I will not discuss off label use and/or investigational use in my presentation.

I have no financial relationships to disclose:

Employee of:
Consultant for:
Stockholder in:
Research support from:
Honoraria from:
The Neural Basis of Response Selection in Schizophrenia: A Potential Endophenotype

Neil D. Woodward Ph.D.
Post-Doctoral Fellow
Psychiatric Neuroimaging Program
Vanderbilt University School of Medicine

2009 International Congress on Schizophrenia Research
March 28-April 1, 2009
San Diego
Genetics of Schizophrenia

• Heritability of schizophrenia is approximately 80%

• Schizophrenia is a complex polygenetic disorder

• Endophenotypes may aid search for liability genes
  – Quantifiable markers of illness closer to underlying neurobiology of a disorder
  – Genetically “simpler”

• Endophenotype criteria:
  – Heritable
  – State Independent
  – Present in unaffected relatives of patients

Gottesman & Gould, 2003
Response Selection in Schizophrenia

- Response Selection: The selection of an appropriate response to a specific stimulus
- Usually assessed with tasks like choice reaction time (CRT)
- CRT is heritable
- CRT impaired in schizophrenia: state independent
- CRT impaired in unaffected MZ twins of schizophrenia probands

Nuechterlein, 1977; Wright et al., 2001; Cannon et al., 2000
fMRI Investigation of Choice Reaction Time in Schizophrenia

• Aims:
  – Confirm that CRT is impaired in both first episode psychosis (FEP) and chronic patients
  – Examine the neural basis of CRT in schizophrenia
  – Determine if the neural changes are present in both FEP and chronic patients
  – Determine if the exact same changes in regional brain activity observed in patients are present in unaffected siblings of patients
Methods

• Subjects:
  – 32 controls: 18 Young Adult (YA) & 14 Middle Aged (MA)
  – 10 Chronic patients
  – 15 Medication free FEP patients (Neuroleptic naïve or lifetime Tx<2 weeks)
  – 12 Unaffected siblings of patients

• Chronic patients treated with atypical antipsychotics

• FEP and Chronic patients matched for age to YA and MA control groups, respectively

• No group differences in parental SES
Methods
Subject Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>YA Ctrl</th>
<th>MA Ctrl</th>
<th>FEP</th>
<th>Chronic</th>
<th>Unaffected Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18</td>
<td>14</td>
<td>15</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>14/4</td>
<td>9/5</td>
<td>12/3</td>
<td>8/2</td>
<td>5/7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22.5</td>
<td>3.3</td>
<td>32.4</td>
<td>10.9</td>
<td>22.5</td>
<td>3.3</td>
<td>33.5</td>
<td>7.5</td>
<td>36.9</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>14.9</td>
<td>1.7</td>
<td>17.4</td>
<td>2.4</td>
<td>13.4</td>
<td>2.5</td>
<td>13.4</td>
<td>2.2</td>
<td>15.0</td>
<td>2.3</td>
<td>A</td>
</tr>
<tr>
<td>Parental SES</td>
<td>2.6</td>
<td>0.5</td>
<td>2.6</td>
<td>0.5</td>
<td>2.5</td>
<td>0.7</td>
<td>3.0</td>
<td>0.5</td>
<td>3.2</td>
<td>0.8</td>
<td>B</td>
</tr>
<tr>
<td>Onset Age</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>22.5</td>
<td>3.2</td>
<td>21.7</td>
<td>6.3</td>
<td>--</td>
<td>--</td>
<td>C</td>
</tr>
<tr>
<td>Duration of Illness</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.4</td>
<td>0.3</td>
<td>11.5</td>
<td>6.4</td>
<td>--</td>
<td>--</td>
<td>D</td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>19</td>
<td>4.6</td>
<td>14.7</td>
<td>3.7</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>18.9</td>
<td>4</td>
<td>10.7</td>
<td>2.4</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>PANSS General</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>38.5</td>
<td>6.8</td>
<td>26.1</td>
<td>4.2</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>GAF</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>45.4</td>
<td>12.2</td>
<td>50.6</td>
<td>15.9</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

Parental SES unavailable for 2 subjects

Planned Contrasts:
A=Controls>Scz
B=YACtrls>FEP
C=MACtrls>Chronic Patients
D=MACtrls>Siblings
E=FEP>Chronic Patients

Abbreviations: FEP: First Episode Psychosis; GAF: Global Assessment of Function; MA: Middle Aged; PANSS: Positive and Negative Syndrome Scale; YA: Young Adult
Methods

Behavioral Task

- Target randomly appeared in one of four spatial locations on each trial
- Each location corresponded to a different button press (e.g. far left location corresponds to left middle finger)
- 60 trials per block interleaved with fixation periods
Methods

• All data collected on a 1.5T Siemens Sonata scanner

• RFX Block design analysis comparing CRT blocks to fixation

• SPMs created comparing patients to controls (p<.05, whole brain corrected)

• Activation extracted from significant clusters and planned contrasts carried out:
  – FEP vs. Young Adult controls (YA Ctrl)
  – Chronic vs. Middle Aged controls (MA Ctrl)
  – Siblings vs. MA Ctrl
Behavioral Results

Reaction Time

Main effect of group:
  p<.005

Pts vs. Ctrls:
  p<.005

FEP vs YA Ctrls:
  p<.05

Chronic SCZ vs MA Ctrls:
  p<.05

siblings vs MA Ctrls:
  p<.15

FEP=First Episode Psychosis; YA=Young Adult Controls;
MA=Middle Age Controls

Woodward et al., in press
Behavioral Results
Accuracy

Main effect of group: 
\[ p < .05 \]
Pts vs. Ctrls: 
\[ p < .005 \]
FEP vs YA Ctrls: 
\[ p < .05 \]
Chronic SCZ vs MA Ctrls: 
\[ p < .05 \]
Siblings vs MA Ctrls: 
\[ p < .05 \]

FEP=First Episode Psychosis; YA=Young Adult Controls; MA=Middle Age Controls

Woodward et al., in press
Imaging Results
Task Related Activations by Group

Young Adult Controls (n=18)

Middle Aged Controls (n=14)

First Episode Patients (n=15)

Chronic Patients (n=10)

Unaffected Siblings (n=12)

Woodward et al., in press
Imaging Results
Controls vs. Schizophrenia

- SCZ>CTRL:
  A: Right Middle Frontal Gyrus (BA 9)*
  B: Right SMA*
  C: Left Middle Frontal Gyrus (BA 9)**
  D: Bilateral Pre/Post Central Gyrus**

* p<.05 cluster level corrected
** p<.01 uncorrected cluster level

Woodward et al., in press
Imaging Results
Group Differences in Right BA 9

Main Effect of Group:
  p<.001
FEP vs. YA Ctrl:
  p<.05
Chronic SCZ vs. MA Ctrl:
  p<.005
Siblings vs. MA Ctrl:
  p<.05

FEP=First Episode Psychosis
YA=Young Adult Controls
MA=Middle Age Controls

Woodward et al., in press
Imaging Results
Group Differences in Right SMA

Main Effect of Group:  
p < .001
FEP vs. YA Ctrl:  
p < .05
Chronic SCZ vs. MA Ctrl:  
p < .005
Siblings vs. MA Ctrl:  
p < .35

FEP=First Episode Psychosis
YA=Young Adult Controls
SCZ=Schizophrenia Controls
MA=Middle Age Controls

Woodward et al., in press
Functional Connectivity Analysis

Individual Time Courses within Seed ROI

Seed ROI: Talairach: x=38, y=36, z=33
Region that showed greater activity in patients and siblings compared to controls

Random FX GLM: ROI Time Course Predictor

Connectivity Map
Imaging Results
Function Connectivity Differences Between Schizophrenia and Controls

- Areas in **RED**: Controls demonstrated greater positive correlation between seed region and PFC and parietal lobe (BA 40) - shown in red colors

- Areas in **BLUE**: Controls demonstrated greater inverse correlation between seed region and Right Inferior frontal gyrus and left medial frontal lobe - Blue colors

- Patients did not demonstrate greater correlations with seed region in any brain region compared to controls

Woodward et al., in press
Imaging Results
Functional Connectivity Differences Between Groups

Woodward et al., in press
Imaging Results
Correlation Between Connectivity and Task Performance

Magnitude of connectivity between right DLPFC seed region and right BA 40

Patients/Siblings: $r=-.43$, $p<.01$
Controls: $r=.00$, $p<.99$

Difference between groups was significant: $t(64)=2.06$, $p<.05$

Woodward et al., in press
Summary

- CRT impairment in patients is state independent; impaired CRT also observed in unaffected siblings

- Abnormal dIPFC BOLD response during CRT may relate, in part, to genetic vulnerability
  - State independent
  - Present in unaffected relatives of patients

- Function of a right fronto-parietal network may be different for patients and unaffected siblings

- CRT is an ideal paradigm to use for investigating the neural basis of response selection deficits in patients and unaffected siblings

- Genes affecting PFC activity and connectivity within a fronto-parietal network may relate to genetic susceptibility for schizophrenia
Limitations

• “Loose” imaging contrast: CRT compared to fixation
  – Isolation of specific processes related to CRT?

• Replication using event-related fMRI

• Sample sizes
Acknowledgements

University of Alberta

Scot E. Purdon, Ph.D
Phil Tibbo, M.D.
Barb Waldie, M.A.
Peter Seres, M.S.
Ian Harding
Lenka Zedkova, M.D.

Vanderbilt

Baxter Rogers, Ph.D.

Funding Support

Alberta Heritage Foundation for Medical Research
Canadian Institute for Health Research

We are grateful to the subjects who participated in this study