

TASK-DEPENDENT DRUG-SPECIFIC EFFECTS OF METHYLPHENIDATE AND ATOMOXETINE ON BRAIN FUNCTION IN MEDICATION-NAÏVE CHILDREN WITH ADHD

Authors: Ana Cubillo¹, Anna Smith¹, Nadia Barrett¹, Vincent Giampietro², Andrew Simmons, Katya Rubia¹

Affiliations: ¹Department of Child and Adolescent Psychiatry ² Department of Neuroimaging, Institute of Psychiatry, King's College London, UK.

Introduction and objectives

Methylphenidate (MPH), a predominant dopamine (DAT) but also noradrenaline transporter (NET) inhibitor, is the first choice treatment for Attention Deficit Hyperactivity Disorder (ADHD). Single doses in functional magnetic resonance imaging (fMRI) have shown to enhance and normalise brain activation in medication-naïve children with ADHD in frontal, striatal and cerebellar brain regions during inhibition, sustained attention and time discrimination [1-3]. Atomoxetine (ATX) is a non-stimulant selective presynaptic NET inhibitor, used as an alternative treatment for ADHD. In healthy adults, a single dose of ATX has shown to enhance right inferior frontal activation during inhibitory control [4]. However, to our knowledge, no fMRI study has investigated the effects of an acute dose of ATX on brain activation in ADHD, or compared its effects with those of MPH. This study investigates the drug-specific effects of ATX and MPH on brain activation in medication-naïve children with ADHD during disorder-sensitive tasks of time perception, motor inhibition and working memory. We hypothesised task-dependent effects, with MPH having stronger effects on dopaminergic fronto-striatal mediated perceptual timing networks and ATX being more associated with upregulation of right inferior frontal activation and of noradrenergic mediated fronto-cortical attention networks in the WM.

Subjects

18 male dextral children with ADHD (DSM-IV)

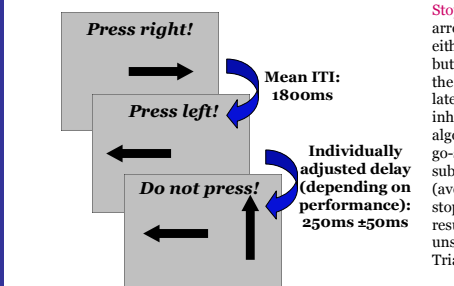
- ✓ aged 10-17 (mean age = 13; SD = 2)
- ✓ never medicated
- ✓ IQ > 70
- ✓ no neurol. deficits, no comorbidity with learning disability, or other major psychiatric illness

Methods

Acquisition: T2-weighted MR images depicting BOLD contrast were acquired in a 3T GE scanner from 16 near-axial slices parallel to the AC-PC plane.

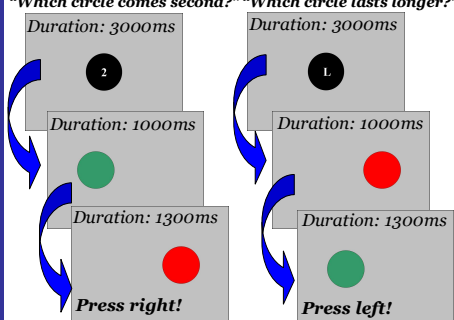
Data analysis: fMRI data were analysed using non-parametric fMRI analysis package of XBAMM (<http://www.brainmap.co.uk/>). For each task, within-group repeated measures ANOVAs were conducted for both fMRI and performance data, with drug condition (MPH, ATX, placebo) as within-subjects factor.

fMRI paradigms



Stop Task: Subjects have to respond to go arrows (79.6% of trials, 294 trials) that point either right or left with a right/left button response. In 20.4% of trials (60 trials), the go-signals were followed (about 250ms later) by stop signals and subjects had to inhibit their motor responses. A tracking algorithm changed the time interval between go-signals and stop-signals according to each subject's performance on previous trials (average percentage of inhibition over previous stop trials, recalculated after each stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials. The mean Inter-Trial Interval (ITI) is 1.8s. 9 min.

Order discrimination blocks "Which circle comes second?" Time discrimination blocks "Which circle lasts longer?"



Time discrimination task: 5x30s alternated blocks each for the time discrimination and temporal order judgement (control) conditions (six trials each). 5min.

Time discrimination blocks: after the appearance of a cue letter 'L' for 3s, subjects are presented with 6 pairs of red and green coloured circles, which appear consecutively left and right from each other. One of them is randomly presented for a standard duration of 1s, and the comparison circle for either 1.3s, 1.4 or 1.5s. Subjects have to decide which of the two circles had the longer duration, by pressing the left/right button. Temporal order judgement blocks: after the appearance of the cue number '2' for 3s, subjects are presented with the same stimuli, but they have now to indicate which circle came second. Response time for both conditions is 2100ms.

N-Back task: The 6 minutes working memory (WM) task consists of 4 different conditions. In the control condition "It is X?" the subject is presented to series of letters, and the subject has to press for every X that appears on the screen. In the conditions "1-back", "2-back" and "3-back", the subject has to press the button whenever the letter presented is the same as one, two or three before it, respectively. Image corresponds to the 3-Back condition.

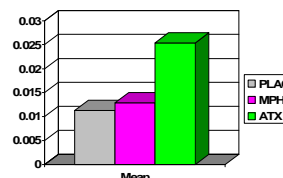
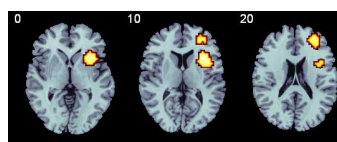
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Results: Performance differences

MPH compared to placebo and ATX improved temporal discrimination. No significant drug effects were observed on WM or Stop task performance.

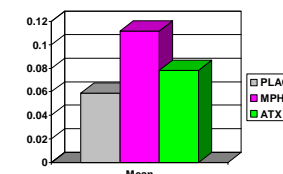
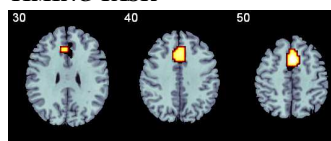
Results: Brain activation differences

STOP TASK



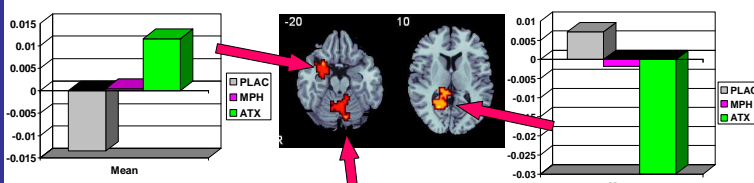
ATX>PLAC, MPH (PLAC=MPH) in right inferior frontal and dorsolateral prefrontal cortices.

TIMING TASK

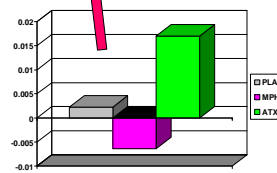


MPH>PLAC (ATX=PLAC) in anterior cingulate/supplementary motor area

WORKING MEMORY (NBACK) TASK (3 back contrast)



ATX>PLAC, MPH (PLAC=MPH) in activation in cerebellar vermis, left superior temporal gyrus and deactivation in the left posterior cingulate.



Conclusions:

➤ These preliminary results show that ATX and MPH had dissociated and task-dependent drug-specific effects on the brain activation of children with ADHD. ATX had stronger upregulating effects on right inferior frontal activation during motor inhibition, and temporal and cerebellar activation during working memory, while MPH had stronger medial frontal upregulation effects during time estimation.

➤ The drug-specific effect of ATX on cerebellar activation during WM is in line with the dense presence of noradrenaline transporters [5] compared to that of dopamine transporters in this area [6].

➤ The observed upregulation effects of ATX in right inferior frontal cortex during motor inhibition and in superior temporal cortex during WM extend, for the first time, previous findings of enhanced activation in the same areas in healthy adults during motor inhibition [4] to a group of medication naïve children with ADHD.

➤ The deactivation in PCC under ATX suggests that part of its effects may be via deactivating the "default-mode" network, and thus allowing the engagement of task-relevant regions.

➤ These upregulation changes could potentially underlie the performance improvement observed in WM and inhibition under prolonged ATX treatment in patients with ADHD [7, 8].

➤ The ACC upregulation with MPH extends previous findings in ADHD [3] by showing that the effect is drug-specific, in line with the dopamine hypothesis for timing.

➤ In conclusion, the findings confirm the hypothesis that ATX has stronger effects on noradrenergically mediated cortical inhibition, working memory and attention networks [9, 10, 11], while MPH appears to be more potent in upregulating dopaminergically innervated fronto-striatal timing functions [3].

References:

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