Methamphetamine’s Effect on the Brain and Behavior

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Outline

1. Review of brain and behavioral dysfunction in methamphetamine
   1. Neural substrates
      1. Anterior cingulate
      2. Orbitofrontal cortex
      3. Insula
   2. Behaviors
      1. Inhibition
      2. Reward processing
      3. Decision-making
2. Prediction of relapse in methamphetamine dependent individuals

What Does Dopamine Do?

- Signal for:
  - Stimuli that predict reward
  - Probability of reward
  - Reward magnitude (expected - observed)
Anterior Cingulate

- Action–outcome associations:
  - Guiding decisions about whether the expected value of a reward means that it is worth acting (Rushworth, 2004)
- Monitoring and evaluating the outcomes of actions
  - Conflict
  - Errors (Botvinick, 2004)

Orbitofrontal Cortex

- Represents the affective value of reinforcers as they relate to learning and state-dependency (Kringelbach 2005)
- During choice OFC neurons encode the value of offered and chosen options. (Padoa-Schioppa & Assad, 2006)

Insular Cortex

- Interoception: the sense of the physiological condition of the entire body (Craig 2002)
- Interoceptive state processing in the anterior insula is relayed to the anterior cingulate cortex, the OFC, and striatum

Inhibition

- Inhibition is the process by which the execution of a thought, action, or emotion is overridden or reversed.
- Stop-signal reaction time (SSRT) - latency to inhibit an initiated motor response: longer for MA abusers than for control groups (Monterosso et al 2005).
- MA show greater interference on computerized single-trial version of the Stroop test despite intact priming (Salo et al 2002).
- MA individuals make more errors on trials that required inhibition of distracting information (Salo et al 2005).
Reward Processing

- Amphetamine administration activates:
  - Medial orbitofrontal cortex.
  - Anterior cingulate cortex.
  - And the ventral striatum (Vollm et al 2004a; Vollm et al 2004b).
- MA users show dopamine transporter reduction in the caudate/putamen and nucleus accumbens (Sekine et al 2001).

Decision-making - Overview

- Decision-making:
  - The process of making choices or reaching conclusions.
- Comprises temporally and functionally distinct processes:
  - (1) the assessment and formation of preferences among possible options
  - (2) the selection and execution of an action
  - (3) the experience or evaluation of an outcome

Decision Making Factors

- Decision-making:
  - Person has to select among several options
  - Each option can be associated with positive or negative outcomes, which may be uncertain.
  - Key elements of decision situations:
    - Probability of an outcome associated with an option
    - Positive versus negative consequence
    - Magnitude of the consequence
    - The time delay between the action selection and the consequence

Decision-making & Methamphetamine

- Amphetamine abusers show
  - Suboptimal decisions (correlated with years of abuse)
  - Deliberated for significantly longer before making their choices (Rogers et al 1999)
- MA subjects are more influenced by the immediately preceding outcome (Paulus et al 2002)
- Decision-making by MA individuals is characterized by a rigid stimulus-response relationship:
  - Shift from processing "success" toward processing the degree of stimulus "predictability." (Paulus et al 2003)
Relapse

- An important public health problem
- Predicting relapse may help to deliver targeted interventions to those individuals at risk
- Current methods to predict relapse have
  - Low specificity (many false positives)
  - Moderate sensitivity (frequent false negatives)

Study Goals

- Neurobiology of decision-making dysfunctions in stimulant dependent subjects.
- Can functional magnetic resonance imaging be used as a tool to predict relapse?

Subjects

- 46 methamphetamine dependent subjects sober for a median of 25 days
- 6 lost to follow up
- 40 subjects followed up a median of 370 days
- NO RELAPSE: 22
- RELAPSE: 18
- 279 days median sober time

Functional Magnetic Resonance Imaging

- Magnetic resonance imaging
- Behavioral task
- Changes in blood oxygenation
- Identify brain areas involved in task-related processing
Assessment Protocol

Baseline Assessment:
- Diagnostic: SCID
- Symptom: BPRS / HDRS / YMRS
- Neuropsychology: DKEFS
- Decision-making: Two-choice Prediction task, Iowa Gambling Task

fMRI:
- Block Design: Two-choice Prediction Task versus Two-choice Response Task

Subjects’ Socio-demographics

<table>
<thead>
<tr>
<th></th>
<th>Non-relapsers</th>
<th>Relapsers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.3 ± 8.8</td>
<td>41.9 ± 9.0</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Never Married</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Education (years)</td>
<td>12.9 ± 1.2</td>
<td>13.5 ± 1.0</td>
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Subjects’ Use Characteristics

<table>
<thead>
<tr>
<th>Use Characteristics</th>
<th>Non-relapsers</th>
<th>Relapsers</th>
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</thead>
<tbody>
<tr>
<td>Years of use</td>
<td>14.9 ± 10.0</td>
<td>17.3 ± 8.0</td>
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<tr>
<td>Sober days before imaging</td>
<td>27.4 ± 8.3</td>
<td>27.8 ± 11.0</td>
</tr>
<tr>
<td>Current Alcohol / Marijuana abuse</td>
<td>5 ± 7</td>
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<tr>
<td>Follow up characteristics</td>
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<tr>
<td>Follow up duration [days]</td>
<td>437 ± 165</td>
<td>440 ± 304</td>
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<tr>
<td>Marijuana use during follow up [n]</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Cocaine use during follow up [n]</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Symptom Ratings</td>
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<tr>
<td>HDRS 21</td>
<td>7.1 ± 7.8</td>
<td>10.2 ± 7.6</td>
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<tr>
<td>BPRS</td>
<td>27.3 ± 7.9</td>
<td>30.4 ± 6.8</td>
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<tr>
<td>YMRS</td>
<td>1.7 ± 2.7</td>
<td>5.4 ± 6.9</td>
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Brain Activation: Choice Versus Response Task

Brain Activation Graph

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Brain Activation and Relapse

Prediction Accuracy

<table>
<thead>
<tr>
<th>Region</th>
<th>Non-Relapsers</th>
<th>Relapsers</th>
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</thead>
<tbody>
<tr>
<td>R Insula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Middle Frontal Gyrus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Middle Frontal Gyrus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Middle Temporal Gyrus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Inferior Parietal Lobule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Cingulate Gyrus</td>
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% Signal Difference

Summary & Conclusions

• Functional magnetic resonance imaging results predict relapse.

• Relapse = less activation in structures that are critical for decision-making

• Poor decision-making: “setting the stage” for relapse

Prediction Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Relapse</th>
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<tbody>
<tr>
<td>YES</td>
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<tr>
<td>NO</td>
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N (40 after a median of 370 days)

Correctly Predicted by Imaging

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<tr>
<th></th>
<th>Sensitivity 94.4%</th>
<th>Specificity 86.4%</th>
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<tbody>
<tr>
<td>17</td>
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<tr>
<td>20</td>
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Thanks

• Support from:

See also: [http://koso.ucsd.edu/~martin/index.html](http://koso.ucsd.edu/~martin/index.html)