The National Methamphetamine Symposium

Making Research Work in Practice

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NCETA

Neural and cognitive effects of methamphetamine and implications for treatment

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Neural and cognitive effects of methamphetamine and implications for treatment

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Importance of Cognition

- Cognitive function is related to treatment success
  - Cognition is fundamental for the ability to inhibit the immediate pursuit of pleasurable stimuli, and for the development of adaptive patterns of behaviour – both key factors in drug dependence (Kalivas and Volkow, 2005)
- Treatment to assist with cognitive dysfunction may directly assist with these difficulties
- Also provide indirect benefits to treatment such as greater cognitive capacity for engagement in cognitive behavioural therapy, the principal treatment for MA dependence.

MA and cognition

- Chronic MA use has been associated with significant impairments (relative to age/education matched controls) in a range of cognitive domains
  - (Scott et al., 2007; Nordahl et al., 2003; Dean et al. 2013; Meredith et al. 2005)
  - Poor verbal memory
  - Slowed Processing speed
  - Executive function
    - Disinihibted – poor self control
    - Selective attention – inability to avoid distraction
    - Decision making – biased toward immediate desires, myopia for future negative consequences
    - Cognitive flexibility – difficulty switching between different activities

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MA and cognition

- Chronic MA use has been associated with significant impairments (relative to age/education matched controls) in a range of cognitive domains
  - (Scott et al., 2007; Nordahl et al., 2003; Dean et al. 2013; Meredith et al. 2005)
  - The magnitude of impairment across the domains is significant
    - Medium effect sizes for learning (d' = -.62), executive function (d' = -.63) and memory (d' = -.59) (Scott et al. 2007)
    - Meta-analyses of cognitive sequale of other drugs suggest smaller impairments
      - Cocaine – d' = -.035 (Jovanovski et al. 2005)
      - Marijuana – d' = -.15 (Grant et al. 2003)
      - **Alzheimers Disease – d = -.8-1.0 (Backman et al. 2005)**

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MA and cognition

- Chronic MA use has been associated with significant impairments (relative to age/education matched controls) in a range of cognitive domains
  - (Scott et al., 2007; Nordahl et al., 2003; Dean et al. 2013; Meredith et al. 2005)
  - Use behaviour (frequency, duration, quantity) does not predict the level of cognitive impairment
    - Cherner et al. 2010; Iudicello et al 2010
    - Not clear what does predict
      - Hypotheses include individual (potentially genetic) variation in susceptibility to MA toxicity
      - Impairment seems to be worse in
        - » Older participants
        - » Men
        - » Confounded by comorbidity (e.g., other psychiatric conditions)

MA and cognition

- For those chronic MA users who enter treatment, cognitive function worsens in the early stages of abstinence
  - First 14 days of abstinence (particularly 5-14 days) (Kalechstein et al. 2003; Simon et al. 2004; 2010)
  - Attention, memory, executive function all decline from already poorer function levels
    - Deprived of acute benefits of MA to cognition, ‘’self-medicating’ hypothesis (see Newton et al. 2014)
    - Sleep disturbance during acute withdrawal (see McGregor et al. 2008)
    - Dysphoric mood, agitation, slowness of movement also contribute (Kalechstein et al.)

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MA and cognition

- Research on longer-term improvements in cognitive performance are mixed at best
  - After 6 months of abstinence, performance on cognitive measures was worse than comparable groups of MA users who either relapsed or continued to use (Simon et al. 2004)
  - After 13 months (range 6-42 months) Iudicello et al. 2010 found improvement in cognitive performance returning to levels that were not significantly different to healthy matched controls
    - Improvements were domain specific
      - Improved: Motor abilities, information processing speed
      - No improvement: learning and memory, executive function
    - Only those who showed ‘impairment’ at baseline benefited from abstinence
  - Volkow et al. 2001 and Wang et al. 2004
    - At 9-12 months no significant improvement in cognitive performance

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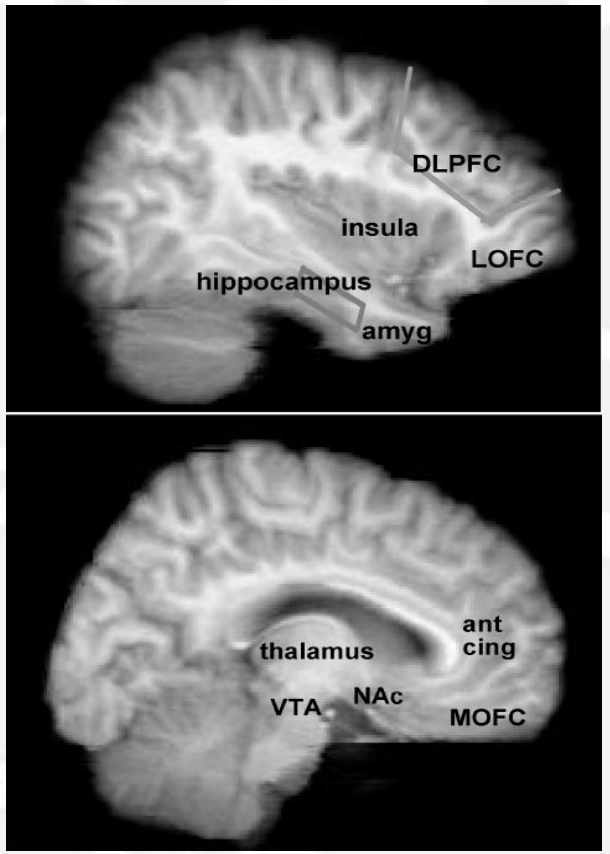
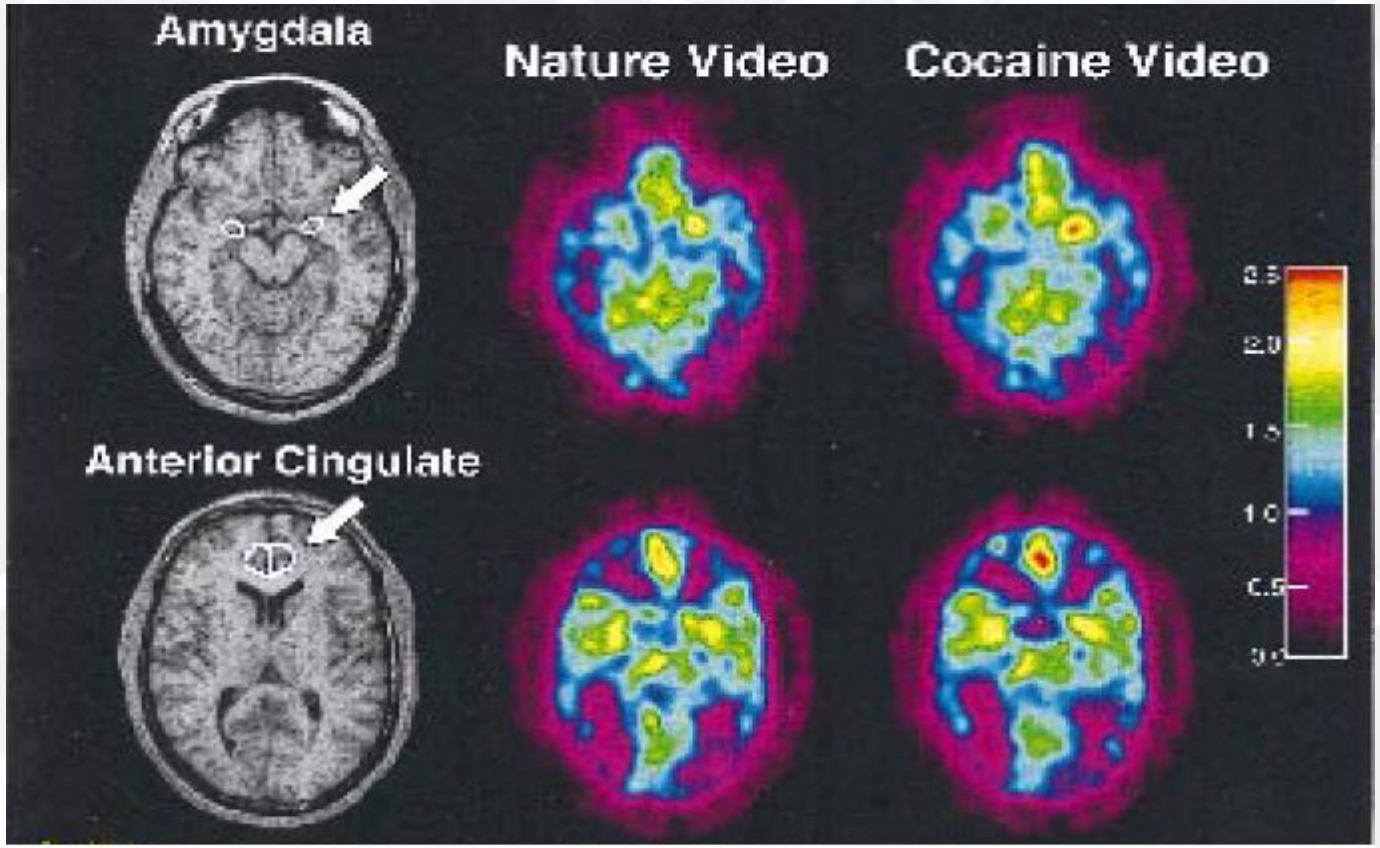
Drug-related brain changes?

- drugs, like natural rewards such as sex, food, water, produce euphoria by overactivating 'pleasure/limbic' centres in the brain, via the release of dopamine in the nucleus accumbens (NAc)
- The limbic system is closely tied to learning centres such as the hippocampus, and repeatedly pairing drug-induced euphoria with drug-related stimuli creates an association



Cue-induced brain activation

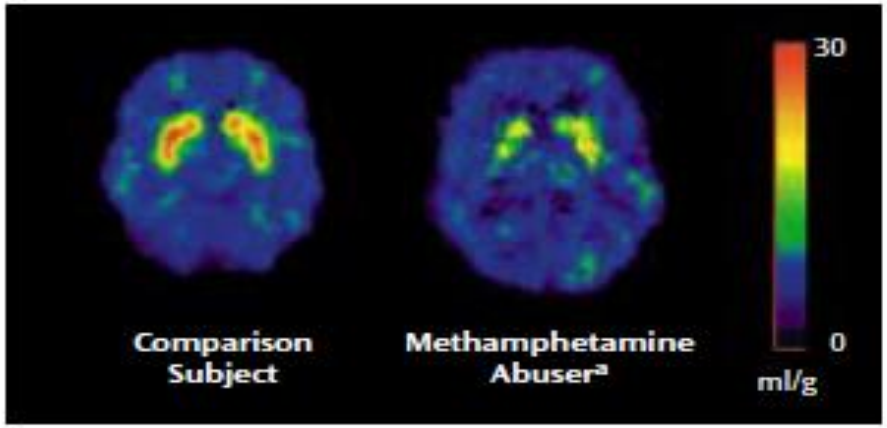
- In both active and abstinent users, showing drug-related stimuli activates limbic regions usually associated with the effects of the drug



The availability of D2 receptors, specifically when there is a low availability, in the human midbrain has been linked to vulnerability to addiction

Conversely, high d2 receptor levels has shown to be a protective factor in siblings of drug dependent individuals

FIGURE 1. Striatal Distribution Volume of the Dopamine Transporter Ligand [^{11}C]*d-threo*-Methylphenidate in a 33-Year-Old Male Comparison Subject and a 33-Year-Old Male Methamphetamine Abuser



[a] PET scan was performed 80 days after detoxification.

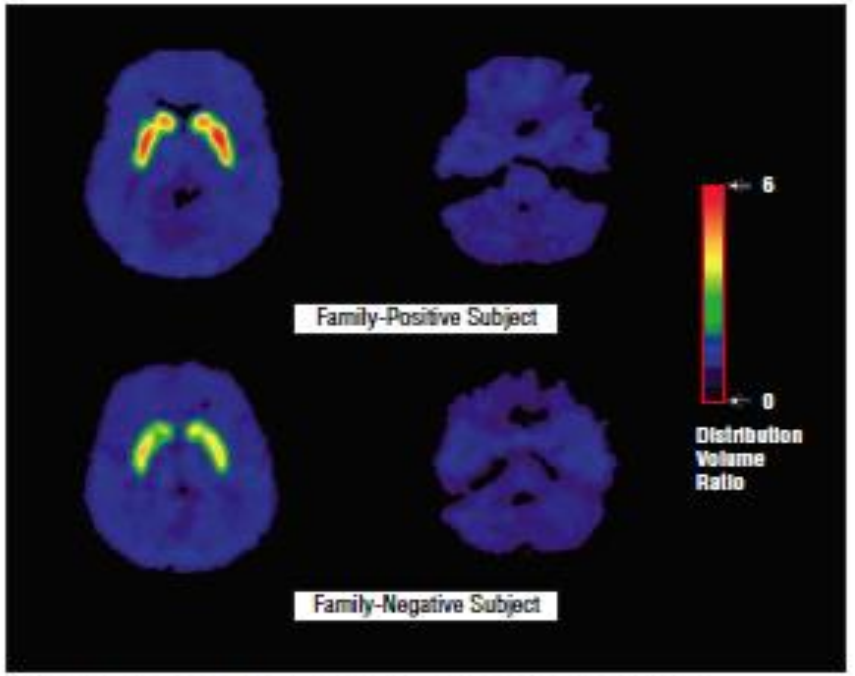
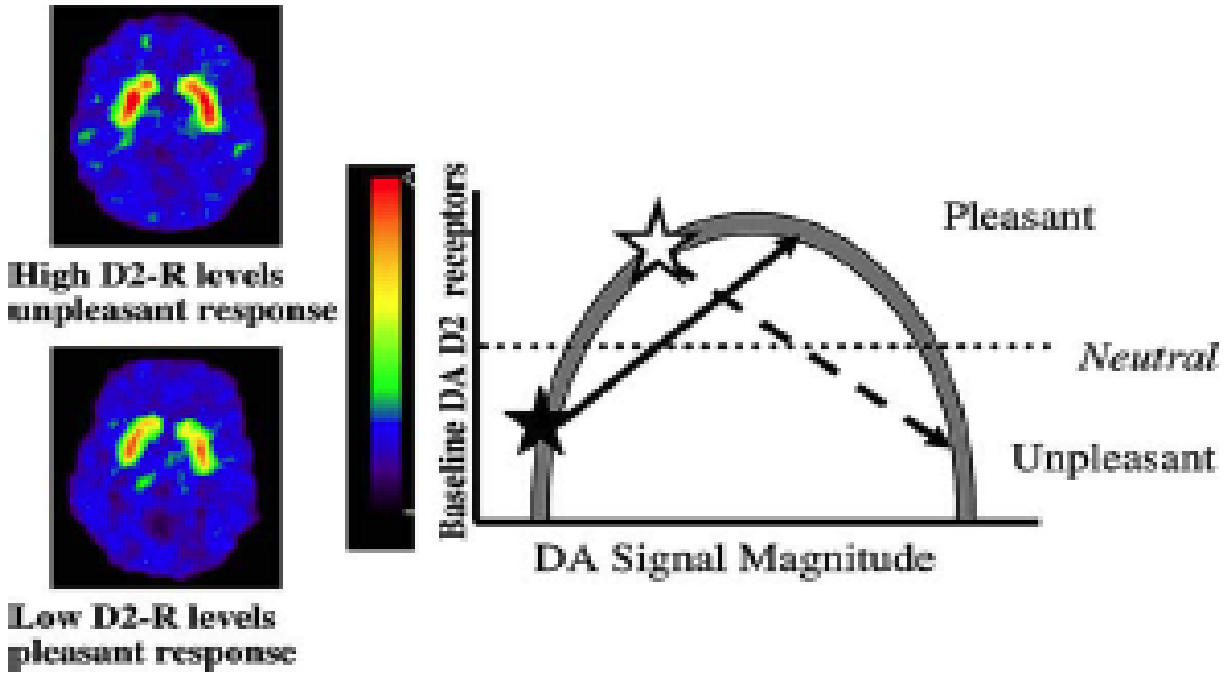


Figure 1. Images for the distribution volume ratios of carbon 11 (^{11}C)–labeled raclopride showing higher dopamine D_2 receptor availability in a family-positive than in a family-negative subject. Images shown correspond to levels where the striatum and cerebellum are visualized.

An inverted U-shape curve has been hypothesised by Volkow, suggesting that there is an optimal level of Dopamine stimulation for the drug to be perceived as 'pleasant'

In people with low level of d2 receptors (closed star on the figure) the large drug-induced increases in DA result in optimal stimulation

In people with high levels of d2 receptors (open star) the large increase pushes them to far and into the unpleasant range of the curve



Dopamine changes in MA

- Dopamine D2 receptor levels and metabolism are significantly depleted in MA users – Volkow et al. 2001
- The level of dopamine metabolism depletion
  - is a predictor of relapse risk – Wang et al. 2012
  - Development of Parkinsonian symptoms – Wang et al. 2004
  - Associated with nearly four times greater risk of developing Parkinson's Disease – Curtin et al 2015
    - No greater risk for dependent cocaine users
  - Associated with greater impulsivity for reward

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'Impulsivity for reward'

- DSM-V acknowledges this component in its criteria for substance use disorder
  - "substance is often taken in larger amounts or over a longer period than was intended" and
  - "there is a persistent desire or unsuccessful efforts to cut down or control substance use"
- Loss of control is relative, not absolute

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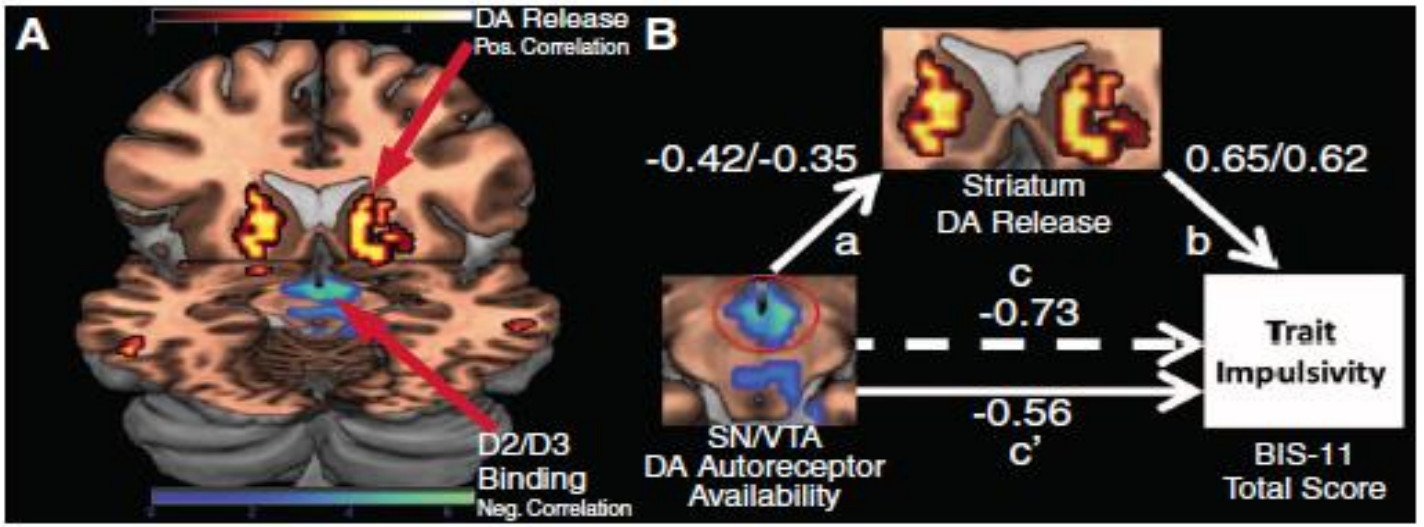
- People who self-report being highly impulsive have low levels of D2 (and D3) receptor availability in midbrain areas such as the striatum
- Giving them a small amount of amphetamine results in significantly greater dopamine release in the striatum
  - The pattern of response to dopaminergic stimulation is consistent with the hypothesis
    - These individuals have low dopamine levels
    - Individuals who describe themselves as having poor self-control have an enhanced response to dopaminegeric stimulation
    - The elevated response is associated with stronger subjective desire or ‘wanting’ of the drug



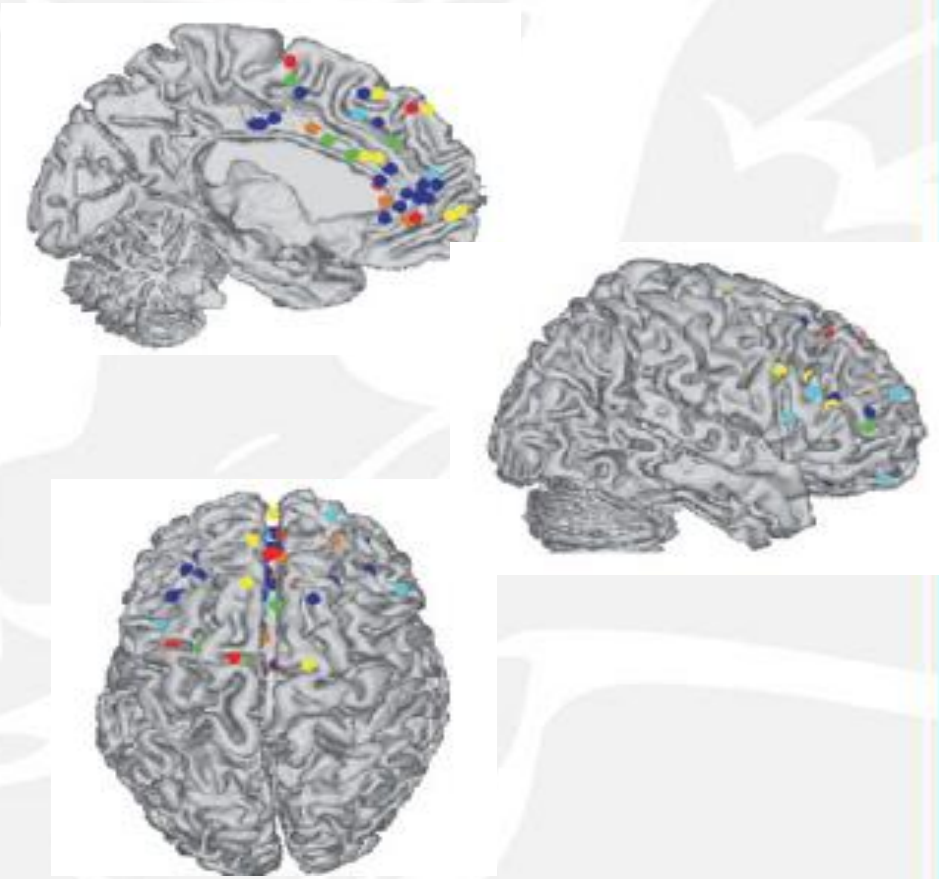
Dopaminergic Network Differences in Human Impulsivity

Joshua W. Buckholtz,[1,2*†] Michael T. Treadway,[1†] Ronald L. Cowan,[3,4] Neil D. Woodward,[3,4] Rui Li,[5] M. Sib Ansari,[5] Ronald M. Baldwin,[5] Ashley N. Schwartzman,[1] Evan S. Shelby,[1] Clarence E. Smith,[3] Robert M. Kessler,[5] David H. Zald[1,3]

30 JULY 2010 VOL 329 SCIENCE

Control dysfunction

- Dependent MA users and show significantly poorer performance on self-control tasks (such as the GNG, SST)
- The cognitive deficits are associated with significantly lower activity in both the prefrontal and anterior cingulate regions
- The presence of brain and behaviour differences in problem gamblers raises the question as to what extent dysfunction is caused by, or causes drug use
- See Dean et al. 2013 for a discussion of the cause/effect issue in MA users



Goldstein and Volkow (2011) review of neuroimaging studies in drug addiction. Regions associated with inhibitory control deficits are marked in yellow

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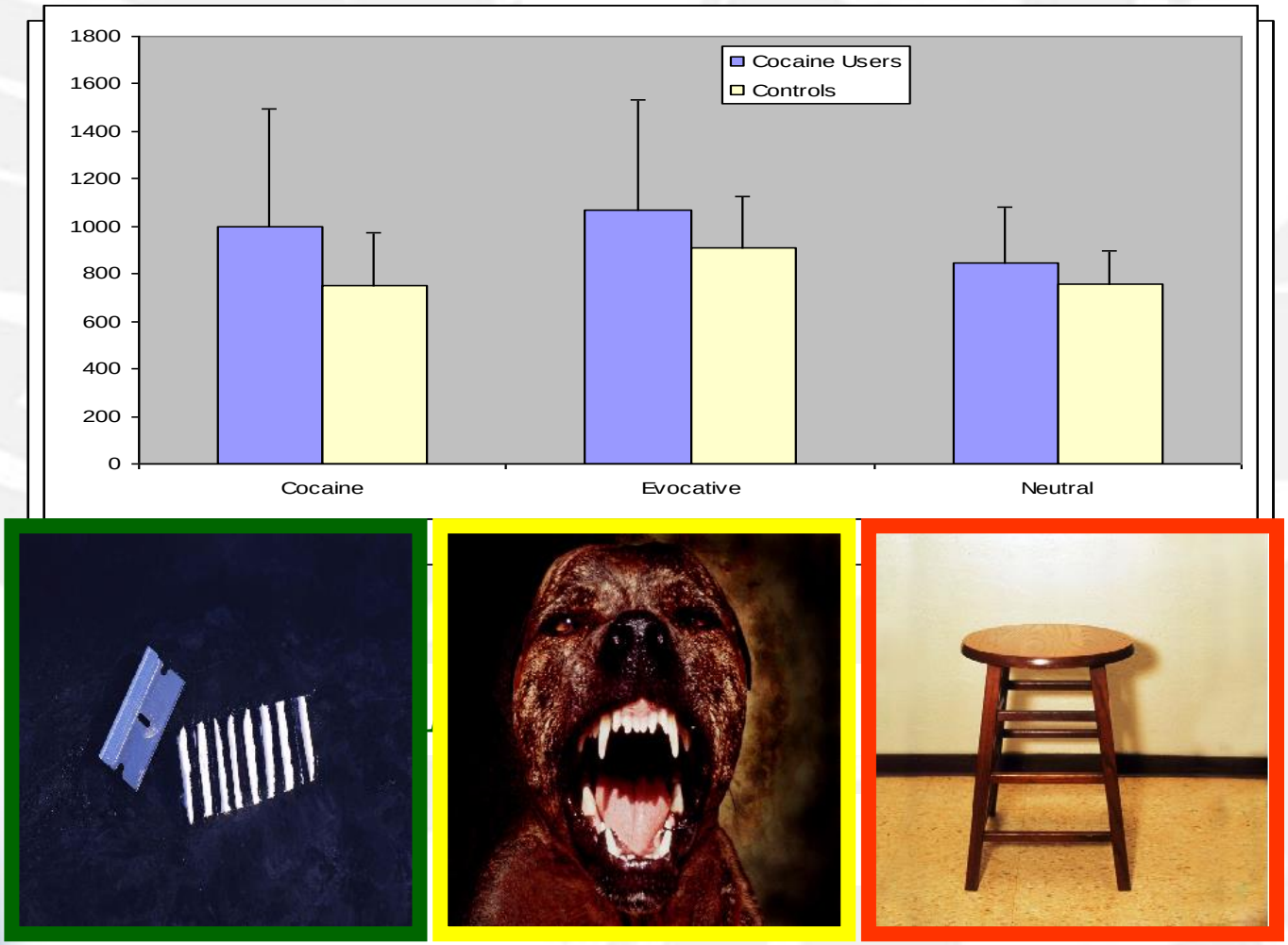
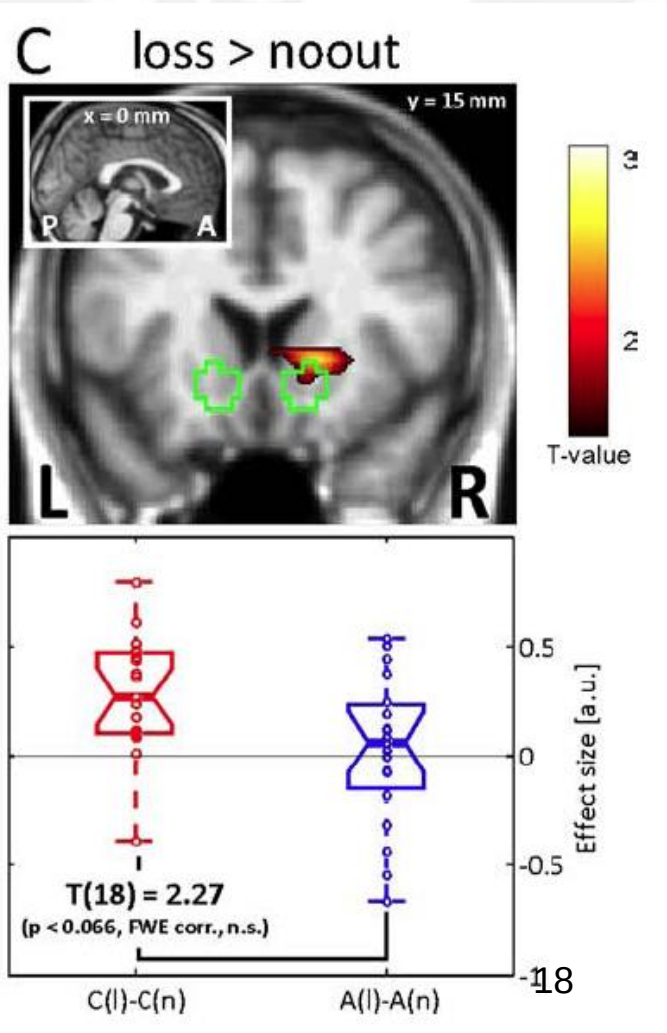
- Psychostimulant users demonstrate an attentional bias for drug-related stimuli (Copersino et al. 2004; Franken et al. 2000, Hester et al. 2006)
- Greater bias predicts poorer treatment outcomes (Carpenter et al. 2005)
- Inhibitory or cognitive control correlates with magnitude of bias



- Increase in limbic brain response to anticipation of reward
- Reduction in limbic response to monetary loss
- Regions such as striatum, insula
- See Bjork et al 2011 for a review



Control and treatment outcomes

- Cognitive impairment is generally associated with poorer treatment retention
  - Aharonovich et al. 2003, 2006, 2008, Carroll et al., 2011
- Cognitive control performance specifically has been linked with treatment outcomes and retention rates
  - Brewer et al. 2008, Streeter et al., 2009, Verdejo-Garcia et al., 2012
  - Paulus et al (2005) found that poor cognitive control performance (decision making task) in MA users and associated hypoactivity in dorsolateral prefrontal, parietal, temporal cortices and anterior insula accurately predicted relapse in 89% of relapsers and 95% or nonrelapsers (at 12 month follow-up).
- Cognitive performance has had less predictive power of response to treatment from interventions
  - Carroll et al. 2011, Aharaonvich et al. 2008

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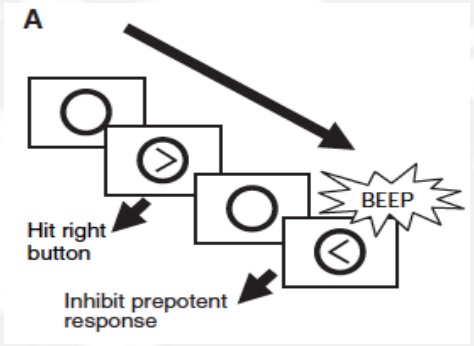
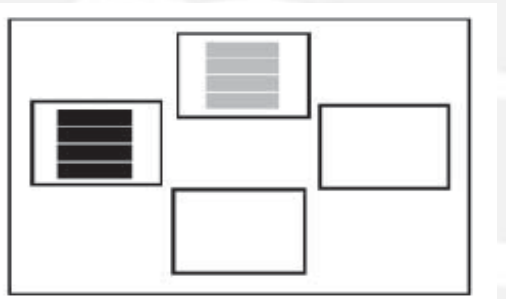
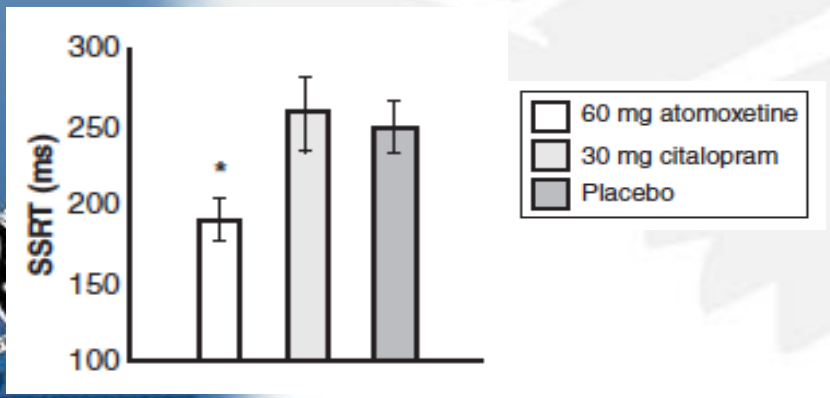
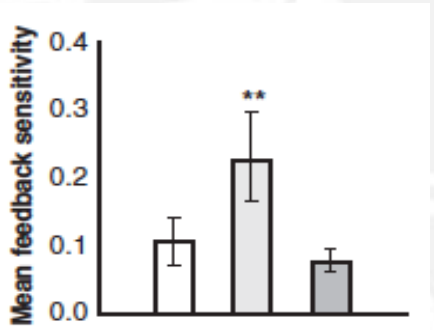
Can you improve control?

- Psychopharmacological approaches to this question have pondered what neurochemical drivers underlie self-control
  - Chamberlain et al. 2006 (Science) gave people the stop-signal and reward learning tasks while under the influence of either atomoxetine (noradrenergic) or citalopram (serotonergic)
  - SST performance was improved by noradrenergic, but not serotonergic, modulation
  - The opposite pattern was found for reward learning performance







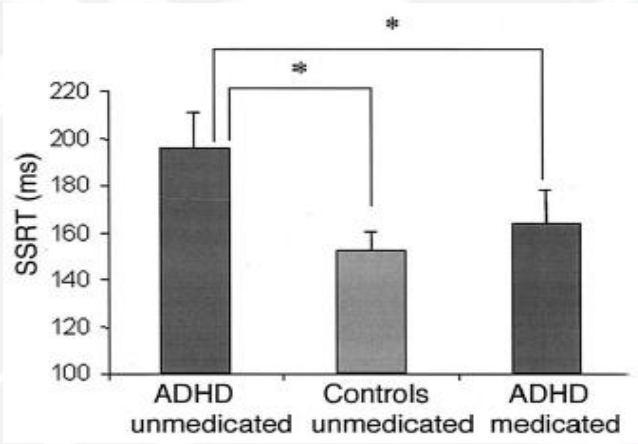


On the probablistic reward learning task, participants must choose one of the two coloured tiles, and receive a monetary reward 80% of the time. Once a participants chooses the correct tile on 8 consecutive trials, the contingencies change (or swap)

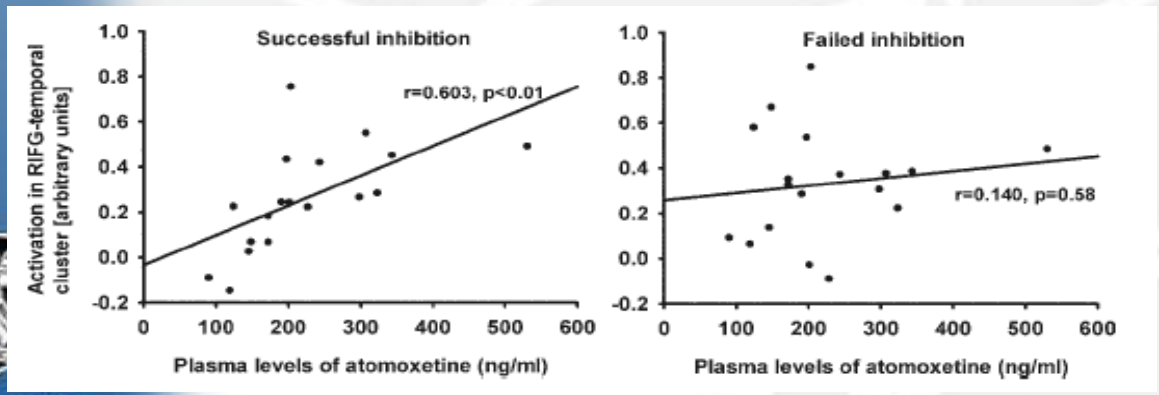
Improving control in disease?

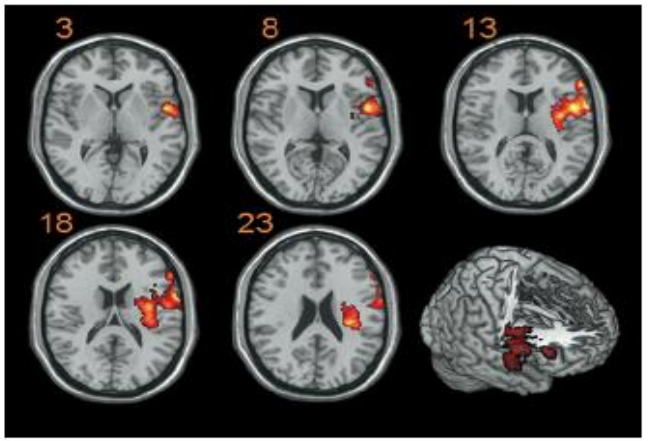
- Clinical studies have consistently demonstrated that atomoxetine and methylphenidate (ritalin) to children diagnosed with ADHD, results in significant improvments to performance on cognitive control tasks
- Aron et al. 2003, demonstrated that stop-signal performance significantly improved in children with ADHD taking Ritalin
- Chamberlain (2009) subsequently showed that these improvements were associated with significant increases in right IFG activity during Stop trials

Aron et al (2003) Biological Psychiatry



Chamberlain et al (2009) Biological Psychiatry





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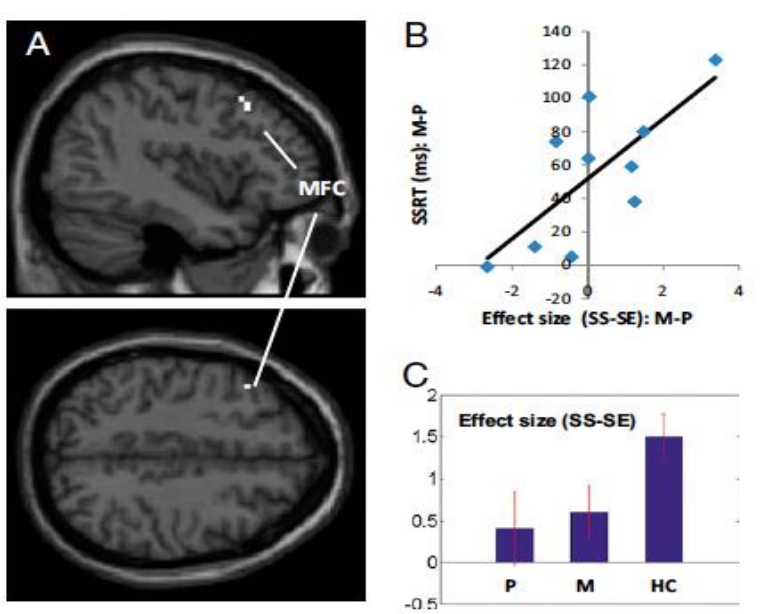
Improving control in PS Users?

- Similar benefits of methylphenidate and other psychostimulant medications have been seen in dependent psychostimulant users
- Li et al. 2010, demonstrated that stop-signal performance significantly improved in adult dependent cocaine users taking Ritalin
  - improvements were associated with significant increases in ventromedial prefrontal activity during Stop trials
- Specific benefits to cognitive control performance have been seen for both
  - Cocaine dependent participants
    - Moeller et al., 2012; Goldstein et al., 2010; Goldstein and Volkow, 2011; Kalechstein et al., 2012
  - Methamphetamine dependent
    - Dean et al., 2011, Gharemani et al. 2010

Li et al (2010) PNAS



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The Effects of Modafinil Treatment on Neuropsychological and Attentional Bias Performance During 7-Day Inpatient Withdrawal From Methamphetamine Dependence

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Turning Point Alcohol and Drug Centre, Australia; Monash University, Australia

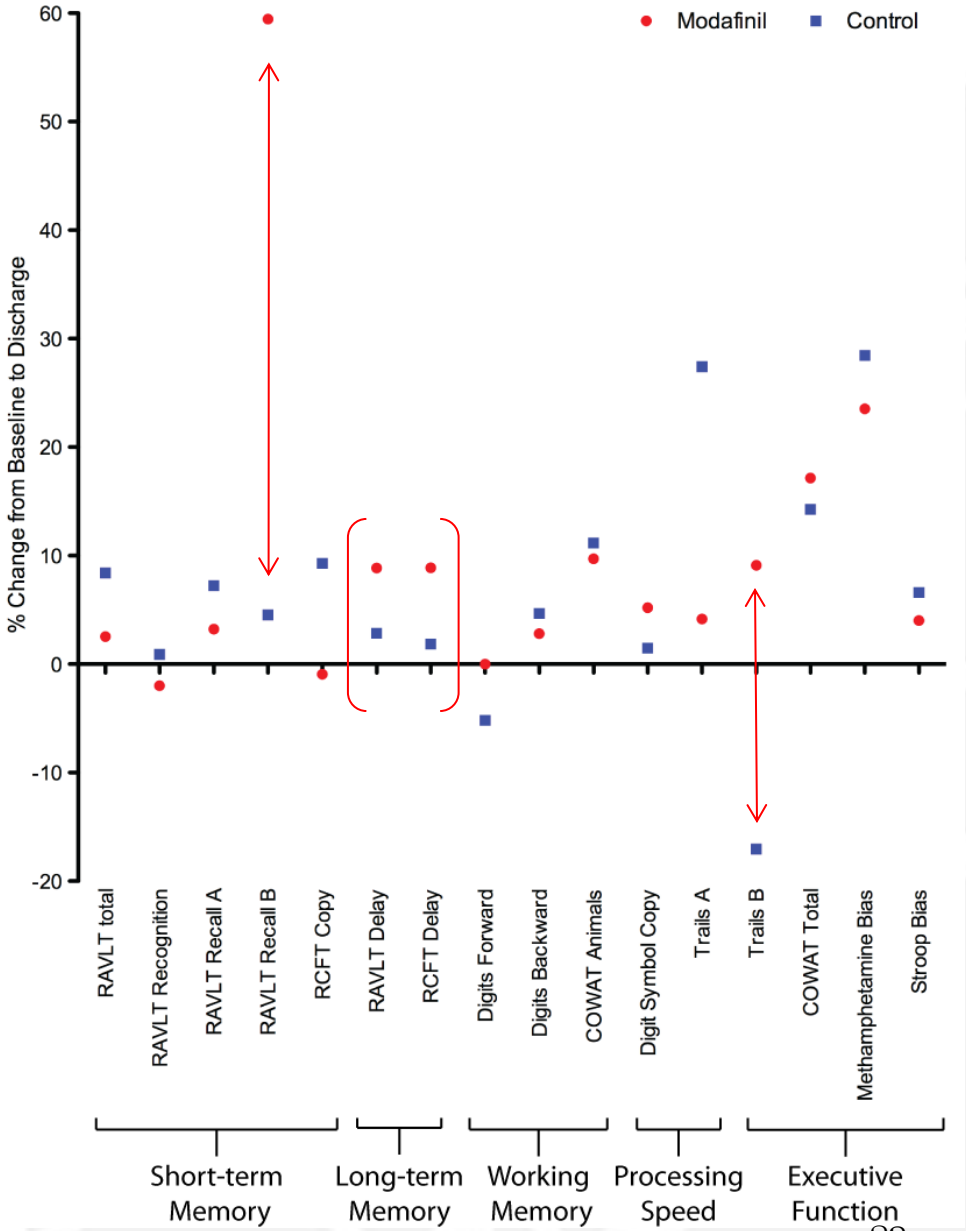
Experimental and Clinical Psychopharmacology
2010, Vol. 18, No. 6, 489–497

Baseline attentional bias scores were related to:

- number of days retained in treatment ($r = .60$, $p = .02$)
- self-reported relapse at follow-up ($r = -.42$, $p = .17$)

Discharge attentional bias scores were related to:

- Self-reported methamphetamine uses during the period since discharge ($r = .54$, $p = .07$)



Neuroenhancers and treatment outcomes

- Cognitive enhancers have NOT generally improved treatment outcomes for psychostimulant users in RCTs, or have mixed results at best
  - Modafinil
    - Improved abstinence – Dackis et al. 2003, Hart et al., 2008
    - No difference – Shearer et al. 2008, Anderson et al., 2009, Heinzerling et al., 2010, Dackis et al., 2012, Anderson et al., 2012
  - Methylphenidate
    - No difference – Schubiner et al. 2002, Grabowski et al. 1997; Dackis et al., 2005
  - Cochrane review (Castells et al. 2010), 16 studies and 1345 patients, 7 psychostimulant drugs including modafinil and MPH for cocaine use
    - Did not reduce cocaine use (Standardised Mean Diff = 0.11)
    - Trend for improving abstinence (Relative Risk = 1.41)
    - No influence on treatment retention (RR = 0.97)

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Neuroenhancers and treatment outcomes

- Two recent trials in MA dependent patients with dexamphetamine have shown positive treatment outcomes
  - Galloway et al. 2011; Longo et al 2010
- New trial beginning in St Vincents Hospital in Sydney with a new non-abuse variant of dexamphetamine
  - http://www.abc.net.au/news/2014-10-14/adhd-drug-trialled-in-ice-addiction-treatment/5808540

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Improving control in MA Users?

- Long-term abstinence and 'Super-normal'
  - Cross-sectional research in long-term abstinent psychostimulant users (and other dependent groups such as cigarette smokers – see Nestor et al., 2011) suggests that successful abstinence is associated with significantly better cognitive control performance (and CC network activity) than matched users and controls
  - see Connolly et al. 2012 for review
- The challenge for my/our field is to build evidence to determine whether this is the correct paradigm to pursue
  - If so, what treatment outcomes and over what duration are an appropriate measure?
  - Like CBT and antidepressants, do we need to use cognitive enhancers to provide short-term enhancement of a control system under extreme duress, while longer-term psychological interventions are used to overcome potentially life-long deficiencies in 'self-control'?

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Predicting adolescent alcohol misuse – 'binge drinking' Whelan et al. 2014 Nature

- 2000 children tested every 2 years from the age of 10
- 7 sites across Europe – called the IMAGEN project
- They identified 115 - 16 year old binge drinkers in their sample
  - A min of three lifetime binge drinking episodes leading to drunkeness
- They could correctly identify 73% of the binge drinkers at age 16 using a model of parameters from age 14 (prior to binge drinking) that included prefrontal activity during inhibitory control (both successful and failed)

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