Long-term medication effects on inhibitory brain function in ADHD (#38080)

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1) Have any data been collected for this study already?
It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in this study?
Our primary hypotheses are as follows:
(1) We hypothesise differences in functional connectivity across typically developing controls, medication-naïve boys with ADHD, and medicated boys with ADHD (Cubillo et al., 2010; Massat et al., 2018; van Rooij et al., 2015). Specifically: 1) reduction in functional connectivity in medication-naïve children with ADHD compared to typically developing controls; 2) enhanced functional connectivity in children with ADHD on medication compared to medication-naïve children with ADHD; 3) we will also test the comparison between children with ADHD on medication and typically developing controls which may not reveal impairment in functional connectivity.
(2) We predict that participants with ADHD will show performance deficits compared to controls based on the strong evidence of inhibitory performance deficits in ADHD (Alderson et al., 2007; Rubia et al., 2007, 2013; Willcutt et al., 2005; Wright et al., 2014). We predict greater deficits in patients who are medication-naïve compared to the medicated ADHD group and compared to controls.
(3) We hypothesise that treatment-naïve participants with ADHD will show deficits in brain activation compared to controls in line with past research (Cortese et al., 2012; Hart et al., 2013; Lei et al., 2015; Lukito et al., in press; McCarthy et al., 2014; Norman et al., 2016). We expect to see underactivation of key nodes of the right-hemispheric inhibitory network (inferior frontal cortex, insula, pre-supplementary motor area, caudate, supramarginal gyrus, and subthalamic nucleus; Aron et al., 2007; Duann et al., 2009; Hung et al., 2018; Zhang et al., 2017). Based on evidence from single dose studies (Rubia et al., 2014) and from meta-regression analyses between long-term medication use and brain activation in ADHD, which show increased activation in right inferior frontal cortex, caudate, and medial frontal regions (Norman et al., 2016), we hypothesise that long-term medicated patients will show less underactivation in these regions relative to controls and more activation in these regions relative to medication-naïve patients.
Additionally, we will conduct the following exploratory analyses: (4) A comparison of controls, treatment-naïve patients, and medicated patients using a whole brain activation analysis to provide an unbiased assessment of the brain areas involved in stop task performance. (5) The influence of ADHD symptoms on brain function and performance will be explored.

3) Describe the key dependent variable(s) specifying how they will be measured.
(1) Imaging: Blood Oxygen Level Dependent (BOLD) signal of contrasts comparing successful stop > go trials and failed stop > go trials. Brain function will be analysed by investigating brain activation and functional connectivity (beta-series correlations method).
(2) Behavioural: Go process: Mean Reaction Time (MRT) to go trials, intra-subject standard deviation of MRT (SDRT), omission errors, premature responses. Inhibitory control: Stop Signal Reaction Time (SSRT) using the integration method (Verbruggen et al., 2019). Error-monitoring measures: post-error reaction time to go signals (PERT), post-error slowing (PES). PES will be calculated as the difference between the reaction time to correct go responses after correct trials and reaction time to correct go responses after error trials, which is the most common approach used in ADHD research (Balogh & Czobor, 2016).
(3) Clinical: ADHD symptom count (inattentive, hyperactive/impulsive, or combined) assessed by Conners Parent Rating Scale (Conners, 2008).

4) How many and which conditions will participants be assigned to?
This study will include a group of boys with ADHD (10-18 years old) and an age-matched group of typically developing boys. Participants with ADHD will be asked to maintain their treatment as usual schedule for the duration of their participation in the study. The following subgroups are expected to form within the ADHD group, however, number of participants in each group cannot be determined prior to recruitment:
Primary ADHD groups: (1) Medication-naïve (never used ADHD medication or have not been using medication for at least a year); (2) On methylphenidate (stable medication for at least two weeks before the study enrolment). Secondary ADHD groups: (3) Medication-free (defined as not using ADHD medication for a minimum of two weeks); (4) On non-stimulant medication (stable medication for at least two weeks before the study enrolment); (5) On stimulant medication (this group will include group (2) and those taking other stimulant medication; stable medication for at least two weeks before the study enrolment); (6) On any ADHD medication (this group will be composed of groups (4) and (5))
Since this study does not include an experimental manipulation of medication, the final formation of groups will be dependent on the medication status of the recruited participants. Thus, there may be specific contrasts that are not possible due to low numbers; for practical purposes we define this as <15 participants. Since methylphenidate is the first line pharmacological treatment for ADHD in the UK (National Institute for Health and Care Excellence, 2018), we expect that the majority of participants will be receiving methylphenidate.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
1. Behavioural data: Hypothesis 2: Behavioural data analyses of all dependent variables will match the group comparisons conducted on fMRI data.

2. MRI data: Structural and functional MRI data will be processed using SPM 12. First, we will preprocess (see section 8) and model the neuroimaging data on a single subject level. The first level models will include the following conditions and covariates: (1) Go trials; (2) Successful stop trials; (3) Failed stop trials; (4) Missed go trials and go trial errors; (5) Motion parameters estimated during preprocessing
First level model contrasts will be: (1) Successful stop > go trials; (2) Failed stop > go trials. These will be used at the second level to test the hypotheses. An exploratory analysis will also compare successful stop > failed stop trials.
Hypothesis 1:Beta-series correlations will be used to investigate task-related functional connectivity (Rissman et al., 2004). The following ROIs will be used: inferior frontal cortex (MNI coordinates [x, y, z]: 50, 18, 6), insula (36, 18, 0), pre-supplementary motor area (6, 18, 48), supramarginal gyrus (52, -46, 36), subthalamic nucleus (derived from probabilistic subthalamic nucleus atlas), and caudate (defined from the Harvard-Oxford probabilistic atlas). These regions have shown involvement in motor inhibition paradigms (Aron, 2007; Zhang et al., 2017) and have been observed to exhibit lower activation in ADHD individuals relative to controls (Cortese et al., 2012; Hart et al., 2013; Lei et al., 2015; Lukito et al., in press; McCarthy et al., 2014; Norman et al., 2016).
Hypothesis 3: We will use an independent samples t-tests with an input from the first level contrasts, specifying the groups described below. An ROI analysis will be performed on the same nodes as used in testing hypothesis 1 to investigate the differences in brain activation between groups during stop task performance, following steps detailed above. Covariates will be mean centred and include age in months. The following groups comparisons will be performed:
-ADHD medication naïve vs healthy controls
-ADHD on methylphenidate vs heathy controls
-ADHD on methylphenidate vs ADHD medication naïve
Hypothesis 4: A whole brain analysis will be performed to provide an unbiased assessment of the differences in brain activation between the groups specified above during stop task performance, following steps detailed above.
Hypothesis 5: ADHD symptoms will be regressed against changes in activation or functionality pattern observed in testing of hypotheses 1, 3 and 4.
The pipelines for the above fMRI analyses will be developed on independent data.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
This project will include boys with ADHD (10-18 years old) without major psychiatric or neurological comorbidities (oppositional defiant and conduct disorders will be allowed but a sensitivity analysis will be performed). Participants who have discontinued their ADHD medication treatment less than two weeks before the scan will be excluded.
Participants with extreme movements will be excluded. Using ArtRepair, more than 5% of slice artefact or more than 25% of volume artefacts will lead to the exclusion of the participant.
Participants whose performance data indicate that they did not follow/understand the task instructions (i.e. probability of inhibition <0.25 or >0.75 (Verbruggen et al., 2019) and rate of omission error to go trials >30%) will be excluded.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
This project will include baseline data collected for two studies investigating the effects of fMRI neurofeedback in ADHD. The majority of the data will be derived from an ongoing study investigating the mechanism and clinical efficacy of real-time fMRI neurofeedback of the right inferior frontal cortex in ADHD. This study is aiming to recruit 100 ADHD adolescents. This study will also include existing data (N=31) from a proof of concept study of fMRI neurofeedback for ADHD (Alegria et al., 2017). The current study will therefore include a maximum of 131 ADHD participants, prior to data quality checks. Additionally, 20-30 healthy controls will be recruited (The recruitment might be challenged by the COVID-19. We are hoping to reach a decent number of participants but we aware that this might be complicated with the new guidelines of March 2020). For a power of 90% and p<0.008 (0.05/6 ROIs) on an ANOVA testing hypotheses (1) assuming minimum total number of participants of 100 with three groups and one covariate, an effect size of f=0.46 is estimated.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
The data for this project will come from two other studies exploring the mechanism and clinical efficacy of real-time fMRI neurofeedback of right inferior frontal cortex in ADHD. One of those studies has already been completed (N=31) (Alegria et al., 2017), while the other (predicted N=100) is ongoing (see section 7). The following preprocessing steps will be performed on fMRI data in the order listed. Default options will be used except where otherwise indicated. Data preprocessing will include: (1) Slice-timing correction with the middle slice in the time series used as reference; (2) Realignment; (3) Co-registration with T1-weighted images; (4) Tissue segmentation of the structural data into three different tissue types (grey matter, white matter and cerebrospinal fluid) using unified segmentation. The resultant upsampled grey and white matter segmented images will be used to create an unbiased intermediate study-specific template using DARTEL (Ashburner, 2007); (5) Normalisation of functional data to MNI template using deformation flow field parameters produced in step (4); (6) Spatial smoothing at 6mm FWHM; (7) *Depending on the data quality, ArtRepair (Mazaika et al., 2005) will be used to clean the data for some participants. a. First, the raw data will be assessed; b. Then, noise filtering will be applied to detect and repair slice artefacts. This will be done only if less than 5% of slices show artefacts; c. Finally, we will detect and repair volume artefacts (>1.5% variation in global intensity or >0.5mm/time repetition scan-to-scan motion) for up to 25% of the functional runs. If more than 20% of participants will show volume artefacts in more that 25% of functional runs, the threshold for scan-to-scan motion will be relaxed to 1mm.