Experimental fMRI study on the comparison of the brain function effects of a single dose of guanfacine and lisdexamfetamine relative to placebo in children and adolescents with ADHD

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1. PROTOCOL FULL TITLE: Experimental fMRI study on the comparison of the brain function effects of a single dose of Guanfacine and Lisdexamfetamine relative to placebo in children and adolescents with ADHD.

Protocol Short Title/ Acronym: AGUALIS

Study Identifiers

ClinicalTrials.gov ID:			
REC Number:			
UKCRN Number:			
Protocol Version Number:	5	Date:	27/03/2019

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2. Study Synopsis

TITLE OF EXPERIMENTAL STUDY:	Experimental fMRI study on the comparison of the brain function effects of a single dose of Guanfacine and Lisdexamfetamine relative to placebo in children and adolescents with ADHD.
Protocol Short Title/Acronym:	AGUALIS
Study Type:	Basic Science Study
Sponsor Name:	King's College London
Chief Investigator:	Oliwia Kowalczyk
UKCRN Number:	
REC Number:	18/LO/0472

Medical Condition or Disease Under Investigation:	Attention Deficit Hyperactivity Disorder (ADHD)
Purpose of Experimental Study:	To compare single dose effects of Guanfacine extended release (GXR) and Lisdexamfetamine (LDX) relative to placebo and compared to controls on ADHD fMRI brain function during typically compromised cognitive tasks that are modulated by these drugs (motor inhibition, working memory, and sustained attention).
Primary Objective:	To investigate the common and drug-specific effects of single-dose GXR and LDX, compared to placebo on brain function in ADHD using fMRI.
Secondary Objective(s):	To assess the effects of the two drugs on performance on the tasks.
Study Design:	Cross-sectional, Case-control, Crossover, Placebo Controlled, Randomised, Single-dose and Single-site study
Endpoints:	1) Brain activation as measured by blood−oxygen−level−dependent (BOLD) response as obtained by functional magnetic resonance imaging for each of the 3 tasks and the resting state. 2) Dependent variables extracted from performance on tasks.
Sample Size:	20 ADHD adolescents, 8-20 years 20 healthy controls, 8-20 years
Summary of Eligibility Criteria:	ADHD patients: Meeting clinical diagnosis for Attention-Deficit Hyperactivity Disorder (ADHD); age range 8-20 years; medication-naïve or non-medicated in the 3 months; no comorbid conditions other than autism, phobias, eating disorders, oppositional defiant and conduct disorder or mild anxiety and depression; IQ > 70; heart rate > 65 beats/minute; systolic blood pressure > 90 mm Hg, diastolic blood pressure < 90 mm Hg. Healthy controls: No clinical diagnosis of ADHD or any other major psychiatric disorder; age range 8-20 years; psychoactive medication-free; no mental health conditions; IQ > 70.
Intervention (Description, frequency, details of delivery)	Each ADHD patient will be scanned 3 times, under either LDX, GXR, or placebo, in randomised order (visits 1, 2, 3). Each patient will receive one single clinical oral dose of GXR, LDX, and placebo and undergo a fMRI scan 4.5 hours after ingestion. Then they will receive nothing for a week and then be scanned again one week later on the single dose of the other conditions (placebo or drug) (visits 1, 2 and 3). Healthy controls will be tested once, unmedicated.
Comparator Intervention:	Not applicable
Maximum Duration of the Study for a Subject:	3 weeks

Version and Date of Final Protocol:	Version 5 27/03/2019
Version and Date of Protocol Amendments:	

3. Revision History

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date

4. Glossary of terms (Optional)

ADHD = Attention Deficit Hyperactivity Disorder

fMRI= functional Magnetic Resonance Imaging

IoPPN = Institute of Psychiatry, Psychology & Neuroscience

KCL = King's College London

LDX = Lisdexamfetamine

GXR = Guanfacine Extended Release

5. Protocol Contents

6. Background & Rationale

Attention Deficit/Hyperactivity Disorder (ADHD) is defined by age-inappropriate problems with inattention, impulsiveness, and hyperactivity. ADHD is one of the most common childhood disorders affecting 5-10% of children. Currently, stimulants are first-line treatment for ADHD (Wilens, 2008). A meta-analysis of fMRI studies of single Methylphenidate (MPH) effects shows consistent upregulation and normalisation of the ventral attention system (IFC and basal ganglia; Rubia et al., 2014a) which is consistently reduced in ADHD relative to controls causing attention and inhibition deficits (Rubia et al., 2014b, Hart et al., 2013). MPH also deactivates areas of the default mode network (Rubia et al., 2014a), representing mind wandering, which is typically enhanced in ADHD, causing attention lapses and impairing performance (Rubia et al., 2014b, Christakou et al., 2013). The mechanisms of action of more recently licenced stimulant (Lisdexamfetamine - LDX) and nonstimulant (Guanfacine Extended Release - GXR) drugs on ADHD brain function, are, however, unknown. LDX is efficacious in reducing ADHD symptoms with larger effect sizes than MPH (Soutullo et al., 2013). In animal studies, LDX produces more substantial increases in catecholaminergic neurotransmission in prefrontal cortex and striatum (Rowley et al., 2014). Cognitively, it also improves academic performance, executive functions and attention in ADHD (Turgay et al., 2010). However, the effect of LDX on brain function in ADHD is unknown. GXR reduces ADHD symptoms (Wilens et al., 2015) with larger effect size than Atomoxetine (ATX; Sikirica et al., 2013). It is a selective α2-adrenoceptor agonist, enhancing noradrenaline neurotransmission in the prefrontal cortex (Wang et al., 2007). Guanfacine improves planning, working and emotional memory, associative learning (Jakala et al., 1999, Swartz et al., 2008), selective and flexible attention (Fox et al., 2015), while in ADHD it improves sustained attention and interference inhibition (Scahill et al., 2001). fMRI and PET studies in humans (and animals) show that guanfacine enhances DLPFC, striato-thalamic and parietal activation (Swartz et al, 2010) during working memory (McAllister et al., 2011), choice behaviour (Kim et al., 2012), selective attention (Clerkin et al., 2009), stress (Fox et al., 2012), and emotion processing (Schultz et al., 2013; Schultz et al., 2014). GXR and LDX thus have positive effects on ADHD behaviour and cognition, but their underlying brain mechanisms are unknown. It is paramount to understand the differential mechanisms of action of these two drugs on ADHD brain function relative to each other.

7. Study Objectives and Design

7.1 Study Objectives

Aim of the study

The aim of this study is to understand the mechanism of action of two recently licensed drugs for ADHD on brain function and cognition. We will compare the brain activation changes elicited by Guanfacine extended release (GXR; a non-stimulant drug) with the brain activation changes elicited by Lisdexamfetamine (LDX; a stimulant drug) and by placebo in 20 currently non-medicated patients with ADHD using functional Magnetic Resonance Imaging (fMRI). Additionally, we will test 20 unmedicated healthy controls to test for potential normalisation of the two drugs on ADHD cognition and brain function. For this purpose, we intend to scan participants during their performance of tasks of attention, working memory, and inhibition, which we know from previous studies to elicit abnormal brain activation patterns in ADHD patients (Rubia et al., 2005; Smith et al., 2006). Additionally, prior to each scanning session participants will complete a battery of neurocognitive tasks, which were previously shown to be impaired in ADHD (Rubia et al., 2007). ADHD participants

performance on the neurocognitive tasks will be compared across sessions and to the performance of healthy controls.

Objectives of the Study

The proposal is for a suitably powered experimental randomised placebo-controlled double-blind study to test the mechanism of LDX and GXR compared to placebo in ADHD children.

7.1.1 Primary endpoints

Brain activation as measured by blood−oxygen−level−dependent (BOLD) response as obtained by functional Magnetic Resonance Imaging (fMRI) for each of the 3 tasks and a resting state scan.

1) A working memory task (N-back task) (6 min)

2) A tracking stop task (9 min)

3) A parametric sustained attention task (12 min)

4) A resting state scan (8 min)

7.1.2 Secondary endpoints

Dependent variables extracted from performance on the above listed tasks completed in the scanner. Dependent variables extracted from performance on the neurocognitive battery of tasks:

1) Go/No-go (5 min)

2) Interference inhibition (Simon task) (5 min)

3) Continuous performance task (8 min)

4) Time discrimination task (5 min)

5) Vigilance task (7 min)

7.2 Study Design

Cross-sectional, Case-control, Crossover, Placebo Controlled, Randomized, Single-dose and Single-site.

7.3 Study Flowchart

For ADHD patients:

	Pre-assessment	Visit 1	Visit 2	Visit 3
Date				
Start / End time				
Researcher Administered				
Eligibility checklist				
K-SADS (P/C)				
Self-Administered				
Background Information (P)				
Edinburgh Handedness (C)				
SCQ (P)				
CPRS (P)				
ADHD-RS (P)				
Adverse Effects Scale (P)				
Neurocognitive Measures				

WASI (30-40min)				
Go/No-go task (5min)				
Interference inhibition (Simon) (5min)				
Continuous performance task (8min)				
Time discrimination task (5min)				
Vigilance task (7min)				
fMRI Working Memory task (6min)				
fMRI Tracking Stop task (9min)				
fMRI Sustained Attention task (12min)				
fMRI Resting State (8min)				
Forms				
Consent form child				
Consent form parent				
MRI safety form				
MRI request form				
Receipt of payment				

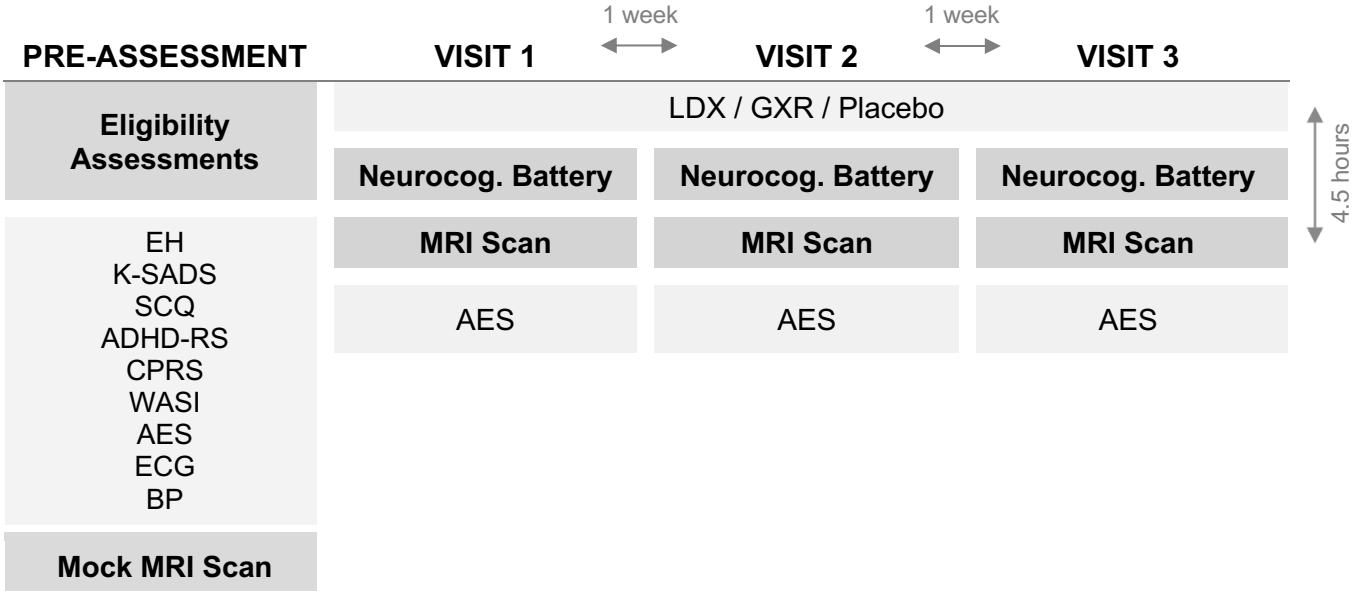

Figure 1. Schematic overview of the design of the study. ADHD-RS, Attention Deficit Hyperactivity Disorder-Rating Scale; AES, Adverse Effects Scale; BP, Blood Pressure; CPRS, Conners' Parent Rating Scale; ECG, Electrocardiogram; EH, Edinburgh Handedness; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; Neurocog. Battery, Neurocognitive Battery of tasks; SCQ, Social Communication Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence.

For healthy controls:

	Pre-assessment	Visit 1
Date		
Start / End time		

Researcher Administered		
Eligibility checklist		
Self-Administered		
Background Information (P)		
Edinburgh Handedness (C)		
SCQ (P)		
CPRS (P)		
Neurocognitive Measures		
WASI (30-40min)		
Go/No-go task (5min)		
Interference inhibition (Simon) (5min)		
Continuous performance task (8min)		
Time discrimination task (5min)		
Vigilance task (7min)		
fMRI Working Memory task (6min)		
fMRI Tracking Stop task (9min)		
fMRI Sustained Attention task (12min)		
fMRI Resting State (8min)		
Forms		
Consent form child		
Consent form parent		
MRI safety form		
MRI request form		
Receipt of payment		

PRE-ASSESSMENT

Eligibility Assessments

EH
SCQ
CPRS
WASI

Mock MRI Scan

VISIT 1

Neurocog. Battery

MRI Scan

Each session of cognitive tasks will consist of the below:

Go/No-go (5min)	Interference inhibition (Simon task; 5min)	Continuous Performance (8min)	Time Discrimination (5min)	Vigilance (7min)

Each MRI scan will consist of the below:

Structural Scan (10min)	fMRI Working Memory (N-back; 6min)	fMRI Tracking Stop Task (6min)	fMRI Parametric Sustained Attention (12min)	fMRI Resting State (8min)

Figure 1. Schematic overview of the design of the study. ADHD-RS, Attention Deficit Hyperactivity Disorder-Rating Scale; CPRS, Conners' Parent Rating Scale; EH, Edinburgh Handedness; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; Neurocog. Battery, Neurocognitive Battery of tasks; SCQ, Social Communication Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence.

8. Study Design

8.1 Study Details

There will be two groups. The first group will comprise 20 ADHD patients between 8 and 20 years who will participate in the double-blind, randomised, active drug condition, within-group, placebo-controlled experimental fMRI study. The second group will consist of 20 healthy young people between 8 and 20 years old, who will act as a control group and be scanned only once under no drug. Each ADHD participant will be assessed in baseline measures during the pre-assessment. Then the ADHD patient will be scanned 3 times under each of these 3 drug conditions: GXR, LDX, and placebo. We will compare the patient groups under the acute dose of LDX and GXR with placebo in a randomised, within-group, placebo-controlled design. Every patient will receive a single typical clinical weight-adjusted dose of GXR (0.05mg/kg, being rounded to the closest dose of 1mg, 2mg, or a maximum of 3mg GXR), LDX (30mg for participants under 30kg, 50mg for participants over 30kg body weight) and placebo (10mg Vit C) in one of the scans, in a randomised order. Advice regarding drug dosage has been specifically obtained from an experienced child psychiatrist with expertise in paediatric psychopharmacology. For fMRI studies of single dose effects, it is common practice to use the standard typical clinical target dose that is given to patients after a period of titration rather than the initial dose that would be given clinically on the first day in continuous clinical drug administration where patients are titrated up to the optimal dose. This is to test for the brain effects of a typical dose of the medication under investigation in the patient population. This was also done in our previous fMRI studies where we tested the single dose effects of a standard clinical dose of Methylphenidate (0.03mg/kg) and Atomoxetine (1mg/kg) (Cubillo et al., 2012).

It is generally agreed that for Guanfacine to show clinical effects, it should be administered continuously for approximately 6 weeks. In the case of a single dose study this is a clear limitation. Nonetheless, while behavioural effects might need long term administration to appear, it has been shown in previous fMRI studies that brain function changes will be apparent after a single dose. This is based also on similar observations in studies investigating the related drug Atomoxetine, which is also a noradrenalin agonist. Atomoxetine is also a non-stimulant medication for ADHD that shows behavioural effects after several weeks but we have shown brain function effects after one single dose in ADHD patients (Cubillo et al., 2013; Smith et al., 2013).

ADHD patients will be scanned 4.5 hours after drug administration (where drugs have shown to have maximum plasma concentration). They will be scanned 3 times, one week apart, under each drug condition (LDX, GXR, placebo). Scanning session duration: 60 min.

Healthy controls will be scanned once, under no drug condition, and complete the same protocol as ADHD patients.

Each participant will receive £20 for the pre-assessment visit and £50 for each scanning session to reimburse them for their time (i.e. £170 in total for ADHD patients and £70 for healthy controls). We will also reimburse any travel expenses and can arrange taxis or other travel if required. After each visit participants will receive a token showing the amount that he or she will be paid for the session (i.e. £20 or £50). Payments will be given at the end of the patient's participation in the study, i.e. they will exchange the tokens they collected for money.

8.2 Frequency and Duration of Intervention

Each ADHD subject is expected to visit the IoPPN for a pre-assessment and 3 testing sessions performed at 4 separate visits one week apart.

The scans will be performed at intervals of 7 days to allow for sufficient washout periods. The literature shows that GXR has a half-life of approximately 17 hours (Cruz, 2010) and LDX of approximately 9 hours (Boellner et al., 2010). Following the general guideline of calculating washout period as 6.5 times the half-life of the drug, the appropriate washout period for GXR is 4.6 days and for LDX 2.4 days. Consequently, there should be no drug interactions if the scans are performed at 7-day intervals.

The first scan will be performed approximately a week after the initial assessment (described in section 11 of this document). Each ADHD patient will receive a single typical clinical weight adjusted oral dose of GXR (0.05mg/kg, being rounded to the closest dose of 1mg, 2mg, or a maximum of 3mg GXR), LDX (30mg for participants below 30kg, 50mg for participants above 30kg body weight), and placebo (10mg Vitamin C) in one of the scans, in a randomised order. Patients will be scanned 4.5 hours after drug administration (where drugs have shown to have maximum plasma concentration). In each testing session participants will complete a 60-minute-long MRI scan consisting of various tasks (described in section 11 of this document). Total time for which each subject will be enrolled in this study is 3 weeks during which he or she will complete one 4-hour long pre-assessment and 3 hourly scanning sessions (a total of approximately 7 hours).

Healthy controls will visit IoPPN twice: for a pre-assessment and for one fMRI and cognitive testing session.

8.3 Subject Compliance

Young people with ADHD included in the study will be medication naïve (or not have had medication in the past 3 months) and they will have to wait to start their medication (if they are planning to have medication) until the end of the study. This may be inconvenient for some patients but we will only include participants who are prepared to do this. Furthermore, we will attempt to keep the length of the testing period for each patient to a minimum, by scanning participants with minimum intervals (1 week) between scans.

8.4 Study Adherence

No adherence issues are expected as this is a single dose study with the medication being provided by the researcher on the day of the scan.

8.5 Concomitant Medication

Patients included in the study will be medication naïve or not have taken medication in the past 3 months.

9. Research Environment

The study will be conducted at an academic institution, the Institute of Psychiatry, Psychology & Neuroscience, at King's College London, UK. The medication will be provided by Shire Pharmaceuticals Limited and given to Maudsley Pharmacy who will perform the overencapsulation for blinding and dispensing. The PhD student will collect and administer the drugs to participants; this will be done under clinical supervision. A Child Psychiatrist (Dr Celine Ryckaert) will prescribe the medication, will be present at the end of the session and will be on-call during the scan. Additionally, there will be a second psychiatrist working on the study who will be able to provide cover for times when Dr Ryckaert is unavailable. All

fMRI scans will be completed at the 3T GE scanner at the Centre for Neuroimaging Sciences (CNS) at the IoPPN.

10. Selection and Withdrawal of Subjects

10.1 Inclusion Criteria

Twenty young people with ADHD, 8-20 years old, medication-naïve or medication free for at least three months, recruited from local clinics, meeting DSM-5 criteria for ADHD using ADHD Diagnostic Interview and rating scales.

- Age range: 8-20 years

- Medication-naïve or on non-medicated for at least 3 months

- Meeting DSM-5 diagnosis of ADHD

- Score above clinical cut-off on the ADHD module of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1996)

- Score above clinical cut-off for ADHD on the short forms of the Conners Parent Rating Scales, CPRS (Conners et al., 2008)

- Score above cut-off on the ADHD Rating Scale, ADHD-RS (DuPaul, et al., 1998)

- IQ > 70 as tested on the WASI-II (Wechsler et al., 1999)

Mood and depression symptoms, autism, phobias, anxiety, conduct disorder, oppositional defiant disorder, and eating disorders will be allowed.

Twenty healthy young people, 8-20 years old, will be recruited.

- Age range: 8-20 years

- Not using psychoactive medications

- Score below cut-off for ASD on the Social Communication Questionnaire (SCQ) (Rutter et al., 2001)

- Score below cut-off for ADHD or other disorders on the short forms of the Conners Parent Rating Scales, CPRS (Conners et al., 2008)

- IQ > 70 as tested on the WASI-II (Wechsler et al., 1999)

10.2 Exclusion Criteria

Exclusion criteria for ADHD participants:

- IQ < 70 (Wechsler et al., 1999)

- Currently on ADHD medication or has been on ADHD medication in the past 3 months

- Comorbidity with schizophrenia, bipolar disorder, learning disability, OCD, severe depression with current suicidal behaviour (as assessed by a clinical interview)

- Neurological problems, i.e. a history of severe neurological illness, e.g. brain tumour, epilepsy or a history of symptomatic seizures, polyneuropathy etc.

- Substance abuse history

- Other illness (cardiovascular, renal, hepatic, metabolic) that would impact the data integrity or safety of the subject (i.e. contraindicated to any of the treatments) as determined by the investigators

- Contraindication to MRI. i.e., previous implantation of metallic material, pacemaker, implanted medication pumps, neural stimulators, claustrophobia

- Unable to give informed assent or consent in the case of the parent

- Contraindications for LDX and GXR use (i.e. advanced arteriosclerosis, agitated states, hyperexcitability, hyperthyroidism, moderate or severe hypertension, symptomatic cardiovascular disease, heart rate < 65 beats/minute, systolic blood pressure < 90 mm Hg, diastolic blood pressure > 90 mm Hg)

Exclusion criteria for healthy controls:

- IQ < 70 (Wechsler et al., 1999)

- Currently on psychoactive medication treatment

- Diagnosis of a mental health disorder

- Scoring high on the questionnaires for ADHD (CPRS) or Autism (SCQ)

- Neurological problems, i.e. a history of severe neurological illness, e.g. brain tumour, epilepsy or a history of symptomatic seizures, polyneuropathy etc.

- Substance abuse history

- Other illness (cardiovascular, renal, hepatic, metabolic) that would impact the data integrity or safety of the subject (i.e. contraindicated to any of the treatments) as determined by the investigators

- Contraindication to MRI. i.e., previous implantation of metallic material, pacemaker, implanted medication pumps, neural stimulators, claustrophobia

- Unable to give informed assent or consent in the case of the parent

10.3 Selection of Participants

Patients will be recruited through Child and Adolescent Mental Health Services, via advertisement, social media, parent support groups as well as via Trust Consent for Contact mechanisms. Potential participants will be identified within the participating NHS Trusts (South West London and St George's Mental Health Trust, Oxleas NHS Foundation Trust, Camden and Islington NHS Foundation Trust, Central and North West London NHS Foundation Trust, Barnet, Enfield and Haringey Mental Health NHS Trust, Great Ormond Street Hospital, City and Hackney CAMHS, South London and Maudsley NHS Foundation Trust, East London NHS Foundation Trust, Whittington Health NHS Trust, Guy's and St Thomas' NHS Foundation Trust, North East London NHS Foundation Trust, West London Mental Health NHS Trust).

The healthy controls will be recruited through advertisement on social media and other online platforms, community spaces (e.g. libraries), schools, and newspaper adverts.

10.4 Withdrawal of Subjects

There is little evidence for side or adverse effects of the single dose LDX and GXR, hence withdrawal due to adverse effects is not expected. Nevertheless, potential adverse effects have been listed in the participant information sheet which will be provided to participants and their parents for their information. Participation will be discontinued if

- *the participant decides they no longer wish to continue*
- *recommended by the investigator*

Should a patient decide to withdraw from the study, the reason for withdrawal will be recorded as detailed as possible.

Participants who wish to withdraw from the study will be asked to confirm whether they are still willing to provide the study specific data at visits that were completed.

10.5 Expected Duration of Study.

1st May 2018 – 31st December 2020

Provided a timely reception of ethical approval we will begin recruitment in May and expect to begin testing the first participant by June 2018. We predict that we will be able to test one participant a month, depending on participant and scanner availability. We aim to finalise data collection by 31st December 2020 latest. Following that, we will begin data analysis, preparation of publications, and the PhD student will begin thesis write up.

11. Study Procedures

The following procedure will be followed in this study:

We will recruit 20 young people aged between 8 and 20 years with a current diagnosis of ADHD, who have never taken medication for ADHD (medication-naïve) or who have not been on ADHD medication for at least 3 months. All participants will have no history of substance abuse and no neurological deficits, learning disability, reading, speech, or language disorder, no other major clinical psychiatric disorder other than ADHD and autism, and no contraindications for LDX or GXR. These patients will be identified within SLaM and other clinics and will have already received a diagnosis of ADHD from a clinician or will be on a community waiting list awaiting clinical ADHD assessment. The family will be given a letter inviting the patient to participate as well as an information sheet.

If participants are interested in taking part their informed consent (or that of their parents where participants are under 16) will be sought and recorded by the PhD student. The PhD student will make sure that the participants have no contraindications to participation in this study (including MRI and drug related contraindications). Once they have agreed to participate in the study, we will invite parents and their child to come for a pre-assessment meeting at the Institute of Psychiatry, Psychology and Neuroscience where we will perform the following assessments:

1) Edinburgh Handedness Inventory (Oldfield, 1971)

2) IQ (WASI-II) (Wechsler et al., 1999)

3) Social Communication Questionnaire (Rutter et al., 2001)

4) Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), ADHD module (Kaufman et al., 1996); this assessment will be audio-recorded for reliability purposes, consent will be sought

5) ADHD Rating Scale (ADHD-RS) to measure ADHD symptom severity (DuPaul et al., 1998)

6) The Conners-Third Edition: Parent Rating Scales, Short Form [Conner 3- P(S)] to assess ADHD severity (Conners, 2008)

7) ECG; this will be performed to ensure the participants have no cardiac contraindications to using LDX or GXR, the results will be reviewed by a doctor; patients who have a heart rate below 65 beats/minute will be excluded

8) Blood pressure; this will be measured in order to be able to exclude patients with systolic

blood pressure of < 90 mm Hg and diastolic blood pressure of > 90 mm Hg

9) Physical measurements (i.e. weight); this will be taken to accurately calculate the medication dosage

Additionally, the patient will be familiarised with the scanner environment by visiting the "mock scanner" and trained on the tasks he or she will later complete in the actual scanner. If eligible the patient will be invited to come back to the IoPPN to complete the three fMRI scans. Each patient will participate in three testing sessions performed at three separate visits one week apart. Each patient will receive a single typical clinical weight adjusted dose of GXR (0.05mg/kg, being rounded to the closest dose of 1mg, 2mg, or a maximum of 3mg GXR), LDX (30mg if below 30kg, 50mg if above 30kg body weight), and placebo (10mg Vitamin C) in one of the scans, in a randomised order. After approximately 3.5 hours and an hour prior to the scan the participant will complete a battery of the following neurocognitive tasks lasting approximately 40 minutes:

1) Go/No-go - 5 min, assessing the participant's ability to inhibit a motor response and selective attention (Rubia et al., 2007)

2) Interference inhibition (Simon task) - 5 min, involving a stimulus-response incompatibility effect. The task measures interference inhibition and selective attention. In this task, subjects have to execute a motor response according to iconic information and to inhibit the tendency to make an incorrect response that is triggered by an interfering, and predominant, spatial information (Rubia et al., 2007)

3) Continuous performance task - 8 min, measuring target detection, sustained attention, as well as selective attention (Rubia et al., 2007)

4) Time discrimination task - 5 min, measuring the participant's ability to discriminate between time intervals that differ by several hundreds of milliseconds (Rubia et al., 2007)

5) Vigilance task - 7 min, assessing vigilance on the detection of signals that are difficult to identify (Mackworth, 1948).

Subsequently, patients will be taken to the MRI suite to undergo a brain scan. Patients will be scanned 4.5 hours after drug administration (where drugs have shown to have maximum plasma concentration). The researcher at the scan (i.e. PhD student) will not know which tablet is given on each occasion. This has been designed this way to minimise bias. Medication details will be kept by the supervisor, and will be given to the parents after the three scans have taken place, and to the PhD student to group the data once all the subjects have been scanned.

In each scanning session, the participants will complete the following tasks that have shown to elicit underactivation in task-relevant regions in ADHD and to be modulated by MPH and ATX:

1) Working memory task (N-back task) - 6min, measuring 3 levels of working memory difficulty and will also assess the default mode network decrease with progressively increasing working memory (Cubillo et al., 2013, Chantiluke et al., 2014)

2) Tracking stop task - 9min, measuring motor response inhibition and error monitoring (Rubia et al., 2005, 2011; Cubillo et al., 2013)

3) Parametric sustained attention task - 12min, investigating the effects of increasing load on sustained attention on brain activation (Christakou et al., 2013, Murphy et al., 2015)

4) Resting state fMRI - 8min, measuring intrinsic connectivity networks associated with ADHD (default mode network, cognitive control network, dorsal and ventral attention,

saliency, and motor networks).

Total scanning time for each session will be approximately 60 minutes. The duration of testing for each subject will be 3 weeks.

Additionally, a group of 20 healthy age-matched controls will be recruited. Healthy controls will have no diagnosis of ADHD or other major psychiatric conditions, they will be psychoactive-medication free, have no history of substance abuse and no neurological deficits, learning disability, reading, speech, or language disorder. Healthy controls will be assessed using the following measures during their first visit at the IoPPN:

1) Edinburgh Handedness Inventory (Oldfield, 1971)

2) IQ (WASI-II) (Wechsler et al., 1999)

3) Social Communication Questionnaire (Rutter et al., 2001)

4) The Conners-Third Edition: Parent Rating Scales, Short Form [Conner 3- P(S)] to assess ADHD and other disorders (Conners, 2008)

Additionally, the participant will be familiarised with the scanner environment by visiting the "mock scanner" and trained on the tasks he or she will later complete in the actual scanner. If eligible the participant will be invited to come back to the IoPPN for a testing session that will involve the same cognitive and fMRI tasks as conducted with ADHD patients. The duration of testing for each healthy control will be one week or less.

12. Assessment of Safety

12.1 Specification, Timing and Recording of Safety Parameters.

MRI is considered safe and non-invasive and there are no reported side effects. However, there is a slight risk that the scanner is sometimes perceived as unpleasant and uncomfortable. The researchers will be sensitive to this possibility and will suspend testing sessions at the request of the participant or at the first signs of distress and discomfort. The participant will be informed that he or she is free to terminate the scanning session whenever they wants to. Alerting mechanisms ensure easy communication and radiographers will constantly check that the participant is content to remain in the scanner.

Adolescents are sometimes anxious about the scanner. To familiarise them with this new environment they will participate in a "mock scan" in an inactive scanner beforehand and be trained on the tasks included in the study. They will also be able to tell in the first scan whether they are happy to be scanned 3 times. Every effort will be made to ensure that they do not feel anxious or claustrophobic. However, if they feel that the scanner is frightening to them, they will not have to participate. The same applies for adolescents who feel claustrophobic in the scanner.

The scanner is also noisy and this may be unpleasant for some children. We will, therefore, expose them to the noise beforehand in the mock scanner. If the children feel that they dislike the noise, they do not have to participate. Also, in order to minimize the discomfort of the noise, we will provide all participants with headphones that are specifically designed to reduce the noise level. This is standard procedure for all scanning subjects at the IoPPN.

Participants will be informed of the non-invasiveness and safety of the MRI scan.

Because we require 3 scanning sessions of 60 minutes of repeated scanning for this project, we decided to only scan older children, i.e. young people between 8 and 20 years. If the patients for whatever reason are not happy or do not tolerate the repeated scans and decide to drop-out of the research they are allowed to do so at any time.

During a research MRI scan, information is sometimes obtained about neurological abnormalities. This will be assessed by a clinical radiographer who will then inform the patient's GP about any unusual anomalies which appear to be a cause for concern. The participant's parent/guardian will then be informed about these by the GP.

Young people with ADHD included into the study will be medication naïve or not had medication for at least 3 months and they will have to wait to start their medication (if they are planning to have medication) until the end of the study. This may be inconvenient for some patients but we will only include participants who are prepared to do this. Furthermore, we will attempt to keep the length of the testing period for each patient to a minimum, by scanning participants with a minimum intervals (1 week) between scans. Taking medication for the first time is a sensitive issue but this study will be under the strict guidance of a clinician, i.e. a child psychiatrist (Dr Celine Ryckaert) will be responsible for prescribing the medication and for discharging patients, the psychiatrist will also be on call on the day of each scan. The side effects (listed in the information sheet) may or may not be experienced by patients and this may be uncomfortable and/or distressing for both patient and parents. However, we expect that the majority of our participants will be recruited via clinics where they will be expecting to be prescribed medication for ADHD in the near future. This will mean they will most likely have had full and frank discussions about the advantages and disadvantages of medication with the clinician and will have thought carefully about this issue before being recruited for this study.

The medication will be overencapsulated for blinding. To make it easy for patients to ingest the capsules the smallest size was chosen after consultation with Maudsley Pharmacy.

The 3T MRI scanner, which is CE marked, will be used for functional neuroimaging protocol as well as the conventional structural neuroimaging protocol. One of the functional imaging protocols will involve the use of multi-echo scanning sequence. The multi-echo sequence will significantly improve the quality of the resting state data, as it will reduce motion, respiration, cardiac function, and other non-neuronal artefacts. The sequence will be applied to the resting state scan only as the resting state data is highly sensitive to such artefacts. The enhanced functional multi-echo neuroimaging protocol used in the Institute of Psychiatry Centre of Neuroimaging Studies includes minor modification of the conventional use of the CE marked scanner. A customised pulse sequence program (i.e. software) has been developed to allow enhanced functional multi-echo imaging on the General Electric Magnetic Resonance Imaging (MRI) scanner to be used for this study. As application of this sequence involves using the MRI scanner outside its CE marking, a formal risk assessment was undertaken in order to investigate the safety implications of the use of this sequence (and in particular any additional risks relative to the manufacturer provided version) and to ensure appropriate procedures were in place to manage such risks. No additional risks were identified, and the sequence can therefore be used with standard precautions. Since its implementation, the sequence has been successfully applied in studies involving human participants

12.2 Procedures for Recording and Reporting Adverse Events

While there are side effects associated with long-term use of LDX and GXR, the single dose administration is unlikely to cause side effects. Nonetheless, any adverse effects will be monitored with a standardised parental questionnaire developed by Hill and Taylor (2001), extended to include GXR and LDX related side effects. Furthermore, a clinician will be on call for the scanning day in the unlikely case of any adverse effects. Moreover, potential side effects associated with the drugs (such as: drowsiness, headache, dizziness, dry mouth, fatigue, gastrointestinal problems, loss of appetite, palpitation, elevated blood pressure,

muscle spasm, euphoric mood) have been included in the information sheets for patient's and their parents' information.

In case of any serious adverse events (SAE) standard HRA reporting procedures will be followed. Related and/or unexpected SAE will be reported to the relevant Research Ethics Committee within 15 days of the Chief Investigator becoming aware of the event. All other safety reporting, including progress reports, declaration of conclusion, and summary of final report, will be performed according to the HRA guidelines.

12.3 Stopping Rules

Changes in safety rules are very unlikely and there are no reasons why the study should be stopped.

13. Statistics

13.1 Sample Size

For fMRI comparisons, a minimum N of 20 has been recommended (Thirion et al., 2007). Based on a previous fMRI comparison using whole brain analysis of acute effects of the ATX and MPH on the fMRI brain function in the same working memory task as proposed in this study, we calculated that for a power of 80% we would need an N of 15 subjects for a $p < 0.05$ and N of 20 for a $p < 0.01$ (Cubillo et al., 2013). A sample size of 20 is proposed to account for the fact that the novel contrast of GXR and LDX may potentially have a smaller effect size than the previous comparisons of MPH and ATX. Therefore, to obtain 20 complete datasets 50 patients or more will be screened. This is done to ensure enough participants meet the recruitment criteria and to account for potential dropouts.

13.2 Randomisation

This is a within-patient experimental randomisation design. Each patient gets a single dose of each of the 3 drugs and will be scanned thereafter. The order of drug administration (LDX, GXR, placebo) will be randomised controlling for order effects and the testing will be performed in a double-blind fashion. The supervisor will be responsible for the randomisation and neither the researcher present at scan (i.e. PhD student) nor the parents and patients will know which drug is tested in any given session.

The unblinding will occur at the end of data collection on approval by the Chief Investigator and supervisors. A copy of the blinding will be provided by pharmacy for each study visit to the study team for emergency unblinding. A further copy will be provided to a member of the Department of Neuroimaging unrelated to the study. They can be called at any time to unblind a specific session out of hours if an alternative unblinding option is unavailable.

Unblinding protocol and reporting will be applied according to the local pharmacy procedures.

13.3 Analysis

Analyses of brain activation for the fMRI data will be conducted using SPM (www.fil.ion.ucl.ac.uk/spm) and FSL (www.fsl.fmrib.ox.ac.uk). All performance data will be analysed using SPSS and R. The hypotheses relating activation changes within patients after the acute drug administration will be tested using repeated measures ANOVAs with each of the 3 drug conditions as repeated measures (placebo, GXR, LDX).

Comparison between healthy controls and ADHD patients under placebo and under the two drugs will be conducted by 3 ANOVAs to test for brain abnormalities in ADHD relative to controls at baseline and to test for potential normalisation of the 2 drugs on brain activation.

14. Study Steering Committee

Supervisors will oversee the study.

15. Data Monitoring Committee

As this is an experimental study and not a clinical trial we will not have an external data monitoring committee. The supervisors of the study will form a data monitoring committee and assess the study progress and all other aspects of the study. They will meet once every 6 months.

16. Direct Access to Source Data and Documents

Only the research team and named collaborators will have access to the data.

17. Ethics & Regulatory Approvals

This protocol and related documents will be submitted for review to an NHS Research Ethics Committee (REC).

18. Quality Assurance

Monitoring of this study will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team.

19. Data Handling

The supervisor will act as custodian for the study data. The following guidelines will be strictly adhered to:

- Patient data will be anonymised.
- All anonymised data will be stored on a password protected computer.
- All study data will be stored in line with the Data Protection Act.
- All study data will be archived in line with Sponsor requirements.
- Audio-recordings will be taken on a password protected encrypted smartphone provided by KCL for the purpose of this study. Only the study team will have access to the smartphone. Participants will provide an opt-in consent to have their recordings taken. Where participants will decide not to have their recordings taken this will not disqualify them from the study. The recordings will be kept on a password protected KCL PC in an anonymised format (as described in the above). Audio-recordings will be destroyed upon completion of the study. Nonetheless, participants will have the option to request to have their information (i.e. audio-recordings and any other material generated by the study) destroyed at any time.

20. Data Management

The data will be behavioural data, cognitive performance data, and fMRI data in electronic format and password protected.

The data to be analysed will be inputted into an SPSS datasheet in a linked-anonymised format.

Data management will follow KCL guidelines.

21. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

22. Insurance/Indemnity

A professional indemnity policy is in place from the sponsor (KCL) for all studies conducted at KCL.

23. Financial Aspects

Funding to conduct the study is provided by Shire Pharmaceuticals Limited.

24. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Statistician (if applicable) Date

Print name

25. References

Chantiluke, C. et al. (2014). Psychological Medicine 8, 1-18.
Christakou, A. et al. (2013). Molecular Psychiatry 18, 236-44.
Clerkin, S.M. et al. (2009). Biological Psychiatry 66, 307-312.
Conners, C.K. et al. (2008). Toronto, Canada: Multi-Health Systems.
Cubillo, A. et al. (2012). Cerebral Cortex, 24(1), 174-185.
Cubillo, A. et al. (2013). Psychological Medicine 44, 633-646.
DuPaul, G. K. et al. (1998). New York, NY: Guilford Press.
Fox, H.C. et al. (2012). Journal of Psychopharmacology 26, 958-972.
Fox, H.C. et al. (2015). Journal of Psychopharmacology 29, 312-323.
Hart, H. et al. (2013). JAMA Psychiatry 70, 185-198.
Hill, P. et al. (2001). Archives of Disease in Childhood, 84(5), 404-409.
Jakala, P. (1999). Neuropsychopharmacology 20, 460-470.
Kaufman, J. et al. (1996). Pittsburgh: University of Pittsburgh Press.
Kim, S. et al. (2012). Psychopharmacology 219, 363-375.
Mackworth N. H. (1948). Quarterly Journal of Experimental Psychology 1(1), 6-21.
McAllister, T.W. et al. (2011). International Journal of Psychophysiology 82, 107-114.
Murphy, C.M. et al. (2015). American Journal of Psychiatry 71(10), 1107-16
Oldfield, R. C. (1971). Neuropsychologia, 9(1), 97-113.
Rowley, H.L. et al. (2014). Journal of Psychopharmacology 28, 254-269.
Rubia, K. et al. (2005). American Journal of Psychiatry 162, 1067-75.

Rubia, K., et al. (2007). Child Neuropsychology, 13(3), 276-304.
Rubia, K. et al. (2014a). Biological Psychiatry 7, 616-628.
Rubia, K. et al. (2014b). Expert Review of Neurotherapeutics 14, 519-538.
Rutter, M. et al. (2001). Los Angeles, CA: Western Psychological Corporation.
Scahill, L. et al. (2001). American Journal of Psychiatry 158, 1067-1074.
Schulz, K.P. et al. (2013). Psychopharmacology 226, 261-271.
Schulz, K.P. et al. (2014). European Neuropsychopharmacology 24, 1444-1453.
Sikirica, V. et al. (2013). CNS Drugs 27, 943-953.
Smith, A. B. (2006). American Journal of Psychiatry 163(6), 1044-1051.
Smith, A. et al. (2013). Biological Psychiatry, 74(8), 615-622.
Soutullo, C. et al. (2013). CNS Drugs 27(9), 743-751.
Swartz, B.E. et al. (2008). Clinical Neuropharmacology 31, 251-260.
Swartz, B.E. et al. (2010). Neuropsychopharmacology 23, 263-275.
Thirion, B. et al. (2007). Neuroimage 35, 105-20.
Turgay, A. et al. (2010). Journal of Child and Adolescent Psychopharmacology 20, 503-511.
Wang, M. et al. (2007). Cell 129(2), 397-410.
Wechsler D. (1999). San Antonio, Texas: The Psychological Corporation.
Wilens, T.E. (2008). Journal of Clinical Psychopharmacology 28, S46-53.
Wilens, T.E. (2015). Journal of the American Academy of Child & Adolescent Psychiatry 54(11), 916-925.
Williams, E. J. (1949). Australian Journal of Scientific Research, Ser. A 2, 149-168