A randomized controlled clinical trial of real-time functional magnetic resonance imaging neurofeedback for adolescents with attention deficit hyperactivity disorder (ADHD)

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Introduction:
Right inferior frontal cortex (rIFC) is one of the most consistently underactivated brain regions in ADHD children during cognitive control tasks (Norman et al., 2015, Hart et al., 2012). Furthermore, we found this region to be a disorder-specific neurofunctional biomarker of ADHD relative to other childhood disorders (Rubia, 2011, Norman et al., 2016). rIFC is also the brain region that is most consistently upregulated with psychostimulant medication, which is the benchmark treatment for ADHD as it is effective in 70% of patients (Rubia et al., 2014). However, stimulant medication has side effects and long-term efficacy has not been demonstrated. In this study, we wanted to teach ADHD adolescents to self-upregulate this brain region which is consistently underactivated and most consistently upregulated with stimulant medication using real-time Neurofeedback with functional magnetic resonance imaging (rtfMRI-NF). For this purpose, we conducted a proof of concept randomised controlled trial (RCT) of rtfMRI-NF of rIFC in ADHD adolescents. We hypothesised that rtfMRI-NF would improve clinical symptoms of ADHD, cognitive control functions that are mediated by rIFC (such as sustained attention, inhibition, temporal discounting, time estimation) and the activation of rIFC during a motor inhibition stop task that is typically underactivated.

Methods:
Thirty-one ADHD boys were randomized in a single-blind RCT (only patients and parents were blind, but not researchers for practical reasons) to rt-fMRI-NF (14 sessions) of the rIFC (active group) or the left parahippocampal gyrus (lPHG, control group). Visual feedback was presented via a video-clip of a rocket that had to be moved from the ground to the space. Main outcome measures were changes in parents’ rating of clinical ADHD symptoms which were assessed at pre, post, and on average 11 month follow-up. A computer-based test battery and a fMRI Stop task were also used to assess NF effects on cognition and IFC brain function.

Results:
Both NF groups showed significantly linearly progressive increased activation with increasing session numbers in their respective target regions relative to the other group. Both groups also showed reduced ADHD symptoms from pre to post with no significant group differences; these changes, furthermore correlated significantly with the brain changes in their respective target regions. Only the active group, however, showed a transfer effect, whereby they showed increased activation in rIFC without the neurofeedback. Also, only the active group maintained the achieved improvements in ADHD symptoms at an average of 11 month follow-up. Furthermore, only the active group improved in intra-subject response variability and (trend-wise) in sustained attention. Lastly, only the active group showed significantly enhanced rIFC activation after the training relative to before the training during a Stop motor inhibition task, relative to the control group, who did not show this effect. The rIFC upregulation effect was similar to the one we have previously observed with stimulant medication (Rubia et al., 2014).

Discussion:
The proof of concept study shows that ADHD adolescents can learn to self-up-regulate rIFC activation and this is associated with improved ADHD symptoms, cognition and inhibitory rIFC activation.