrenia) as the between subjects variable, and Encoding Orientation (Semantic, Non-Semantic) and Cueing (Cued, Uncued) as the within-subjects variables. I predicted a significant Group x Encoding Condition x Cueing interaction, such that retrieval-related brain activity among schizophrenia participants would be most similar to that of control participants in left inferior frontal gyrus (BA 45/47), middle frontal gyrus (BA 6/44), anterior prefrontal cortex (BA 10/46), and hippocampus during Cued (relative to Uncued) retrieval of words encoded Semantically (relative to Non-Semantically). Under this hypothesis, participants with schizophrenia would show significantly more retrieval-related activity in these regions when oriented to the semantic relationship between words and scenes (as compared to not) and when provided with retrieval cues (as compared to not provided with cues). Furthermore, I predicted that these brain activity differences would be significantly greater than those found in the control group.

Contrary to my hypotheses, there were no regions that showed significant Group by Cueing by Encoding Orientation interactions and survived the threshold and clustering analysis, although subthreshold activity was detected in bilateral inferior frontal regions and a left inferior temporal lobe region, among others.

*Retrieval-Related Brain Activity: Summary*

Overall, the majority of my hypotheses regarding retrieval-related brain activity were unsupported. Cueing had virtually no impact on between-group differences in brain activity at retrieval. Controls demonstrated significantly greater activity than schizophrenia participants in a number of brain regions during both Cued and Uncued retrieval. Finally, both groups showed greater brain activity during retrieval of Non-Semantically encoded items, whereas the opposite contrast (Semantic > Non-Semantic) revealed few significant regions, suggesting that the increased activity seen for retrieval of Non-Semantically encoded items reflected increased retrieval effort by both groups.

## Effect of Signal-to-Noise Ratio on Task-Related Brain Activity

One potential confounding factor related to neuroimaging analyses (particularly involving psychiatric populations, such as individuals with schizophrenia) is poor signal-to-noise ratio (SNR). Specifically, the fMRI signal that is derived from brain tissue in individuals with schizophrenia is often less strong than the signal from control participants. This may be due, at least in part, to inherent properties of the brain tissue itself, as well as factors related to participant behavior during the data acquisition process (e.g., excessive head movement in scanner). Between-group discrepancies in brain signal, therefore, make it difficult to interpret differences in brain activity, as such differences could reflect genuine variation in brain activity between groups or simply an artifact.

In order to address this issue, I first compared the peak SNR values for control and schizophrenia participants in each of the 9 scanning runs. In 7 of the 9 runs, control participants had significantly higher peak SNR values than schizophrenia participants (all $p$'s < .04), with trend-level effects for the remaining 2 runs (p-values of .06 and .11,

respectively). Therefore, I created 2 groups (n = 15 for each) that were matched on peak SNR (control = 503.3; schizophrenia = 514.9). Using these groups, I compared control and schizophrenia participants on brain activity within each of the regions that showed significant between-group differences in the analyses described above.

*Effect of Signal-to-Noise Ratio on Encoding & Subsequent Memory Analyses*

With regard to between-group differences observed during Semantic encoding, all regions that previously demonstrated significant group differences (control > schizophrenia or schizophrenia > control) remained significant with the matched groups. The analysis for Non-Semantic encoding revealed that all regions in the schizophrenia > control contrast remained significant, while 9 out of 12 regions in the control > schizophrenia contrast remained significant. Left parahippocampal gyrus, right fusiform gyrus, and left cerebellum were no longer significant when SNR was matched across groups.

The Group x Encoding Condition analysis revealed that 10 out of 14 regions remained significant, including anterior and posterior cingulate gyrus, right inferior parietal lobule, and right fusiform gyrus, while left middle frontal (BA 8) and precentral gyrus (BA 4) activity was no longer significant. Lastly, 18 of 20 regions demonstrating a Group x Subsequent Memory interaction remained significant when SNR-matched groups were used. Only regions in left and right cerebellum were non-significant, while areas including left middle frontal gyrus (BA 46), right inferior parietal lobule (BA 40), and left medial frontal gyrus (BA 9) continued to show a significant interaction.

*Effect of Signal-to-Noise Ratio on Retrieval Analyses*

Comparison of the matched groups in the previously defined regions for Uncued retrieval revealed that 19 of the 33 regions remained significant (control > schizophrenia). These included left middle frontal gyrus (BA 9), right inferior frontal gyrus (BA 45), and bilateral inferior parietal lobule (BA 40), all of which are known to contribute to successful retrieval. Similarly, 15 of the original 29 regions identified for between-group differences in Cued retrieval (control > schizophrenia) remained significant. Among these were left middle frontal gyrus (BA 9), right superior frontal gyrus (BA 8), left inferior parietal lobule (BA 40), and right fusiform gyrus (BA 18).

Analysis of the between-group differences (control > schizophrenia) in retrieval for items encoded Non-Semantically revealed that 16 out of 31 regions remained significant, while 16 of 30 regions remained significant for the Semantic retrieval analysis (control > schizophrenia). For items encoded both Non-Semantically and Semantically, controls continued to demonstrate significantly greater retrieval-related brain activity in bilateral inferior frontal gyrus (BA 44, 45/47), left middle frontal gyrus (BA 9), and right superior parietal lobule (BA 7), among a number of other regions.

*SNR-Matched Analyses: Summary*

The Encoding and Subsequent Memory brain activity analyses using groups of control and schizophrenia participants matched on signal-to-noise ratio revealed few discrepancies compared to the original findings. Most (or all) regions of between-group differences that were originally identified remained significant. This is likely related, at least in part, to the fact that many of the differences were in the direction of schizophrenia participants > controls. Thus, it is logical that when using only schizophrenia participants with higher SNR, the differences would remain significant.

The analyses of Retrieval-related brain activity revealed somewhat different results. In the four contrasts described, roughly half of the regions that were originally found to be more active in controls than schizophrenia participants were no longer significant when SNR was matched between groups. This suggests that some of the between-group differences observed at retrieval may be artifactual in nature, possibly due to head movement, speaking in the scanner, or other factors. However, as approximately half of the regions remained significant, it is logical to conclude that there are likely true differences between groups during episodic memory retrieval, particularly in frontal and parietal regions.

## Individual Difference Measures: Results

The fourth set of results outlined below concerns the effect of individual differences on behavior and brain activity. Specifically, the focus of the following predictions relates to the influence of inherent semantic processing ability on episodic memory and task-related brain activity in individuals with schizophrenia and healthy controls. The specific questions used to address this area of interest are as follows:

*1. I predicted that participants from both groups who scored higher on measures of semantic processing ability would show greater subsequent memory benefits for semantically-encoded items (relative to items encoded non-semantically) than participants who scored lower on semantic processing measures.*

In order to address this hypothesis, I first created a verbal semantic processing composite variable by summing z-scores from performance on the WAIS Vocabulary, WAIS Similarities, and Pyramids and Palm Trees tests for each participant (alpha = 0.92). I then conducted Pearson's *r* correlations between recall measures and the semantic

processing composite variable. Results are displayed in Table 17. Control participants demonstrated significant correlations between semantic processing ability and nearly all recall measures: percent correct for Non-Semantically-encoded words, Uncued words, Cued words, total percent correct, and total percent correct of previously-seen items. Consistent with predictions, schizophrenia participants also demonstrated significant correlations between semantic processing ability and Semantically-encoded percent correct, as well as semantic processing ability and Non-Semantically-encoded percent correct, total percent correct, total percent correct of previously-seen items, and Uncued percent correct. None of the correlations differed significantly between groups.

Inspection of the scatterplot showing the relationship between semantic processing ability and recall of semantically-encoded items (Figure 7) suggested more variance in recall performance and semantic processing ability among schizophrenia participants. However, it is also clear that individuals with schizophrenia who are higher on semantic processing ability perform more similarly to controls on recall of semantically-encoded items than schizophrenia participants who are lower on semantic processing ability.

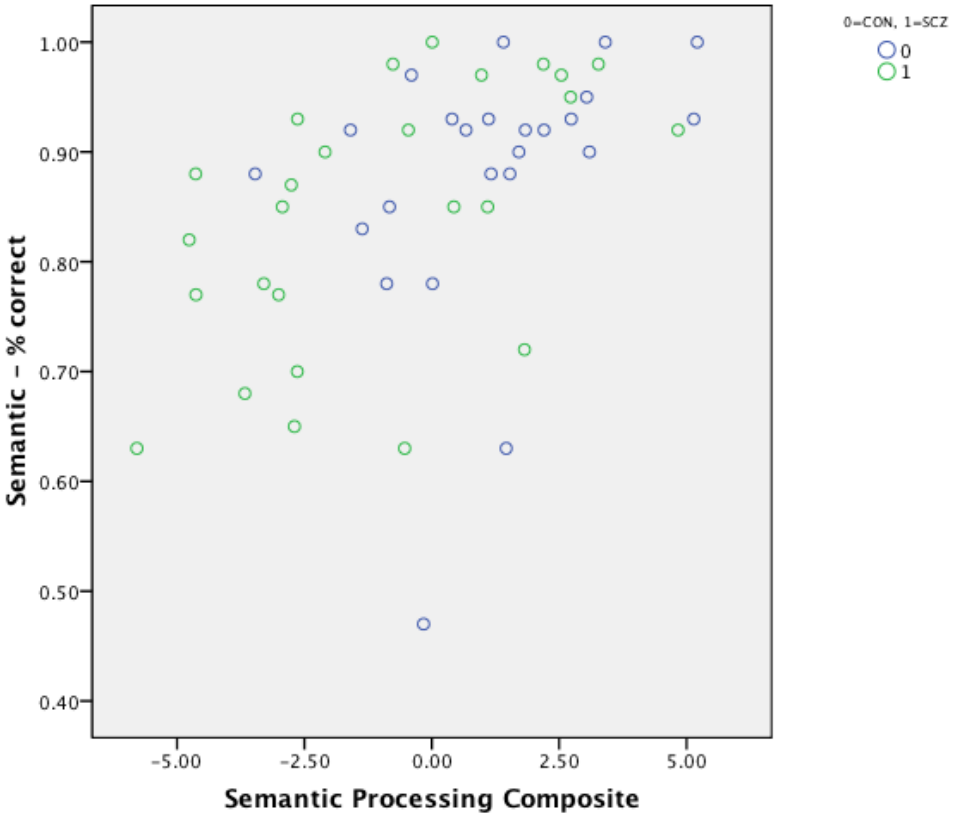
***Table 17. Correlations between symptoms & semantic processing and recall performance***

| | Total % Correct | Total % Correct (of old) | % Correct Rejections | Non-Semantic % Correct | Semantic % Correct | Uncued % Correct | Cued % Correct |
|---|---|---|---|---|---|---|---|
| ***Control*** | | | | | | | |
| Semantic Processing | ***.48**** | ***.46**** | .29 | ***.49**** | .35 | ***.48**** | ***.43**** |
| Positive Symptoms | .02 | .05 | -.20 | .06 | .00 | .04 | .05 |
| Negative Symptoms | -.15 | -.09 | ***-.47**** | -.10 | -.09 | -.14 | -.04 |
| Disorganized Symptoms | -.19 | -.21 | .08 | -.31 | .09 | -.21 | -.19 |
| ***Schizophrenia*** | | | | | | | |
| Semantic Processing | ***.52***** | ***.50**** | .24 | ***.41**** | ***.55***** | ***.41**** | .39 |
| Positive Symptoms | .00 | .03 | -.11 | .01 | .06 | .22 | .17 |
| Negative Symptoms | -.06 | -.11 | .15 | -.10 | -.09 | -.18 | -.13 |
| Disorganized Symptoms | -.32 | -.32 | -.10 | -.21 | ***-.42**** | -.16 | -.16 |

-Neuropsychological and symptom data unavailable for 2 participants (1 control, 1 schizophrenia)

*p < .05
**p < .01
***p < .005

***Figure 7. Scatterplot demonstrating association between Semantic Processing Composite measure and recall of Semantically-encoded items in both groups***



Next, I created symptom summary scores for three symptom clusters (positive, negative, and disorganized) by summing global rating scores for each domain from the SAPS and SANS. I then performed correlations between the symptoms summary measures and recall performance, given the established relationship between symptomotology and cognition in schizophrenia. Results are displayed in Table 17. The control group showed a significant positive correlation between the negative symptom cluster and the number of correct rejections at recall. Among schizophrenia participants, there was a significant correlation between disorganization symptoms and number of Semantically-encoded words that were recalled. Further correlations were conducted between each of the disorganization symptoms (global bizarre behavior, global formal thought disorder, global attention) and correct Semantic recall, in order to more fully characterize the nature of this relationship among schizophrenia participants. These analyses revealed trend-level correlations between Semantic recall and global attention ratings ($r$ = -0.39, $p$ = .052), as well as Semantic recall and global bizarre behavior ($r$ = -0.35, p = .07), while the correlation between Semantic recall and global formal thought disorder was significantly lower (p > .96).

I also performed correlations between the symptom summary measures and the semantic processing composite variable, in order to evaluate the relationship between symptomotology and semantic processing ability. Among controls, semantic processing ability correlated significantly with disorganized symptoms ($r$ = -0.59, $p$ < .005), while the correlations with positive and negative symptoms were non-significant ($p$'s > .37). In the schizophrenia group, semantic processing ability also correlated significantly with

disorganized symptoms ($r$ = -0.67, $p$ < .001), while the other correlations were non-significant ($p$'s > .68).

Lastly, I performed correlations between a measure of abstract reasoning ability (Matrix Reasoning) and memory performance in each group separately, in order to evaluate the specificity of the relationship between semantic processing ability and memory in this sample. Neither the participants with schizophrenia (all $p$'s > .22) nor the control participants (all $p$'s > .19) showed significant associations between performance on the Matrix Reasoning subtest and any of the recall measures.

*2. Participants from both groups who scored higher on measures of semantic processing ability would show greater activation enhancements (Semantic encoding > Non-Semantic encoding) in brain regions typically associated with semantic encoding, including left inferior frontal gyrus (BA 45/47).*

To address this hypothesis, I conducted a regions-of-interest (ROI) analysis. To do this, I correlated semantic processing ability with average brain activity in each of the ROIs that previously showed main effects of Encoding Orientation (Semantic > Non-Semantic). Results are displayed in Table 18. Contrary to my predictions, only schizophrenia participants demonstrated significant correlations between Semantic encoding-related brain activity and the semantic processing composite measure, whereas controls did not demonstrate such relationships. The schizophrenia participants showed significant negative correlations in three regions: two areas of left middle frontal gyrus (BA 6) and left inferior frontal gyrus (BA 9). Thus, better semantic processing abilities were associated with less activation in these regions. Inspection of the scatterplots showing the relationship between semantic processing ability and brain activity during

Semantic encoding (Figures 8, 9, and 10) suggested a similar relationship between these two variables for participants with schizophrenia and controls alike. Although the significant correlation observed in the schizophrenia group in one region (-41, 3, 29) may have been driven by outlying data points, results of the correlational analyses suggest that schizophrenia participants who are higher on semantic processing ability show brain activity during encoding that is similar to that of controls who are high on semantic processing ability. Furthermore, semantic processing ability reliably differentiates the magnitude of encoding-related brain activity in schizophrenia participants with high versus low semantic processing ability.

***Table 18. Regions demonstrating significant correlations between semantic encoding-related brain activity and the semantic processing composite variable***

| Region of Interest | Brodmann Area(s) | X | Y | Z | r | p-value |
|---|---|---|---|---|---|---|
| ***Control participants*** | | | | | | |
| *no significant correlations* | | | | | | |
| ***Participants with schizophrenia*** | | | | | | |
| Left inferior frontal gyrus | 9 | -41 | 3 | 29 | -.45 | .033 |
| Left middle frontal gyrus | 6 | -45 | 2 | 49 | -.48 | .019 |
| Left middle frontal gyrus | 6 | -28 | 15 | 57 | -.55 | .007 |

***Figure 8. Scatterplot demonstrating association between Semantic Processing Composite measure and average brain activity in left middle frontal gyrus (BA 6)***

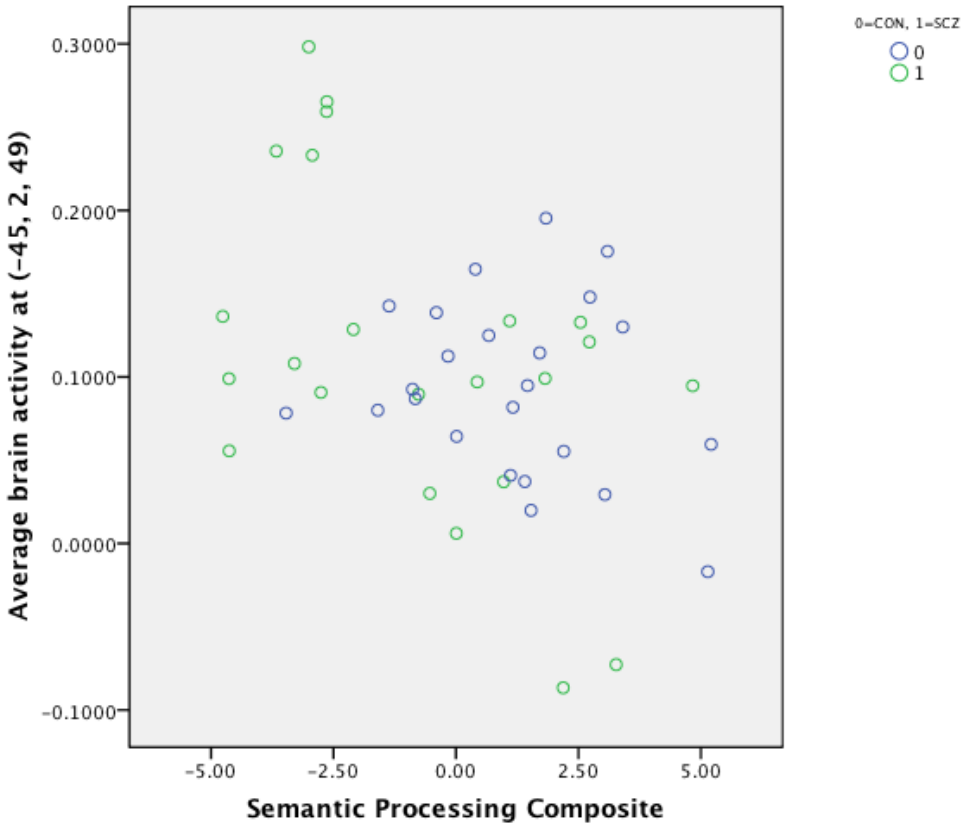


***Figure 9. Scatterplot demonstrating association between Semantic Processing Composite measure and average brain activity in left inferior frontal gyrus (BA 9)***

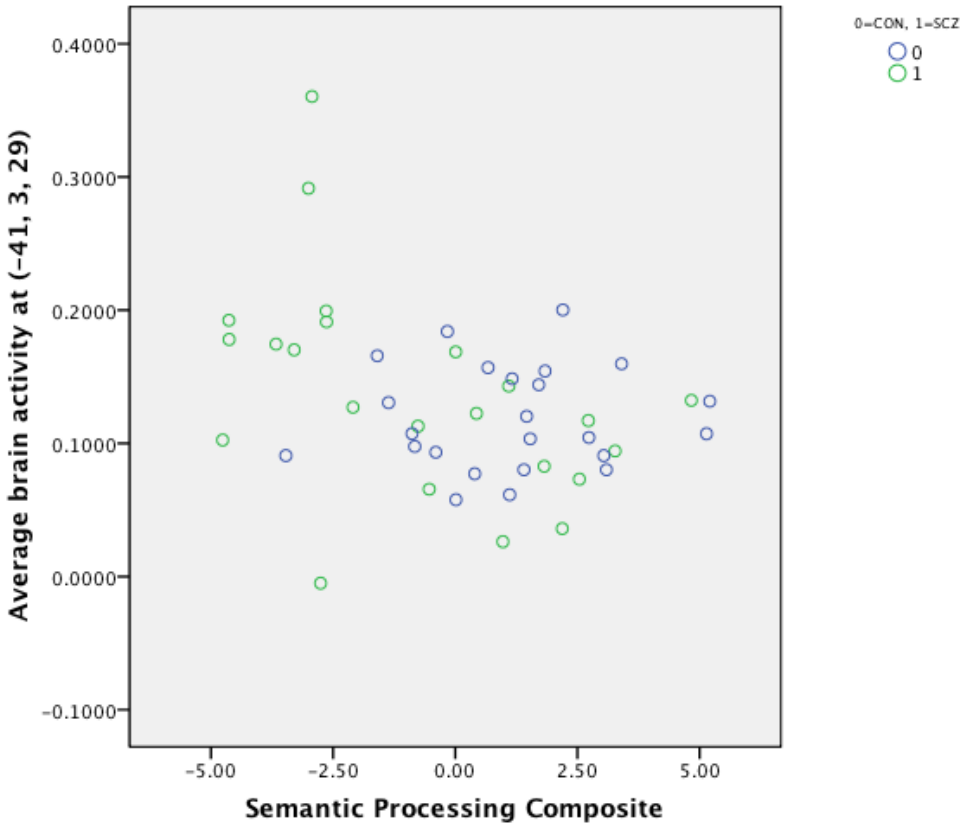
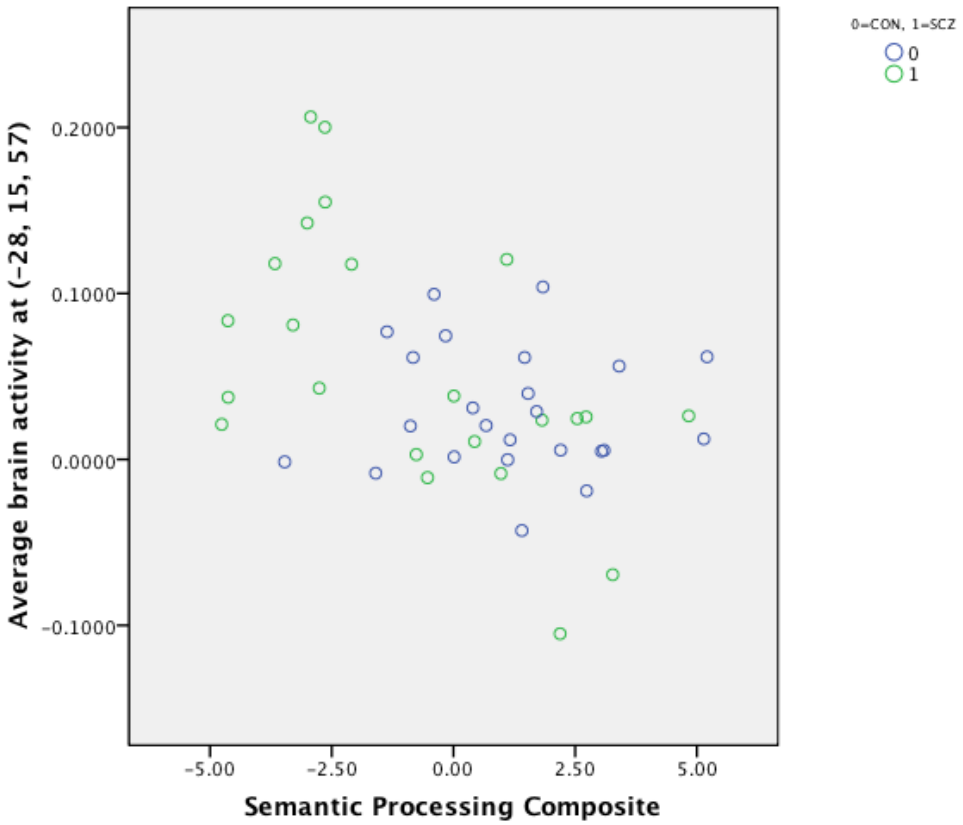


***Figure 10. Scatterplot demonstrating association between Semantic Processing Composite measure and average brain activity in left inferior frontal gyrus (BA 6)***



To verify the specificity of the relationship between semantic processing ability and task-related brain activity, I conducted similar correlational analyses between performance on the Matrix Reasoning subtest and brain activity in regions showing a main effect of Encoding Orientation in each group separately. Results of these analyses indicated that participants with schizophrenia demonstrated a significant relationship between Matrix Reasoning performance and brain activity ($r = -0.44$, $p = .037$) in one region [left middle frontal gyrus (-45, 2, 49)], while control participants did not demonstrate significant correlations in any areas.

In order to assess potential effects throughout the brain, rather than constraining effects to certain regions of interest, I conducted whole-brain correlations between task-related brain activity during Semantic encoding and the semantic processing composite variable. In order to reduce the false-positive rate associated with conducting whole-brain correlations, I increased the cluster size ($n = 29$) and activation threshold ($z = 3.25$) from the previous correlations, thus maintaining an overall false-positive rate of .05. The analysis revealed that participants with schizophrenia demonstrated a significant negative correlation in left middle frontal gyrus (BA 6), whereas controls did not demonstrate significant correlations in any brain regions.

Lastly, I examined the role of semantic processing ability on encoding-related brain activity in both participants with schizophrenia and control participants. Of particular interest was whether diagnostic group (control vs. schizophrenia) continued to predict encoding-related brain activity when semantic processing ability was taken into account, and whether group interacted significantly with semantic processing ability in predicting brain activity. To address these questions, I conducted hierarchical regressions

in each of the regions showing significant between-group differences in encoding activity with the average magnitudes of brain activity in each group in each region as dependent variables. For each regression, the semantic processing composite variable and group were entered in step 1, followed by the interaction between semantic processing in group in step 2. Regressions were conducted for all brain regions showing significant between-group brain activity differences during either Semantic or Non-Semantic encoding.

Results of the analyses for Semantic encoding are summarized in Table 19 and results of the Non-Semantic encoding analyses are summarized in Table 20. As evidenced by the significant beta values at each region of interest, diagnostic group remained significantly predictive of brain activity during both Semantic and Non-Semantic encoding even when semantic processing ability was included in the regression. In contrast, semantic processing ability was only predictive of encoding-related brain activity during Semantic encoding in four regions and was not predictive of brain activity during Non-Semantic encoding. Additionally, there were significant Group x Semantic Processing interactions in a 7 regions in both hemispheres (2 left, 5 right), suggesting that the relationship between intrinsic semantic processing ability and encoding-related brain activity differed to some degree between groups.

*Individual Difference Measures: Summary*

Both groups demonstrated significant positive associations between semantic processing ability and episodic memory performance, and inspection of the scatterplots confirmed a similar relationship between semantic processing ability and memory performance in both controls and schizophrenia participants. Furthermore, among schizophrenia participants semantic processing ability was negatively correlated with

***Table 19. Results of hierarchical regression: Regions showing significant between-group differences in Semantic Encoding***

| Region of Interest | $R^2$ Model 1 | $R^2$ Model 2 | $R^2$ change | p-value of $R^2$ change | Beta: Group | Beta: Semantic Processing |
|---|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | | |
| Left cerebellum | .219*** | .221 | .002 | ns | -0.50*** | -0.12 |
| Left cerebellum | .166* | .185 | .019 | ns | -0.38* | .07 |
| ***Schizophrenia > Control*** | | | | | | |
| Left inferior frontal gyrus | .218** | .272 | .054 | ns | .35* | -0.20 |
| Left middle frontal gyrus | .219*** | .242 | .023 | ns | .37* | -0.18 |
| Left medial frontal gyrus | .200** | .242 | .042 | ns | .39* | -0.13 |
| Left superior frontal gyrus | .401**** | .484* | .083 | .012 | .45*** | -0.31* |
| Left anterior cingulate gyrus | .246*** | .255 | .009 | ns | .51*** | .05 |
| Left precentral gyrus | .323**** | .353 | .030 | ns | .41*** | -0.27* |
| Left precentral gyrus | .269*** | .303 | .035 | ns | .47*** | -0.11 |
| Left superior temporal gyrus | .404**** | .413 | .009 | ns | .61**** | -0.06 |
| Left inferior parietal lobule | .315**** | .353 | .037 | ns | .57**** | .02 |
| Left superior parietal lobule | .367**** | .402 | .035 | ns | .56**** | -0.10 |
| Left middle occipital gyrus | .300**** | .444*** | .144 | .002 | .31* | -0.36* |
| | | | | | | |
| Right medial frontal gyrus | .265*** | .341* | .077 | .031 | .45*** | -0.13 |
| Right precentral gyrus | .375**** | .499*** | .124 | .002 | .32* | -0.41*** |
| Right precentral gyrus | .239*** | .266 | .028 | ns | .44*** | -0.11 |
| Right paracentral lobule | .302**** | .369* | .067 | .039 | .52**** | -0.08 |
| Right paracentral lobule | .290*** | .406** | .116 | .006 | .50*** | -0.09 |
| Right insula | .254*** | .257 | .003 | ns | .51*** | .01 |
| Right inferior parietal lobule | .251*** | .297 | .045 | ns | .50*** | .01 |
| Right superior parietal lobe | .306**** | .379* | .073 | .029 | .52**** | -0.08 |

-Model 1: Semantic processing composite, Group; Model 2: Semantic processing composite, Group, Semantic x Group

*p < .05; **p < .01; ***p < .005; ****p < .001; ns = non-significant

***Table 20. Results of hierarchical regression: Regions showing significant between-group differences in Non-Semantic Encoding***

| Region of Interest | $R^2$ Model 1 | $R^2$ Model 2 | $R^2$ change | p-value of $R^2$ change | Beta: Group | Beta: Semantic Processing |
|---|---|---|---|---|---|---|
| ***Control > Schizophrenia*** | | | | | | |
| Left middle frontal gyrus | .191** | .202 | .010 | ns | -0.41** | .06 |
| Left medial globus pallidus | .221*** | .233 | .012 | ns | -0.39** | .15 |
| Left thalamus | .163* | .168 | .005 | ns | -0.37* | .07 |
| Left parahippocampal gyrus | .223*** | .223 | .000 | ns | -0.36** | .20 |
| Left middle temporal gyrus | .199** | .203 | .004 | ns | -0.43** | .04 |
| Left fusiform gyrus | .316**** | .319 | .003 | ns | -0.59**** | -0.09 |
| Left cerebellum | .147* | .150 | .003 | ns | -0.40* | -0.06 |
| | | | | | | |
| Right putamen | .177* | .179 | .002 | ns | -0.41** | .03 |
| Right thalamus | .215** | .216 | .001 | ns | -0.47** | -0.02 |
| Right pons | .192** | .214 | .022 | ns | -0.42** | .04 |
| Right posterior cingulate gyrus | .203** | .207 | .004 | ns | -0.40** | .11 |
| Right fusiform gyrus | .216** | .220 | .004 | ns | -0.50*** | -0.13 |
| | | | | | | |
| ***Schizophrenia > Control*** | | | | | | |
| Left precentral gyrus | .234*** | .236 | .002 | ns | .37* | -0.21 |
| Left superior temporal gyrus | .341**** | .351 | .010 | ns | .56**** | -0.05 |
| Left inferior parietal lobule | .208** | .208 | .000 | ns | .44*** | -0.04 |
| Left superior parietal lobule | .286** | .286 | .000 | ns | .44*** | -0.18 |
| | | | | | | |
| Right postcentral gyrus | .211** | .212 | .001 | ns | .46*** | .00 |
| Right superior temporal gyrus | .254*** | .283 | .029 | ns | .54**** | .14 |

-Model 1: Semantic processing composite, Group; Model 2: Semantic processing composite, Group, Semantic x Group

*p < .05; **p < .01; ***p < .005; ****p < .001; ns = non-significant

Semantic encoding-related brain activity in a number of left prefrontal cortex areas, such that greater semantic processing ability was associated with decreased left frontal cortex activity. Notably, correlational analyses with a putative measure of abstract reasoning (Matrix Reasoning) suggested that the effect of semantic processing ability on memory performance and brain activity demonstrated here is relatively specific and does not simply reflect a more global effect of intelligence on cognitive performance or task-related brain activity. Furthermore, controls did not show any such relationships between encoding activity and the semantic processing measure. To my knowledge, this is the first study to show that individuals with schizophrenia who possess greater semantic processing abilities show better performance in semantic encoding conditions and alterations in brain activity during supportive encoding conditions. Such results point to the importance of examining and understanding individual differences in cognitive ability among individuals with schizophrenia, as these may strongly influence the results of both behavioral and imaging studies.

## Chapter 6: Discussion

In the present study, I investigated the effects of strategies provided during encoding and retrieval on episodic memory performance and task-related brain activity in individuals with schizophrenia and healthy controls. This investigation revealed a number of notable findings. Like controls, schizophrenia participants recalled more words that were encoded Semantically than Non-Semantically, as well as more words that were Cued than Uncued at recall. Analyses of the functional neuroimaging data revealed that during Semantic encoding schizophrenia participants activated many brain regions that have frequently been associated with semantic processing and successful encoding.

Furthermore, schizophrenia participants activated many of these regions to a significantly greater degree than control participants. The subsequent memory analyses revealed significant overlap in activity between the control and schizophrenia participants in posterior regions. Furthermore, individuals with schizophrenia showed significantly greater activation for remembered than missed items in a number of frontal cortex regions, whereas controls largely showed either no differences between remembered and missed items or greater activity for missed than remembered items in those areas. In contrast to the encoding analyses, analyses of the retrieval neuroimaging data revealed that controls demonstrated significantly greater activity than schizophrenia participants across many brain regions during both Cued and Uncued retrieval. Both groups also showed more robust brain activity during retrieval of Non-Semantically encoded items (relative to Semantically-encoded items). Lastly, the individual difference analyses revealed that both groups showed significant associations between inherent semantic processing ability and episodic memory performance. Furthermore, schizophrenia participants demonstrated significant associations between semantic processing ability and Semantic encoding-related brain activity in left prefrontal cortex, whereas controls did not show any such relationships.

Below, I will review the findings from the present study and interpret them in the context of the literature in this research area. I will first discuss the specific findings from the behavioral data, followed by a discussion of the functional neuroimaging findings and the individual difference measures. Finally, I will provide a global overview of the results of the present study and attempt to reconcile them with the relevant empirical literature.

## Behavioral Findings

*Encoding Orientation Effects*

The results of the current study provide additional strong evidence for the hypothesis that the memory performance of individuals with schizophrenia can be significantly improved by providing support for effective encoding strategies.

Similar to controls, participants with schizophrenia demonstrated significantly better recall for items that were encoded Semantically (relative to items encoded Non-Semantically). Thus, orientation to the semantic relatedness of the word-scene pairs significantly improved subsequent recall of the words in both groups. This finding is in line with previous studies of EM in schizophrenia that have reported memory improvement following orientation to beneficial encoding conditions (Bonner-Jackson et al., 2005; Chan et al., 2000; J. M. Gold et al., 1992; Koh & Peterson, 1978; McClain, 1983; Paul et al., 2005; Ragland et al., 2006; Ragland et al., 2003). Such findings have been attributed to an enhancement of strategic memory processes through the manipulation of encoding conditions, as individuals with schizophrenia typically show deficits in generating and applying effective encoding and organizational strategies (Brebion et al., 1997; Brebion et al., 2004; Hutton et al., 1998; Iddon et al., 1998; Koh, 1978; Russell et al., 1975; Russell & Beekhuis, 1976; Traupmann, 1980). For example, Russell and colleagues (1976) reported that even for word lists with highly related items, participants with schizophrenia demonstrated significant deficits in using the inherent semantic relatedness of the items to enhance recall. Thus, it is likely that individuals with schizophrenia can only benefit from semantic relationships between to-be-learned items

when they are oriented to such relationships. The results of the present study support this claim.

Most of the previous studies in this area have reported improvements in *recognition* memory following orientation to beneficial encoding conditions, often utilizing yes/no recognition paradigms. Although such findings are promising, it has been argued that recognition memory tasks are less rigorous than recall and can be completed on the basis of familiarity, rather than recollection (Yonelinas & Jacoby, 1994). Furthermore, some authors have stated that conscious recollection is impaired and underlies memory deficits in schizophrenia, whereas familiarity processes are relatively intact (Danion et al., 1999; Huron et al., 1995). Thus, the memory benefits described by previous studies following encoding manipulations could be attributable, at least in part, to enhancements in familiarity, without increased rates of recollection on the part of the schizophrenia participants. The results of this study extend previous findings in this domain by demonstrating significant enhancements in subsequent *recall* memory among individuals with schizophrenia following orientation to a Semantic encoding task, suggesting that conscious recollection (as opposed to only familiarity) was improved.

In addition to the main effect of Encoding Condition, I found a significant Group x Encoding Condition interaction for subsequent recall accuracy, such that between-group differences in recall were dramatically reduced following Semantic Encoding, relative to Non-Semantic encoding. Thus, individuals with schizophrenia benefited from the Semantic Encoding condition to a greater degree than control participants. Importantly, this finding also suggests that the semantic processing system in schizophrenia is relatively intact, as schizophrenia participants were able to profit from

encoding strategies when they were provided. Moreover, these findings further implicate strategic and executive processes in the EM deficits observed in schizophrenia, rather than memory capacity itself, since the provision of memory strategies was effective in eliminating between-group differences in recall. Thus, the shortcomings on the part of individuals with schizophrenia appear to lie in the ability to spontaneously generate and apply beneficial memory strategies, as they demonstrated significant gains when such strategies were externally provided.

The results of the present study also extend previous findings by demonstrating that orientation to beneficial encoding strategies improves associative (or relational) memory, as well as item memory, which have been reported by prior studies. Researchers have previously demonstrated associative memory deficits in individuals with schizophrenia (Kopp & Reischies, 2000; Titone et al., 2004; Waters et al., 2004), and some have suggested that such deficits outstrip impairments observed in memory for individual items (Achim & Lepage, 2003; Lepage et al., 2006). However, memory performance also increases among individuals with schizophrenia for semantically-related (relative to arbitrary) stimulus pairs (Achim *et al.*, 2007). Thus, results of the current study add to this literature and suggest that the benefits of advantageous encoding conditions can improve memory for associations between items, in addition to memory for individual items. One could argue that the memory paradigm used in the present experiment assessed item memory, rather than associative memory, as only individual items (words) were recalled during retrieval. Still, successful recall of the individual items was dependent on processing the relationship between the scene and the to-be-recalled word. I propose that this type of memory retrieval requires associative

processing and evaluation of semantic relationships, making it qualitatively distinct from classic tests of item memory (e.g., word list learning paradigms).

In contrast to the effects of the Encoding Orientation described above, the groups did not perform equivalently on all memory measures. Controls were significantly more accurate than schizophrenia participants in correct identification of new items. In light of the results described previously, I interpret these findings to suggest that although the encoding manipulation was successful, certain memory deficits continue to persist in the schizophrenia group. This finding raises the question of whether identification of new items poses a greater challenge to individuals with schizophrenia than recall of previously seen items. Initially, identifying new items appears to be easier and require less effort than recalling old items, as new items can be identified on the basis of familiarity alone. In support of this notion, EM studies in schizophrenia have found no differences between controls and individuals with schizophrenia for correct rejection of new items (Bonner-Jackson et al., 2005; Ragland et al., 2004).

However, identification of new versus old items places significant emphasis on retrieval processes, which are impaired in schizophrenia. Given such retrieval deficits, it may be difficult for individuals with schizophrenia to draw clear distinctions between different classes of items, such as differentiating between poorly encoded items and new items. It is possible that these two types of items seem very similar to individuals with schizophrenia, making it more difficult to identify those items that are actually new. The present study provides evidence in support of this notion. Specifically, calculation of effect sizes for between-group differences in hits (old items) and correct rejections (new items) revealed a larger between-group difference in correct rejection rates (effect size =

.65) than hit rates (effect size = .52). Relatedly, d-prime (measuring discriminability of old vs. new items) was calculated for each group separately, and the groups were then compared. Results revealed a significantly larger d-prime value for controls than schizophrenia participants. Both of these findings suggest that schizophrenia participants had more difficulty than controls in discriminating old from new items at recall, which may underlie the observed deficits in correct identification of new items by the schizophrenia group.

The present findings are also in line with previous research demonstrating a disproportionate deficit in correct identification of new items by individuals with schizophrenia (A. P. Weiss *et al.*, 2008; A. P. Weiss et al., 2004). For example, using a source memory paradigm, Weiss and colleagues (2008) found that individuals with schizophrenia had more difficulty than controls in distinguishing old from new items. Another study from the same group (A. P. Weiss et al., 2004) reported significantly higher false alarm rates for novel items among schizophrenia participants compared to controls, despite equivalent hit rates for previously-seen items. Thus, the memory trace that is available for individuals with schizophrenia may be weaker for certain items, making it more difficult to discriminate them from items that were never seen.

*Retrieval Cue Effects*

The present findings demonstrate that the provision of retrieval cues is effective in improving EM performance in individuals with schizophrenia. Furthermore, the beneficial effects provided by retrieval cues were comparable for control and schizophrenia participants alike.

The analysis of the behavioral data for the effect of Retrieval Cues demonstrated a significant main effect of Cueing. Schizophrenia participants, like controls, recalled significantly more items that were Cued at recall, relative to those that were Uncued. Similar to the Encoding Orientation results, this finding supports previous literature in this area that has demonstrated significant memory benefits conferred by retrieval cues to individuals with schizophrenia (Culver et al., 1986; McClain, 1983; Sengel & Lovallo, 1983; Tompkins et al., 1995). Tompkins and colleagues (1995) found that cueing aided schizophrenia participants in various tests of memory. Using categorized word lists that were either cued or uncued at recall, Sengel and Lovallo (1983) also found that retrieval cues substantially enhanced memory performance in individuals with schizophrenia. Thus, this finding adds to the empirical evidence supporting the crucial role of retrieval cues for memory function in schizophrenia.

In addition, the results of the Retrieval Cue analysis suggest that the memory system underlying EM retrieval in individuals with schizophrenia can function in a similar manner as that of healthy controls under supportive conditions. More specifically, the presence of retrieval cues conferred approximately the same memory benefits to both controls and participants with schizophrenia. This finding suggests that when strategic mnemonic processes are controlled, the underlying cognitive architecture of memory retrieval in controls and individuals with schizophrenia is relatively similar. Taken together with the results from the Encoding Orientation analysis, my findings demonstrate that individuals with schizophrenia are receptive to strategic memory manipulations during both the encoding and retrieval stages, and they may help to elucidate some of the memory deficits that are often associated with schizophrenia.

The suggestion that individuals with schizophrenia show the same benefits of cueing as controls is further supported by the non-significant Group x Cueing interaction for recall. Although schizophrenia participants showed significant memory benefits from the retrieval cues, these benefits were comparable to those seen in the control group. Interestingly, others have reported significant interactions between Group and Cueing in studies of recall. For example, McClain (1983) reported that retrieval cues (relative to no cues) benefited schizophrenia participants to a greater degree than controls. Although few studies have found such an effect, it is worthwhile to explore why such an effect was not found in the present study. It is possible that the discrepancy between my findings and those of McClain (1983) lies in the type of retrieval cues used. While my experiment used the first letters of words as cues, the McClain (1983) study used semantic categories as cues. In fact, many other studies of retrieval cues in schizophrenia have used category cues at recall (Culver et al., 1986; Sengel & Lovallo, 1983). Arguably, the difference between the presence and absence of category cues represents a greater difference than present versus absent one-letter cues, and the magnitude of this difference may depend on group membership (control vs. schizophrenia). Thus, different cue types may differentially affect the likelihood of recall in control and schizophrenia participants.

A second explanation regarding the failure to find the predicted Group x Cueing interaction may be related to the number of stimulus presentations at encoding. In the present study, participants viewed each word-scene pair a total of four times, whereas most EM studies of this type presented each word only once prior to recall (Culver et al., 1986; McClain, 1983; Sengel & Lovallo, 1983). Multiple presentations of each item in the present study might have increased the likelihood of recall independent of the

retrieval cues, potentially dampening the effect that the cues had on recall success. In contrast, retrieval cues following a single presentation of a word might have been disproportionately more helpful, particularly for schizophrenia participants. Taken together, a significant Group x Cueing interaction may have been found using category cues and fewer presentations of each word-scene pair.

*Encoding Condition & Retrieval Cue: Combined Effects*

These results suggest that the highest rate of recall is found in both diagnostic groups when both advantageous encoding and retrieval strategies are utilized simultaneously. The data also indicate that for both groups, cueing at retrieval is most effective for items that were initially encoded poorly.

In examining the collective effects of Encoding Condition and Retrieval Cue presence on subsequent recall, individuals with schizophrenia (like controls) demonstrated the highest rate of recall for Semantically encoded items that were Cued at retrieval. Thus, my prediction with regard to the presence of both encoding and retrieval cues was upheld. Both groups showed a positive linear increase in recall performance across the four conditions, with the lowest recall for Non-Semantic Uncued items and the highest recall for Semantic Cued items. Notably, the effect of Encoding Condition appears to be stronger than the effect of Cueing, as there was a substantial increase in recall from the two Non-Semantic recall conditions (Uncued and Cued) to the two Semantic recall conditions (Uncued and Cued). This notion is supported by a comparison of effect sizes: for the effect of Encoding Orientation, the effect size was 1.65, whereas the effect size for the effect of Cueing was .50. As discussed above, it is possible that the presence or absence of one-letter cues represented a less dramatic manipulation than

semantic versus non-semantic processing of the word-scene pairs. Regardless of this possibility, however, both groups demonstrated greater recall success as the conditions became progressively more supportive.

The combined effect of supportive encoding and retrieval conditions in schizophrenia in is line with similar studies that have examined this question. Other researchers (Culver et al., 1986; McClain, 1983) have found that although encoding manipulations alone are beneficial for memory performance, free recall in schizophrenia participants is equivalent to that of controls only when retrieval cues are provided as well. The exception to this line of research is one study (Larsen & Fromholt, 1976) which reported equivalent free recall performance for control and schizophrenia participants following only an encoding manipulation. However, this result is somewhat unusual and relatively rare in this literature.

Such findings in individuals with schizophrenia also parallel memory research in the healthy aging literature. The memory impairments observed in older adults, like those in individuals with schizophrenia, have been attributed in part to strategic memory deficits (Sanders *et al.*, 1980). Furthermore, the experimental manipulations that have been shown to improve memory in schizophrenia are also known to enhance memory in older adults (Grady *et al.*, 1999; Logan *et al.*, 2002). Importantly, research with older adult populations indicates that advantageous retrieval conditions must be present to reveal the benefits of strategic encoding conditions (Naveh-Benjamin *et al.*, 2007; Naveh-Benjamin et al., 2002), and the results of the present study suggest a similar notion regarding individuals with schizophrenia. Although the neural systems underlying memory impairment in schizophrenia and older adulthood likely differ to some degree,

experimental behavioral paradigms have tapped into a common mechanism to improve memory and cognition in both groups. This functional overlap may indicate future targets for psychopharmacological interventions or cognitive remediation.

Notably, I also found a significant Encoding Task x Cueing interaction, such that there were greater differences between Uncued and Cued recall for items encoded Non-Semantically (relative to those encoded Semantically). Put a different way, the retrieval cues conferred a greater benefit to participants from both groups following Non-Semantic encoding, whereas retrieval cues following Semantic encoding did not improve recall to such a significant degree. Such results are uncommon, as most studies of this type do not manipulate retrieval conditions. One study (McClain, 1983) reported an Encoding Task x Cueing interaction, although it was in the opposite direction of the results presented here: they reported greater benefit from retrieval cues for blocked relative to unblocked stimulus presentation. Another study (Culver et al., 1986) found a similar pattern of results, such that strong retrieval cues improved recall for deeply-encoded material, but not for material encoded more poorly. Thus, the findings of the present study diverge from previous findings on this point. It is currently unclear why this is the case. One possibility is that in the McClain (1983) and Culver et al (1986) studies, the shallow encoding condition made recall disproportionately more difficult than in the deep encoding condition. Thus, very few words from the shallow encoding condition were recalled, regardless of whether they were cued or not, whereas the deep encoding condition was substantially easier and the presence of retrieval cues served to further boost recall.

Lastly, I did not detect the predicted three-way interaction between Group, Encoding Condition, and Cueing. Although schizophrenia participants did show a significantly greater recall benefit than controls following Semantic encoding, they did not show a differentially greater benefit when provided with Retrieval Cues. In contrast to my predictions, both groups showed a linear improvement in recall over the four conditions, rather than the schizophrenia group showing a greater recall benefit (compared to controls) for Semantically-encoded Cued words. This negative finding might be partially attributable to a lack of power, as the number of participants may have been too small to detect a significant three-way interaction. A more likely explanation, however, is that individuals with schizophrenia often demonstrate encoding or retrieval manipulation effects that are comparable to, not greater than, those of control participants. Therefore, detecting interactions of the nature predicted is very difficult and rare.

## Functional Neuroimaging Findings

### *Encoding Orientation Effects*

The present results provide further support for the hypothesis that use of beneficial encoding strategies is effective in enhancing encoding-related brain activity in individuals with schizophrenia.

Schizophrenia participants activated a network of typical semantic processing regions during Semantic (relative to Non-Semantic) encoding, including a number of areas in left prefrontal cortex (BA 6, BA 9/46). The opposite contrast (Non-Semantic > Semantic) revealed only two regions of significant activity (left superior temporal gyrus, left insula). This pattern of results mirrors those found in healthy control participants, in

which robust prefrontal cortex activation has been reported in response to supportive encoding paradigms (Baker et al., 2001; Fletcher et al., 1998; Kapur et al., 1994; Savage et al., 2001), supporting the notion that individuals with schizophrenia recruit similar brain regions as controls when provided with beneficial encoding strategies. The fMRI findings are also compatible with the Encoding Orientation behavioral findings in the schizophrenia group, which demonstrated robust effects of encoding condition on subsequent recall among schizophrenia participants. Behaviorally and neurobiologically, therefore, individuals with schizophrenia show the capacity to modulate memory function in response to encoding manipulations to a similar degree as healthy individuals.

Notably, however, the Semantic > Non-Semantic encoding contrast in schizophrenia participants did not reveal significant task-related activity in left inferior frontal gyrus (BA 45/47), a region that supports verbal semantic processing functions (Demb et al., 1995; Fletcher et al., 1998; Kapur et al., 1994). This finding was somewhat surprising, given the crucial role of this region in semantic tasks. In order to more strongly verify the lack of between-task activation differences in the schizophrenia participants, I conducted an ROI-based contrast of Semantic versus Non-Semantic encoding activity, using the coordinates from two regions of interest in left inferior frontal gyrus (-40, 39, 0; -52, 27, -3) identified in a previous manuscript (Bonner-Jackson *et al.*, 2007). This analysis revealed a trend-level difference (Semantic > Non-Semantic, $p = .07$) in one region and a non-significant difference between conditions in the other. Furthermore, visual inspection of the separate Semantic and Non-Semantic encoding activation maps revealed similar patterns of activity in the vicinity of left inferior frontal gyrus. Thus, it appears that schizophrenia participants did not activate left inferior frontal

gyrus to a significantly greater degree during Semantic than Non-Semantic encoding. In contrast, within-group analyses revealed that controls did activate areas of bilateral inferior frontal gyrus significantly more during Semantic than Non-Semantic encoding. Although unlikely, it is possible that left inferior frontal gyrus was being recruited by schizophrenia participants during the Non-Semantic task, as well as during the Semantic task, despite the fact that it did not explicitly require semantic processing. Controls, on the other hand, showed more typical Encoding Orientation effects, activating inferior frontal gyrus preferentially during Semantic processing. This discrepancy between groups was not predicted and may suggest that the groups were engaged in somewhat different cognitive activities during encoding. Importantly, however, these observations only represent differences in within-group, rather than between-group, brain activation patterns. Thus, these data should be interpreted with caution.

With regard to between-group contrasts, I detected a number of predicted activation differences during Non-Semantic encoding, the majority of which were in the direction of controls > schizophrenia participants. My findings partially replicate previous reports of underactivation among individuals with schizophrenia during standard EM paradigms (Barch et al., 2002; Hofer et al., 2003b; Ragland et al., 2001). Notably, controls activated regions that are supportive of EM function, including parahippocampal gyrus, to a greater degree than schizophrenia participants. Interestingly, however, there were few between-group differences found in frontal cortex during Non-Semantic encoding, despite the wealth of research reporting hypofrontality in individuals with schizophrenia. One explanation for this finding could be related to the nature of the orienting task itself, which was a comparatively “shallow” encoding task that emphasized

spatial relationships between words and scenes. In line with this fact, between-group differences (control > schizophrenia) *were* detected in more posterior brain regions that support such functions. For example, greater Non-Semantic encoding activity was found in controls relative to schizophrenia participants in bilateral fusiform gyrus, an area that has been implicated in processing of scenes (Johnson & Rugg, 2007), as well as in "shallow" encoding that resulted in successful subsequent memory (L.J. Otten & Rugg, 2001). Thus, controls recruited a set of posterior brain regions to complete the more visually guided encoding task, in addition to subcortical regions that typically subserve memory function (i.e., medial temporal lobe).

In contrast to the Non-Semantic encoding findings, the between-group analysis for brain activity associated with Semantic encoding revealed that schizophrenia participants activated a large network of frontal, temporal, and parietal cortex regions to a significantly greater degree than control participants. As stated in the Results, 19 of the 21 regions showing between group differences in Semantic encoding were activated more by schizophrenia participants than by controls. This finding is in line with previous work demonstrating enhancements in brain activity in individuals with schizophrenia relative to controls under supportive encoding conditions (Bonner-Jackson et al., 2005; Ragland et al., 2005), as well as reports of normal modulation of brain activity during encoding of related associate pairs (Achim et al., 2007).

The precise mechanisms that lead patients with schizophrenia to show greater activity than controls under supportive encoding conditions are not clear. As described above, the results of the regression analyses suggested that the between-group differences in encoding-related brain activity did not simply reflect differences in semantic

processing ability. One possibility for these differences is that under beneficial encoding conditions, schizophrenia participants are able to engage regions of frontal cortex (as well as other brain regions) not utilized by controls, which act in a compensatory manner and aid in successfully completing the orienting task. In addition to frontal cortex regions, schizophrenia participants also showed greater activity than controls in bilateral parietal cortex, an area postulated to act in a compensatory manner during EM encoding in schizophrenia (Heinze et al., 2006). In contrast to this hypothesis, however, post-hoc analyses from the current study indicated that low-performing participants with schizophrenia showed the most enhanced brain activity during Semantic encoding, relative to higher-performing schizophrenia participants or controls. This finding may suggest that the pattern of over-activation is a function of an underlying pathological process, rather than a compensatory mechanism. Further study of this question is clearly required to more fully understand the nature of activation enhancements seen in schizophrenia under supportive memory conditions.

However, controls and schizophrenia participants did not rely on entirely different brain systems during supportive encoding. The main effect of Encoding Condition demonstrated that the groups activated a number of regions to similar degrees during Semantic encoding, in addition to a few similar regions during Non-Semantic encoding. Among the regions recruited by both groups during Semantic encoding were multiple areas of prefrontal cortex (left inferior frontal gyrus, bilateral middle frontal gyrus) and medial temporal lobe (bilateral parahippocampal gyrus). This result further suggests that individuals with schizophrenia and healthy controls engage similar and overlapping neural systems when oriented to process semantic relationships between items.

*Subsequent Memory Effects*

Data from the subsequent memory neuroimaging analyses represent a relatively novel indication that the neural systems underlying successful subsequent memory in individuals with schizophrenia partially overlap those in controls. Additionally, results of the present study demonstrate that subsequent memory activity varies depending on the nature of the encoding task used.

Both groups demonstrated robust subsequent memory effects (remembered items > missed items) in regions of frontal cortex, including bilateral inferior frontal gyrus (BA 44) and left precentral gyrus (BA 6), which support subsequent memory in healthy controls (Brewer *et al.*, 1998; Buckner et al., 2001; Fletcher et al., 2003; Kirchhoff *et al.*, 2000). Although this pattern of results was predicted for the control group, it was unexpected in the schizophrenia group. The few functional neuroimaging studies that have examined subsequent memory effects in schizophrenia have identified posterior regions, rather than frontal regions, as likely candidates to support successful memory encoding in individuals with schizophrenia (Bonner-Jackson *et al.*, 2008; Heinze et al., 2006). Consistent with these previous findings, subsequent memory effects in the present study were identified in posterior brain regions as well as frontal regions (e.g., right superior parietal lobule, left fusiform gyrus, left precuneus). However, the presence of such effects among individuals with schizophrenia in frontal cortex was surprising given past research. My findings, therefore, represent the first demonstration (to my knowledge) of subsequent memory effects among schizophrenia participants localized in areas of frontal cortex. Although these data should be interpreted with caution, the results described here may serve as an additional indication that the neural systems underlying

successful memory in individuals with schizophrenia overlap with those of healthy controls. Further examination of this notion is needed in future research.

In contrast to the effects in frontal cortex, however, I did not find the predicted main effects of subsequent memory in hippocampus, despite previous indications that this region is crucial for EM formation and subsequent memory (Bernard *et al.*, 2001; Brewer et al., 1998; Fernandez *et al.*, 1998; Reber *et al.*, 2002; Stark & Okado, 2003), although schizophrenia participants did show subsequent memory effects following Non-Semantic encoding in right parahippocampal gyrus. One possible explanation for this negative result could be that hippocampus was equally active during encoding of both remembered and non-remembered items, as participants were explicitly instructed to memorize items for a later memory test. A second factor may stem from the fact that the medial temporal lobes are often difficult to image and typically produce poorer quality functional images. The anatomical location of medial temporal lobe structures also renders successful functional imaging of this region more difficult, as it is more susceptible to movement and other artifact (Ojemann *et al.*, 1997). Significant task-related activation in this area could have been attenuated by the presence of adjacent sinus cavities or other brain structures. However, this scenario is less likely, given the significant medial temporal lobe activity identified in other analyses.

With regard to the effects of orienting task on subsequent memory-related activity, it was somewhat surprising that nearly all the regions that showed a main effect of subsequent memory were for items encoded Non-Semantically, as opposed to Semantically. This finding represents a departure from previous work examining subsequent memory effects as a function of encoding condition, which have largely

reported greater subsequent memory effects following “deeper” encoding tasks (Baker et al., 2001; Fletcher et al., 2003; L. J. Otten et al., 2001). Fletcher and colleagues (2003) found subsequent memory effects in left and medial prefrontal cortex that were larger in magnitude following semantic (deep) than alphabetical (shallow) encoding tasks (Fletcher et al., 2003). Similarly, two other studies (Baker et al., 2001; L. J. Otten et al., 2001) reported overlap between regions showing subsequent memory effects for deep and shallow encoding, with a suggestion that deep encoding was associated with more subsequent memory regions than shallow encoding. In contrast, one study showed that rote rehearsal produced stronger subsequent memory effects than semantic processing at encoding (Davachi *et al.*, 2001). However, this finding does not appear to be widely replicated in this literature. Overall, therefore, the results of the present study regarding encoding orientation effects on subsequent memory activity are, for the most part, unsupported by previous research.

One must, therefore, pose the question of why subsequent memory effects were detected more often following Non-Semantic than Semantic encoding in this study. Some insights into the current results may be provided by the study described above (Davachi et al., 2001), which reported greater subsequent memory effects for items encoded using rote rehearsal, as compared to semantic encoding. Of the five regions that showed greater subsequent memory effects following rote rehearsal in the Davachi et al. (2001) paper, three were identified in the current study (left inferior prefrontal cortex, right superior parietal lobe, left cerebellum). This raises the intriguing possibility that, in the absence of external encoding support, participants utilized a rote memorization strategy in order to commit the word-scene pairs to memory. A second consideration is related to the number

of regions identified in this analysis that are thought to support vision and visual imagery. Areas of left inferior and bilateral middle occipital gyrus showed subsequent memory effects, as did left precuneus and fusiform gyrus bilaterally. Precuneus has been implicated in visuo-spatial imagery, among other functions (Cavanna & Trimble, 2006), while Otten and Rugg (2001) reported subsequent memory effects in bilateral fusiform gyrus following a syllable-counting task. These data support the notion that participants in this study relied heavily on visual processing areas to support subsequent memory for Non-Semantically encoded items and likely adopted a visually based memory strategy to learn the associations between the words and pictures. Lastly, it should be noted that Semantic encoding was associated with better subsequent recall, and therefore fewer missed items, than Non-Semantic encoding. With fewer trials from which to calculate miss-related activity (relative to recall-related activity), it is possible that the subsequent memory effects identified for Semantically encoded items in this study underestimated the actual subsequent memory response. In contrast, Non-Semantic encoding was associated with a larger number of missed items, thereby allowing for a more accurate estimate of subsequent memory activity across groups.

Consideration of the Group x Subsequent Memory brain activation interactions also revealed an unexpected pattern of results. Specifically, in nearly all of the regions identified in the analysis, schizophrenia participants demonstrated greater encoding activity for subsequently remembered items than missed items, with the majority of these regions found for Non-Semantic encoding. In contrast, controls showed either no difference between remembered and missed items, or greater encoding activity for missed items than remembered items, in the regions showing Group x Subsequent Memory

effects. Notably, controls did show subsequent memory activity in other brain regions, but not in regions showing the interaction. Surprisingly, controls did not demonstrate any of the predicted subsequent memory effects (remember > miss) in the interaction regions, and even showed the opposite pattern (miss > remember) in certain brain areas.

Interestingly, a number of the areas showing significant miss > remember activity in controls were in frontal cortex (e.g., left middle frontal gyrus, right inferior frontal gyrus). Although this result was not predicted, one possible explanation for this finding is the fact that each word-scene pair was presented to participants at four separate times over the course of the scanning runs. Therefore, the brain signal that was used in these analyses was averaged across the four presentations of the stimuli. This analysis strategy could have inadvertently attenuated the signal associated with successful subsequent memory, as task-related brain responses in healthy controls decrease over repeated presentations of a stimulus (Demb et al., 1995). Such findings have been interpreted to suggest that repeated processing of identical stimuli requires less neuronal activity following the initial presentation. In support of this notion, analyses comparing first presentation of stimuli to subsequent presentations in the control group revealed that the first presentation was associated with significantly more widespread and robust activity than subsequent presentations combined.

Individuals with schizophrenia, however, do not show the same relationship between repeated stimulus presentations and attenuated brain response. Both fMRI (Kubicki et al., 2003) and ERP studies (Patterson *et al.*, 2008) have shown that individuals with schizophrenia fail to show typical priming or habituation effects. Data from the current study corroborate these findings. Brain activation during first and

subsequent presentations of stimuli were quite similar in schizophrenia participants, suggesting that they did not habituate as easily as controls and continued to require additional neuronal activity to complete the encoding tasks. Such a pattern of data would make it more likely to find subsequent memory effects in the schizophrenia group, which is what was reported above.

*Retrieval: Cueing Effects*

Results from the present study indicate that retrieval cues were ineffective in enhancing retrieval-related brain activity among individuals with schizophrenia. Rather, schizophrenia participants demonstrated underactivation across all recall conditions.

Between-group contrasts of the brain imaging data during Uncued retrieval revealed that individuals with schizophrenia demonstrated a widespread pattern of underactivation (relative to controls) during Uncued recall. My findings in this regard support previous research indicating activation deficits in various brain regions among individuals with schizophrenia during EM retrieval, including tests of item recognition (Barch et al., 2002; Hofer et al., 2003a; Hofer et al., 2003b; Jessen et al., 2003; Ragland et al., 2001; Ragland et al., 2004), associative recognition (Lepage et al., 2006), and word list recall (Crespo-Facorro et al., 1999). Notably, however, the majority of studies in this area have also reported impaired memory performance, in combination with deficits in retrieval-related brain activity, in individuals with schizophrenia. In the present study, the brain activation deficits observed among the schizophrenia participants were accompanied by recall performance that did not differ significantly from that of controls. This result raises the intriguing question of how the schizophrenia participants were able

to perform equivalently to controls during subsequent recall, in spite of massive underactivation.

Although the literature provides little guidance in this regard, one potential explanation for this phenomenon is that the neural systems underlying EM retrieval in schizophrenia are fundamentally different from those in healthy individuals. Therefore, the lawful relationship between behavior and brain activity that is observed in controls during memory retrieval may not exist in individuals with schizophrenia. It is possible that the increases in brain activity that accompany increases in recall success in controls are not present in schizophrenia. In support of this notion, analyses of brain activation in the schizophrenia group during correct retrieval (correct recall of Old > correct rejection of New) revealed a failure to activate typical "correct retrieval" regions, such as right anterior (BA 9/10) or right dorsal (BA 9/46) prefrontal cortex (McDermott *et al.*, 2000). These data contrast with findings from Ragland et al. (2004), however, who reported that retrieval success in schizophrenia participants was associated with activity in a variety of frontal, temporal, and parietal cortex regions (Ragland et al., 2004). Thus, there are currently mixed findings regarding this question. Future research should address the issue of how individuals with schizophrenia can achieve behavioral performance equivalent to that of controls, despite differential brain activity patterns.

In contrast to the predicted brain activation deficits during Uncued retrieval, it was hypothesized that Cueing would serve to "normalize" brain activity between groups and minimize between-group differences. Despite the provision of retrieval cues, however, brain activity patterns among individuals with schizophrenia did not change noticeably, relative to brain activation in the control participants. Contrary to my

hypotheses, widespread underactivation persisted in schizophrenia participants during Cued retrieval, even though recall performance was improved. As discussed in the Behavioral Results section, it is possible that the retrieval cues were helpful in modestly improving recall but did not provide sufficient support to enhance brain activity in the schizophrenia participants, whereas category cues or word stems might have been more effective in promoting increased brain activity in the schizophrenia group. However, little empirical work has focused on the effects of retrieval cues on brain activity in schizophrenia, making interpretation of these findings somewhat more challenging. A discussion of potential factors that may have influenced the retrieval brain imaging findings is below (see *Retrieval: Other Issues*).

*Retrieval: Encoding Condition Effects*

Data from the present study suggest that orientation to an advantageous encoding strategy was ineffective in enhancing retrieval-related brain activity in schizophrenia or equating retrieval-related brain activity across groups.

An additional way to examine the retrieval-related brain activity data is to compare the groups on brain activity during retrieval of Semantically- versus Non-Semantically-encoded items. Similar to the findings from the Uncued and Cued retrieval data, recall of items seen during both Non-Semantic and Semantic encoding was associated with hypoactivation in multiple frontal and temporal brain regions in schizophrenia participants, as well as more posterior areas. Once again, this pattern of underactivation in individuals with schizophrenia during EM retrieval represents a partial replication of previous findings in this domain. For example, work from the Heckers group (Heckers et al., 1998; A. P. Weiss et al., 2003) has consistently reported impaired

hippocampal recruitment in schizophrenia participants during retrieval following deep encoding, although they also found overactivation of prefrontal regions following shallow encoding, despite equivalent memory performance. Similarly, Ragland and colleagues (2005) described overactivation in the left frontal pole during recognition among individuals with schizophrenia following a levels-of-processing manipulation. Studies examining the effect of encoding condition on retrieval-related brain activity in healthy populations have made similar conclusions (Rugg *et al.*, 1997; Schacter *et al.*, 1996; Tsukiura *et al.*, 2005). For example, a study by Schacter and colleagues (1996) found that hippocampal activity at retrieval was associated with recollection of studied words, whereas activity in frontal regions was associated with elevated retrieval effort. Thus, in this context the empirical data would predict a pattern of dysregulation among schizophrenia participants, with greater than normal activity in frontal cortex during retrieval of poorly encoded items and hypoactivation in medial temporal lobe regions during retrieval of deeply-encoded items.

As stated above, this hypothesis was not fully supported. Although schizophrenia participants did not activate frontal regions to a greater degree than controls, the present study did provide some evidence of hyperactivation during retrieval of poorly encoded items. Within-group contrasts revealed that individuals with schizophrenia showed substantially more retrieval activity for items encoded Non-Semantically (relative to those encoded Semantically), suggesting more effort was being exerted while attempting to recall poorly-encoded items. Regions showing this pattern included left (BA 44) and right (BA 45) inferior frontal gyrus, as well as right middle frontal gyrus (BA 9). Similarly, the main effect of Encoding Condition demonstrated that both schizophrenia

participants and controls activated a number of regions to a greater degree during retrieval of Non-Semantically encoded items, including bilateral prefrontal cortex (BA 44, 47, 9/46). In contrast, there were no regions demonstrating greater retrieval-related activity for Semantically encoded items than Non-Semantically encoded items. Thus, the data indicates that the differences in retrieval-related activity were in the expected direction (Non-Semantic > Semantic), although they did not reach significance at the between-group level.

*Retrieval: Other Issues*

With regard to the retrieval brain imaging findings, the pattern of underactivation observed during recall in participants with schizophrenia could be more generally related to impairments in post-retrieval monitoring, which refers to a cognitive process that is posited to evaluate the accuracy of potential memory responses (Koriat & Goldsmith, 1996). Most functional neuroimaging studies of post-retrieval monitoring in healthy populations have shown that this process is supported largely by frontal brain regions (e.g., (Achim & Lepage, 2005a). To my knowledge, no functional neuroimaging studies of post-retrieval monitoring in individuals with schizophrenia exist. However, it seems likely that individuals with schizophrenia would show impairments in monitoring the contents of memory or making judgments about the likelihood of having previously seen an item, as meta-cognitive processes in this group are faulty (Moritz *et al.*, 2006). Furthermore, the dysfunction in this cognitive process could potentially reveal itself in reduced brain activity during EM retrieval. If control participants were actively monitoring their recall responses during retrieval, while schizophrenia participants were engaged in this activity to a lesser degree, brain activation differences in frontal cortex

could differ between groups, regardless of actual recall accuracy. Although this hypothesis does not account for the between-group differences in other brain regions, it could represent one factor underlying the failure to find overactivation in prefrontal regions that is common in schizophrenia during retrieval tasks.

A second issue that merits discussion is the between-group difference in task-related brain activity during viewing of New (not previously-seen) word-scene pairs. Control participants activated bilateral medial temporal lobe regions (centered in left and right parahippocampal gyrus) during correct identification of New items (relative to correct identification of previously-seen items). Structures in the medial temporal lobes are known to respond to novelty (among other features). In particular, parahippocampal gyrus appears to be involved in detection of novel stimuli (M. W. Brown & Aggleton, 2001; Gabrieli *et al.*, 1997; Kohler *et al.*, 2005). For example, Kohler et al. (2005) reported increased right parahippocampal gyrus activity in response to novel stimuli. Similarly, Gabrieli and colleagues (1997) found that activity in parahippocampal gyrus *decreased* for more familiar scenes (relative to unfamiliar scenes). Thus, the activity in bilateral parahippocampal gyrus observed in controls during viewing of New items may represent a neural response that signals novelty and helps them to correctly classify items as New. In contrast, schizophrenia participants did not show any activity in medial temporal lobe regions during correct identification of New items, which is likely related to their lower accuracy rates in identifying items that were not seen before. This hypothesis is supported by data from Weiss and colleagues (2004), who reported increased false alarm rates during a test of EM recognition, in conjunction with impaired hippocampal function, among individuals with schizophrenia (A. P. Weiss et al., 2004).

Taken together, it appears that the neural systems underlying identification of new materials in individuals with schizophrenia may continue to show deficits, despite supportive encoding and retrieval environments.

Lastly, it is important to address the issue of signal-to-noise ratio (SNR) as it relates to observed differences in task-related activity between groups. Losses of SNR in psychiatric populations can be attributed to a variety of causes, many of which are unrelated to cognitive task performance *per se*. These include brain structure abnormalities, increased signal artifact related to subject movement, and effects of psychotropic medications (G. G. Brown & Eyler, 2006). Therefore, one must attend to this potential confound in order to properly interpret patterns of functional brain activation. As reported above, the subgroups of control and schizophrenia participants continued to demonstrate significant between-group differences in retrieval-related brain activity, despite being matched on mean SNR. Across retrieval tasks, areas of bilateral frontal cortex, inferior parietal lobe (particularly left), and bilateral middle temporal gyrus (among others) remained significantly more active in controls than schizophrenia participants, even after controlling for differences in SNR. Altogether, approximately half of the regions of between-group differences identified in the retrieval analyses remained significantly different. This finding suggests two ideas, both of which are likely accurate: 1) some of the observed between-group differences in retrieval-related brain activity were due to artifactual causes, such as increased head movement on the part of schizophrenia participants; 2) some of the observed between-group differences in retrieval-related brain activity reflected genuine discrepancies in task-related activation and represent true underlying neurobiological differences between control and schizophrenia participants

during EM retrieval. Above, I have outlined potential mechanisms that may cause such differences, although a number of factors remain unclear in this regard (e.g., how equivalent recall performance was found between groups, despite substantial retrieval-related brain activation differences). Future research may profit by examining this issue in more detail.

## Individual Difference Measures

The analyses examining the effects of individual differences highlighted the importance of understanding the influence of individual differences in semantic processing ability on individual differences in episodic memory performance and brain activation in schizophrenia. Of central interest were the correlations between recall accuracy and the semantic processing composite variable. Both groups demonstrated significant positive correlations between semantic processing ability and a number of the recall measures, including total items correct. Notably, I also detected a significant correlation between semantic processing ability and recall of Semantically encoded words in the schizophrenia group ($r = .55$, $p < .005$), whereas no such correlation was found in the control group. These findings provide strong evidence that premorbid cognitive functioning and inherent cognitive abilities in individuals with schizophrenia play a significant role in how they respond to cognitive interventions. Like controls, individuals with schizophrenia show a lawful relationship between intrinsic semantic processing ability and memory benefits from a semantic orienting task. Additionally, the relationship between semantic processing ability and memory performance was somewhat specific, as I found no evidence of a significant association between abstract reasoning ability and memory performance.

Previous work has examined the relationship between memory function and various cognitive abilities in schizophrenia. For example, Ragland and colleagues (2003) found that group differences in premorbid verbal intellectual ability contributed to less accurate word classification during the encoding phase, but did not appear to influence recognition accuracy. Kareken and co-workers (1996) found that poor semantic organization was related to EM deficits in schizophrenia, while Goldberg et al (1998) suggested that thought disorder in schizophrenia might be related to the severity of semantic processing deficits (Goldberg *et al.*, 1998). To my knowledge, however, the current study is the first to demonstrate a significant relationship between individual differences in semantic processing ability and episodic memory function following an encoding orientation manipulation in individuals with schizophrenia.

Few (if any) studies have examined individual differences in semantic processing ability in schizophrenia and have related them to behavioral measures. The work referenced above suggests that semantic processing ability represents a cognitive domain of great importance for individuals with schizophrenia, as well as a topic of great interest for those studying this disease. Based on my results and the findings of others, it appears that the intrinsic semantic processing ability possessed by individuals with schizophrenia impacts many aspects of their lives and can have wide-reaching implications in terms of functional outcome and quality of life.

Regarding other notable correlations, schizophrenia participants showed a significant negative correlation between disorganized symptoms and recall of Semantically encoded items. Disorganized symptoms are associated with executive function (Daban *et al.*, 2002; Moritz *et al.*, 2001), lower verbal IQ and poor concept

attainment (O'Leary *et al.*, 2000), and working memory (Daban et al., 2002) in schizophrenia. It is likely that some (or all) of these factors are involved in successful semantic processing and subsequent memory function, further supporting the notion that individuals with schizophrenia possess inherent traits and cognitive abilities that can determine the outcome of cognitive interventions.

Finally, negative symptoms were not significantly correlated with any of the recall measures. Traditionally, negative symptoms have been associated with poor EM function in schizophrenia (Aleman et al., 1999; Brazo *et al.*, 2002; Cirillo & Seidman, 2003; S. Gold *et al.*, 1999; Pelletier *et al.*, 2005; Thoma et al., 2006), so it was somewhat surprising that a significant correlation between negative symptoms and recall was not detected. This may have been a consequence of the individuals with schizophrenia who participated in the study, as many of them were high functioning and relatively free of symptoms. It is conceivable that studying participants with a wider range of symptomotology would have produced a different pattern of correlational results.

In addition to its effect on episodic memory performance, a further topic of interest was the relationship between semantic processing ability and task-related brain activity during Semantic encoding. This relationship was assessed in two ways for each group separately. An ROI-based approach, using brain regions that showed significant task-related activity during Semantic encoding, identified significant negative correlations for schizophrenia participants in three brain areas – two areas in left BA 6 (-45,2, 49 & -28, 15, 57) and one area in left BA 9 (-41, 3, 29). A second approach, in which semantic processing ability was correlated with brain activity throughout the entire brain, identified one significant negative correlation among individuals with

schizophrenia in left BA 6 (-27, 5, 55). This region was somewhat close to one of the left BA 6 regions identified in the previous analysis.

As stated in the Results, there has (to my knowledge) been relatively little work done in this domain (i.e., examining individual differences in semantic processing ability as they relate to brain activity), either in individuals with schizophrenia or healthy populations. Thus, the precise localization of such correlations was difficult to predict. In light of my findings, however, there is evidence that this area of prefrontal cortex (BA 6) plays a role in various processes that may contribute to semantic processing in healthy individuals. For example, it has been suggested that left BA 6 is involved in word retrieval and phonological processing (Kubicki et al., 2003; Thompson-Schill *et al.*, 1997), functions that would likely be tapped in making decisions about relationships between words and scenes. Left PFC has also been implicated in working memory function in healthy controls (Smith & Jonides, 1999), as well as effortful memory retrieval (Naghavi & Nyberg, 2005). Given the fact that all of the correlations were negative, it appears that schizophrenia participants with less intrinsic semantic processing ability may require and recruit regions of left prefrontal cortex in order to successfully complete the Semantic encoding task, whereas those with more semantic processing capacity did not need to bring these regions online. Furthermore, it is noteworthy that a degree of overlap was found across correlational analyses, which may suggest converging evidence for a specific role of left PFC (particularly left BA 6) in semantic processing in schizophrenia. As with the analysis of the behavioral data, I also found that the relationship between semantic processing ability and encoding-related brain activity

among schizophrenia participants was relatively specific, such that I detected a much weaker relationship between abstract reasoning ability and brain activity.

It was somewhat unexpected, however, that control participants did not demonstrate a significant relationship between semantic processing ability and brain activity during Semantic encoding. It is the case that the range (-3.47 – 5.21) and standard deviation (2.07) of semantic processing scores for control participants was more restricted than those of schizophrenia participants (range: -5.79 – 4.83, SD = 2.86), potentially reducing the likelihood of finding significant correlations. Brain activity among individuals with schizophrenia also tends to be more variable relative to patterns of brain activity in control participants (Barch *et al.*, 2003), which may have also contributed to the detection of stronger relationships between semantic processing and brain activity in schizophrenia participants.

Importantly, these findings suggest that individuals with schizophrenia respond differently at a neurobiological level to memory interventions depending on their inherent ability to take advantage of those interventions. Specifically, schizophrenia participants who had higher levels of semantic processing ability (as measured in this study) activated regions in left frontal cortex to a lesser degree during Semantic encoding, in a sense making them more like control participants. In contrast, schizophrenia participants who were low on semantic processing ability recruited the left frontal regions significantly more, possibly representing either a compensatory or pathological process. This heterogeneity in the intrinsic skills of individuals with schizophrenia, and the underlying brain systems that they affect, represents a rich source of knowledge and potential future research area, as well as a potential approach to parsing the heterogeneity in behavior and

brain function shown by individuals with schizophrenia. More research is needed to clarify the differential relationship between semantic processing ability and task-related brain activity in healthy controls and individuals with schizophrenia.

## Limitations

The present study had a number of limitations that merit discussion and should be addressed in future research. First, the participants with schizophrenia in this study demonstrated a somewhat limited range of psychopathology. The schizophrenia participants who volunteered to be involved in this research were high functioning, relative to a typical schizophrenia sample. Furthermore, I was only able to include participants with schizophrenia (as well as control participants) who were able to tolerate a 2-hour cognitive battery and 2-hour MRI scanning session while adhering to the instructions the entire time. Thus, it is possible that the participants with schizophrenia who successfully completed this study were not necessarily representative of the general schizophrenia population. Therefore, conclusions that are drawn from this work must be made cautiously.

Secondly, although sample sizes of the control and schizophrenia groups used in the neuroimaging analyses (24 and 23 participants, respectively) were relatively large compared to many studies in the functional neuroimaging literature, they did not provide high power to detect more subtle group differences, such as those that might be apparent in behavior. For example, it is possible that more of the correlational analyses (relating semantic processing ability and memory performance) would have been significant if larger groups were used. A similar case can be made for the two- and three-way

interactions in the behavioral data. Although many of the findings were in the predicted direction, a larger N might have helped to further clarify some of the results.

A third limitation posed by the present study was the nature of the retrieval task used in the scanner. Specifically, participants were required to recall words and say them aloud while being scanned. Although recall tasks have been used successfully in fMRI studies, they can introduce potential problems. For example, speaking in the scanner resulted in additional head movement in both groups, particularly the schizophrenia participants, which degraded the quality of the functional images and even rendered certain scanning runs unusable. Furthermore, repeated opening and closing of the mouth can alter the properties of the cavities surrounding the brain, making it more difficult to obtain quality images. Therefore, the valuable information that was obtained by using a cued recall paradigm also led to certain difficulties in data collection and analysis.

Finally, and related to the previous point, it is worth reiterating that the schizophrenia group had lower signal-to-noise ratios (SNR) on most of the scanning runs, somewhat limiting the conclusions that can be drawn from these data. Above, I have described a number of steps that were taken to address this issue on a post-hoc basis, including matching subgroups of control and schizophrenia participants on SNR and re-analyzing the neuroimaging data. However, such fundamental differences in the signal derived from the brains of the control and schizophrenia participants are problematic, especially when attempting to interpret the relationship between brain activation and behavior. Given the results of the contrasts using matched groups, it seems somewhat safe to conclude that some of the initial findings were spuriously influenced by SNR

artifacts, whereas others represented real between-group differences in brain activation. This issue is of key importance and should be monitored in all studies of this type.

## Future Directions

The results from the present study suggest a number of avenues and directions for future research in the domain of memory-related brain function in individuals with schizophrenia. One topic which was unexplored in this study, but which is of great interest and importance in this field, is the relationship between brain structure and cognition in individuals with schizophrenia. For my purposes, I would be interested to investigate the relationship between brain structure, brain function, and strategic memory processing. Specifically, a question that arises from this line of research is whether the size or integrity of brain structures in schizophrenia constrains the ability to benefit from memory strategies, and whether these factors are related to inherent cognitive abilities, such as verbal processing. One could postulate that individual differences in gray matter integrity in prefrontal cortex, for example, may differentiate those individuals with schizophrenia who are able to benefit from strategic instruction from those who are not. Hippocampal size and its relation to memory function have also been investigated in this population. Future research could examine the relationship between the size of structures in the medial temporal lobe and relational memory performance, among other topics.

A second issue to be further explored in future work is the effect of different retrieval cue types on recall success and retrieval-related brain activity, in both schizophrenia participants and healthy controls. As discussed previously, it is possible that the use of different retrieval cues (e.g., category cues, word stems, etc.) has an impact on the likelihood of retrieval success. Furthermore, the pattern of differences may

vary across groups depending on which retrieval cues are being used. Thus, future research endeavors should assess whether the use of different retrieval cues significantly alters patterns of brain activity or memory performance, and whether such differences show interactions with group (i.e., control vs. schizophrenia).

Furthermore, the findings from the present study regarding the effects of individual differences on behavioral performance and brain activity warrant further exploration. Specifically, follow-up work should be conducted to examine how differences in cognitive abilities and demographic variables (among other factors) influence memory performance and memory-related brain function, as well as how these relationships differ between individuals with schizophrenia and healthy individuals. For example, in a noteworthy finding not discussed above, the parental education of schizophrenia participants was predictive of a number of recall measures, while such a relationship was not detected in controls. Findings such as these may help to uncover some of the factors that are involved in the development of schizophrenia.

Finally, future work in this area would profit from the use of a psychiatric control group, such as individuals with major depressive disorder (MDD). Individuals with MDD, like individuals with schizophrenia, are known to have memory deficits, although the precise mechanism underlying such deficits has not been fully uncovered. The proposed design can be used to explore the question of whether the effects of strategy manipulation on brain activity apply to individuals with schizophrenia alone or to individuals with severe mental illness more generally. Furthermore, it would be possible to compare the groups on other measures as well, such as brain structure and inherent cognitive abilities. Investigations of this type would provide further insight into the

neural mechanisms underlying cognitive deficits in schizophrenia, and they may help to shed light on neurobiological factors that trigger impairments in severe mental illness more generally.

## Summary

Overall, results of the behavioral and neuroimaging data analyses suggested that the schizophrenia participants benefited from the encoding condition manipulation. Behaviorally, they recalled more words following Semantic (relative to Non-Semantic) encoding, and the interaction with Group indicated that this recall benefit was greater among schizophrenia participants than controls. These behavioral benefits were accompanied by increases in task-related brain activation among schizophrenia participants. Whereas between-group differences were detected in both directions (control > schizophrenia and schizophrenia > control) for Non-Semantic encoding, nearly all of the between-group differences during Semantic encoding were in the direction of schizophrenia > control. The behavioral and neuroimaging findings in this regard replicate previous research showing significant enhancement of memory performance and brain activity in schizophrenia participants following deep encoding tasks. Additionally, the current data extend previous work by demonstrating these effects using a recall (rather than recognition) test and an associative (rather than item) memory paradigm.

The current study also showed that the retrieval cue manipulation was equally beneficial for the memory performance of controls and individuals with schizophrenia. Furthermore, retrieval cues conferred greater memory benefits for both groups following Non-Semantic encoding, suggesting that cueing is more beneficial for poorly encoded

information. Regarding the neuroimaging data, however, all retrieval conditions were associated with widespread hypoactivation in the schizophrenia group. There were indications that reduced signal-to-noise ratios in the schizophrenia group influenced the retrieval neuroimaging results, although post-hoc analyses suggested that some of the results reflect true between-group differences in retrieval-related brain activity.

Novel findings from this study included the detection of subsequent memory effects in frontal cortex in schizophrenia participants, in addition to effects detected in posterior areas that have been reported in previous studies. Furthermore, a number of interesting relationships were detected between behavioral performance and individual differences in semantic processing ability, including a significant positive correlation between the semantic processing composite measure and recall of Semantically encoded items. This correlation was significant only in the schizophrenia group, not the control group. In addition, significant negative correlations were detected between Semantic encoding activity and the semantic processing composite measure, once again only in the schizophrenia group. Taken together, these data provide evidence that individual differences in cognitive abilities among individuals with schizophrenia can significantly affect behavioral and neurobiological responses to strategic memory interventions.

Despite the presence of encoding and retrieval cues, however, schizophrenia participants did not show enhancements in memory and brain activity under all conditions. This was most obvious during the retrieval tasks, in which the schizophrenia group showed patterns of underactivation across all retrieval conditions. In addition, correct identification of New items was poorer in schizophrenia participants and associated with brain activation deficits, most notably in medial temporal lobe.

Individuals with schizophrenia appear to have difficulty in discriminating old from new items, and this conclusion is supported by the effect size and d-prime analyses. Furthermore, it is conceivable that activity in medial temporal lobe regions in controls signals novelty and aids in detection of new items, whereas the absence of such activity in individuals with schizophrenia may be associated with deficits in identifying new items.

Finally, the current findings suggest that, despite the differences in brain activity described above, individuals with schizophrenia and healthy individuals rely on partially overlapping networks of brain regions to support EM processes. In analyses of brain activity associated with EM encoding, subsequent memory, and retrieval, controls and schizophrenia participants consistently demonstrated commonalities in the neural systems that were recruited to subserve memory functions. I interpret these findings to further support the notion that constraining memory strategy use in individuals with schizophrenia is effective in enhancing and "normalizing" memory-related brain activity patterns. Although certain deficits in memory performance and brain activation persist, it is clear that orientation to advantageous memory strategies can partially ameliorate EM function among individuals with schizophrenia.

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