Opioid Withdraw and Cognitive Impairment from Stimulant Use Disorder

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- METHAMPHETAMINE NEUROTOXICITY
- METHAMPHETAMINE WITHDRAWAL
- NEUROCOGNITIVE EFFECTS OF METHAMPHETAMINE

- We are often taught there is no major withdrawal from stimulants and therefore hospitalization is not required
- It is not as intense as withdrawal from opioids, alcohol or benzos
- The main effects of methamphetamine are dopamine release related and the main problem with methamphetamine is excessive stimulation of the reward pathway
- We are given the impression that after a week of stopping methamphetamine the person returns to “normal” functional state

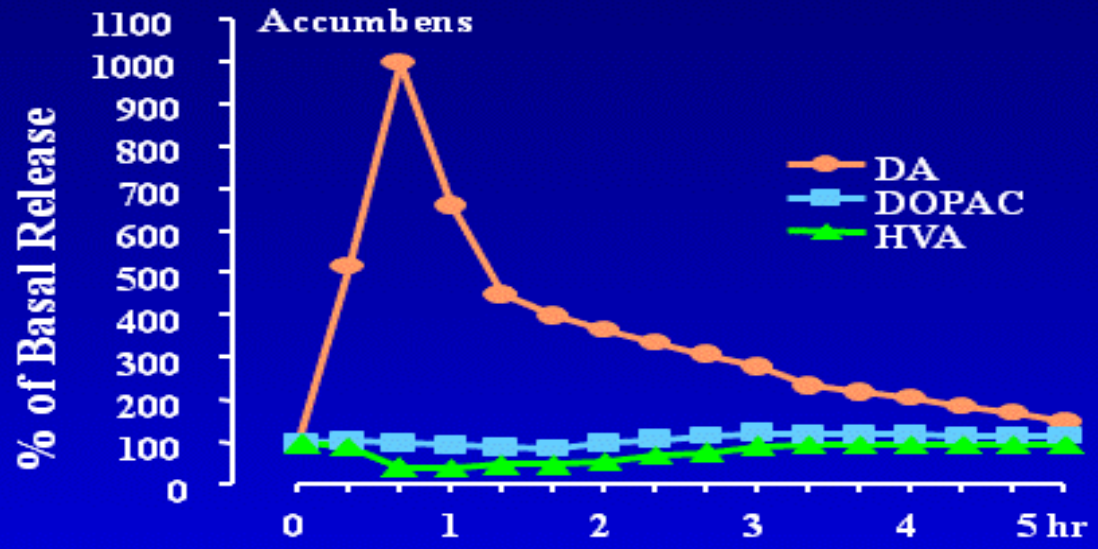
Reward Pathway (Nucleus acumbens/ventral striatum)

Cocaine
- blocks the reuptake of dopamine

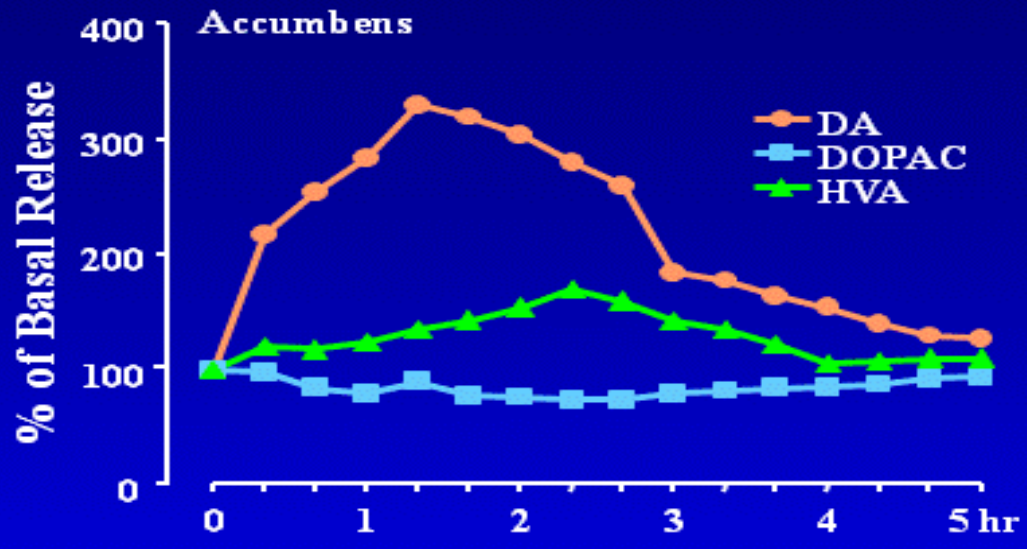
Methamphetamine
- blocks the reuptake of dopamine and
- binds to presynaptic DA neuron membranes and cause release
- binds to the presynaptic DA vesicles (VMAT)and causes release DA
- binds to the presynaptic DAT and causes release of DA
- blocks the breakdown of dopamine via the MAO pathway

Effects of Drugs on Dopamine Release

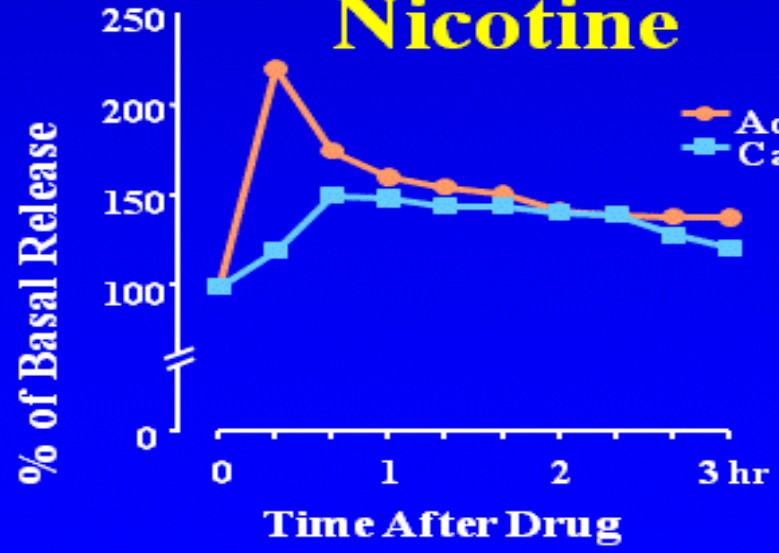
Amphetamine



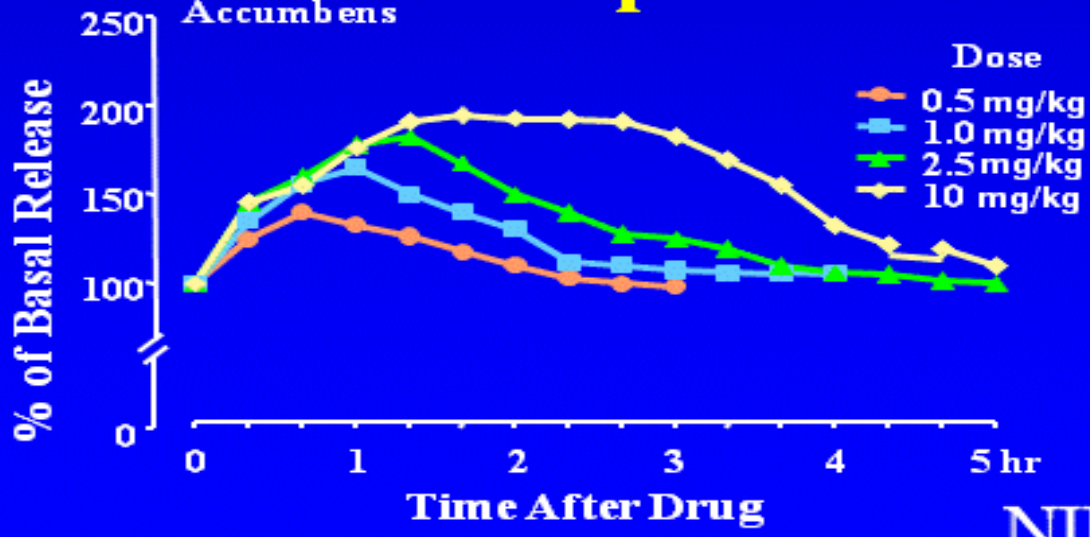
Cocaine



Nicotine



Morphine



Di Chiara and Imperato, PNAS, 1988

NIDA

BUT THERE IS MUCH MORE

- Dopamine is found in throughout the brain therefore the effects are not limited to the reward pathway
- Evidence of reduction of dopamine transporters and dopamine receptors:

-Orbital Frontal Cortex (cognitive process of decision making)
-Anterior Prefrontal Cortex (abstract Complex problem-solving and planning)
-Dorsolateral Prefrontal Cortex (execution, order and timing of sequential acts toward a goal)
-Dorsal Striatum (planning, execution, and automatization of motor behavior.
-Amygdala (controls emotions/positive and negative)

DOPAMINE IS NOT THE ONLY MONOAMINE NEUROTRANSMITTER

- Loss of serotonin transporter (SERT) resulting in serotonin release and eventual depletion from the presynaptic neurons
- ? Excessive 5HT during acute use
- Norepinephrine reuptake (hyperthermia, tachycardia, dilated pupils)

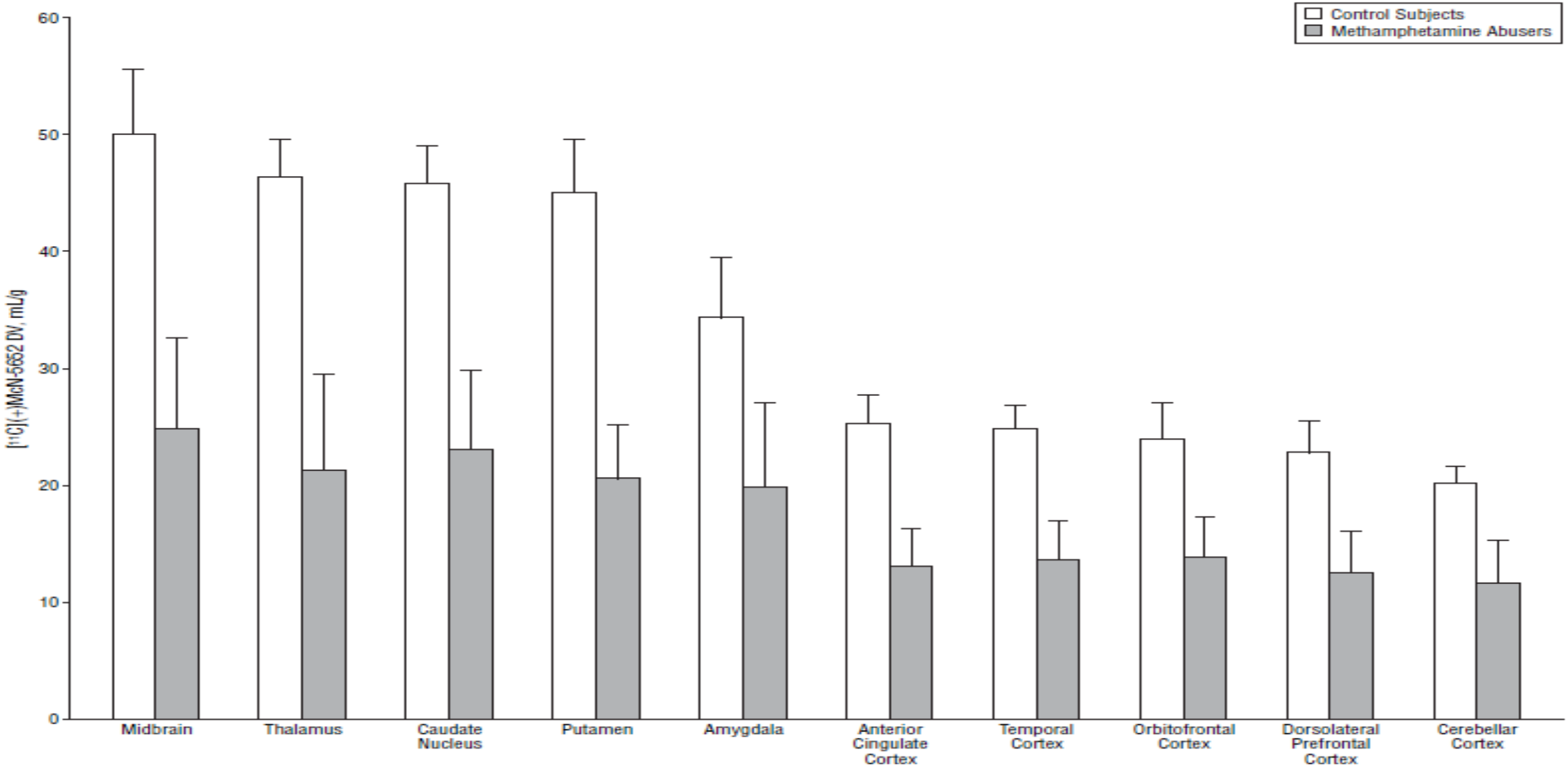


Figure 2. Mean regional brain *trans*-1,2,3,5,6,10-beta-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-[2,1-a]isoquinoline ([^{11}C](+)McN-5652) distribution volumes (DVs) in control subjects and methamphetamine abusers. Methamphetamine abusers had significantly decreased [^{11}C](+)McN-5652 DVs in the global regions compared with controls (Wilks $\Lambda = 0.001$; $P = .003$, by multivariate analysis of variance). Univariate analysis of variance revealed that methamphetamine users had significantly lower [^{11}C](+)McN-5652 DVs than controls in all regions studied ($P < .001$ for all). Error bars represent SE.

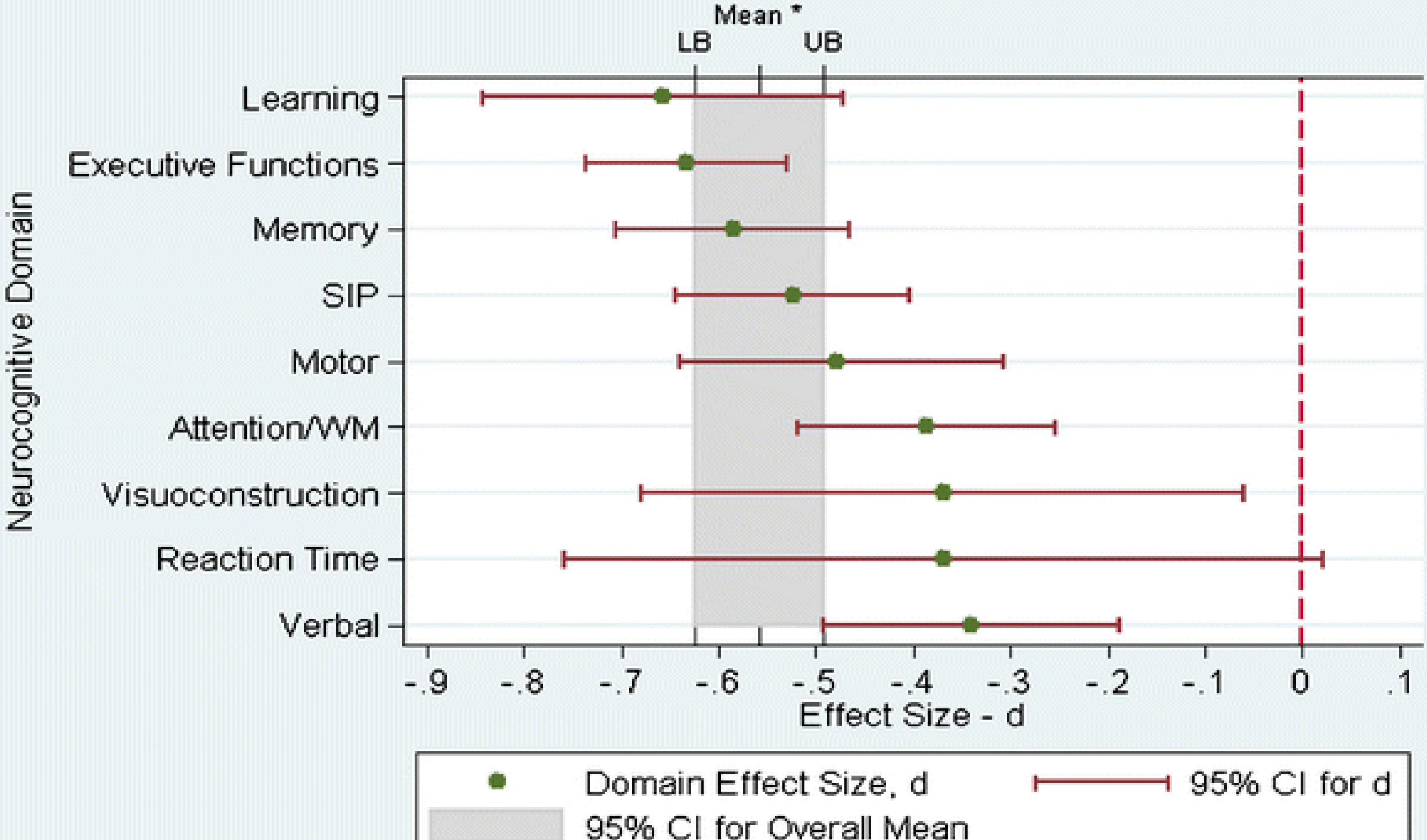
AND IT IS NOT JUST NEUROTRANSMITTERS

- Increased evidence of neuroinflammation (increased microglial activation) resulting in neurotoxicity
- Disruption of the blood brain barrier that blocks toxins
- Mitochondrial dysfunctionresulting in oxidative stress
- Breaks in the DNA single and double strands
- Increase in inflammatory ct
- Focal cerebral perfusion deficits

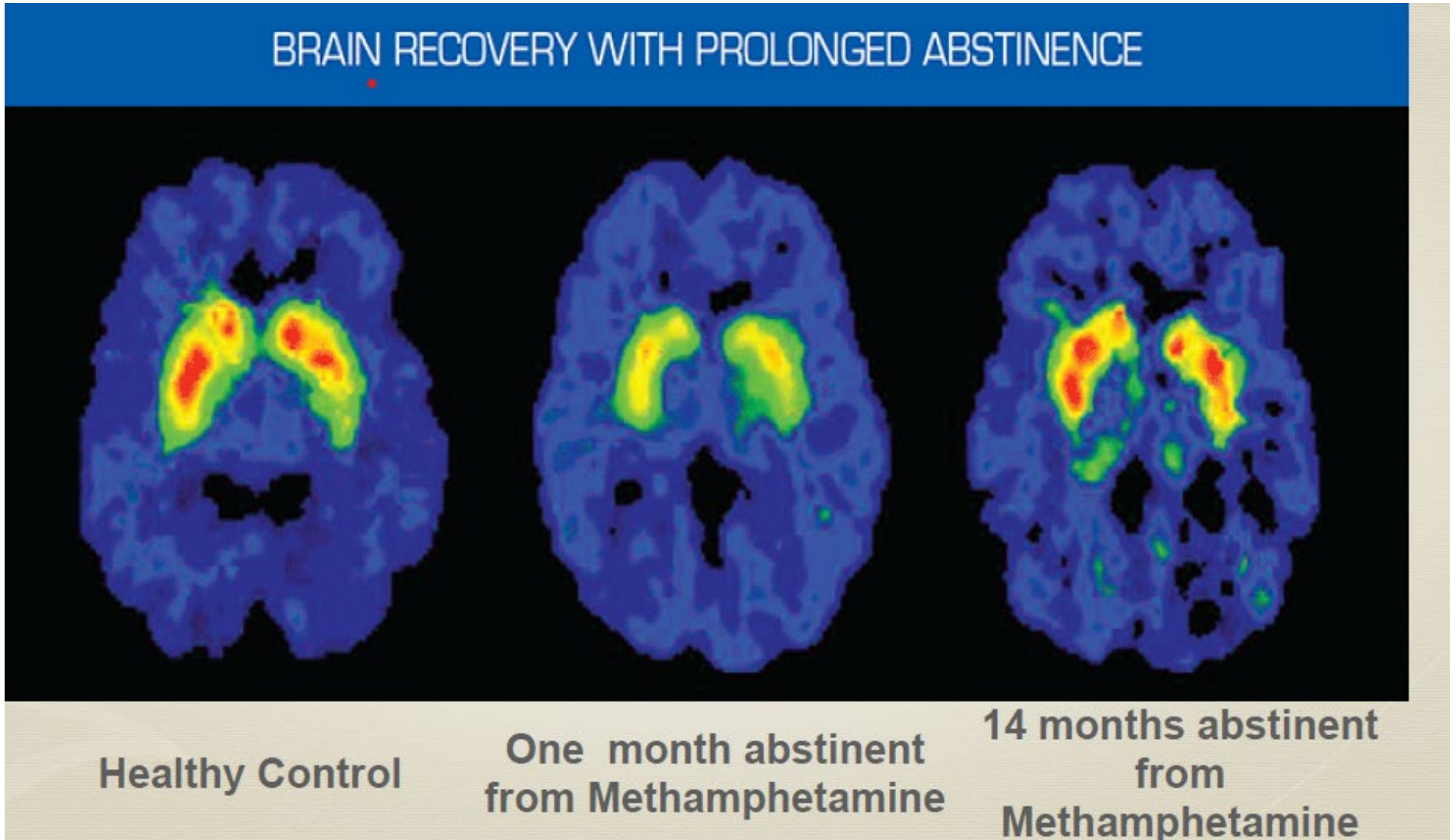
METHAMPHETAMINE IS A NEUROTOXIC AGENT

Neurocognitive Effects of Methamphetamine : A Critical Review and Meta-analysis. Scott JC., et al., Neuropsychology Review 17, 275-297 (2007)

- Review of literature that had neuropsychological testing results
- 18 studies (487 subjects, 464 controls)


Mean *
LB
UB
Learning
Executive Functions
Memory
SIP
Motor
Attention/WM
Visuoconstruction
Reaction Time
Verbal
Neurocognitive Domain
-.9
-.8
-.7
-.6
-.5
-.4
-.3
-.2
-.1
0
.1
Effect Size - d
Domain Effect Size, d
95% CI for d
95% CI for Overall Mean

HOW LONG WILL THE IMPAIRMENTS LAST



DURATION OF THE DEFICITS

- Persist into abstinence
- May worsen initially (5-14 days)
  * one study suggested individuals in early abstinence actually performed worse than those who continued to use methamphetamine)

Dopamine transporter (DAT) levels may return to normal in 12 months but mild cognitive impairments may persist longer

ARE THERE IMPLICATIONS FOR TREATMENT

- Unclear how much these impairments impact cognitive driven treatments
- Evidence based treatment
  - contingency management (immediate reward)
  - cognitive based treatments (matrix model)
- Need to develop specific strategies that address the deficits of impaired memory, learning and executive function

Some observations regarding treatment

- Longer term then 12 weeks of IOP
- Trigger identification
  - people (sex partners, “friends who understand”)
  - places (specific using environment)
  - things (stimulus checks)
  - times (weekends→ daily)
- Cyclical pattern: use—anhedonia---cravings—use (immediate reward)
- More frequent follow up
- Isolation from positive support systems and activities
- Paranoia and difficulty in getting into treatment
- More concurrent mental health issues (bipolar, ADHD, depression)

DSM-V METHAMPHETAMINE WITHDRAWAL

- Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after Criterion A:
- Fatigue.
- Vivid, unpleasant dreams.
- Insomnia or hypersomnia.
- Increased appetite.
- Psychomotor retardation or agitation.
- **C**. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

METHAMPHETAMINE WITHDRAWAL

- Acute phase (crash) : 1-7 days
  -increased sleep
  -increased appetite
  -fatigue
  -depression / anhedonia
  -inactivity
  -cravings
- Subacute phase 1-2 weeks
  -anxiety
  -poor sleep +/-
  -cravings
  -anhedonia
  -poor concentration, irritability

MANAGEMENT

- No standard treatment approach
- Predominately psycho-social support
- Outpatient
- No approved medications
  -mirtazapine
  -modafanil