Imperial College London

Clinical Study Report

The control of brain networks after traumatic brain injury: a neuroimaging and neuropsychological study of dopamine and cognition

2013-004244-37

19 September 2018

CONFIDENTIAL

Imperial College London

Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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1 TITLE PAGE

Study title: **The control of brain networks after traumatic brain injury: a neuroimaging and neuropsychological study of dopamine and cognition**

Name of Test Drug: Methylphenidate

Indication studied: To test whether imaging techniques (SPECT scans) can be used to predict whether patients will respond to methylphenidate (a drug which increases dopamine levels).

Study description: A double-blind, placebo-controlled, crossover design study was undertaken in patients who had suffered a traumatic brain injury and had persistent cognitive impairments. Patients received either 0.3mg/kg (to the nearest 5mg and capped at a maximum dose of 25mg) of methylphenidate twice a day or placebo, each for 2 weeks. Primary outcome was whether response to treatment could be predicted by abnormalities on a SPECT scan.

Sponsors: Imperial College London

Clinical Phase: Phase IV

Study dates: 10th July 2014 to 29th September 2016

Investigators: Dr Peter Jenkins, Professor David Sharp

Sponsor signatory: Gisela Barreto, Clinical Trials Manager, Imperial Joint Research Compliance Office

GCP Statement: This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential documents

Date of report: 19th September 2018

2 SYNOPSIS

NAME OF SPONSOR Imperial College London **NAME OF MEDICINAL PRODUCT** Methylphenidate	
Title of Study	**The control of brain networks after traumatic brain injury: a neuroimaging and neuropsychological study of dopamine and cognition**
Investigator(s)	Dr Peter Jenkins, Professor David Sharp
Study centre(s)	Imperial College London
Publication	N/A
Study period	From: 10th July 2014 To: 29th September 2016
Objectives	Primary Objective: To test whether SPECT imaging techniques can be used to predict whether patients will respond to dopaminergic treatment with methylphenidate. Secondary Objective: 1. To measure dopamine tranpsorter levels following traumatic brain injury using the SPECT radioligand 123I-FP-CIT. 2. To investigate whether alterations in striatal dopamine transmission reflect disconnection between brainstem dopamine nuclei and the striatum by studying the patterns of traumatic axonal injury using diffusion tensor imaging.
Methodology	A single-centre double-blind, placebo-controlled, crossover design study
Number of patients	Planned: 40 Analysed: 40
Diagnosis and main criteria for inclusion	• a diagnosis of a moderate-severe traumatic brain injury (as defined by the Mayo TBI severity classification system) at least 3 months prior to recruitment into the study • age between 20 and 65 years • capable of giving written informed consent • subjective complaint of cognitive difficulties by the participant, treating clinician, or caregiver
Test product, dose and mode of administration	Methylphenidate, 0.3mg/kg (to the nearest 5mg and capped at a maximum dose of 25mg) twice a day, oral
Duration of treatment	2 weeks
Criteria for evaluation	Primary: Improvement in the 'Choice Reaction Time' with methylphenidate in patients with low volume of distribution of the dopamine transporter in the caudate. Secondary:
Statistical methods	Complete case analysis, no imputation for missing data.

SUMMARY CONCLUSIONS

EFFICACY RESULTS:
Patients with low caudate dopamine transporter levels as measured by SPECT showed improvement in reaction times with methylphenidate compared to placebo (median change = -16ms; P=0·02, a 27% improvement). Patients with normal dopamine transporter levels did not improve (1ms; 95% CI [-10, 10ms]; P=0·84).

SAFETY RESULTS: There were no serious adverse events. One participant discontinued methylphenidate and withdrew from the trial due to unpleasant feelings of restlessness that were considered likely secondary to the treatment. Heart rate was significantly increased on methylphenidate compared to placebo (median change = 5·5 beats per minute; 95% CI [3, 12]; P<0·001). Systolic blood pressure was not different between methylphenidate and placebo (median change = 1·5mmHg; 95% CI [-2·5, 8]; P=0·21).

CONCLUSION: SPECT scans can be used to determine which patients who have suffered a traumatic brain injury will respond to treatment with methylphenidate.

DATE OF THE REPORT: 19th September 2018

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS & DEFINITION OF TERMS

CIF	Clinical Imaging Facility, Imperial College London
CNS	Central Nervous System
CT	Computed Tomography
DAT	Dopamine transporter
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
INR	International Normalised Ratio
IV	Intravenous
LFT	Liver Function Tests
MRI	Magnetic Resonance Imaging
NHS	National Health System
SPECT	Single Photon Emission Computed Tomography
PT	Prothrombin Time
REC	Research Ethics Committee
TBI	Traumatic Brain Injury
U&E	Urea and Electrolytes
V_T	Volume of distribution

5 ETHICS AND REGULATORY APPROVAL

5.1 INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments, and the patient information sheets were reviewed and approved by the appropriate independent ethics committees as detailed in table one below.

Table I: Ethics committees

Centre name and number	West London and GTAC NRES Committee (14/LO/0067)
Investigator	Professor David Sharp
Ethics committee	West London and GTAC NRES Committee (14/LO/0067)
Chairman	Dr Catherine Urch
Date of approval of the final protocol	21st February 2014
Date of approval of amendment 1	5th March 2014
Date of approval of amendment 2	13th June 2014
Date of approval of amendment 3	21st October 2014
Date of approval of amendment 4	12th November 2014
Date of approval of amendment 5	19th July 2016

5.2 ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the current version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practise (GCP)

5.3 PATIENT INFORMATION AND CONSENT

All patients provided written informed consent to participate in the study prior to being screened.

The patient information sheet detailed the procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and the investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patient was then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records. A sample of the patient information sheet and consent form can be found at appendix 16.1.2.

5.4 REGULATORY APPROVAL

The study was performed in compliance with the requirements of the Medicines and Heatlhcare Products Regulatory Agency (MHRA). The study gained full regulatory approval

from the MHRA on 6th February 2014. Imperial College was issued with the following EudraCT number 2013-004244-37.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table II shows the principal study personnel involved in the study.

Table II: Principal study personnel

Title	Name and affiliation
Principal investigator	Professor David Sharp
Sponsor	Imperial College, London
Project Leaders	Dr Peter Jenkins
Clinical Research Associate(s)	Mr Niall Bourke Dr Sara De Simoni Ms Jessica Fleminger
Medical Adviser	Professor David Sharp
Data Management	Dr Peter Jenkins Dr Sara De Simoni

7 INTRODUCTION

Traumatic brain injury (TBI), injury to the brain caused by trauma to the head, is the commonest cause of death and disability in young adults (1). It is commonly caused by road traffic accidents and assaults. In military personnel, TBI may occur following blast injury, which has become the signature injury from the current conflicts in Iraq and Afghanistan. Patients can experience significant cognitive and psychiatric problems (2). This cognitive impairment poses an immense burden to the well-being of an individual, and has significant economic and social consequences. Crucially, we have no treatments to improve cognitive impairment and brain repair. The results of trials of drugs following TBI have been disappointing. A detailed review of the literature in 2011 concluded: “In the absence of clear evidence of benefit from acute neuroprotective drug use (drugs to protect the brain soon after injury), there is an urgent need to explore other potential modulators of late outcome from TBI.” (3). A drug therapy that improves brain function and quality of life after TBI would have a major effect on patient well-being and dramatically reduce the cost of their care.

Patient outcome after TBI is highly variable (2). Approximately 25% of patients improve but an equal number deteriorate over time. We know little about why patients vary and how much the brain recovers following injury. Patients may deteriorate years after the injury and develop late complications including epilepsy or dementia (4,5). These observations suggest that, rather than a single event causing static damage, TBI can trigger a longstanding process, which may progress over many years.

Despite substantial investment, the results of trials of acute neuroprotection have been disappointing. An alternative strategy is to enhance the function of brain regions that remain intact but function inefficiently after TBI. Targeting neuromodulatory systems such as dopamine is a promising strategy to achieve this. Dopamine is known to influence many cognitive functions, such as attention and working memory (6).

Synaptic dopamine levels are highly regulated by the dopamine transporter (DAT). Levels of the transporter in the striatum are a marker of dopaminergic neurotransmission, and are reduced both in TBI patients and in animal models of TBI (7,8-9). In animals, administration of the dopaminergic and noradrenergic agent methylphenidate (a dopamine reuptake inhibitor) reverses this deficit, and improves the cognitive impairments produced by the model (8-11). In humans, the drug is already widely used to treat attentional impairment in conditions such as attention deficit hyperactivity disorder (ADHD), and is a promising candidate for a cognitive enhancer in TBI (12-13). However, the mechanism by which methylphenidate improves cognitive function after brain injury is unclear, and patient response is highly variable with difficulty predicting who is likely to benefit. Thus, what is needed in the clinic is a way to target the use of these drugs to patients who are likely to respond. In addition, the evidence of improvement is not consistent (14). This is likely to be because dopamine levels relate in a non-linear way to cognitive function. Too much as well as too little can cause impairment. Therefore, a more detailed understanding of the mechanism by which dopamine influences cognitive function after TBI is required.

Levels of DAT in the striatum can be assessed using the single photon emission computed tomography tracer 123I-FP-CIT. In Parkinson’s disease, the tracer provides a well-validated diagnostic tool that is widely available (15). In humans, binding of 123I-FP-CIT is reduced in the striatum after TBI, providing direct evidence for damage to dopaminergic pathways (8). Hence, 123I-FP-CIT imaging has the potential to be used to assess striatal dopamine dysfunction after TBI. Directly identifying dopaminergic dysfunction using SPECT is likely to be useful because the response of patients to treatment with dopaminergic drugs is not consistent.

This study used SPECT scans in TBI patients to investigate the whether they could predict which TBI patients would improve with methylphenidate treatment.

8 STUDY OBJECTIVES

Primary Objective:
To test whether the MRI or SPECT imaging techniques can be used to predict whether patients will respond to dopaminergic treatment with methylphenidate.

Secondary Objective
To measure DAT levels following TBI using the SPECT radioligand ^{123}I-FP-CIT.

9 INVESTIGATIONAL PLAN

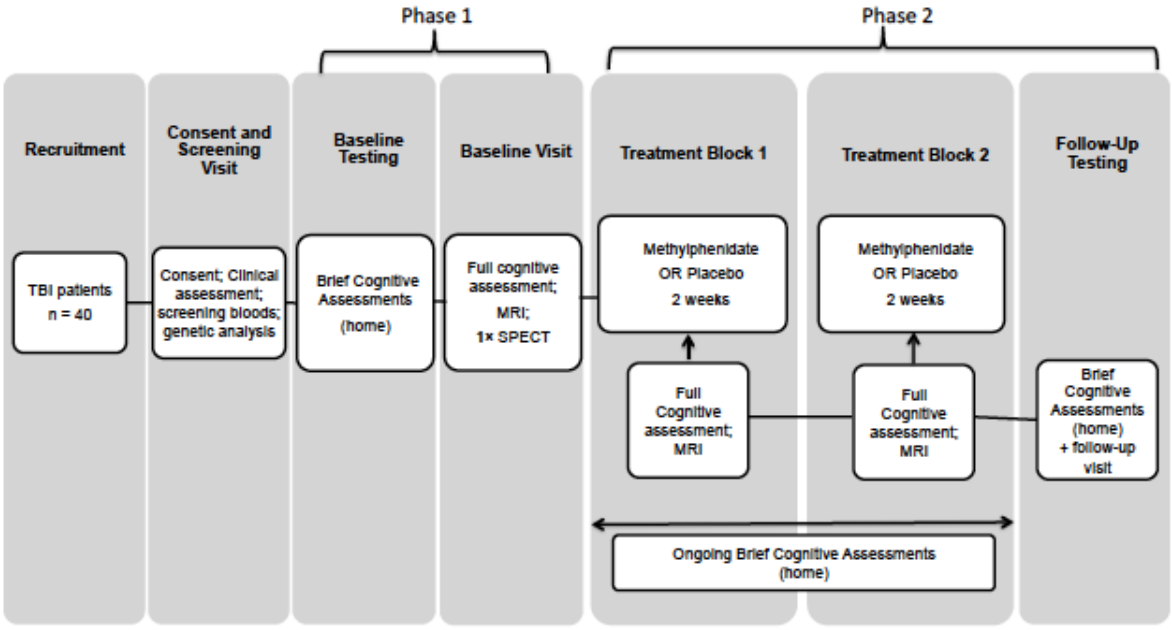
9.1 OVERALL STUDY DESIGN AND PLAN

Overview
The study was a single centre study of dopaminergic transmission, brain damage, brain function, and cognitive impairment following TBI.

Study Design
A double-blind, placebo-controlled, crossover design study was undertaken in a TBI patient group. Patients received either 0.3mg/kg (to the nearest 5mg and capped at a maximum dose of 25mg) of methylphenidate twice a day or placebo, each for 2 weeks. A full battery of cognitive tests were administered at each MRI visit, with a more select battery completed at home prior to, during and following treatment administration (see Figure 1).

STUDY TIMING

Figure I Schematic chart of Protocol



STUDY LOCATION

All procedures involving study participants were undertaken within the sites of the hospitals that form part of Imperial Academic Health Sciences Centre (AHSC) i.e. the Hammersmith Hospital, St Mary's Hospital and Charing Cross Hospital.
All research SPECT scanning were performed at clinical imaging facilities within the Imperial College NHS Trust. MRI scanning was performed at the Imperial College Clinical Imaging Facility (CIF).

9.2 SELECTION OF STUDY POPULATION

INCLUSION CRITERIA

- a diagnosis of a moderate-severe traumatic brain injury (as defined by the Mayo TBI severity classification system) at least 3 months prior to recruitment into the study
- age between 20 and 65 years
- capable of giving written informed consent
- subjective complaint of cognitive difficulties by the participant, treating clinician, or caregiver

EXCLUSION CRITERIA

- unwillingness or inability to follow the procedures required
- significant neurological or psychiatric illness diagnosed prior to the TBI
- family history of a first degree relative with a psychotic illness
- currently participating in a clinical trial or has done so within 1 month before screening

- use of any medication or substance that, in the opinion of the investigators, would interfere with the study or compromise participant safety
- history of a drug or other allergy that, in the opinion of the investigators, contraindicates their participation in the study
- history of current or past drug or alcohol addiction
- female participants who are breast feeding or pregnant (positive pregnancy test) or plan to become pregnant during the study
- positive urine drug screen
- contraindication to MRI scanning, assessed by a standard pre-MRI questionnaire
- contraindication to the use of methylphenidate (including medications deemed to have a potentially serious interaction with methylphenidate as per the British National Formulary)
- clinical evidence of motor symptoms of Parkinsonism as assessed by a Neurologist

WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences.

The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be to be detrimental to the well-being of the patient. Patients who did not complete the study through to the final visit were replaced

Full documentation was made of any withdrawals that occurred during the study in the CRF. The Investigator documented the date and time of the withdrawal and results of any assessments made at this time. If the patient withdrew because of an adverse event (AE) or a serious adverse event (SAE) then details were forwarded to the Ethics committee as required. The investigator also forwarded details to the sponsor, Imperial College. The sponsor, Imperial College, forwarded details to the regulatory authorities as appropriate.

9.3 TREATMENTS

TREATMENTS ADMINISTERED

Methylphenidate

DESCRIPTION OF INVESTIGATIONAL PRODUCTS

Methylphenidate is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not completely understood but its effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine.

METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Subjects were randomised into the trial provided they have satisfied all subject selection criteria. Each subject is assigned to a sequence of treatment administrations by means of a computer-generated, pseudo random code. The randomisation code is a blocked design with block size of four to achieve balance in allocation of drug order.

SELECTION OF DOSES IN THE STUDY

The treatment dose of methylphenidate (0.3mg/kg twice daily) was selected as per previous trials (12) and British National Formulary dosing guidelines.

SELECTION AND TIMING OF DOSE FOR INDIVIDUAL PATIENTS

All patients were asked to follow the same timing of dose.

TREATMENT COMPLIANCE

All study treatment was provided to the patient by the study investigator or designated member of staff. To ensure drug accountability the investigator or designated deputy maintained accurate records of the dates and amounts of drug received, to whom it was dispensed and accounts of any supplies which were accidentally or deliberately destroyed; these details were recorded on a drug accountability form. All unused clinical supplies were returned to the pharmacy.

9.4 EFFICACY AND SAFETY VARIABLES

EFFICACY AND SAFETY MEASUREMENTS ASSESSED

Performance status:

Primary Outcome Measure

Cognitive and Behavioural Testing:
Performance on the Choice Reaction Task (CRT) was assessed using median reaction times. The change in performance between the placebo visit and the methylphenidate visit was used.

Secondary Outcome Measures

Cognitive and Behavioural Testing:
A range of neuropsychological tests were used to explore effects of methylphenidate treatment and their relationship to DAT levels. We assessed memory, processing speed, executive function and fluid intelligence/reasoning. Change in performance on a subset (6/12) of a brief computerized battery of cognitive tests and the following validated neuropsychology assessments will be measured:

- The Trail Making Test
- The Delis-Kaplan Executive Function System Colour-Word Interference Test (Stroop)
- The logical memory subtests I and II from the Wechsler Memory Scale (Third Edition, WMS-III)
- The People Test (PT) from the Doors and People Test
- The Wechsler Abbreviated Scale for Intelligence (WASI) Matrix Reasoning test

Patients were asked to complete the brief computerized battery including a CRT on a tablet at home throughout the four-week trial. We analysed these home data. We also assessed changes in attention by measuring the change in reaction time between the first third and last third of the CRT as well as the intra-individual response variability.

The effects of methylphenidate on the following behavioural measures were also assessed using questionnaires

- Fatigue and apathy (Lille Apathy Rating scale and Visual Analogue Scale for Fatigue)
- Quality of life (SF36 Health survey)
- Functional outcome (Glasgow Outcome scale – extended (GOSE))
- Psychiatric state (Hospital Anxiety and Depression Scale (HADS))
- Behavioural impact (Frontal Systems Behaviour Scale (FrSBE), Barratt Impulsivity scale (BIS), Cognitive Failures Questionnaire)

Objective measures of change in behaviours will be assessed using the following validated caregiver questionnaires:

- Apathy (Lille Apathy Rating scale)
- Behavioural impact (Frontal Systems Behaviour Scale (FrSBE), Cognitive Failures Questionnaire, Rating Scale of Attentional Behaviour)

Vital Signs:
Blood pressure
Heart rate

Table III shows the schedule of examinations and procedures.

Table III Schedule of examinations and procedures

Protocol Activity	**Screening visit**	SPECT Scan day	Baseline Assessment	End of Treatment Block 1	End of Treatment Block 2
Informed Consent	X				
General Medical History and Physical Examination	X				
MRI Screening and suitability check	X				
Weight	X				
Blood Tests	X				
Drugs of Abuse Testing	X				
ECG	X				
Heart Rate and Blood Pressure	X		X	X	X
Adverse Event Assessment		X	X	X	X
Concomitant Medication	X	X	X	X	X
Lifestyle Guidelines Compliance		X	X	X	X
SPECT Scan		X			
Full Neuropsychological Testing			X	X	X

9.5 STATISTICAL METHODS PLANNED IN THE PROTOCOL & DETERMINATION OF SAMPLE SIZE

STATISTICAL AND ANALYTICAL PLANS

Time-points for analysis
Final analyses were performed when 40 participants completed the trial.

Methods for handling missing data
A complete case analysis was conducted (i.e. for each analysis only cases with the relevant outcome data were included). There was no imputation for missing data.

Adjustments for covariates
We adjusted the DAT volume of distribution for subject age.

Multiple Comparisons
Adjustment for multiplicity was considered unnecessary because the trial had a single pre-specified outcome measure. The secondary outcome measures were exploratory and provided additional methods to investigate the central hypothesis that neuroimaging measures of nigrostriatal integrity will inform response to methylphenidate treatment.

DETERMINATION OF SAMPLE SIZE

The study was primarily powered for the effect of methylphenidate on cognitive function. A prior study of ^{123}I-FP-CIT imaging in patients after TBI suggests that <10 subjects would be necessary to find reliable differences in striatal DAT (7). Analysis of methylphenidate effects on cognitive function suggest an effect size of >0.44 for a range of neuropsychological measures (e.g. 12). This indicates that group sizes of between 30-40 patients would be adequate to detect an effect of methylphenidate across the whole patient group. It was anticipated that the stratification of patients on the basis of ^{123}I-FP-CIT imaging would make the treatment effect sizes of methylphenidate considerably larger, although there was no previous work to guide the power analysis.

9.6 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

PROTOCOL AMENDMENTS

There were 5 substantial amendments to the Protocol, all approved by the ethics committee. There were no changes to the planned analyses.

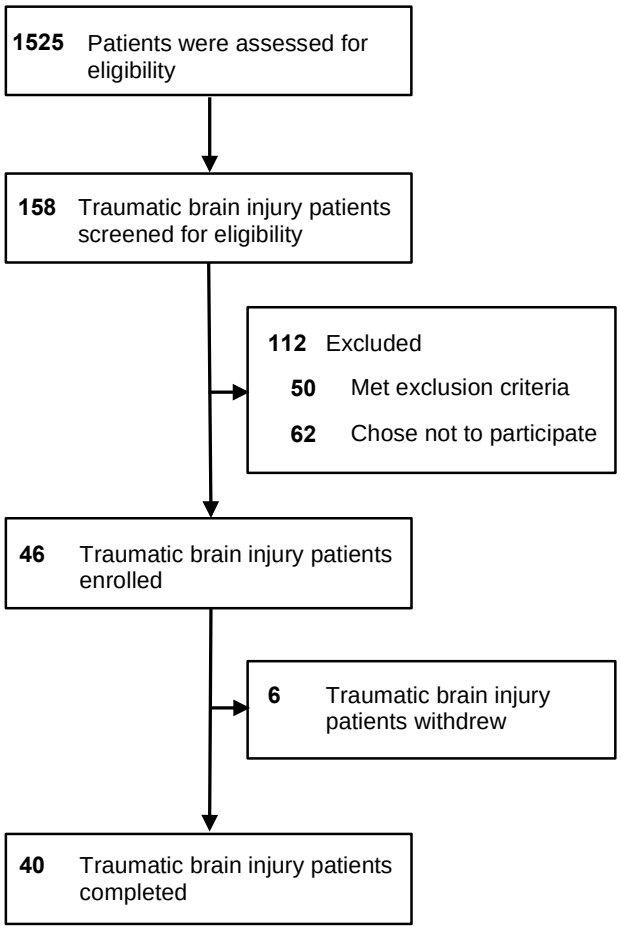
9.7 DATA QUALITY ASSURANCE

All investigators underwent training and standardisation of conducting assessments. Standard operating procedures were written for all necessary elements. Cross-checking and audit of inputted data was carried out to monitor for errors.

10 STUDY POPULATION

10.1 DISPOSITION OF PATIENTS

Table IV Disposition of patients



Reasons for withdrawal:
1 started methylphenidate before ^{123}I-ioflupane SPECT scan, 1 withdrew due to side effects of medication, 4 withdrew due to time commitments

10.2 PROTOCOL DEVIATIONS

Table V Protocol deviations

Deviation	
Entry criteria	0
Withdrawal criteria	1
Incorrect dosing regimen	2
Concomitant treatment/medication	0
Other	2

11 RESULTS

11.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table V Demographics of the Study Patients

Characteristic	Placebo First (N=20) *Mean ± SD*	Methylphenidate First (N=20) *Mean ± SD*	Normal caudate DAT levels (N=22) *Mean ± SD*	Low caudate DAT levels (N=18) *Mean ± SD*
Age – yr	39 ± 12	40 ±12	40 ± 11	39 ± 12
Male sex – no. (%)	16 (80)	18 (90)	17 (77)	17 (94)
Weight – kg	85 ± 13	76 ± 12	81 ± 15	79 ± 11
Traumatic brain injury details				
Time since injury – months	67 ± 85	83 ± 93	67 ± 86	86 ± 93
Length of post-traumatic amnesia – days	61 ± 120	75 ± 157	37 ± 41	106 ± 197
Days in hospital	48 ± 52	51 ± 54	35 ± 45	67 ± 56
Lowest recorded Glasgow Coma Scale	8·3 ± 5·4	8·3 ± 5·2	9·4 ± 5·4	7·1 ± 4·8
Cause of injury				
RTA – no. (%)	7 (35)	14 (70)	10 (45)	11 (61)
Incidental Fall – no. (%)	7 (35)	1 (5)	5 (23)	3 (17)
Violence – no. (%)	5 (25)	4 (20)	6 (27)	3 (17)
Other non-intentional injury – no. (%)	1 (5)	1 (5)	1 (5)	1 (6)

11.2 EFFICACY RESULTS

Methylphenidate improves information processing speed in patients with caudate dopamine transporter abnormalities

For the primary end point of reaction time (CRT), there was a significant improvement in the low caudate DAT group during methylphenidate treatment compared to placebo (median change = -16ms; 95% confidence interval [CI], -28 to -3ms; P=0·02). There was no significant change in the normal caudate DAT group (1ms; 95% CI [-10, 10ms]; P=0·84). Direct comparison of low and normal caudate DAT groups showed improvement in reaction times was significantly greater in the low-binding group (W=96, P=0·049).

Across all patients, there was no statistically significant difference in reaction times between those taking methylphenidate in the first block and those taking it in the second

block (W=114, P=0·13). In addition, across the whole patient group, there was no improvement in CRT on methylphenidate compared to placebo (W=434, P=0.11).
There was no speed/accuracy trade-off associated with changes in reaction time seen on methylphenidate. Errors and misses on CRT performance were similar for methylphenidate and placebo in both the normal and low caudate DAT groups. If outliers were not removed from the analysis, the effect of methylphenidate in the low caudate DAT group compared to placebo was of borderline significance (95% CI [-25 to 3ms]; P=0·06). The normal caudate DAT group still showed no significant change (95% CI [-12, 8ms]; P=0·92) and direct comparison of low and normal caudate DAT groups did not show a difference between the groups (W=135, P=0·15).
In addition to testing patients in the laboratory, we also conducted daily home CRT assessment using tablet devices. This provided a complementary assessment of information processing speed assessed at many more time points. This confirmed that the effect of methylphenidate was only seen in the low caudate DAT group. Patients with low caudate DAT showed a significant improvement in reaction times on methylphenidate compared to placebo (-19ms; 95% CI [-23, -7ms]; P=0·002). Again, there was no significant change in reaction time in the normal caudate DAT group (6ms; 95% CI [-10, 9ms]; P=0·50). Direct comparison of low and normal caudate DAT groups again showed that improvement in reaction times was significantly greater in the low DAT group (W=53, P=0·004).

Methylphenidate improves apathy in patients with caudate dopamine abnormalities

Patients with low caudate DAT also showed significant improvements in self-reported apathy (LARS-self) (median change = -2 points; 95% CI [-9, 0]; P=0·03), as well as on caregiver-reported apathy (LARS-other) (-3.5 points; 95% CI [-7, 0]; P=0·02). Patients with normal caudate DAT did not show improvements in either apathy measure, although self-reported apathy approached significance (-1 point; 95% CI [-6·5, 0·5]; P=0·07 and -0·5 points; 95%CI [-10·0, 7·5]; P=0·98, respectively). Self-reported fatigue (VAS-F) was reduced in both the low and normal DAT groups (median change = -7·5; 95% CI [-23·4, -3·2]; P=0·007 and -6·6; 95% CI [-18·6, -0·7]; P=0·03, respectively). Methylphenidate did not significantly affect any of the other cognitive or behavioural measures.

End Point	Normal caudate ^{123}I-ioflupane specific binding ratio (N=22)				Low caudate ^{123}I-ioflupane specific binding ratio (N=18)				Difference between low and normal binding groups (W, P value)
	Placebo *Median (IQR range)*	Methylphenidate *Median (IQR range)*	Treatment Difference* *Median (95% CI)*	P Value	Placebo *Median (IQR range)*	Methylphenidate *Median (IQR range)*	Treatment Difference* *Median (95% CI)*	P Value	
Efficacy									
Neuropsychological Tests									
Choice Reaction Time task median reaction time - ms	357 (325–392)	362 (331–378)	1 (-10–10)	0·84	382 (359–429)	369 (347–398)	-16 (-28–-3)	0·02	(96, 0·049)
Choice Reaction Time task – Intra-individual variability**	0·18 (0·14–0·22)	0·18 (0·14–0·22)	0·00 (-0·04–0·03)	0·71	0·17 (0·15–0·21)	0·16 (0·15–0·19)	-0·01 (-0·03–0·02)	0·51	(126, 0·49)
Trail Making Test A (s)	21·0 (19·0–30·8)	22·0 (16·3–34·0)	-1·0 (-3·5–4·0)	0·84	25·0 (16·8–34·0)	25·0 (20·3–33·8)	0·0 (-5·0–5·0)	1	(174, 0·91)
Trail Making Test B (s)	49·0 (37·8–69·0)	55·0 (35·3–81·3)	3·0 (-8·0–11·5)	0·58	48·0 (42·5–68·3)	54·0 (50·3–65·8)	10·0 (-5·0–16·5)	0·28	(205, 0·62)
Trail Making Test B-A (s)	22·0 (16·3–38·5)	23·0 (16·0–46·0)	2·0 (-8·5–8·5)	0·95	31·0 (25·3–32·8)	28·0 (25·3–41·5)	4·0 (-5·0–17·0)	0·28	(211·5, 0·34)
Stroop Color Naming & Word Reading	27·8	28·8	0·0	0·43	28·5	29·0	0·5	0·92	(208, 0·56)

Composite Score (s)	(24·8–31·4)	(24·6–20·0)	(-2·8–1·3)		(25·0–33·6)	(25·1–31·4)	(-1·8–1·8)		
Stroop Inhibition (s)	55·5 (44·5–59·0)	57·5 (47·3–62·0)	1·0 (-4·0–4·0)	0·97	55·0 (44·3–61·0)	54·5 (43·3–67·8)	-4·5 (-6·5–3·5)	0·34	(177·5, 0·58)
Stroop Inhibition-Switching (s)	59·0 (51·3–71·8)	63·0 (52·3–67·8)	2·0 (-6·0–2·0)	0·40	69·5 (60·0–75·3)	65·0 (52·0–79·5)	-3·0 (-9·5–2·0)	0·13	(166, 0·56)
Stroop Inhibition-Switching vs Baseline Contrast (s)	31·5 (26·0–42·8)	31·5 (25·3–39·3)	-1·5 (-5·5–2·5)	0·43	40·0 (32·5–45·8)	33·5 (25·0–50·5)	-4·0 (-10·0–1·5)	0·12	(162, 0·33)
People Test Immediate Recall	32·0 (28·3–35·5)	32·0 (27·3–33·8)	0·0 (-4·0–4·0)	0·87	34·0 (30·0–36·0)	34·0 (29·0–36·0)	0·0 (-5·0–9·0)	0·85	(182, 0·89)
People Test Delayed Recall	12·0 (10·0–12·0)	11·0 (9·0–12·0)	0·0 (-3·5–2·0)	0·59	12·0 (12·0–12·0)	12·0 (10·0–12·0)	0·0 (-4·5–1·5)	0·21	(196·5, 0·78)
People Test Forgetting	0·0 (0·0–2·0)	0·0 (0·0–2·0)	0·0 (-2·5–3·0)	0·87	0·0 (0·0–0·0)	0·0 (0·0–2·0)	0·0 (-4·0–2·0)	0·18	(218·5, 0·35)
WASI Matrix Reasoning* **	29·0 (28·0–31·0)	28·5 (26·0–31·5)	0·0 (-2·0–1·0)	0·48	30·0 (27·0–32·0)	30·0 (26·0–32·0)	1·0 (-1·5–1·5)	0·71	(159, 0·43)
Functional outcome									
Glasgow Outcome scale – extended	6·0 (5·0–6·0)	6·0 (5·0–6·0)	0·0 (-1–1)	1	5·0 (5·0–6·0)	6·0 (5·0–6·0)	0·0 (0·0–1·0)	0·06	(144, 0·08)
Behavioural									

Questionnaires									
Lille Apathy Rating Scale Self: Total	-26·5 (-29·8–-15·3)	-29·5 (-30·8–-20·5)	-1·0 (-6·5–0·5)	0·07	-23·0 (-28·0–-17·0)	-29·0 (-31·0–-24·0)	-2·0 (-9·0–0·0)	0·03	(154·5, 0·36)
Lille Apathy Rating Scale Caregiver: Total	-25·5 (-29·5–-10·0)	-27·0 (-30–-12)	-0·5 (-10·0–7·5)	0·98	-21·0 (-26·8–16·8)	-27·5 (-33·0–18·5)	-3·5 (-7·0–0·0)	0·02	(48·5, 0·18)
Visual Analogue Scale for Fatigue	56·1 (28·7–63·6)	34·5 (23·1–46·8)	-6·6 (-18·6–-0·7)	0·03	45·8 (36·8–54·8)	24·5 (15·1–38·3)	-7·5 (-23·4–-3·2)	0·007	(161, 0·61)
Frontal Systems Behaviour Scale (Self): Total (Now)	107·0 (96·3–134·0)	109·8 (91·3–141·0)	-5·0 (-7·5–1·0)	0·08	102·0 (85·0–106·0)	94·0 (83·0–107·0)	-3·0 (-9·0–4·0)	0·44	(201, 0·70)
Frontal Systems Behaviour Scale (Other): Total (Now)	107·5 (80·3–124·3)	98·0 (77·8–108·3)	-0·5 (-26·5–3·5)	0·47	99·0 (94·0–111·5)	92·0 (86·8–101·5)	-8·5 (-11·0–6·0)	0·27	(69·5, 0·47)
Hospital Anxiety and Depression Scale – Anxiety	7·0 (4·0–11·8)	6·0 (3·0–14·0)	1·0 (-2·0–1·5)	0·75	4·0 (1·0–6·0)	3·0 (2·0–6·0)	-1·0 (-2·0–1·5)	0·48	(164, 0·67)
Hospital Anxiety and Depression Scale – Depression	5·0 (4·0–11·5)	6·0 (3·0–9·0)	-1·0 (-2·5–1·0)	0·55	3·0 (2·0–8·0)	3·0 (1·0–6·0)	-1·0 (-6·0–2·0)	0·28	(154, 0·47)
Cognitive Failures Questionnaire – self	50·5 (37·5–63·8)	48·0 (34·5–60·8)	-2·0 (-9·0–5·5)	0·50	30·0 (22·0–51·0)	30·0 (22·0–45·0)	0·0 (-7·0–5·0)	0·92	(203·5, 0·65)
Cognitive Failures Questionnaire – other	16·0 (14·0–	14·0	0·0	0·41	14·0 (12·0–	14·0	-3·0	0·11	(77·5, 0·73)

	18·0)	(9·0–19·0)	(-6·5–2·0)		19·0)	(9·0–16·0)	(-6·0–1·0)		
Rating Scale of Attentional Behaviour – Other	16·0 (9·0–24·0)	15·5 (12·8–18·5)	1·0 (-15·0–7·5)	1	13·0 (8·0–18·0)	12·0 (8·8–15·8)	-2·0 (-6·0–2·5)	0·28	(58·5, 0·45)
Physical examination									
Systolic blood pressure – mmHg	122 (115–138)	132 (118–138)	2 (-3–10)	0·28	123 (114–131)	127 (121–131)	2 (-5–9)	0·51	(213, 0·69)
Heart rate – beats/min	63 (58–76)	71 (66–84)	6 (3–15)	0·002	60 (55–68)	67 (62–77)	6 (3–11)	0·008	(206·5, 0·82)

12 SAFETY EVALUATION

12.1 ADVERSE EVENTS (AE's)

Subject No.	Adverse Event Description	Severity	Relationship to study medication	Action taken	SAE Classification
001	Felt dizzy, sleepy and slight nausea after SPECT scan	1 (Mild)	Unrelated	None	No
002	Insomnia. Present for last 2 months	1 (Mild)	Unlikely	None	No
003	Discomfort in scanner due to head rest	1 (Mild)	Unrelated	None	No
006	Feeling of a "heavy head" / light headache	1 (Mild)	Probable	None	No
009	Dizzy	2 (Moderate)	Possible	None	No
009	Feeling flat/drained/confused	1 (Mild)	Possible	None	No
015	Felt sluggish most days, lethargic	1 (Mild)	Unlikely	None	No
016	Feeling more tired around midday for the last 2 weeks. Otherwise well.	1 (Mild)	Unrelated	None	No
018	Bereavement - patients mother passed away	1 (Mild)	Unrelated	None	No
019	Difficulty swallowing tablets	1 (Mild)	Definite	None	No
020	Vasovagal during venepuncture	1 (Mild)	Unrelated	None	No
023	Increased thirst. No increased urine output. No nocturia.	1 (Mild)	Possible	None	No
023	Metallic taste in mouth. Comes on c. 40mins after medication then wears off	1 (Mild)	Probable	None	No
023	Viral sinus infection	1 (Mild)	Unrelated	None	No
025	Increased thirst, bloated stomach	1 (Mild)	Unrelated	None	No
031	Headache. 3 in total over 2 weeks. bitemporal throbbing, Migrane	1 (Mild)	Unlikely	None	No
040	Headache: intermittent, around scar	1 (Mild)	Unrelated	None	No

040	Little bit drowsier, otherwise felt well. Uncertain related to medication.	1 (Mild)	Unlikely	None	No
041	Anxiety	1 (Mild)	Unlikely	None	No
042	Dry Mouth, Anxious, Increased heart rate during exercise	1 (Mild)	Possible	None	No
043	Nausea	1 (Mild)	Unrelated	None	No
048	Felt heart beating stronger - 1/2 day. no on going symptoms	1 (Mild)	Possible	None	No
056	Viral cold - sore throat	1 (Mild)	Unrelated	None	No
058	Participant felt increased stimulation on tablets	2 (Moderate)	Definite	Permanent discontinuation of study medication	No
065	Felt warm, dry mouth.	1 (Mild)	Unrelated	None	No
067	Anxious	1 (Mild)	Possible	None	No
067	Haematuria - normal abdominal examination, normal bloods	2 (Moderate)	Unrelated	GP contacted	No
068	Complex partial seizure. This is known to occur since injury	2 (Moderate)	Unrelated	None	No
071	Increased irritability	1 (Mild)	Possible	None	No

BRIEF SUMMARY OF ADVERSE EVENTS

No significant adverse events. One patient discontinued the study as they felt “over-stimulated” on the tablets

TREATMENT RELATED ADVERSE EVENTS

One patient felt over-stimulated. Other adverse events possibly related to medication were anxiety, increased heart rate, dry mouth, headaches, metallic taste in mouth and feeling dizzy.

12.2 SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

None

12.3 DEATHS

None

12.4 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Heart rate was significantly increased on methylphenidate compared to placebo (median change = 5·5 beats per minute; 95% CI [3, 12]; P<0·001). Systolic blood pressure was not different between methylphenidate and placebo (median change = 1·5mmHg; 95% CI [-2·5, 8]; P=0·21).

12.5 SAFETY CONCLUSIONS

A well-tolerated medication. Caused an increase in heart rate but only one patient withdrew because of perceived side-effects of the medication.

13 DISCUSSION AND OVERALL CONCLUSIONS

The results show that patients with low caudate DAT levels as measured by ^{123}IFP-CIT SPECT scan after TBI, experience improved reaction speeds with methylphenidate treatment and reduced apathy. The results provide a proof-of-principle that measuring the integrity of the neurotransmitter system upon which a cognitive enhancer acts can stratify the selection of treatment for common clinical problems seen after TBI.

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15 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

16.1.2 Patient information sheet and consent form

16.1.3 Regulatory Approval

16.1.4 Statistical Analysis Plan

16.2 CASE REPORT FORMS

16.2.1 CRFs for deaths, other serious adverse events and withdrawals for AE