Parametric Variation in Working Memory Demand in Patients With Schizophrenia: 
A Behavioral and Neuroimaging Pilot Study

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1. Objective
- A substantial literature has demonstrated deficits in working memory (WM) performance in patients with schizophrenia (Lee & Park, 2005), and WM is a major target for attempts to improve cognition in this patient group (Barch & Smith, 2008).
- Functional imaging studies of patients with schizophrenia performing WM tasks have produced contradictory findings (see Van Snellenberg et al., 2006, for review).

2. Self-Ordering Task

- On each trial, participants are presented with eight stimuli like those shown above.
- Participants are instructed to select each object exactly once, in any order.
- Thus, each trial is completed in eight steps. After each step, the spatial location of the objects is randomly rearranged.
- Participants are given ten (behavioral task) or seven (imaging task) seconds to complete each step, with a two-second delay between steps.
- If an error or no response is made, the program selects an object for the participant.
- In the fMRI study, participants also carried out a control task in which they simply had to select the object marked by an asterisk on each step.

3. Demographic Data (Both Experiments)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% Female</th>
<th>Age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>9</td>
<td>44.4%</td>
<td>29.7 (10.5)</td>
</tr>
<tr>
<td>Patients</td>
<td>10</td>
<td>20.0%</td>
<td>34.7 (12.4)</td>
</tr>
<tr>
<td>Imaging Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>7</td>
<td>28.6%</td>
<td>28.3 (1.8)</td>
</tr>
</tbody>
</table>

4. Results for Behavioral Experiment

- All groups performed significantly better than chance on steps 3 - 8 (all p < 0.05). Both control groups also performed significantly better than chance on step 2.

5. Methods for fMRI Experiment

- Whole-brain fMRI data was acquired on 7 subjects with a 3T Phillips scanner at the Program for Imaging and Cognitive Science center at the Neurological Institute of New York. Functional data were acquired with an EPI BOLD sequence using a TR of 2000 ms, TE of 20 ms, flip angle of 77°, field of view of 192 mm, 45 slices, and 1 mm isotropic voxels. High resolution structural scans were acquired using an MPRAE sequence using a field of view of 256 mm, 165 slices, and 1 mm isotropic voxels. Data underwent reconstruction, slice-timing correction, realignment, normalization to a template image (MNI), and smoothing (8 mm FWHM) in SPM 5.

- First-level models for each subject were analyzed using a canonical-HRF model in SPM 5, with seperate regressors for the control task and each step, as well as button clicks and incorrect responses. Spikes in the fMRI timecourses were modelled as nuisance regressors, along with the image global mean.

- A DLPFC ROI was determined from meta-analytic data (Wager & Smith, 2003). These data were re-analyzed using Multi-level Kernel Density Analysis (Wager et al., 2009). All voxels showing significant activation during ‘executive’ WM tasks that had absolute x coordinate values > 20, y coordinate values > 5, and z coordinate values > 15 (MNI coordinates) were used to make up the ROI. These coordinate ranges were selected to exclude medial (e.g. anterior cingulate), premotor, and anterior insula activations. Percent signal change in the ROI was calculated for each step, relative to the control task.

6. Results for fMRI Experiment

- A regression of signal change on step number revealed a significant quadratic parameter (p = 0.017; F(1,47) = 6.12). The linear parameter was not significant.

- No pairwise comparisons were significant, likely due to low power.

7. Discussion

- Both experiments suggest that the self-ordering task may be a useful tool for investigating WM dysfunction in schizophrenia.

- The behavioral data demonstrate that the self-ordering task elicits a range of levels of performance in both patients and controls, and substantial deficits in patients...

- The fMRI data suggest that DLPFC activation in control participants is non-monotonic, possibly due to poor performance or disengagement from the task with high WM demand.