An fMRI Investigation of Procedural Learning in Unaffected Siblings of Individuals with Schizophrenia

Neil D. Woodward M.A.
Phil Tibbo M.D.
Scot E. Purdon Ph.D.

International Congress on Schizophrenia Research
March 28-April 1
Colorado Springs
Introduction

• Schizophrenia (SCZ) is a highly heritable disorder

• SCZ characterized by abnormalities in cognition, cerebral structure, and neurophysiology

• Examination of unaffected family members may provide insight into the underlying pathophysiological mechanisms related to genetic vulnerability for SCZ

• Unaffected family members demonstrate deficits in:
  – Neuropsychological functioning: working memory, attention, verbal learning
  – Cerebral structure: temporal and frontal lobe volume/cortical thickness
Introduction

- Unaffected first-degree relatives demonstrate alterations in cerebral function that are similar to those observed in patients—few studies carried out

- Unaffected siblings demonstrate over-activation of PFC during WM when matched with controls for performance

- Unaffected siblings fail to activate caudate during anti-saccades despite performing normally on the task

Callicott et al., 2003; Raemaekers et al., in 2006
Introduction

- Procedural learning (PL) and schizophrenia
- Compared to other areas of cognitive functioning, PL has received less attention
- PL relies on distributed circuits involving frontal lobe, striatum, cerebellum; all of which have been implicated in schizophrenia
- Serial Reaction Time (SRT) task frequently used to assess PL (Nissen & Bullemer 1987)

During some blocks target appears pseudorandomly (R blocks) and during others target follows a repeating pattern (S blocks)- subjects are unaware of pattern

Reaction time advantage between S and R blocks evidence of PL
Introduction

• Reports of impaired PL on the SRT task in SCZ have been equivocal

• Inconsistent findings may relate to medication status of patients
  – Typical antipsychotics (APDs) are potent striatal D2 receptor antagonists and impair PL
  – Atypical APDs are less potent D2 antagonists and may spare PL

• In contrast to behavioral findings, imaging studies of PL on the SRT task have yielded fairly consistent findings
• Three prior imaging studies of PL on SRT task in SCZ produced consistent findings

Kumari et al., (2002): Patients did not demonstrate PL on typicals
Failed to activate PFC, striatum, cingulate, precuneus

Reiss et al., (2006): Patients demonstrated normal PL on atypical
Controls demonstrated greater activity in regions of PFC, striatum, and cingulate
Introduction

- Prior study by our group using identical methods described herein

Zedkova et al., (2005):
Patients demonstrated normal PL on atypicals
Controls demonstrated greater activity in PFC, angular gyrus, and striatum
Patients demonstrated greater activity in ant. cingulate, globus pallidus, and temporal lobe
Introduction

• Goal of current experiment to identify neural correlates of PL on the Serial Reaction Time SRT task in unaffected siblings of patients with SCZ

• Alterations in cerebral activation observed in patients during performance of SRT may reflect:
  – Deleterious effect of typical antipsychotics (APDs)
  – Atypical APD induced alteration
  – Illness specific alteration
  – Genetic liability for schizophrenia

• Deficits in cerebral activity observed in patients may relate to genetic liability if unaffected siblings also demonstrate alterations during performance of SRT
## Methods

### Subjects
- 15 controls with no family history of schizophrenia and 12 unaffected relatives of patients; all right handed
- Psychopathology ruled out using SCID

### Table 1: Sample characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Siblings</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>31.3 (11.2)</td>
<td>36.9 (13.3)</td>
<td>t(25)=1.19, p&lt;.248</td>
</tr>
<tr>
<td>Education</td>
<td>17.2 (2.6)</td>
<td>15.0 (2.3)</td>
<td>t(25)=2.37, p&lt;.027</td>
</tr>
<tr>
<td>Parental SES**</td>
<td>2.6 (0.5)</td>
<td>3.2 (0.8)</td>
<td>t(25)=2.18, p&lt;.040</td>
</tr>
<tr>
<td>Sex (Men/Women)</td>
<td>10/5</td>
<td>5/7</td>
<td>x²=1.68, p&lt;.195</td>
</tr>
<tr>
<td>SPQ Scores (n=8)</td>
<td>--</td>
<td>5.8 (2.9)</td>
<td>--</td>
</tr>
</tbody>
</table>

* Mean and (SD)

** Parental Socioeconomic Status (SES). Note: Lower scores equal higher status.
Methods

• **Serial Reaction Time Task**
  – Target appears in one of 4 locations: subject must respond to location as quickly as possible
  – On each trial stimulus appears for 800ms followed by 200ms inter-trial interval
  – 60 trials per block
  – During sequenced (S) blocks the stimulus follows a repeating 12 step pattern
  – During random blocks (R) stimulus location is pseudorandom
Methods

- **Experiment Protocol**
  - Pre-scan Training Session: 5 consecutive S blocks
  - Scanning: 2 imaging runs with 3 S and 3 R blocks interleaved within each run. 18 s fixation between blocks
  - Scanning parameters
    - MPRAGE structural scan for each subject (1x1x1mm voxel size)
    - Single shot EPI sequence for functional runs
      - 156 volumes, TR=3000, TE=50, 4mm thick slices
Methods

• **Functional Imaging Analysis**
  – Preprocessing steps:
    • Motion correction, spatial smoothing (8mm), linear and non-linear drift removal, slice scan timing correction
    • images warped to Talairach space
  – **Statistical Analysis:**
    • Within groups analysis: Fixed effects GLM S vs. R blocks
    • Masks created for neocortex and basal ganglia ROI
      – SPM thresholds: Cortex \( p < 0.005, 162 \text{ mm}^3 \)
      – Basal Ganglia \( p < 0.01 \), no cluster size constraint
    • Between groups analysis: Random effects GLM S vs. R blocks restricted to voxels that showed an effect of condition in the within groups analysis
      – SPM threshold: \( p < 0.05 \)
Methods

- Cortex and Basal Ganglia ROI masks

Cortex Based Analysis
- Structural MRI
- Segmented White Matter
- Cortex-based Mask

Sub-cortical ROI analysis
- Talairach Mask
- Segmented sub-cortical
- Sub-cortical Mask
Groups demonstrated equivalent RT improvement during pre-scan session.

During scanning: Main effect of condition (RT advantage 24ms; p<.001): RT advantage equivalent between groups (p>.160).

RT advantage unrelated to demographic variables (age, gender, education, SES).
Results

• Imaging Results: Within Group Activations

CTRLS

SIBS
Results

- **Imaging Results: Group Differences**

Differences between controls and unaffected siblings in procedural learning related activity on the SRT task. Controls demonstrated greater activity during procedural learning in (A) prefrontal regions corresponding to right superior and middle frontal gyri (BA 9 and 10), left middle frontal gyrus (BA 9), left angular gyrus (BA 39), and (B) right medial globus pallidus. Note, left/right orientation reversed on axial slice.
Conclusions

- Both siblings and controls demonstrated an RT advantage to S blocks during scanning - there were no differences between groups with respect to behavioral performance on the SRT task.

- Controls activated a broad network consisting of PFC, anterior cingulate, basal ganglia, and parietal cortex.

- Siblings demonstrated activity in some of these regions, but not to the same extent as controls - significant differences in brain activations remained after covarying for performance.
Conclusions

- **Similarities with previous study of same task in patients**
  - Patients and siblings demonstrated less activity than controls in regions of the PFC and parietal cortex. Magnitude and spatial extent of differences was generally less in siblings.
Summary

- In addition, both patients and controls demonstrated significantly greater activity during R blocks, relative to S blocks, in the PFC.
- This idiosyncratic pattern was less prevalent in siblings.
Conclusions

• **Summary:**
  - Some aspects of the abnormal neurophysiological responses observed in patients may relate to genetic vulnerability for schizophrenia
  - However, some aspects appear specific to the illness

• **Caveats:**
  - No check of explicit contributions to the task
  - Siblings and controls may have been at different stages of learning
  - Additional endophenotype criteria remain to be filled
    • E.g. Heritability
Acknowledgements

Lenka Zedkova M.D. University of Alberta
Ian Harding University of Alberta
Peter Seres University of Alberta

We would also like to thank all subjects for their participation in the study.