Future Directions in Cognitive Impairment Associated with Schizophrenia: Social Cognition

Michael F. Green, PhD
- Department of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine at UCLA
- UCLA Semel Institute
- VA Desert Pacific Mental Illness, Research, Education and Clinical Center (MIRECC)

ISCTM 2014
Disclosures for Michael F. Green

Consultant
AbbVie, DSP, Forum, Mnemosyne (scientific board), Roche

Research Support
Amgen

Officer in non-profit
MATRICS Assessment, Inc. – but receive no financial compensation
Outline

• Separability of social and non-social cognition
• Relationship to functional outcome
• Adapting measures from social neuroscience for schizophrenia clinical trials
Social Cognition Research in Schizophrenia – At the moment

- Emotion perception
- Emotion understanding
- Emotion regulation

- Emotional empathy
- Cognitive empathy
- Empathic responding
Evidence for the Distinction

• Is social intelligence just “general intelligence applied to social situations”? (David Wechsler).

• Most social processing involves brain regions distinct from non-social processing.

• Some regions are a “neural see-saw” with reciprocal activation with non-social processing regions (e.g., default mode, mentalizing).

• In MATRICS we did not appreciate distinction between social and non-social cognition. (can influence the type of composite used)
<table>
<thead>
<tr>
<th>Study &amp; year</th>
<th>Patients</th>
<th>Analysis</th>
<th>Support?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sergi, et al. 2007, Sz Res</td>
<td>100 Sz and Sz-Aff</td>
<td>Structural equation modeling</td>
<td>Yes</td>
</tr>
<tr>
<td>Allen et al. 2007 Sz Res</td>
<td>169 Sz</td>
<td>Confirmatory Factor Analysis (CFA)</td>
<td>Yes</td>
</tr>
<tr>
<td>van Hooren et al. 2008, Sz Res</td>
<td>44 psychotic dx; 47 familial risk; 41 psychom. risk</td>
<td>Exploratory (EFA) groups separately and together</td>
<td>Yes</td>
</tr>
<tr>
<td>Williams et al. 2008, Sz Res</td>
<td>56 first episode Sz patients</td>
<td>Exploratory (PCA)</td>
<td>Yes</td>
</tr>
<tr>
<td>Bell et al. 2009, Sz Bulletin</td>
<td>151 Sz and Sz-Aff</td>
<td>CFA</td>
<td>Yes</td>
</tr>
<tr>
<td>Hoe et al. 2012, Psych Medicine</td>
<td>130 Sz at BL, 105 at 1 yr follow up</td>
<td>CFA</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Social cognition and community functioning in schizophrenia meta-analysis of 52 studies; 2692 subjects

Estimated average correlation (and confidence interval) by social cognitive domain:
• Mentalizing / Theory of Mind = .48 (.32 - .61)
• Social perception = .41 (.14 - .63)
• Emotion perception/processing = .31 (.21 - .40)

Social cognition explained relatively more variance in community outcome (16%) than non-social neurocognition (6%)

Fett et al. Neuroscience and biobehavioral reviews. 2011
Social cognition as a mediator for functional outcome

- At least 15 separate studies supported social cognition mediation between neurocognition or perception and functional outcome
- Average of 25% variance in functional outcome explained in the mediation model

### Oxytocin (nasal spray) in Schizophrenia

At least 6 studies of oxytocin effects on social cognition performance in schizophrenia.
- Results are inconsistent / a couple studies are encouraging.

<table>
<thead>
<tr>
<th>OT as augmentation for social cognitive skills training</th>
<th>Social cog results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al. 2014</td>
<td>27 pts, parallel group design: 40 IU, 30 min before social cog skills training groups.</td>
</tr>
<tr>
<td>Cacciotti-Saija et al. in press</td>
<td>52 pts with early psychosis, parallel group design: 24 IU BID for 6 weeks</td>
</tr>
</tbody>
</table>

Many unknowns regarding OT studies:
- Target engagement
- Effective dose
- Single vs repeated administrations
- Outcome measures
Social Cognition and Functioning (NIMH SCAF Study) in Schizophrenia

Rationale

• Social cognition is an core aspect of schizophrenia and has strong connections to functional outcome
• It is becoming a target for interventions (both pharmacological and training)
• There is a paucity of reliable, validated social cognitive endpoints for clinical trials
• This area is not well informed by the impressive developments in social neuroscience.
• Similar to the rationale for CNTRICS
**Aim:** To adapt and evaluate measures from social neuroscience for use in schizophrenia clinical trials
- Los Angeles and North Carolina
- 173 stable schizophrenia outpatients 88 controls; Patients retested at 4-weeks
- Data collection recently completed.

**For social cognitive domains:**
1. Performance metrics for use in clinical trials
2. Relevant to social functioning in schizophrenia.

**For social cognitive paradigms:**
1. Can assess a large range of difficulty
2. Tolerable length of time (e.g. 30 min or less)
3. No complex or time consuming scoring
4. Equipment is practical for a clinical trial (no EEG/fMRI)
5. No excessive demands on reading / verbal intelligence
Lower-level Social Cognition: Social / Emotion Cue Identification
Higher level Social Cog: Mentalizing
SCAF Selected Domains / Paradigms

Domain 1: Nonverbal social cues:
1. Basic Biological Motion
2. Emotion in Biological Motion

Domain 2: High-level inferences:
1. Self-Referential Memory
2. Empathic Accuracy
Biological Motion

Do you see human motion?

100% coherent

70% coherent
Emotion in Biological Motion

What emotion do you see:
- Fear
- Anger
- Happiness
- Sadness
- Neutral
Emotion in Biological Motion

What emotion do you see:
- Fear
- Anger
- Happiness
- Sadness
- Neutral
Memory sensitivity (d’) for each group (HC = healthy controls; SZP = schizophrenia patients) for Structural, Others-general, and Self-referential.

P-O Harvey et al. *Schizophrenia Res.* 2011
Empathic Accuracy
How to Create an Ecologically Valid Assessment

Ratings from a target

Ratings from a subject

Empathic Accuracy Correlation (r)
SCAF Measure Evaluation

For each measure we examined:
- patient – control group differences
- test-retest reliability
- utility as a repeated measure (e.g., practice effects, ceiling or floor effects)
- tolerability (patients’ perspective), admin. time

Selected a representative dependent measure
- Biological Motion (85%)
- Emotion in Biological Motion (accuracy)
- Self-referential memory (self condition)
- Empathic Accuracy (9 clip version)
SCAF Study Results
Group Differences (d’)

Kern et al. Schizophrenia Bull. 2013
SCAF Study Results
Test-retest reliability (r)

Kern et al. Schizophrenia Bull. 2013
Within-group effect sizes calculated by dividing mean difference score by its SD.
### SCAF Study Results
#### Practicality and Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Tolerability</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio Motion</td>
<td>5.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Emotion Bio</td>
<td>5.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Self-referential</td>
<td>5.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Empathic accuracy (6-9 clips)</td>
<td>5.4</td>
<td>20-27*</td>
</tr>
</tbody>
</table>

Tolerability on 1-7 scale where 7 = best; 4 = midpoint

* Estimate -- we administered a beta version with more clips. We estimate 20 min for 6 clips and 27 min for 9 clips.
## SCAF Study Results Summary

<table>
<thead>
<tr>
<th>Group Diff.</th>
<th>Test-retest</th>
<th>Utility as repeated measure</th>
<th>Tolerability</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Motion</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Emotion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bio Mot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empathic accuracy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thanks and Acknowledgements

Los Angeles:
• William Horan, PhD
• Junghee Lee, PhD
• Philippe Harvey, PhD
• Robert Kern, PhD
• Steven Marder, MD
• Mike Davis, MD, PhD

Collaborators:
• Kevin Ochsner, PhD
• Jamil Zaki, PhD
• David Penn, PhD

greenlab.npih.ucla.edu