Cognitive deficits in methamphetamine addiction

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OVERVIEW

✧ Methamphetamine (meth) addiction & cognition
✧ Meth self-administration model of addiction
✧ Meth-induced memory and attentional deficits
✧ Future directions and applications
Research center to bridge the gap between basic preclinical science and clinical research

Focus is on the neurobiology and treatment of meth addiction

- Clinical laboratory studies of cue reactivity, attention and cognition
- Medications assessment
- Brain neuroimaging center
- Basic neuroscience
  - Animal models of addiction and relapse
  - Attentional and cognitive deficits
  - Neuronal alterations in corticostriatal pathways
Methamphetamine Effects

Short term
- Wakefulness
- Physical activity
- Increase attention
- Decrease appetite
- Cardiovascular
- Hyperthermia

Long term
- Addiction
- Anxiety
- Confusion
- Insomnia
- Mood disturbances
- Violent behavior
- Psychosis
Cognitive and attentional processes

- Meth addicts show performance deficits in working memory, decision making, and attention.

- All of these functions rely on intact performance of the prefrontal cortex and its connections to the striatum and limbic structures.

How can we systematically determine the impact of chronic meth and the resulting changes in neurobiology that underlie enduring motivational and cognitive dysfunctions?
Self-administration (SA) model of meth addiction in rats

Lever press = Meth i.v. infusion and cues

A) Can we approximate meth addiction and relapse in this model?
B) Does chronic meth use produce cognitive deficits in this model?
Escalated self-administration of intravenous meth over time

![Graph showing meth intake over time with controls receiving daily saline infusions in a yoked manner.](image)

*Note:* Controls receive daily saline infusions in a yoked manner.
Chronic Meth SA reduces dopamine transporter (DAT) levels

ShA = 1 hr/day
LgA = 6 hr/day

(Schwendt et al., JPET, 2009)
Object recognition memory

- Recognition memory requires judgments of the previous occurrence of stimuli made on the basis of:
  A) the relative familiarity of individual objects (novel object recognition), or
  B) by integrating information concerning objects and location (object-in-place recognition memory)

- Novel object recognition memory (dependent upon perirhinal cortex) is impaired after noncontingent (Belcher et al. 2005) and contingent (Rogers et al. 2008) meth administration.

- Object-in-place recognition memory (what and where) is dependent upon a network of medial prefrontal cortex, perirhinal cortex, and hippocampus (Barker et al. 2007).

- Will chronic meth SA affect recognition memory?
Novel object recognition

A) Does chronic meth SA reduce novel object performance?
B) If so, can the deficit be reversed?
Chronic meth SA impairs novel object recognition.

(Reichel et al., Neuropsychopharm, 2011)
Positive allosteric modulation of mGluR5 receptors reverses chronic meth-induced impairment of novel object recognition.

(Reichel et al., Neuropsychopharm, 2011)
Relationship between meth intake during chronic meth SA and mGluR expression in the hippocampus, perirhinal cortex, and prefrontal cortex for mGluR 2/3 (left) and mGluR5 (right).

(Reichel et al., Neuropsychopharm, 2011)
Attentional Set-Shift Task (ASST)

Human / Primate

Wisconsin Card Sort Task: Match the cards (Color, shape, number)

Rodent

Attentional Set-Shift Task (Odor and digging media)

Press 1-4 to sort card
Baseline ASST performance - no differences between groups

Chronic meth SA selectively disrupts ED set shift task performance

(Parsegian et al., Biological Psychiatry, 2011)
Age matched rats with excitotoxic lesions of the medial prefrontal cortex (mPFC) show a specific deficit during the ED shift.

Close similarity of chronic meth SA and mPFC lesion in ED deficit

(Parsegian et al., *Biological Psychiatry*, 2011)
Summary

- A model of prolonged meth self-administration with escalated intake and meth-seeking leads to:
  - deficits in object recognition memory.
  - deficits in extradimensional set-shifting during attentional processing.

- These deficits can be linked to meth-induced neuroadaptations in medial prefrontal and perirhinal cortex function.

- Cognitive enhancers may work to reverse meth-induced cognitive deficits and reduce craving.
Future applicability

- Cognitive assessments for recognition memory and attentional set-shifting can be readily applied across disease models.

- New methods currently being developed in our group are refining cognitive assessment procedures (better automation).

- Endothelin-1 is a vasoconstrictor that produces a local dose dependent ischemic lesion, leading to localized stroke within specific brain circuits. This approach offers the ability to direct focal ischemia into deep and superficial brain compartments in an animal model of stroke in cognitive circuits.