Effects of pharmacotherapy on the ADHD brain: Evidence & future directions

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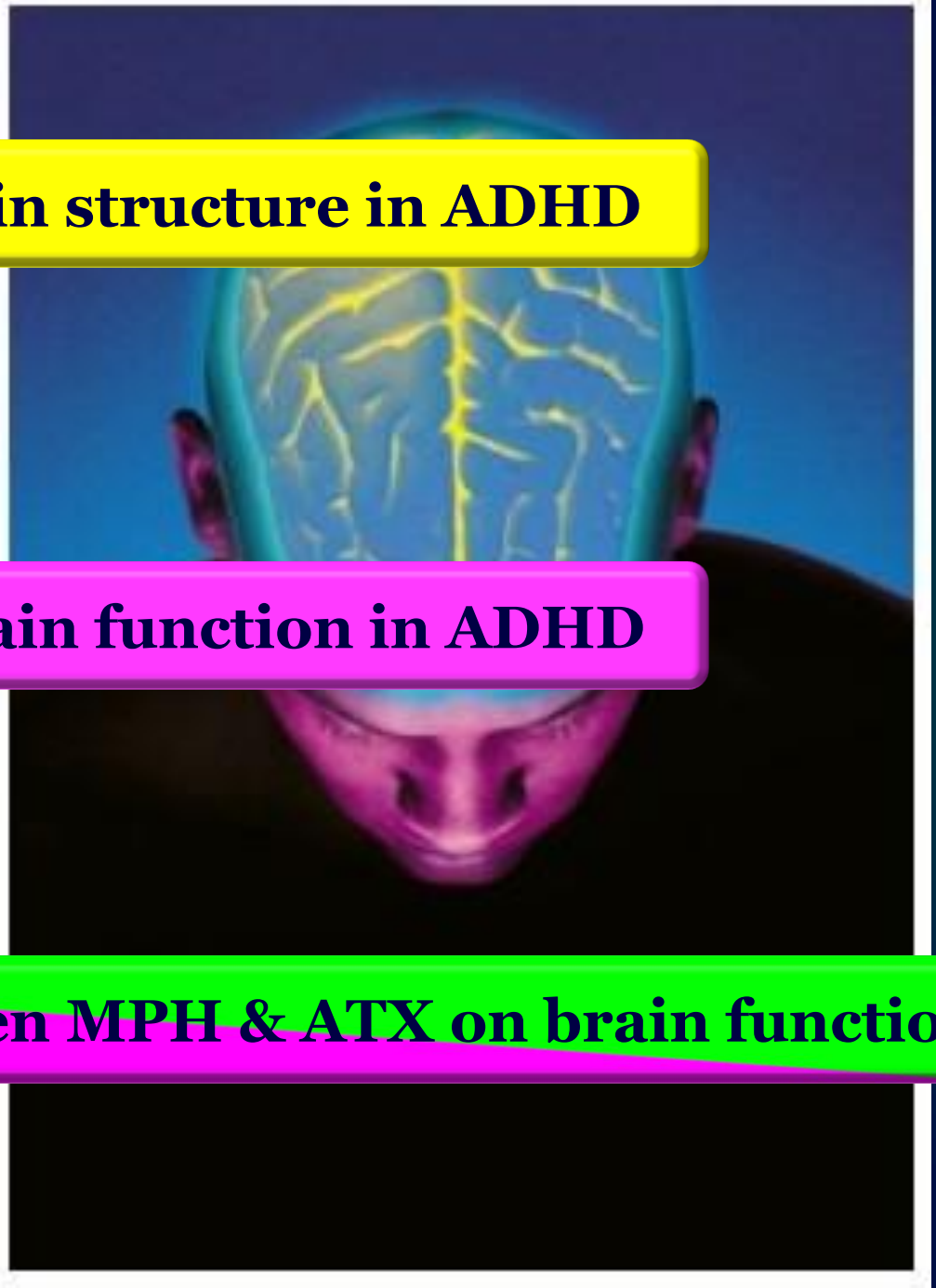
I. Effect of MPH on brain structure in ADHD

II. Effect of MPH on brain function in ADHD

III. Comparison between MPH & ATX on brain function



Methylphenidate

- Stimulant medication "gold-standard" ADHD
- Effective in 70-80% of patients
- In UK, once diagnosed 80% receive MPH

- **DAT**/NET inhibitor in C & ADHD:
  - in BG blocks ~ 70% DAT => ⬆ DA availability
  - in PFC MPH blocks ~ 70% NET & DAT, ⬆ DA & NE
  - Thalamus, TL, Cb

- Disadvantages
  - problematic for Tics => Atomoxetine
  - addictive potential?
  - may stunt growth
  - appetite
  - sleep problems

I. Long-term structural effects?

No prospective studies, no RCT, only naturalistic

Longitudinal studies

- **Castellanos 2006: med ADHD more normal WM overall**
- **Shaw 2009: med ADHD more normal GM in L IFC, PMC, PL**

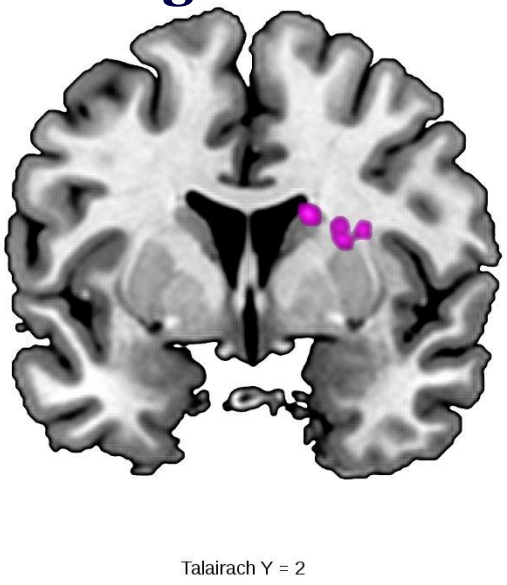
Cross-sectional studies

- **Pliszka 2006: med ADHD > normal ACC volume, caud no diff**
- **Bledsoe 2009: med ADHD more normal post-inf. vermis Cb**
- **Sobel 2010: med ADHD > normal caudate morphology**

Meta-analysis of 13 VBM studies

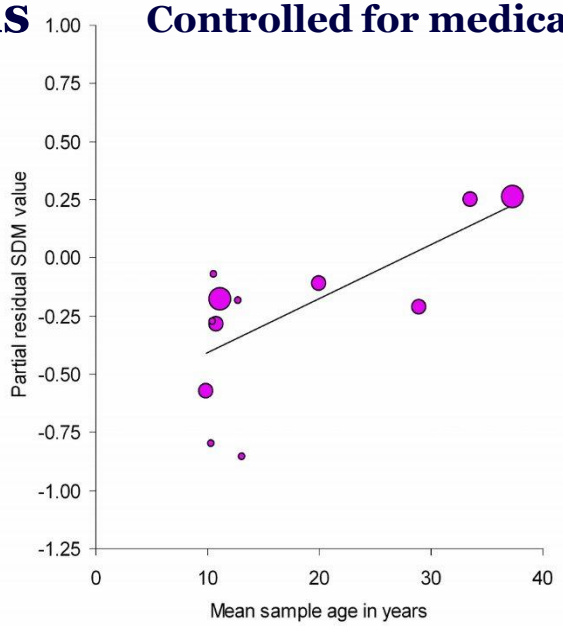
13 studies (4 adult; 9 pediatric)
N combined: 347 ADHD, 313 Controls
Decreased global volume.
Reduced GM volume in caudate, putamen, globus pallidus

Meta-regression analysis

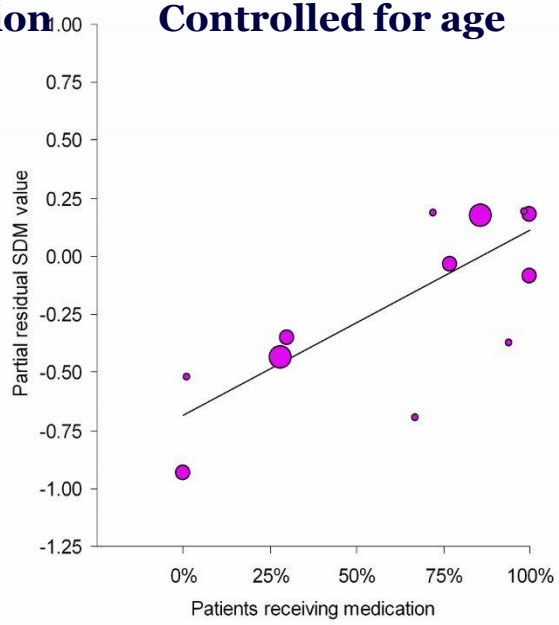


Talairach Y = 2

Controlled for medication



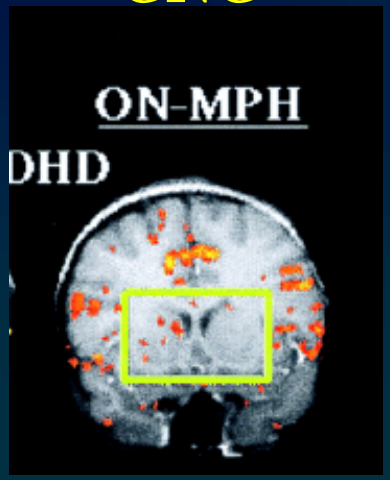
Controlled for age



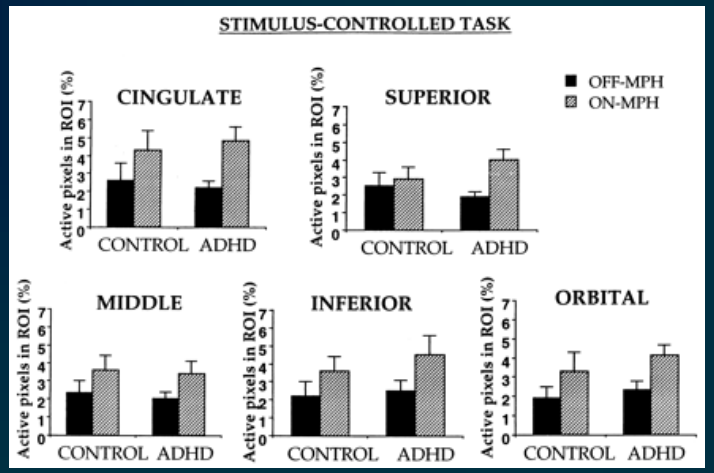
Nakao, Radua, Rubia, Mataix (2011), in re-submission

II. Acute effects of MPH in fMRI of ADHD kids

GNG



Vaidya et al., 1998
Lou et al., 2004



DIV ATT

Caud/ Put

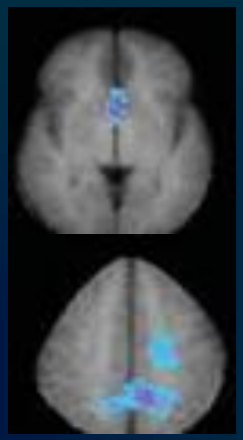
Shafritz et al., 2004

MPH => deact in ACC & PCC

Previously medicated

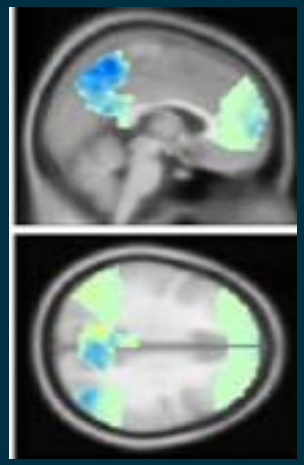
Stroop

Control task



Peterson et al., 2009

GNG



Liddle et al., 2010

II. Acute effects of MPH in med. naive ADHD

N = 13 med-naïve ADHD hyp/inatt combined (DSM IV)
Double-blind, placebo-MPH

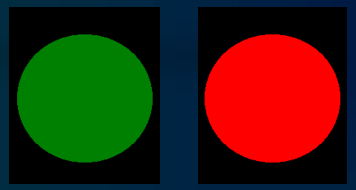
- **Timing functions**
  - **Time discrimination**
- **Response inhibition & errors**
  - **Stop**
- **Interference inhibition**
  - **Simon**
- **Sustained attention & Reward**
  - **Rewarded CPT**

I. Within patient effect:
Comparison Placebo/MPH (0.3mg/kg)

II. Normalisation effect:
Comparison 13 Controls with ADHD (Placebo/MPH)

Normalisation effects by MPH

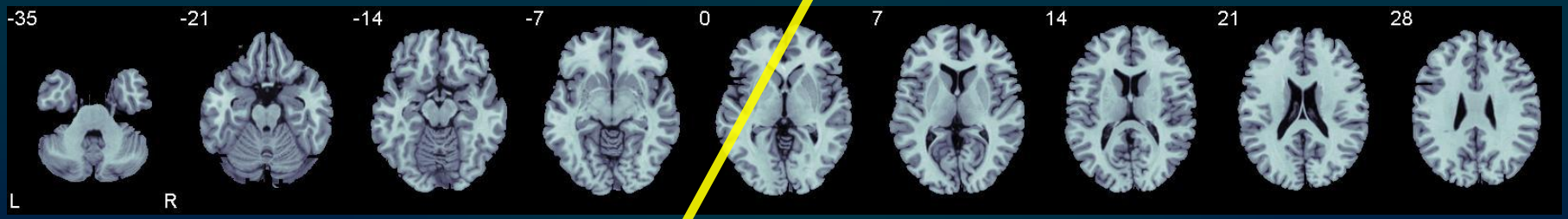
Time discrimination



1s 1.3; 1.4; 1.5s

C > ADHD (Plac)

C > ADHD (MPH)



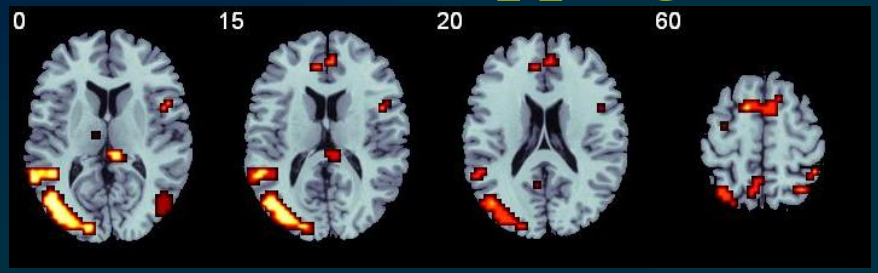
MPH slightly decreased error rate (n.s.).

Rubia et al., Phil Trans B, 2009, 364, 1919-1931.

Normalisation effects by MPH

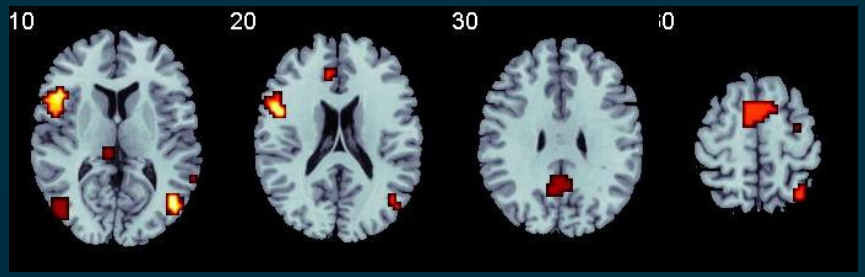
Stop task

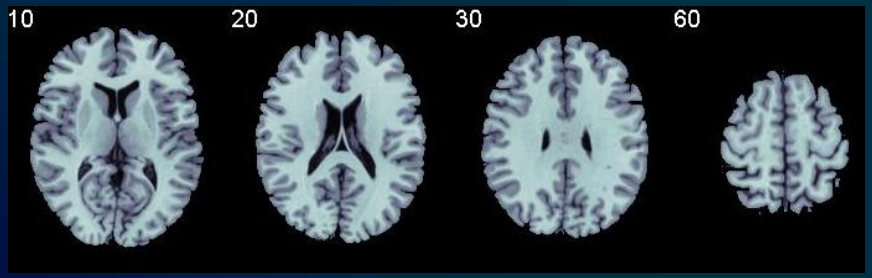
Successful Stopping



C > ADHD (Plac)

Stop errors



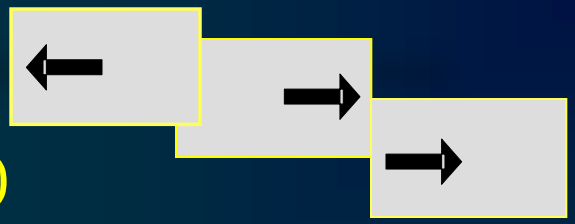


C > ADHD (MPH)

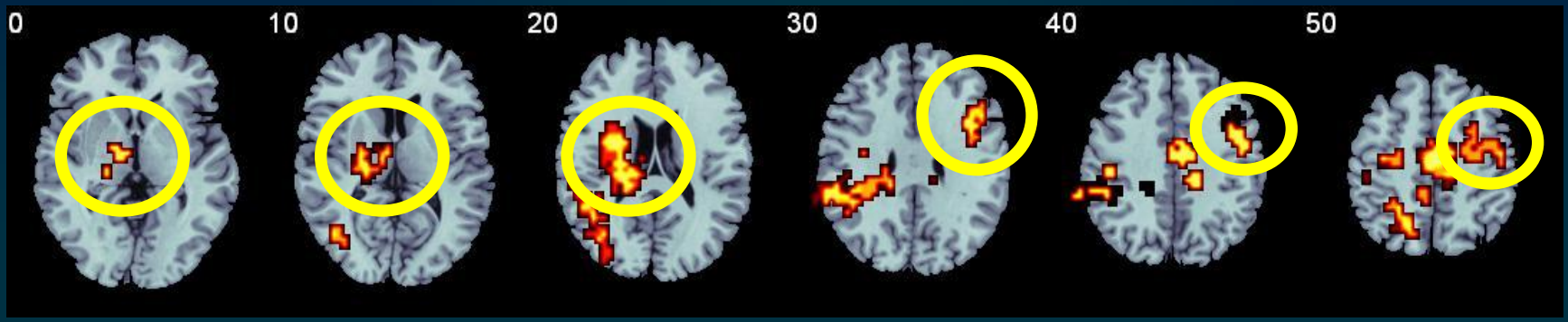
Rubia et al., Biol Psych, in revision

Partial normalisation by MPH

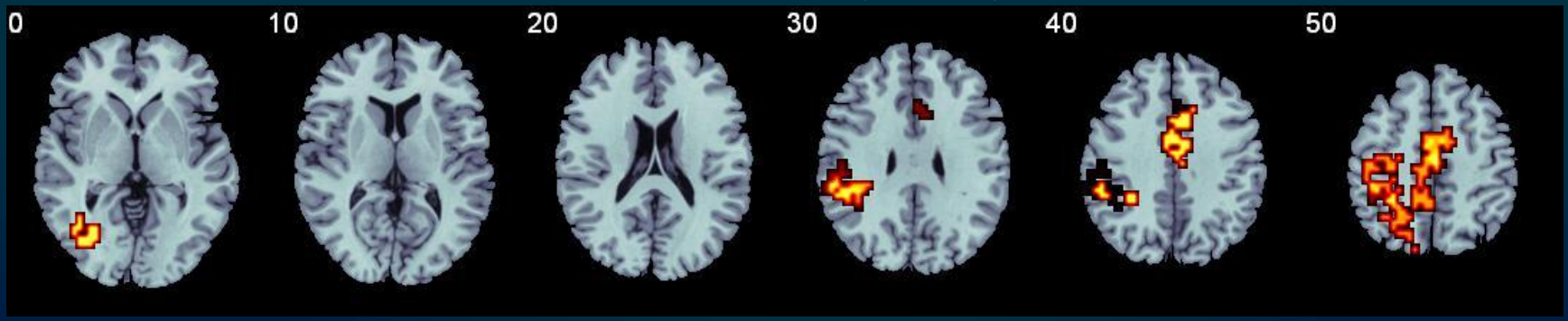
Simon: interference inhibition



C > ADHD (Plac)

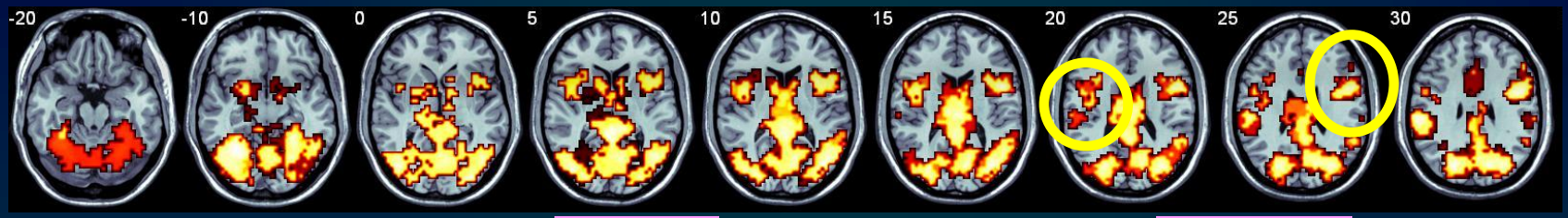


C > ADHD (MPH)



Rubia et al., 2011, Neuropsychopharmacology, in press

Reduced f(x) connectivity in ADHD MPH vs C



L IFC

ACC

R IFC

L BG

R BG

Sustained Attention

L Thal

R Thal

L PL-TL

R PL-TL

PCC

L Cb

Cb vermis

R Cb

Rubia et al., Psychopharmacology, 2009, 57, 640–652.

Atomoxetine

- Only non-stimulant licenced for ADHD
- Effective in 30% non-responders to MPH
- Direct clinical comparisons find equal effectiveness of both drugs in 50% of ADHD (> 40% symptom reduction)

- Selective presynaptic NET inhibitor
- Enhances DA & NE in PFC [= MPH]
- Low effect on caudate, but midbrain, thalamus, cingulate, Cb

- Clinical Advantages
  - Lower likelihood Tics
  - Reduced addictive potential

Atomoxetine

Effects in ADHD cognition

- ↑ Inhibitory processes (SSRT)
- ↑ Sustained attention (COM)
- ↑ Interference inhibition
- ↑ WM

(Chamberlain et al., 2007, Spencer 1998, Faraone 2005, Gau 2010)

In animals (Easton 2007, Swanson 2006, Takano 2009)

- ↑ OFC, hypothal, Thal, Cb, hippoc, OCC
- ↓ caudate, thalamus, putamen

In humans (Wong 2005, Arakawa 2008)

Dose-dep. NET occupancy: Thal, locus coeruleus
ACC, Cb

ATX vs MPH

- 20 medication-naïve dextral boys with ADHD
- Double-blind, cross-over
- 1mg/kg ATX
- 0.3mg/kg MPH

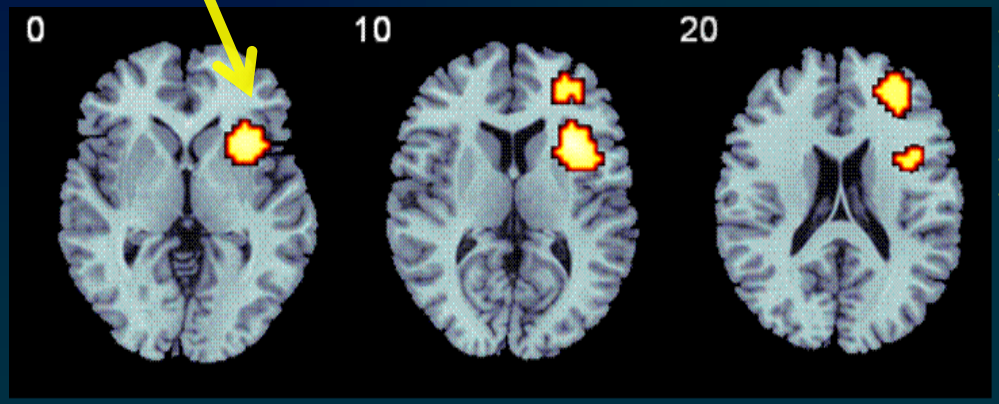
Preliminary data on 18

- fMRI tasks
  - Stop task (motor inhibition) => ATX
  - Time discrimination => MPH
  - Working memory (N-back) => MPH/ATX

Hypotheses:

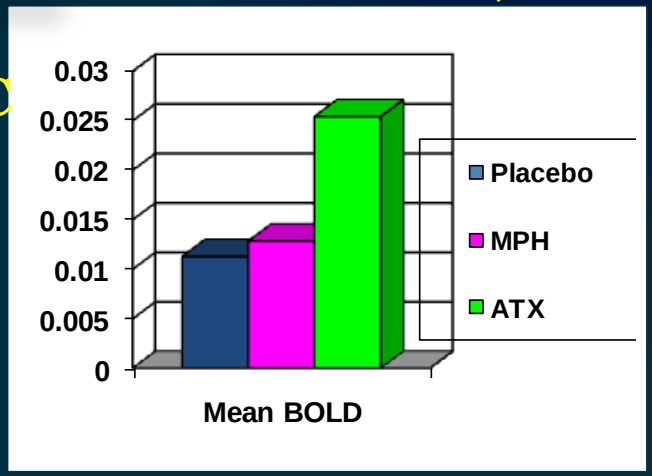
STOP task

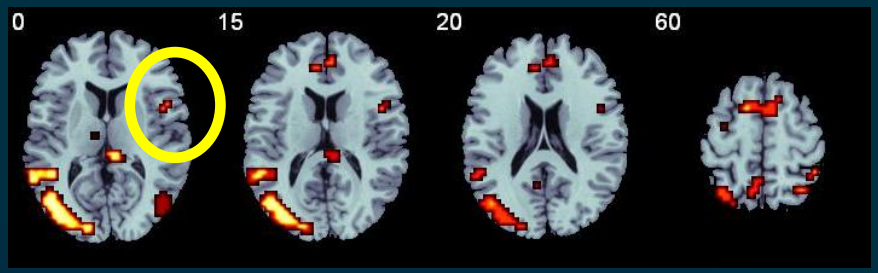
Correlated (neg) with SSRT



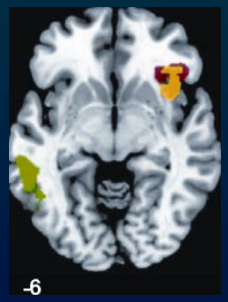
RIFC/ DLPFC Put

ATX > MPH, Plac

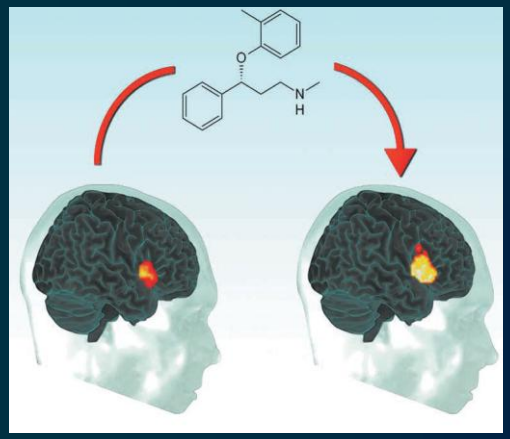




MPH normalises R IFC underactivation (Rubia et al., Biol Psych, 2011)



MPH reduces R IFC activation in healthy adults Pauls et al., in submission



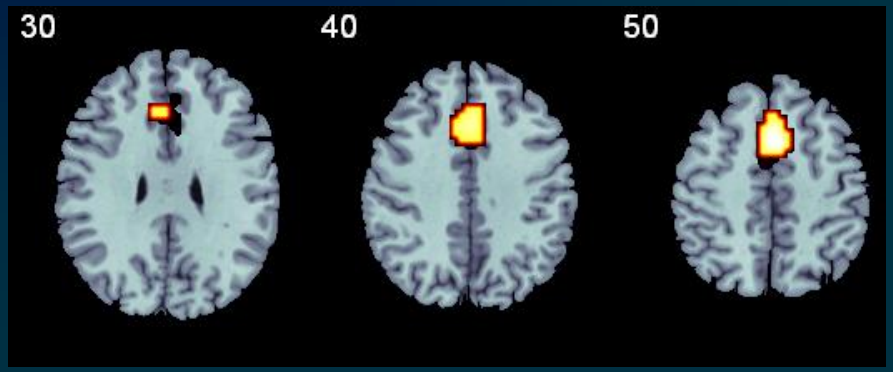
ATX enhances R IFC activation in healthy adults

Cubillo et al., in preparation

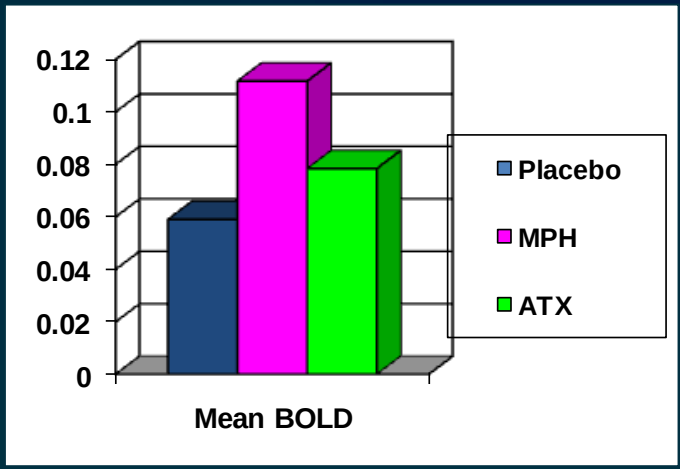
Chamberlain et al., Biol Psych, 2009

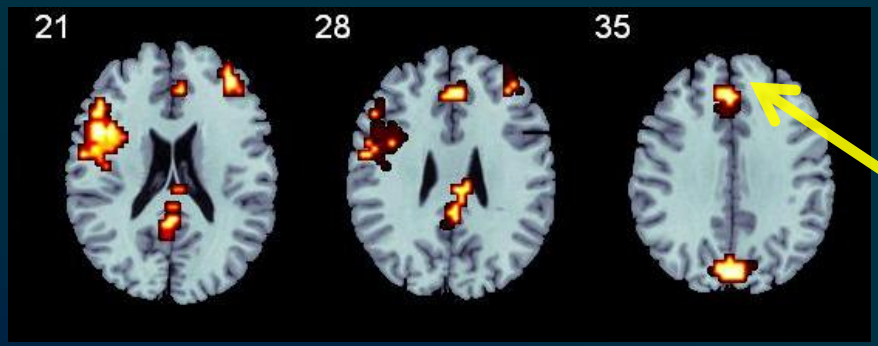
Time discrimination

MPH >Plac, ATX: improved time estimation errors **MPH >Plac, ATX**



ACC/ SMA





Rubia et al., 2009, Phil Trans B

MPH upregulates & normalises ACC underactivation

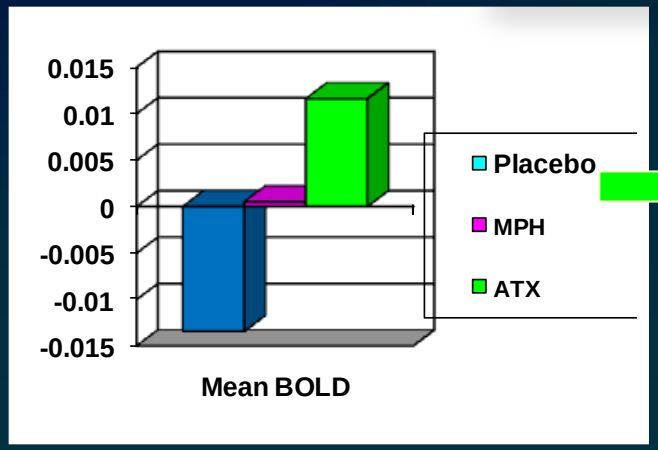
ACC activation corr with errors

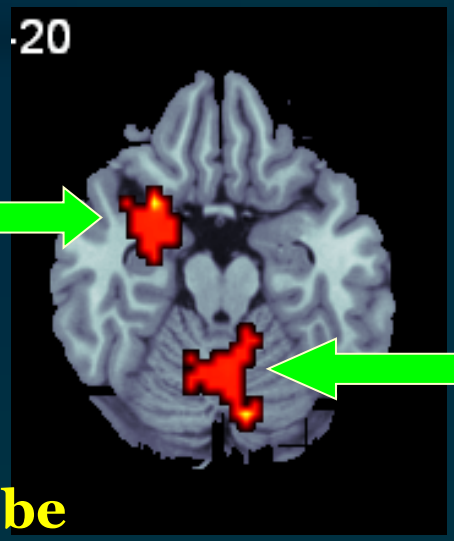
MPH improves time discrimination (Rubia et al., JACAP, 2003).

Cubillo et al., in preparation

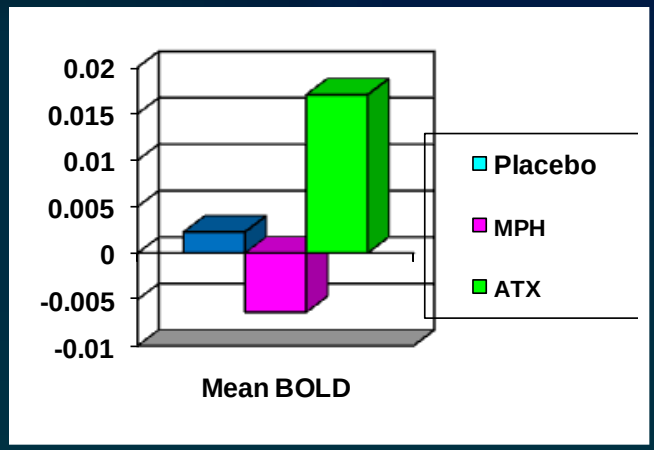
Working memory task

ATX > MPH, Plac



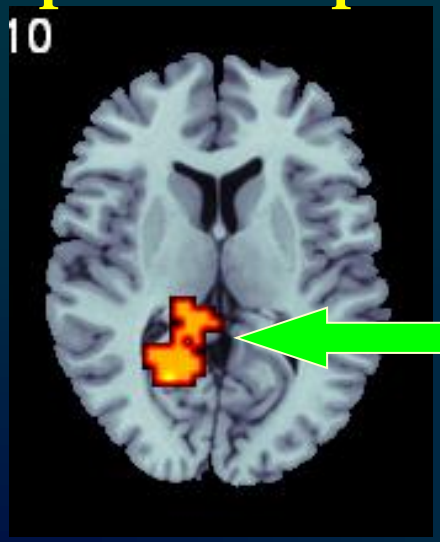


ATX > MPH, Plac

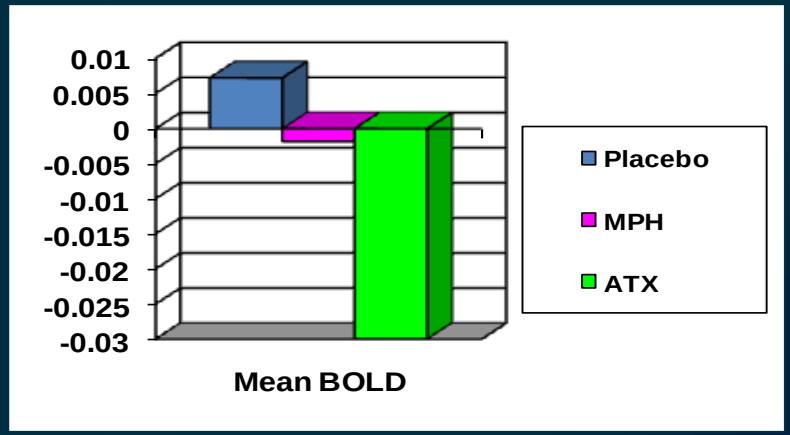


Superior temporal lobe

Cerebellum (vermis)



PLAC > MPH, ATX



correlated (neg with correct response

L PCC => ATX deactivates default mode network

Cubillo et al., in preparation

Conclusions

- Long-term MPH treatment seems to be associated with increased, more normal structural volumes in the basal ganglia (& other regions) in ADHD

- Single clinical doses of MPH improve/normalise abnormal brain function & connectivity in ADHD

- Direct head to head comparison in fMRI between MPH & ATX shows dissociated & task-dependent drug-specific effects

  - MPH has drug-specific ACC upregulation effects in timing

  - ATX has drug-specific upregulating effects on R IFG in Stop, & in superior temporal & cerebellar regions during working memory. ATX also deactivated the default mode network.

Institute of Psychiatry at The Maudsley

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Rozmin Halari
Eric Taylor
Mick Brammer
Vincent Giampietro
Majeed Mohammad
Nadia Barret
Tomo Nakao

All patients

SOMERSET HOUSE AND KING'S COLLEGE BEFORE THE THAMES EMBANKMENT WAS MADE