# Decreased Encoding Efficiency in Schizophrenia

Tara A. Cairo, Todd S. Woodward, and Elton T.C. Ngan

***Background:*** *Working memory deficits are a cardinal feature of schizophrenia that contribute to social and occupational dysfunction.*

***Methods:*** *We used functional magnetic resonance imaging to compare the response to varying task demands during the performance of an item recognition task. Study design and analysis procedures were optimized for the detection of load dependent activity during the encoding phase of working memory.*

***Results:*** *At the lowest load conditions the schizophrenia group performed as well as controls, however to achieve this equivalent performance the schizophrenia group had a significantly higher magnitude of activation compared to the controls. At the higher load conditions, the magnitude of activation between groups became more similar and we began to see performance deficits in the schizophrenic group.*

***Conclusions:*** *These results suggest that patients with schizophrenia have decreased efficiency in the cognitive processes that underlie the early encoding phase of this task. For lower demand tasks, patients with schizophrenia can compensate for decreased efficiency by working harder to achieve equivalent performance. Encoding utilizes attentional and perceptual cognitive operations that are likely common to many other cognitive tasks; therefore, inefficiency may underlie the deficits observed in a wide range of cognitive tasks in schizophrenia compared to healthy controls.*

**Key Words:** Schizophrenia, working memory, encoding, cerebral efficiency, fMRI, mental illness

Working Memory (WM) refers to a cognitive system that allows individuals to maintain and manipulate a limited amount of information in an active state for a brief period of time (Baddeley 1992). WM impairment is considered a fundamental feature of schizophrenia, and can be observed throughout the course of illness, and in medicated, unmedicated, and medication naive patients (Barch et al 2001; Carter et al 1996; Park and Holzman 1992). These deficits are stable (Hughes et al 2002), persistent (Park et al 1999) and resistant to pharmacological treatment (Goldberg and Weinberger 1996), although some of the newer atypical antipsychotic medications seem to offer a degree of improvement (Keefe et al 1999; Meltzer and McGurk 1999). Notably, impaired verbal WM function is a strong predictor of poor quality of life and poor long-term functional outcome (Green 1996).

While the majority of neuroimaging studies have identified reduced prefrontal activity during WM performance, more recent studies have found increased or equivalent prefrontal activity (Manoach 2003). These inconsistencies may be at least in part due to differing levels of memory load (the amount of information to be held in WM) across studies, as WM-related activity has been shown to vary with memory load in many brain regions (Braver et al 1997; Jonides et al 1997; Rypma et al 1999). In healthy subjects, dorsal lateral prefrontal cortex (DLPFC) activity increases with load until WM capacity is exceeded, at which time it decreases (Callicott et al 1999; Goldberg et al 1998). Patients with schizophrenia show greater DLPFC activity compared to nonpatient controls when WM load is low (Callicott et al 2000; Jansma et al 2002; Manoach et al 1999, 2000; Mendrek et al 2004). In contrast, when WM load increases and performance is impaired, subjects with schizophrenia show reduced activation compared to nonpatient controls (Jansma et al 2002; Callicott et al 2003).

These findings suggest that the normal inverted-U relationship between memory load and DLPFC activity may be preserved in schizophrenia, but the curve describing this relationship is shifted to the left, reflecting peak activation at a lower memory load. As increased activity is often associated with increased effort, a left-shifted inverted-U pattern of activity may reflect an inefficient WM system (Callicott et al 2000, 2003; Manoach 2003), whereby people with schizophrenia have to work harder to maintain their performance as load increases, resulting in a WM capacity that is exceeded at a lower level of load. This inefficient response to increasing memory load has been observed not only in the DLPFC but also in right parietal and left cingulate regions (Callicott et al 2000). Manipulation of endogenous dopamine levels with varying dosages of amphetamine in healthy individuals revealed an inverted U-shaped relationship between the amount of amphetamine administered and WM processing efficiency. Low dosages of amphetamine resulted in increased efficiency whereas larger dosages resulted in decreased efficiency (Tipper et al 2005). These results suggest that the observed inefficient WM system in schizophrenia may be the result of increased endogenous dopamine levels.

Although WM is a compound task that can be broken down into three distinct phases: encoding, maintenance, and retrieval; to our knowledge, none of the functional imaging studies comparing WM in healthy controls to patients with schizophrenia have used designs allowing for isolation of phase specific activity. The majority of studies have utilized variations of Cohen's *n*-back WM task, which requires simultaneous encoding, maintenance, updating/manipulation and recall, and there is currently no method for separating the activity associated with these different processes. The studies that have used variations of the Sternberg Item Recondition Task (SIRT) have modeled WM across all task phases, usually emphasizing maintenance related processing with paradigms in which the maintenance phase is much longer in duration than the encoding or retrieval phases. While these studies provide strong evidence for WM deficits in schizophrenia, they cannot directly address whether the memory deficits are related to poor encoding, maintenance or retrieval.

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The SIRT requires subjects to memorize a short list of stimuli, maintain this information in an active state over a brief delay, and then use this information to indicate if a probe is or is not part of the memorized list. As encoding, maintenance and retrieval occur sequentially in the SIRT, it is possible to separate the activity associated with each phase. The few fMRI studies that have attempted to separate out phase specific activity in healthy subjects have demonstrated that the phases are associated with distinct but overlapping patterns of activity. Encoding has been associated with activation in visual and parietal regions (Manoach 2003; Cairo et al 2004; Woodward et al, in press). Maintenance has been associated with activation in visual association, bilateral primary sensory, supplementary motor, ventral prefrontal, and dorsal prefrontal regions (Rypma and D'Esposito 1999; Cairo et al 2004; Woodward et al, in press). Retrieval has been associated with activation in supplementary motor, thalamic, basal ganglia and primary motor regions (Rypma and D'Esposito 1999; Manoach 2003; Cairo et al 2004).

In addition to this spatial separation of phase specific activity, different regions show phase specific responses to variable WM load. In a prefrontal region of interest analysis, Rypma and D'Esposito (1999) found that ventrolateral prefrontal cortex activity decreased with increasing load during encoding, whereas DLPFC activity increased with increasing load during maintenance and retrieval. In a whole brain investigation, we found activity increased with memory load across the majority of regions involved in encoding, with the peak load dependent activity in bilateral occipital and posterior parietal regions. In contrast, more selective load dependent activity was associated with the retrieval phase, primarily in the anterior supplemental motor area (SMA) and the right cerebellum (Cairo et al 2004). As each of the WM phases appears to be associated with a distinct pattern of activity, it is possible that the nature of their contributions to WM impairment may also vary.

Study designs and analysis procedures that allow for separation of phase specific activity provide an opportunity to clarify how WM activity varies with load in schizophrenia in the different brain regions that subserve WM. Because previous studies of WM in schizophrenia have utilized designs that emphasize the maintenance phase of WM, and therefore suggest that the observed deficits are likely maintenance related, the current study and analysis procedures were optimized to assess load dependent activity during the encoding and retrieval phases, with the goal of testing the hypothesis that inefficient encoding contributes to the poor WM performance found in schizophrenia. We used event-related fMRI and a modified version of the SIRT to compare the relationship between phase specific activity across four memory load conditions in patients with schizophrenia and matched nonpatient controls.

## Methods and Materials

### Subjects

Fifteen patients with schizophrenia, recruited from outpatient community care teams (5 females, 10 males, mean age 32.6, SD = 11.04), and 15 healthy volunteers (5 females, 10 males, mean age 32.4, SD = 10.09) participated. One patient and 1 healthy subject were left handed, as assessed by the Annett handedness scale (Annett 1970). Participant groups did not differ significantly on the demographic variables of age, gender, parental socio-economic status (Hollingshead and Redlich 1958), or on estimates of pre-morbid (National Adult Reading Test; Sharpe and O'Carroll 1991) and current (Quick Test; Ammons and Ammons 1962) intellectual functioning ($p < .05$; see Table 1). Written informed consent was obtained from all participants after reviewing a detailed written description of the study, which was approved by the University of British Columbia Clinical Research Ethics board.

**Table 1.** Demographic Data

| | Healthy Participants | | Schizophrenic Participants | |
|---|---|---|---|---|
| | Mean | (SD) | Mean | (SD) |
| Age | 32.40 | (10.09) | 32.60 | (11.54) |
| NART (Pre-Morbid Intellectual Function) | 117.30 | (5.29) | 116.60 | (6.51) |
| Quick Test (Current Intellectual Function) | 109.16 | (7.21) | 103.13 | (9.16) |
| Hollingshead (Parental SES) | 3.60 | (1.69) | 3.50 | (1.55) |

NART, National Adult Reading Test; SES, Socio-economic status.

All patients were interviewed by a psychiatrist independent of the treatment team to confirm the diagnosis of schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (American Psychiatric Association 1994). Symptom severity was assessed by the same psychiatrist using the Signs and Symptoms of Psychotic Illness scale (SSPI) (Liddle et al 2002). The SSPI is a twenty item 5 point rating scale in which 0 represents no pathology, 1 represents questionable pathology and 2–4 represents increasing severity of clear pathology. The average duration of illness was 10.1 years (range 2–31).

All patients were taking oral antipsychotics prescribed by their community psychiatrist. One patient was taking the typical neuroleptic, haloperidol (intramuscularly, every 4 weeks), and the rest were taking atypical neuroleptics. Seven patients were taking risperidone (mean dosage = 3.4 mg/day, range = 1–8 mg), 5 patients were taking clozapine (mean dosage = 350 mg/day, range = 150–600 mg), 4 Olanzapine (mean dosage = 20 mg/day, range = 8–35 mg) and 1 Seroquel (200mg/day).

### Task Design

Each subject completed two 10 min, 53 sec runs of a variable load WM task. A modified version of the SIRT was presented on a personal computer using Presentation Software (Neurobehavioral Systems, Albany, California). Stimuli were projected from an LCD projector onto a screen mounted at the foot of the MRI table. An angled mirror reflected stimuli from the screen into the participants' field of view. During a single trial of this task (Figure 1), subjects saw a string of 2, 4, 6 or 8 different uppercase consonants for four sec. They were instructed to remember these consonants over a short delay (6 sec). A single consonant in lowercase was presented for one sec after this delay, and subjects were required to indicate if this letter had been present in the preceding string. "Present" and "not present" responses were indicted via a fiber-optic response device (Lightwave Medical, Vancouver, British Columbia, Canada). The probability of the test letter having been in the remembered string was .5.

As reduced motivation is a prominent feature of schizophrenia (Schmand et al 1994), interpreting activation differences in the context of poor performance is confounded by the possibility that schizophrenic subjects are not engaged in the task. To encourage maintenance of attention and motivation throughout the study, subjects received financial reward for each correct response for a total possible reward of 10 dollars.

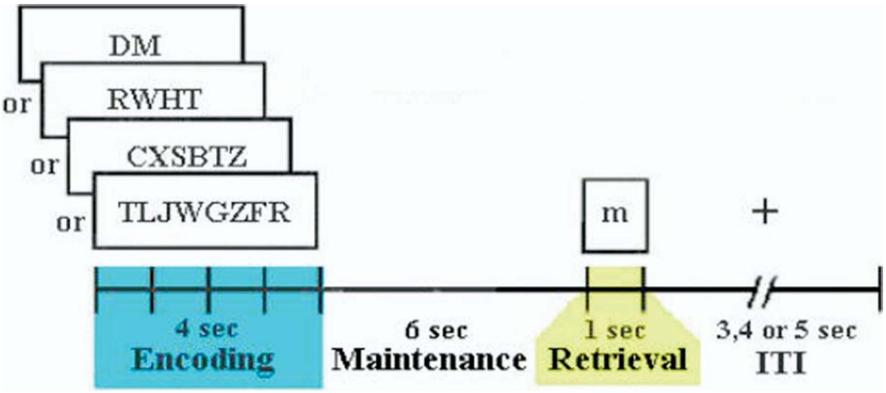


**Figure 1.** Variable load working memory task showing sample stimuli and probe. ITI, intertrial interval.

A rapid event-related design was used in order to maximize the number of trials presented for each memory load condition.

When using rapid event-related designs it is important to ensure the conditions of interest are temporally uncorrelated. In multiple regression analysis it is only the unshared variance within the predictor variables that is useful in separating the signal from each condition of interest. Minimization of multicollinearity between the modeled HRFs is one of the most important but often overlooked study design parameters that contributes to increased accuracy and efficiency in separating overlapping modeled HRFs. The main concern with regard to multicollinearity is increased standard error of the beta estimates and decreased power to detect the real underlying signal. In addition, the adverse consequences of multicollinearity can vary across voxels depending on the relative contributions of the events of interest to the measured signal and the goodness of fit between the model and the signal. For example, in voxels that are activated by only one of two events that have correlated models, in addition to the decrease in power due to increased standard error of the beta estimates, imprecision between the estimated model and the actual signal may lead to underestimation of the signal for the causal event and misattribution of signal to the correlated nonsignal generating event. In the current study, several steps were taken to ensure that our conditions of interest were temporally uncorrelated. First, the intertrial interval (ITI) was variable in duration (3, 4 or 5 sec). Jittering the ITI using noninteger multiples of the TR increases the effective sampling rate by avoiding repeated sampling at TR intervals. Second, blank trials (2 of 27 sec in duration and 3 of 15 sec in duration) were inserted at wide intervals throughout each run. These methods have both been shown to increase to the separability of overlapping functions. Last, we selectively modeled load for the encoding and retrieval phases but not for the maintenance phase. These procedures reduced the maximum correlation between models of any two conditions of interest to .16.

### Imaging

Echo-planar images were collected on a standard clinical GE 1.5 T system fitted with a Horizon Echo-speed upgrade (General Electric Health Care, Chalfont St. Giles, United Kingdom). Conventional spin-echo $T_1$ weighted sagittal localizers were used to view the positioning of the participant's head and to graphically prescribe the functional image volumes. Functional image volumes were collected with a gradient echo sequence (TR/TE 3000/40 msec, 90° flip angle, FOV 24 × 24 cm, 64 × 64 matrix, 62.5 kHz bandwidth, 3.75 × 3.75 mm in plane resolution, 5.00 mm slice thickness, 29 slices, 145 mm axial brain coverage). This sequence is sensitive to the blood oxygen-level dependent (BOLD) contrast. Each stimulus run consisted of 218 scans (encompassing the entire brain). The first 12 sec collected at the beginning of each run were discarded, to avoid variation due to $T_1$ saturation effects.

### Data Processing

Functional images were reconstructed offline. Statistical Parametric Mapping Software (SPM99 – Wellcome Institute of Cognitive Neurology, London, United Kingdom) was used for image realignment, normalization into modified Talairach stereotaxic anatomical space (using affine and nonlinear components, as implemented in SPM99), and smoothing with a Gaussian kernel (8 mm full width at half maximum) to compensate for intersubject anatomical differences and optimize the signal to noise ratio. Maximum rotation and translation estimates from realignment, were no greater than 2 mm and 2 degrees, respectively.

### Statistical Analysis

In the first level (fixed effects) analysis, four memory load conditions were specified for the encoding and retrieval phases, whereas one condition (the average activation across load) was specified for the maintenance phase. The BOLD response for encoding was modeled as the convolution of a 4 sec box-car (beginning at the onset of the letter string to be encoded) with a synthetic hemodynamic response function composed of two gamma functions. Maintenance was modeled as the convolution of a 6 sec boxcar (beginning when the letters to be encoded were turned off) with the synthetic hemodynamic response. Retrieval was modeled as the convolution of a 1 sec boxcar (beginning at the onset of the test letter) with the synthetic hemodynamic response.

To assess load dependent differences between groups for the encoding and retrieval phases, binary masks of voxels that showed a significant (random effects analysis height threshold $t = 6.23$, $p = .01$, corrected for multiple comparisons) activity across all four loads was computed for the encode and retrieval phases. The mean estimated magnitude of response (averaged beta values within each mask) was determined for each subject at each load and entered as dependent variables in separate analyses of variance for the encoding and retrieval phases.

## Results

Whole brain analyses using contrast of averaged activity and load dependent activity (methods detailed in Cairo et al 2004) showed similar load dependent and averaged response activity patterns in both groups. There were no significant between

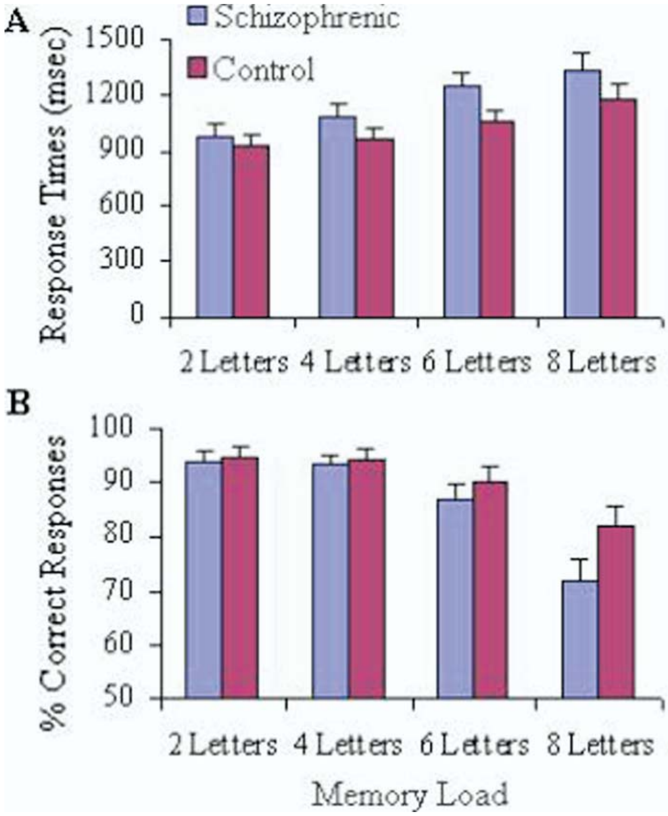


**Figure 2. (A)** Mean response times for each memory load condition for each group. **(B)** Mean percent correct responses for each memory load condition for each group.

group differences that survive correction for multiple comparisons.

### Symptom Severity Ratings

The mean SSPI score for the schizophrenic patients was 7.4 (SD = 3.6) consistent with mild to moderate symptomatology (Liddle et al 2002).

### Task Performance

The mean response times for each memory load condition are shown for both groups in Figure 2A. Response time data were analyzed using a Group (healthy participants, schizophrenic patients) × Load (2, 4, 6 and 8 letters) analysis of variance (ANOVA). Reaction times (RT) from incorrect trials were excluded. The analysis revealed a main effect of load [$F(3,84) = 33.98$, $p < .001$], with both groups showing the expected linear increase in RT with load. Though the main effect of Group did not reach statistical significance [$F(1,28) = 2.31$, $p = .14$], the mean RT was longer in the schizophrenic group for each memory load condition, with differences of more than 100ms for the three higher memory load conditions. There was no significant Group × Load interaction [$F(3,84) = 1.35$, $p = .27$].

The mean percent correct for each memory load condition are shown for both groups in Figure 2B. All of the participants performed above chance in all four memory load conditions. The minimum percent correct for the 8 letter condition was 71.9% in the schizophrenic group and 81.9% (SD = 15), in the healthy group. Accuracy data were analyzed using a Group × Load ANOVA. The analysis revealed a main effect of Load [$F(3,84) = 64.09$, $p < .001$], with both groups showing the expected decrease in accuracy with increasing load. Though the differences were not statistically significant (main effect of Group [$F(1,28) = 1.35$, $p = .25$]), accuracy was lower in the schizophrenic group than in the healthy group for each memory load condition, with the largest difference of 10% for the highest memory load condition. There was a trend towards a Group × Load interaction [$F(3,84) = 2.52$, $p = .06$]. Analyses of specific Group × Load polynomial contrasts revealed a significant linear Load × Group effect [$F(1,28) = 4.63$, $p < .05$].

### Imaging Data

**Encoding Mask.** The encoding mask consisted of 1981 voxels in bilateral occipital cortex, inferior and middle parietal lobules, putamen, caudate, globus pallidus, inferior frontal gyri, supplementary motor cortex and the cerebellum (Figure 3A). The mean activation for each load condition within the encoding mask is shown for both groups in Figure 4. A Group × Load ANOVA revealed a significant increase in activity with increasing load that had both linear [$F(1,28) = 82.22$, $p < .001$] and cubic components [$F(1,28) = 15.53$, $p < .001$]. In addition, there was also a main effect of Group [$F(1,28) = 4.93$, $p < .05$], but no significant Group × Load interaction [$F(3,84) = 2.07$, $p = .11$]. Two-tailed $t$-tests revealed that the schizophrenic group showed significantly greater activation than the healthy group for the low load conditions (2 letters $t(28) = 2.46$, $p < .05$; 4 letters $t(28) = 2.453$, $p < .05$) but a similar magnitude of activation for the high load conditions (6 letters $t(28) = 1.86$, $p = .07$; 8 letters $t(28) = .04$, $p = .96$).

**Retrieval Mask.** The retrieval mask consisted of 3056 voxels in the inferior and middle parietal lobules, right superior central gyrus, left precentral gyrus, left post central gyrus, supplementary motor cortex and the cerebellum (Figure 3B). There were no significant polynomial contrasts for the effects of Load, Group × Load interactions or main effect of Group for the mean activation during the retrieval phase for each load within the retrieval masks.

## Discussion

This study compared the relationship between task difficulty and magnitude of activation during the encoding and retrieval phases of a working memory task in patients with schizophrenia to that in nonpatient controls. Previous research has reported a leftward shift of the inverted-U shape relationship between memory load and DLPFC activity in patients with schizophrenia during the performance of working memory tasks (Callicott et al 2003). Our current study extends this work by identifying that load dependent regions associated with the encoding phase of working memory also show a leftward shift in patients with schizophrenia compared to nonpatient controls. This leftward shift reflects a decreased efficiency in encoding in patients with schizophrenia that may contribute to performance deficits observable as cognitive demands increase.

When memory load was low, no differences in response accuracy or speed were observed between patients with schizophrenia and controls; however, to achieve this equivalent level of accuracy, patients activated a significantly greater number of voxels within the predefined encoding mask. In contrast, when memory load was high, a similar extent of activation was observed in patients and controls, but the schizophrenia group committed significantly more errors. These results indicate that patients with schizophrenia are less efficient at performing the procedures that underlie the encoding of visually presented verbal information. Even for the simplest condition, registering 2

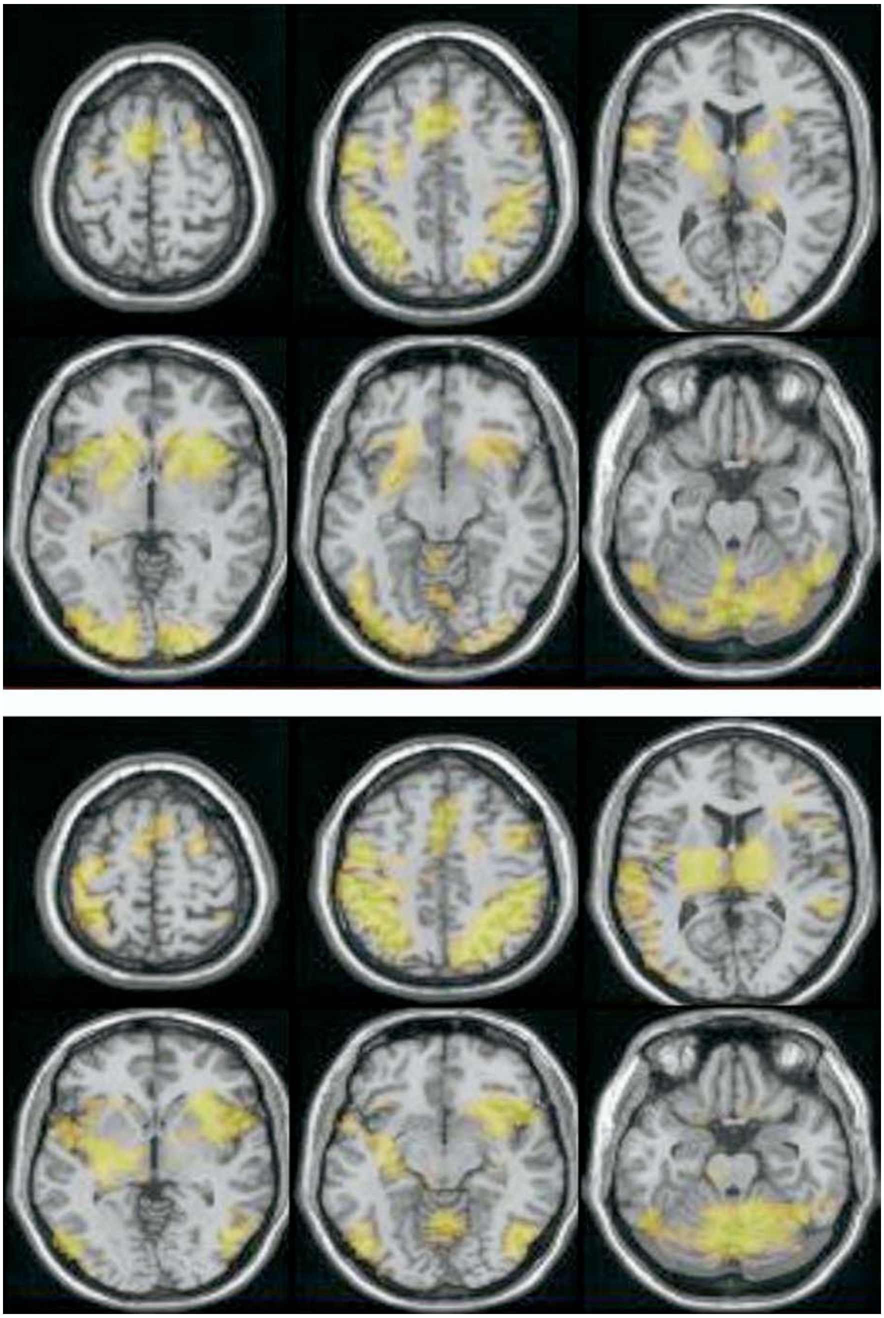

**Figure 3. (A)** Mask of voxels with significant activation during the encoding phase. **(B)** Mask of voxels with significant activation during the retrieval phase.

consonants for later recall, patients with schizophrenia worked harder to achieve a similar level of performance as controls. In other words, increased activity compensates for decreased efficiency to achieve equivalent performance.

This ability to compensate for decreased efficiency by increasing effort (working harder) may be limited by the performance capacity of each subject. As task demand increases beyond the individual's ability to compensate by increasing activity, we begin to see performance differences. This simple relationship between effort and performance can help integrate the discrepancies in the schizophrenia cognition and neuroimaging literature with regard to hypoactivity versus hyperactivity. Our results suggest that patients with schizophrenia would be hyperactive compared to controls for the simplest task for which they can compensate for decreased efficiency by increasing activity (e.g. the 2 letter and 4 letter conditions). Due to decreased efficiency we would expect patients to display a reduction in performance capacity, and to reach ceiling earlier than controls. Thus comparisons of extent of activation controlling for performance (e.g. comparing the extent of activation for 8 letters in controls with the extent of activation for 6 letters in patients), would yield similar (nonsignificant) results between the two groups. Analyses that attempt to standardize activity by subtracting activity associated with a simple task from that associated with a more complex task have the potential for creating a hypoactive pattern that is an artefact of the hyperactive baseline condition (e.g., comparing the difference in activation for 8 letters minus activation for 2 letters between groups).

Metacognitive reviews (Heinrichs and Zakzanis 1998; Johnson-Selfridge and Zalewski 2001), and reports from first episode/early

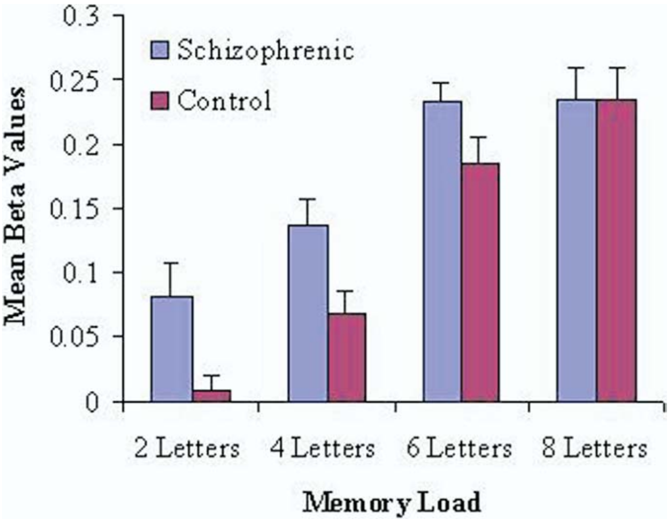


**Figure 4.** The mean estimated magnitude of response within encoding regions for each memory load condition for each group. The schizophrenic group showed an inefficient pattern of encoding activity: an increased activation at low load activity but a similar activity at high load activity. * $p < .05$.

psychosis programs incorporting neurocognitive test batteries (Mohamed et al 1999; Bilder et al 2000) reveal substantial performance deficits across a diverse array of neuropsychological tests that span many cognitive domains. Just as WM is a complex task involving multiple sub processes, the encoding phase itself includes multiple sub processes such as attention, sensory representation, verbal or visual memory processes and some executive functions. Many of these sub-processes are also necessary in most neuropsychological tests, thus decreased efficiency during encoding in schizophrenia is potentially a nontest-specific impairment that contributes to some of the general deficits observable in a diversity of neuropsychological tests when comparing patients with schizophrenia to nonpatient controls.

We have previously reported load dependent activity for the encoding phase of the SIRT task and a load independent activity for the retrieval phase. The current study confirms the previous finding and extends our previous work by showing that the load dependent activity during the encoding phase is present in individuals with schizophrenia but shifted to the left. We cannot exclude the possibility that differential strategies between groups may account for some of these differences. The absence of any significant differences between groups in the magnitude of activation during the load independent retrieval phase suggest that either retrieval is preserved or is less impaired in schizophrenia.

Our patient population consisted of stable medicated individuals living in the community with only mild to moderate symptom severity. Thus we cannot distinguish whether the observed decrease in efficiency at low cognitive load conditions is the result of the illness state or a medication effect. Regardless of whether the observed effect is secondary to medications, or represents residual primary deficits that are only partially responsive to medications, in the absence of a reasonable alternative to neuroleptic treatment, the finding of decreased efficiency at early information processes for even the simplist tasks are pertinent to our understanding of challenges that patients with schizophrenia face day to day.

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