

## Dorsolateral Prefrontal Cortex Dysfunction in Schizophrenia: Relationship to Both Working Memory and Long Term Memory

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### Introduction:

A growing literature suggests that patients with schizophrenia show cognitive deficits in at least two putatively different domains: working memory and long term memory. Deficits in working memory have typically been linked to an underlying disturbance in prefrontal cortex function, while deficits in long term memory (i.e., encoding and/or retrieval) have typically been associated with medial temporal/hippocampal deficits. However, among patients with schizophrenia, it is not yet clear that deficits in working memory and long term memory truly represent two distinct sets of cognitive deficits associated with different underlying neurobiological substrates. An alternative, potentially more parsimonious, hypothesis is that both working memory and long term memory deficits in schizophrenia reflect a dysfunction in the same underlying neurobiological mechanism: a disturbance in prefrontal cortex function. The current study tested this hypothesis by using fMRI to assess the patterns of cortical function and dysfunction associated with the performance of both working memory and long term memory tasks in the same patients with schizophrenia and matched control subjects, during the same scanning session.

### Methods:

Participants were 22 medicated patients with confirmed DSM-IV diagnoses of schizophrenia and 14 healthy controls. All subjects will be scanned while performing three tasks, each with two types of materials (verbal and non-verbal). The first task was a working memory (WM) task: the "2-Back" version of the "N-back" task. In this task, subjects saw a sequence of stimuli presented in the center of a computer screen, and were told to push the target button any time they saw a stimulus that was the same as the stimulus that they saw two trials back, and to push a non-target button otherwise. The second task was an the intentional encoding task in which subjects were presented with a series of stimuli and told to pay careful attention to each item because they would receive a memory test later. To equate for the motor responding required in the other two tasks, subjects were told to press two adjacent buttons as soon as the stimulus appears. The third task was be a yes/no recognition task. Subjects were be presented with a series of stimuli and told to press one button if the stimulus had been seen during either of the two previous tasks (WM or encoding) and another button if the stimulus is new. For the verbal tasks, the stimuli were be visual words and for the non-verbal tasks, the stimuli were non-nameable faces. Stimuli were separated into two lists, and the list used for the encoding versus the WM task were be counterbalanced across subjects.

Subjects perform each task in runs (6 total) comprised of 7 blocks, with 4 "task" blocks and 3 "fixation" blocks in alternating order. Task blocks will last 40 secs and fixation blocks will last 25 secs. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button box was used to record subject's behavioral performance. All scanning was performed on a 1.5T Siemens VISION with a standard head coil. Structural images were acquired using a high resolution (1.25 x 1 x 1 mm) sagittal 3-D MP-RAGE T1-weighted sequence. Functional images were acquired using an asymmetric spin-echo echo-planar sequence (TR=2400 ms, TE= 50 ms, flip = 90°). During each run 102 sets of 16 contiguous, 8 mm thick axial images were acquired parallel to the AC-PC plane (3.75x3.75 mm in-plane). The functional imaging data were movement corrected, co-registered, smoothed, and pooled across subjects. All analyses were performed using ANOVAs treating subjects as a random factor, with group (control, patient) as a between subject factor and condition (task, fixation), task (WM, encoding, recognition), and stimulus (word, face) as within subject factors.

### Results:

Analyses of the behavioral data indicated worse performance among patients with schizophrenia in both the WM and recognition task, with this effect reaching statistical significance for the recognition task ( $p < .01$ ). Both patients and controls demonstrated significant main effects of condition in a number of regions, including bilateral inferior frontal cortex and bilateral posterior parietal cortex. Activation in these regions did not interact with task, and were present in all three tasks. However, as predicted, we found a group x task interaction in dorsolateral prefrontal cortex, with patients showing significantly decreased activation in DLPFC in all three tasks. This finding is consistent with our hypothesis that Additional analyses will focus on examining the relationship between activation in DLPFC as well as control regions, during correct and incorrect trials in both the WM and long term memory tasks, in order to establish a more direct relationships between DLPFC dysfunction and both WM and long term memory performance.