INTRODUCTION AND OBJECTIVES

Methylphenidate (MPH), a predominant dopamine (DAT) but also noradrenergic 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]. Amoxetoxine (ATX) is a non-stimulant selective pre-synaptic norepinephrine uptake inhibitor, used as an alternative treatment for ADHD. In healthy adults, a single dose of ATX has been 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 children with ADHD, in terms of time perception, motor inhibition and working memory. We hypothesised task-dependent effects, with MPH having stronger dopaminergic fronto-striatal mediated perceptive 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.

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

Conclusions:

➢ These preliminary results show that ATX and MPH have dissociated and task-dependent drug-specific effects on the brain activation of children with ADHD. ATX had stronger upregulations of 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 [3] compared to that of dopaminergic 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: