Neurocircuitry of Impulsivity in Psychiatric Disorders

Steven G. Potkin, MD
UC Irvine
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Key Question – What does neuroimaging have to offer?

- Do cross diagnosis symptoms suggest a common underlying mechanism that can be expressed in neurocircuitry?
  - Are brain circuitry dysfunctions underlying cross-diagnostic symptoms are similar?
  - If so, will medication induced circuitry changes alter symptoms?
  - How might such finding influence regulators?
  - Could neuroimaging be a primary outcome measure in a registration study?
Case for Cross Diagnosis
Causes of Symptoms

- Schizophrenia and Bipolar Share Many Risk Genes (e.g. CACNA1C)
- Antipsychotics indicated for bipolar & SCZ
- Antianxiety and insomnia drugs indicated and used in multiple disorders
- Previous indications supported this use but recently are mostly indication specific
Definitions Matter - Impulsivity

**Impulsive behavior**
“actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes” (Reference 1)

- **Reflection impulsivity**
  - the tendency to make a decision without gathering available/足够的 information
  - *IST*

- **Impulsive action**
  - a failure of motor inhibition

- **Impulsive choice**
  - the tendency to choose small immediate or likely rewards versus large delayed or unlikely ones

- **Risk behavior**
  - to place oneself in an unsafe manner that can lead to dangerous consequences
  - *Gambling task*

- **A deficit in waiting**
  - 5-CSRTT/3-CSRTT
  - CPT
  - Go/NoGo task
  - Stroop task

- **A deficit in stopping**
  - SST
  - Go/NoGo task
  - Stroop task

- **Delay discounting**
  - DDT
  - DGT

- **Probability discounting**
  - PDT

Ohmura 2012
Impulsivity is very common behavioral characteristic

- Impulsivity underlies or contributes to suicidality, substance abuse, incarceration, and some violent behaviors.

- Impulsivity increased in substance abuse, schizophrenia, and to a greater extent in dual dx (Zhornitsky et al. Psych Research, 2012).

- Performance deficits related to impulsivity are present (e.g. on the stop-signal task) (Nolan et al. Psych Research, 2011).

- Dopamine release in the ventral striatum and medial prefrontal cortex (mPFC) are believed to play a key role in impulsivity (Ohmura et al. J Pharmacol Sci 2012).
Impulsivity Go/NoGo Paradigm

<table>
<thead>
<tr>
<th></th>
<th>Press</th>
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- NoGo vs Go (inhibition) contrast collapsed across emotion
- Target emotion definition order pseudo-randomized, 2 Happy Go, 2 Neutral Go
- 4 runs of 3min8s
  - 36 Target stimuli
  - 13 Non-target stimuli
  - Stimuli presented for 500ms with a 2-14.5s ISI (fixation cross)
# Impulsivity Go/NoGo Paradigm

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Happy
Impulsivity Go/NoGo Paradigm

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Inhibition (NoGo > Go) task

Fifteen Year Longitudinal follow-up of the Multimodal Treatment Study of ADHD (MTA) – model of impulsivity

BOLD Activation of right ventrolateral PFC related to impulsivity on NoGo task.

Rasmussen et al., in preparation
Cortico-striato-pallido-thalamic loop and motor output (Glutamate-GABA effects on DA)

Pairs of opposing channels within each CSPT loop

Don’t do it!
Do it!

D₁
D₂

Fallon & Potkin

Final common path,
i.e. motor/endocrine/autonomic
The Cortico-Striatal-Thalamo-Cortical loops serve distinct functions but result in a coordinated behavioral output

- The sensorimotor loop is formed by a direct “go” and indirect “no go” pathways
- The others loops, regulating goal-directed behavior in all its aspect (motivational, emotional and cognitive) are organized in the same way

Appropriate behavior requires combining info about motivation and reward with a strategy and action plan to obtain goals; e.g. “to win a card game”
The Cortico-Striatal-Thalamo-Cortical loop balance

*The direct D1 “go” and the indirect D2 “no go” pathways*
Stop-signal paradigm consists of Go- and Stop-signal trials

On Go trials, the subject has 1 s to make a button press in response to the stimulus.
On a Stop trial, a tone is played after the arrow stimulus.
DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

<table>
<thead>
<tr>
<th></th>
<th>Rarely/Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Almost Always/Always</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>I plan tasks carefully.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I do things without thinking.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I make-up my mind quickly.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I am happy-go-lucky.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I don’t “pay attention.”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I have “racing” thoughts.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I plan trips well ahead of time.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I am self controlled.</td>
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(30 items)

Schizophrenia subjects have high levels of impulsivity and more performance impulsivity deficits.

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<th>Controls</th>
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<tr>
<td>BIS TOTAL</td>
<td>61.76 (7.08)</td>
<td>56.00 (9.95)</td>
<td>0.003</td>
</tr>
<tr>
<td>Go RT (ms)</td>
<td>577.26 (82.75)</td>
<td>577.59 (74.16)</td>
<td>ns</td>
</tr>
<tr>
<td>SSRT (ms)</td>
<td>300.32 (50.79)</td>
<td>249.77 (44.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Go Accuracy</td>
<td>0.95 (0.03)</td>
<td>0.98 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stop Accuracy</td>
<td>0.56 (0.11)</td>
<td>0.64 (.07)</td>
<td>&lt;0.001</td>
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</table>

Schizophrenia subjects self-reported high levels of impulsivity and performance impulsivity deficits (e.g. on the stop-signal task) consistent with specific impairments in response inhibition. (Nolan et al. Psychiatry Res. 2011)
Patients, but not HC, positive correlation with BIS-11 and a unique fMRI activation in right ventrolateral prefrontal cortex (VLPFC), a key node of the brain network subserving response inhibition (Kaladjian et al. Psychol Med 2011).
Internet gambling disorder subjects show behavioral impulse inhibition on Go /NoGo task but no right VLPFC inefficacy (Ko et al. Eur Arch Psych Clin Neurosci 2014).
What is the Appropriate Imaging Paradigm? \( \gamma \) Oscillations

Processing of higher order cognitive functions including working memory

Figure 4  Topographic illustration of inhibition of \( \gamma \) oscillations in the DLPFC. Topographic plots illustrate the inhibition of \( \gamma \) oscillations (CI\( \gamma \)) following the application of LiCl\(_{100}\) to the left DLPFC averaged across 14 healthy subjects (HLT), 14 patients with bipolar disorder (BD) and 14 patients with schizophrenia (SCZ). Inhibition is obtained through Equation (1) (see Materials and methods section), and the hot colours indicated the area of maximum inhibition. These plots suggest that patients with schizophrenia have low CI\( \gamma \) in the DLPFC compared to patients with bipolar disorder and healthy subjects. Topographic head plots were obtained by EEGLAB toolbox (Delorme and Makeig, 2004).
What is the Appropriate Imaging Paradigm?

Preattentive info processing related to impaired outcome; NMDA mediated glutamate receptors

Jahshan et al 2012

Sensitivity, specificity, multi-center suitability, ease of measurement?
Do the results extend to unstudied disorders?
Hariri Face and Threat Matching

Amygdala activation during anger or fear face matching
Same trend across diagnosis but significant for BD

Total sample (n=250)  BD sample (n=66)

Tesli et al. PloS One 2013
Would L-type Ca\(^{++}\) channel blocker attenuate amygdala activation and improve symptoms cross diagnoses?

Tesli et al. PloS One 2013
Dot Pattern Expectancy Task
Pleiotropic: Risk variants have different effects on behavioral performance in Sz and BP in memory and CNTRACS context processing

Zhang et al. Neuropsychopharm 2012
Is impulsivity a legitimate pharmacological target?

Impulsivity was limited to poor impulse inhibition measured by motor performance.

We did not consider other aspects of impulsivity such as delayed gratification, risk taking, making decisions with inadequate information, as well as attentional problems.
Questions

- Is impulsivity a legitimate pharmacological target?
- Across diagnoses?
- Could it be approved by FDA?
- Usefulness of imaging as biomarker?
- Mediating pathophysiological marker?
- Neuroimaging as primary outcome measure?