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FULL TITLE OF THE STUDY

Understanding cognition and action in Pick's disease and related disorders

SHORT STUDY TITLE / ACRONYM

Cognition and Action in FTLD

RESEARCH REFERENCE NUMBERS

REC reference number: 10/H0310/59

PROTOCOL VERSION NUMBER AND DATE

version 7, 29th March 2021

OTHER RESEARCH REFERENCE NUMBERS

SPONSOR / CO-SPONSORS / JOINT-SPONSORS

Cambridge University Hospitals NHS foundation Trust and the
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This protocol has regard for the HRA guidance and order of content

RESEARCH REFERENCE NUMBERS

Study Registry Number and Date	ISRCTN10616794 28/06/2018
IRAS Number Project ID:	55856
SPONSORS Number:	N/A
FUNDERS Number:	N/A

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:.

……

Name (please print):

….....

Position:

.....

Chief Investigator:

Signature: .....

Date: .30th March 2021

Name:...Professor James Rowe

KEY STUDY CONTACTS

Chief Investigator	Professor James Rowe Professor of Cognitive Neurology Cambridge University Hospitals co-Lead for Dementia Cambridge University Department of Clinical Neuroscience Herchel Smith Building, Cambridge Biomedical Campus, CB2 0SZ Telephone: +44 (0) 1223 273 630 Secretary: +44 (0) 1223 760 696
Study Co-ordinator	Dr Laura Hughes Cognition and Brain Sciences Unit University of Cambridge 15 Chaucer Road Cambridge CB2 7EF Email: laura.hughes@mrc-cbu.cam.ac.uk Tel: +44 (0) 1223 769 422
Joint-sponsor(s)	The University of Cambridge Research Operations Office Cambridge Biomedical Campus, Box 111 Hills Road Cambridge CB2 0SP Email: croenquiries@admin.cam.ac.uk Tel: +44 (0)1223 333543 Fax: +44 (0)1223 765410
Funder(s)	Wellcome Trust grantenquiries@wellcome.ac.uk Medical Research Council Cambridge Centre for Parkinson Plus direct funding Contact Clinical Lead, Prof James Rowe

	Cambridge NIHR BRC Dementia and Neurodegeneration theme, in-kind support funding Evelyn Trust info@evelyntrust.com Holt Fellowship NIHR Clinical Research Network Research Nurse funding Contact regarding funding: Jackie Green
Key Protocol Contributors	Prof. James Rowe James.Rowe@mrc-cbu.cam.ac.uk +44 (0) 1223 760 696 Dr Laura Hughes Laura.hughes@mrc-cbu.cam.ac.uk Tel: +44 (0) 1223 769 422
Committees	N/A

STUDY SUMMARY

Study Title	Understanding cognition and action in Pick's disease and related disorders
Internal ref. no. (or short title)	Cognition and Action in FTLD
Study Design	Double-blind placebo controlled cross over non-ctimp study As defined by **https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk**
Study Participants	Individuals with a primary diagnosis of a frontotemporal lobar degeneration. Including Progressive Supranuclear Palsy (PSP) and Corticobasal degeneration (CBD), and Frontotemporal dementia (FTD), and matched control participants
Planned Size of Sample (if applicable)	**48 patients and up to 48 control participants added in v7, to total 174 patients and 106 controls**
Follow up duration (if applicable)	Once at 12 months
Planned Study Period	The study commenced 2007. Funding has been renewed by Wellcome Trust and MRC to 2026, with Holt fellowship to 2022 and PI employment contracted to 2035.
Research Question/Aim(s)	1. To examine the neurophysiological consequences of probing the GABAergic and Glutamatergic system using agonists and reuptake inhibitors to modulate neurotransmission. 2. To characterise the neurophysiological changes in FTLD, and link to cognitive and behavioural changes. 2. To identify functional neurocognitive effects of neurodegeneration. 3. To assess the neural determinants of cognitive and behavioural decline.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Wellcome Trust	**Financial (direct)**
MRC	**Financial (infrastructure)**
NIHR	**Financial (infrastructure)**
Holt fellowship	**Financial (direct)**

ROLE OF STUDY SPONSOR AND FUNDER

Cambridge University Hospitals NHS Foundation Trust (CUHT) and University of Cambridge are joint sponsors for this study. They assume overall responsibility for the management of this study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Study Steering Groups

The Chief Investigator meets regularly with the study team to discuss management, safety, data quality, analyses and interpretation prior to dissemination. This is not a clinical trial, as defined by https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

The safe conduct of research, including clinical governance and GCP, are overseen by the site management organisations including the MRC-Cognition and Brain Sciences Unit and the Herchel Smith Clinical Suite Committee.

The work undertaken within this protocol has been, and will continue to be, discussed at PPI groups including our FTD Carer meetings annually, and independent meetings of the PSP Association, including local and national meetings for families and patients.

Protocol contributors

This study has been operating without adverse incident since 2010. The work from it continues to make a major contribution to the understanding of the reference disorders, and has attracted increased interest and funding from government and charitable funding agencies. The protocol has been re-drafted in 2021 to keep in line with changes in guidance, including the HRA, that was established since the start of the study.

The following have contributed to the protocol from the outset.

Prof James B. Rowe (PI, CI and medically qualified), Department of Clinical Neurosciences and MRC Cognition and Brain Sciences Unit, University of Cambridge.

Dr Laura Hughes, Research Associate, Department of Clinical Neurosciences and MRC Cognition and Brain Sciences Unit, University of Cambridge.

Prof Trevor W Robbins, Department of Experimental Psychology, University of Cambridge: advisory only without access to personally identifiable data (PiD)

Ms Julie Wiggins, Research Nurse, Department of Clinical Neurosciences, University of Cambridge.

The following have joined the project since its inception and contributed to the current revision:

Dr Timothy Rittman (medically qualified), Clinical Research Fellow, Department of Clinical Neurosciences, University of Cambridge.

Dr Natalie Adams, Research Associate, Department of Clinical Neurosciences, University of Cambridge.

Ms Michelle Naessens, Research Assistant, Department of Clinical Neurosciences, University of Cambridge.

KEY WORDS: Dementia
FTD - Frontotemporal dementia
FTLD - Frontotemporal lobar degeneration
PSP - Progressive Supranuclear Palsy

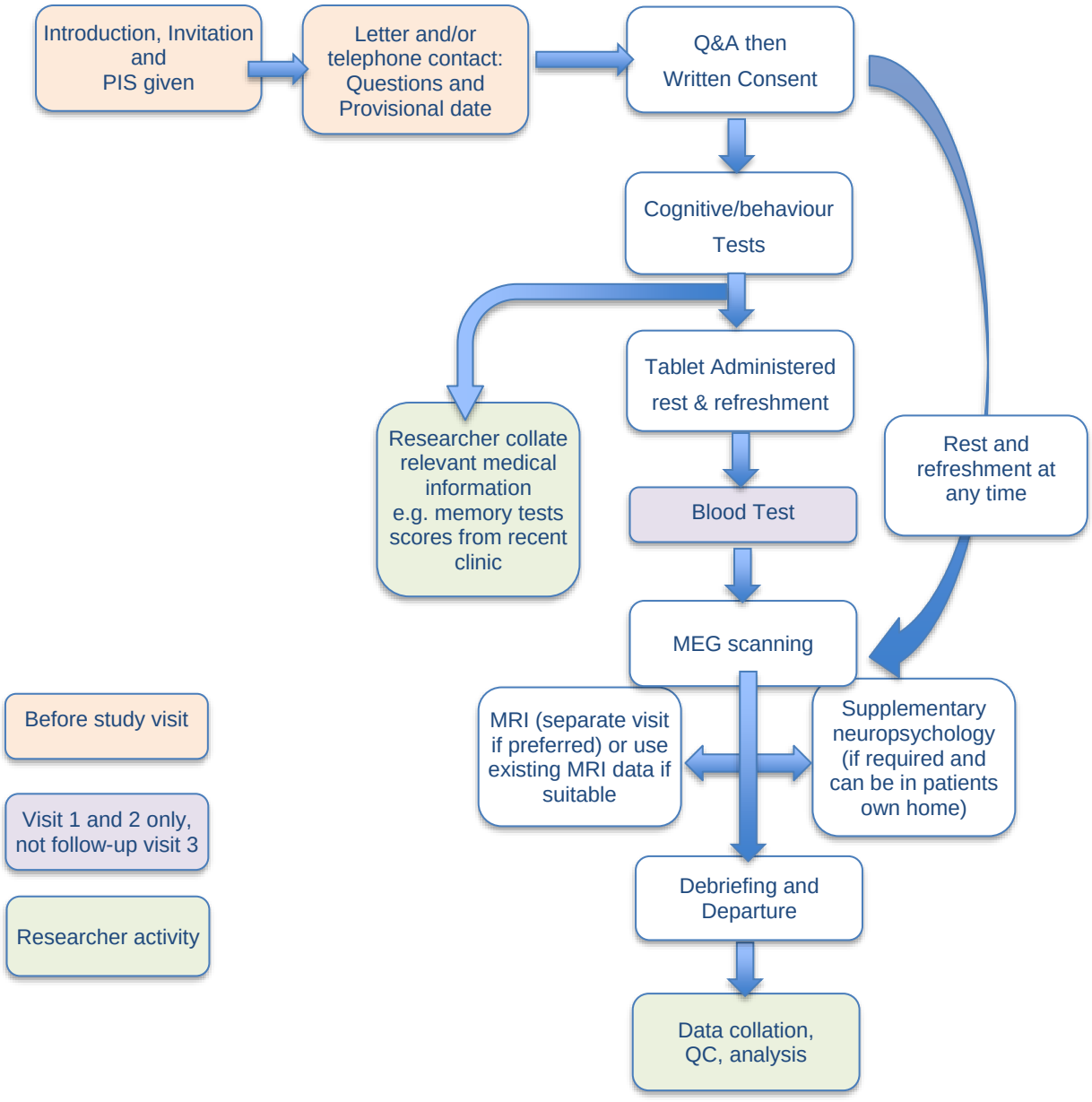
ABBREVIATIONS

ACE-r - Addenbrooke's Cognitive Examination
BCNI – MRC Behavioural and Clinical Neuroscience Institute
BOLD – Blood Oxygen Level Dependent MRI signal (not a blood test)
CBU –Cognition and Brain Sciences Unit
CCNRP - Cambridge Cognitive Neuroscience Research Panel
CRF – Wellcome Trust Clinical Research Facility, Addenbrooke's Hospital
HSB – Herchel-Smith Building (clinical suite)
MMSE - Mini Mental State Examination
MRI – magnetic resonance imaging
MPRAGE (an MRI sequence)
MRC-CBU – Medical Research Council Cognition and Brain Sciences Unit
PiD – Personally identifiable data
PIS – Patient information sheet
UPDRS - Unified Parkinson's Disease Rating Scale
WBIC – Wolfson Brain Imaging Centre

LIST of CONTENTS

STUDY FLOW CHART

Testing steps for each visit. Visits 1 and 2 are the sessions with the drug/placebo. Visit 3 is the 12 month follow-up. All visits follow the same steps.



STUDY PROTOCOL

1 BACKGROUND

Neurodegenerative diseases are major cause of worldwide morbidity and mortality [1]. In the UK, it is estimated that 700,000 suffer from Dementia. In clinical and pathology studies, Frontotemporal dementia (FTD, also called Pick's disease) accounts for ~10% of all dementias [2-4], more so in younger cohorts with estimated prevalence in the middle age range 45-64 years at 15 per 100,000 [5]. FTD has very limited treatment options [6] and no available disease modification treatment.

There are several types of FTD, including the behavioural variant FTD (bvFTD), semantic variant (also called semantic dementia) and progressive non-fluent aphasia (PNFA). All three are types of FTD. In addition, several neurodegenerative disorders overlap with FTD[7] and are included in the spectrum of neuropathological disorders called Frontotemporal lobar degeneration (FTLD). These include motor neuron disease in which a third of patients show significant cognitive changes and 5-10% have combined FTD-MND [8]. Also, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) which often combine a behavioural syndrome overlapping with FTD and shares a similar tau-based neuropathology [9] PSP and CBD are part of the spectrum of this disorders caused by frontotemporal lobar degeneration. Interestingly, there is a separate group of patients who resemble FTD, but who do not appear to have a neurodegenerative syndrome or significant atrophy[10, 11], called "phenocopy" cases.

There is an urgent need to understand better the neurobiology of FTLD. Significant recent advances in molecular biology and genetics of FTLD are nonetheless remote from an understanding of the complex behavioural problems associated with FTLD. It is also premature to study the clinical efficacy of many drugs, even those pertaining to the serotonergic system.

2 RATIONALE

Our approach is to study the important cognitive, structural and neuro-pharmacological features of FTLD at intermediate levels called 'endophenotypes'. These endophenotypes include systems dominated by a handful of neurochemical modulators linked to a set of core cognitive systems. They characterise cognitive and behavioural patterns in FTLD that result from cell loss in frontal cortico-subcortical circuits and loss of neuromodulatory projections from the brainstem to cortex and striatum. These include glutamate, GABA, noradrenaline (NA), serotonin (5HT) and acetylcholine (ACh) as well as dopamine (DA). The cognitive phenotypes of FTLD have features in common with frontal lobe injury [12, 13] affecting attentional control (working memory, planning and rule-switching) and reward based behaviours.

In health, correct actions are made or inhibited according to contexts (rule) and goals (reward). There is a complex relationship between actions, rules, and goals in the brain. Whereas reward representation is associated with orbitomedial frontal cortex, anterior cingulate and ventral striatum [14-

16], cognitive 'rule' functions are often associated with lateral prefrontal cortex [17-19]. We have recently shown how these lateral and ventromedial systems can interact, and how action- and rule-selection processes overlap [20, 21].

The impact of FTLD on these cognitive and motor processes is less well understood, although they are manifest in the core diagnostic features of FTLD such as disinhibition, poor social conduct, emotional blunting, mental rigidity and utilisation. Using the framework of endophenotypes we will study the cognitive and behavioural control in FTLD, focussing on the selection and inhibition of rules and actions. Neurochemical modulation will be studied with magnetoencephalography, to gain sensitivity to the effects of disease and interventions together with insight into the neural mechanism of disease and pharmacological probes. Neuroimaging is therefore a useful supplement to behavioural studies, to understand both the heterogeneity of disease and the functional anatomy or neurocognitive mechanism of drugs.

In addition to impulsivity, and disinhibition, many patients also show marked apathy. This is also part of the dysregulation of behaviour in FTLD, and is not merely a feature of low mood. It is a cause of very high carer burden and stress [22]. The relationship of apathy to the other problems of FTLD is poorly understood, and this has slowed down the development of rational ways to treat apathy. Here we will also monitor apathy by questionnaires, and assess the impact of the drugs on the brain's cognitive systems that may contribute to apathy.

3 THEORETICAL FRAMEWORK

Neural networks for perception and action

Cognitive processes for perception, action, memory and language are supported by specialised brain regions and diffuse brain networks, supporting the segregation and integration of information in the brain. These regions and networks are arranged hierarchically, with information passing forwards and backwards (or up and down the hierarchy), through the activity if nerve cells (neurons) and their connections (synapses).

These networks and regional activity can be revealed by brain imaging. They can be measured to some extent even at rest, but they are more readily seen during "tasks" that call on specific brain functions. These tasks can be passive, like listening to sounds played through earphones. Or they can be active, asking participants to make decisions and actions during the scan. Different tasks reveal different aspects of brain function.

Behavioural control: making and inhibiting actions.

We are often required to inhibit responses. We can restrain an action before it is made e.g. when traffic lights go green we don't drive if there are still children crossing. This inhibition of an action before it is made ('restraint') is characteristic of the Go-No-go paradigm. Alternatively we might 'cancel' an action after it is initiated e.g. if a child runs across the crossing after we have initiated driving. This 'cancellation' forms the basis of the 'stop signal reaction time task (the time needed to stop on 50% of trials is known as the 'stop signal reaction time', SSRT).

These two forms of response inhibition are anatomically and neurochemically distinct across many species [23, 24]. Essentially, No-go inhibition is modulated by serotonin while the SSRT is modulated by noradrenaline. The inferior frontal cortex is activated in association with both forms of inhibition and lesions here or in its basal ganglia connections impair response inhibition [25, 26]. Serotonin modulates action restraint behaviour and activation e.g., acute tryptophan depletion (ATD) may reduce No-go activation in inferior frontal cortex [27] while the selective serotonin uptake inhibitor (SSRI) Citalopram may enhance it [28]. The effects of serotonergic modulations depend on individual differences in trait serotonergic function including trait 5HT2a receptor density.

Behavioural variant FTD (bvFTD) is characterised by obvious failures of inhibition, such as socially disinhibited behaviours, utilisation behaviour and perseveration. This impaired inhibition may be partly due to structural change in critical frontal brain regions [29-31] but also severe reductions in serotonergic projections to frontal cortex [32-34]. SSRI treatment of bvFTD has been tested in small studies [35, 36] but therapeutic trials depend on their clinical outcome rating scales and size. This is problematic in bvFTD [6]. For example, the Neuropsychiatric Inventory is abnormal in FTLD but too unstable over time, and even an optimised clinical dementia rating scale would require n~100 [37]. Priority should therefore be given to the effects of candidate therapies on the FTLD endophenotypes including impaired response inhibition and depleted serotonergic systems. In this setting, pharmacological interventions coupled with neuroimaging are necessary to explore the efficacy *and* mechanism of drug treatment.

Cognitive control: changing and inhibiting rules.

Normal behaviour depends on the context or ‘rules’ which relate actions to outcome or reward. Some rules are very stable e.g. it is all right to undress in private but not in public. Other rules are transient or arbitrary e.g. a driving instruction to turn left at the next traffic lights. Cognitive flexibility is essential to change from one rule to another in an environment with changing reward contingencies and unpredictable outcomes.

The prefrontal cortex is closely associated with rule processes [38]. We have studied how healthy individuals and those with PD or frontal brain injury are able to choose, maintain or make transitions between rules [20, 21, 39]. The effects of neurological disease are sometimes only manifested as changes in network connectivity in fMRI data [39]. Such analyses of connectivity are therefore included in the current proposal. Moreover, the selection of rules is associated with the same pattern of neural responses as the selection of actions themselves [40]. Changing and inhibiting rules may also have anatomical and neurochemical similarities with inhibiting actions.

Cognitive rules may change in different ways. Participants may change from a rule based on one dimension of stimuli (e.g. shapes) to a rule based on a different dimension (e.g. lines: an extradimensional shift, EDS). EDS is abnormal in PD and frontal brain injury [41-43], and modulated by noradrenergic projections to cortex [44-46]. Interestingly, the relatively preserved noradrenergic function in frontotemporal dementia [34] may explain why these patients are not impaired on EDS nor improved by methylphenidate [47, 48]. Alternatively, one can reverse a rule and learn to make the opposite response to a stimulus. Reversal is typically indicated by negative feedback (punishment) to a previously

correct (rewarded) response. Reversal learning requires inhibition of the old rule. It is impaired with frontal cortical lesions, PD and bvFTD [41-43, 47-50]. Unlike EDS, reversal learning is most associated with serotonergic and cholinergic systems: in monkeys, serotonin depletion from PFC impairs reversal learning but not EDS [51, 52] while acute tryptophan depletion impairs human reversal learning [53, 54].

Rule inhibition and EDS can be studied using compound visual discriminations. The Hampshire paradigm [55] includes the type of reversal learning and EDS that has successfully been studied during scanning patients with Parkinson's disease, not bvFTD [56, 57], revealing separate systems for reversal and EDS [55].

This begs the question of whether serotonergic modulation influences reversal learning and rule inhibition in FTLD. Early studies suggested that the SSRI paroxetine did not improve reversal in FTD [58] while escitalopram did not improve reversal learning in healthy individuals [59]. However, both these studies relied on behavioural measures and evaluated small groups. Larger groups are required including neurophysiological indices of the neural effects of treatment.

Neural circuits for behavioural control

Normal behaviour rests on the integrity not only of individual areas or brain cell populations, but on the way in which they are integrated into functional circuits. These circuits can be very small (microcircuits, stretching over a few millimetres) or they can extend across separated brain regions (macrocircuits).

In recent years, it has been recognised that the function of micro- and macro-circuits rests on their ability to support oscillations. Oscillatory dynamics are thought to be critical for normal cognition, including perception, movement and control. The oscillations can be fast (gamma rhythms, occurring over 30 times per second, 30-100Hz), intermediate (alpha and beta 8-12 Hz) or slow (theta and delta < 8Hz). This study focusses on gamma oscillations, and their interaction with lower frequencies.

Gamma oscillations support many cognitive processes, including attention, perception and working memory, and are disrupted in neurological and neuropsychiatric disorders, including FTD [60]. The primary generators of gamma waves are cortical, where inhibitory GABAergic interneuron circuits modulate glutamatergic pyramidal cell activity. Gamma enables both fast local interactions [61] and the translation of local rate-coding to phase-encoding[62], thereby increasing efficiency and integration of large-scale networks. *Ex vivo* and *in silico* studies indicate that superficial GABAergic inhibitory interneurons are critical for the pyramidal post-synaptic potentials that generate gamma waves [63, 64]. Enhanced GABAergic neurotransmission is predicted to modulate gamma oscillations and the precision of connections between hierarchical microcircuits. In a transgenic mouse model of dementia, the return of gamma oscillations restored network synchrony and memory[65].

The effect of FTLD and related disorders on high frequency gamma oscillations (30-100Hz), is not yet established but in healthy humans the peak gamma frequency is highly heritable[64] and determined by GABA concentration[63]. Furthermore, my recent data showing reduced frontotemporal gamma power with age suggest a contribution to age-related neurocognitive inefficiency.

Tiagabine is a selective GABA reuptake inhibitor with a long-established safety record and evidence of improved impulsivity and cognition in animal studies. It has been used in human MEG studies [66] and is licenced for use in treating epilepsy.

NMDA receptor antagonists, such as memantine, have been demonstrated in animal models to increase the power of gamma oscillations [67, 68]. NMDA intervention (including memantine [69]), is widely used to treat dementia, such as Alzheimer's Disease, following favourable open-label studies (and a negative phase II trial [70]). We do not propose to study its clinical efficacy nor pharmacodynamics, but to use its selective properties to probe NMDA's role in cortical circuits in health and disease.

Zolpidem is a short-acting nonbenzodiazepine drug acting on $GABA_A$ receptors and facilitates inhibitory neurotransmission. It has a long-established safety record and is licenced to treat sleeping difficulties. Paradoxically, despite being a sedative, there is evidence of improved motor skills and speech in patients with PSP after a single dose [71-73], perhaps because it resets the balance of excitation and inhibition in the brain. In patients with Parkinson's disease or brain injury, improvements in behaviour are concordant with improvements in abnormal low frequency rhythms [74, 75], and in healthy controls zolpidem also modulates low frequency oscillations [76].

No clinical trials are included in this protocol.

It is possible that these studies will support or motivate future clinical trials in FTLD. However, these studies use either no pharmacological intervention, or selective agents intended to probe neurochemical components of cognitive systems in the context of FTLD and related disorders.

Our principal outcome measures are the neurocognitive architectures of action and behavioural control. We do not expect that these studies will produce clinically significant outcome effects from the single dose regimes, nor symptomatic benefits in patients at the doses/regimens used. Our primary physiological outcome measures do not include clinical assessment scales, or patient based symptom ratings.

From the MHRA clinical trials algorithm and MHRA mock examples, these studies are not clinical trials. Also, in line with the precedent of local studies using MRI and MEG and behaviour to study citalopram and atomoxetine in neuropsychiatric disorders, these are not clinical trials.

Confirmation was sought from the MHRA that these studies are not clinical trials, and their judgement on the protocol was that it was not a clinical trial.

4 RESEARCH QUESTION/AIM(S)

The principal aim of this study is to understand better the neurobiological mechanisms of neurodegenerative disease expressed as regional activity (evoked responses), local oscillatory dynamics (induced oscillatory responses) and large scale network dynamics (connectivity).

4.1 Objectives

Our objectives are to:

1. To examine the neurophysiological consequences of probing the Serotonoergic, GABAergic and Glutamatergic system using agonists and reuptake inhibitors to modulate neurotransmission.
2. To characterise the neurophysiological changes in FTLD, and link to cognitive and behavioural changes.
2. To identify functional neurocognitive effects of neurodegeneration.
3. To assess the neural determinants of cognitive and behavioural decline.

4.2 Outcome

MEG can be extremely sensitive to the presence of brain disease. Where abnormalities are found, we will consider their suitability as surrogate markers (biomarkers) for future clinical trials of candidate therapies. This study however includes no therapeutic intervention. The results will inform the design of such trials, with estimates of biomarker properties (e.g. effect sizes), and evidence of superiority over MRI and cognitive measures alone. The MEG studies also provide the opportunity for 'reverse translation' to use the information from people with diseases to inform and test hypothesis of normal cognition and its neural mechanisms.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

The investigative procedure

Summary

Experiment one was a pilot study, open label (now completed).

The general design of each experiment is exemplified by experiment 2, set out in this protocol in detail below. This was a blinded crossover placebo controlled study of the SSRI citalopram (standard dose 30 mg) to investigate its effect on neurophysiological markers of inhibition, in the context of FTD (Picks disease).

Experiments 3 and 4 extend the clinical phenotype of study populations, to patients with a non-degenerative 'phenocopy' of FTD, and to those with closely related pathologies including Progressive Supranuclear Palsy (PSP) and Corticobasal degeneration (CBD).

Experiments 2-4 use Citalopram 30 mg and dummy pills (closely matching the citalopram tablets in appearance, hereafter called "placebo". Note, tablets of active and inactive substance will not

necessarily be re-processed to be overcoated by an identical capsule if appropriately matched placebo tablets can be directly sourced). The PIS makes the use of a dummy pill clear to participants. Previous versions of the study protocol (v1-v3) also referred to the use of Pindolol, but this has been removed. Experiments 2-4 refer to Citalopram in the individual experimental protocol details below.

Experiment 5 acquired supplementary neuropsychological data.

Experiment 6: Tiagabine 10mg and Experiment 7: Memantine 10mg. Both added under protocol v5, and now completed.

In protocol v7 we introduce:

Experiment 8, which uses Zolpidem 5mg and a dummy/placebo tablet closely matching in appearance. Note, tablets of active and inactive substance will not necessarily be re-processed to be overcoated by an identical capsule if appropriately matched placebo tablets can be directly sourced). The PIS makes the use of a dummy pill clear to participants. This is a single dose cross-over design with neurophysiological endpoints.

Experiment 9 will include a single session follow up after 12 months to assess cognitive and behavioural decline, and changes in neurophysiological measurements.

Details of all experiments are set out below.

Experimental protocol

General procedures

Several linked experiments are proposed, using functional neuroimaging to measure cognition in the context of neurodegenerative disease. Some use pharmacological interventions with drug or placebo, with MEG-based neurophysiological outcome measures. Neuroimaging methods focus on (1) analysis of regional activations and (2) the coupling within hypothesis driven structural models of brain networks. The specific hypotheses tested in each experiment derive directly from the previous discussion of the neurobiology of response and rule inhibition.

Design and randomisation.

The non-pharmacological studies are repeated measures designs (within group) suitable for general linear modelling (ANOVA based t- and F- tests), with normative data from healthy controls, also suitable for general linear modelling of contrasts with patients.

The pharmacological studies of FTLD patients will be crossover studies. Each patient will be scanned on separate sessions, to receive both placebo and drug.

The order of drug/placebo administration in experiments 2-4, and 6-8, will be randomly permuted within blocks of 6, in order of recruitment. We have chosen random permutation, not serial randomisation, to ensure approximate equality of order effects and practice effects for each drug/session. Failure to do so

with low subject numbers would have a high risk of unequal confounding effects of practice. Moreover, in the unlikely event of study termination before all participants were completed, the balanced design imposed by random permutation increases the utility of a smaller dataset. The permutation, packaging and labelling of drugs for the pharmacological studies will be performed independent of the study team, either by a member of the University, Medical School or external drug supplier.

MRI Imaging.

Participants will undergo a standard battery of structural magnetic resonance imaging (MPRAGE, DWI, T2 and PD sequences) as well as Arterial spin labelling, resting BOLD-sensitive echo-planar imaging and a magnetic resonance spectroscopy sequence for GABA. The total imaging time will be typically up to 60 minutes (but possibly up to 90 minutes). These MRI will be undertaken at either the Wolfson Brain Imaging Centre (WBIC) or MRC Cognition and Brain Sciences Unit (CBU) MRI suites. Their approved standard operating procedures will apply. MRI scanning may be undertaken either on the same day as a study visit to the MEG or on a separate day. The decision is made according to participant preference and scanner availability. Patients/carers preferring not to revisit or preferring not to have the full MRI examination can opt to a shorter MRI (limited sequences, 15 minutes) scan on one of the MEG study days. This minimal MRI scan is sufficient for optimal modelling MEG sources but does not enable the supplementary cross-modal comparisons. Again, patient and consultee preference will guide the decision. Both sites have equivalent high performing 3-T MRI scanners operated by clinical radiographers, with fully functional stimulus delivery and response monitoring systems. MRI data pre-processing will use semi-automated processing pipelines and established statistical software (including but not limited to SPM, www.fil.ion.ucl.ac.uk), with quality control assessments at each step.

MEG Imaging

FTLD patients present a greater challenge for phMRI because of movement, disinhibition and the temporal autocorrelations spanning successive trials. We therefore will use the CBU Neuromag Triux 306 channel MEG, combined with up to 128 channel EEG. This works very well even for patients with significant behavioural problems, partly due to the quiet, sitting environment of the MRC-CBU's MEG scanner and the independence of data from trial to trial. The independence of the electrophysiological signal from neurovascular coupling also makes it attractive for pharmacological studies. We have been studying frontotemporal interactions in FTLD related to mismatch negativity responses [77] and semantic response selection [78-80]

The performance and data quality from FTLD patients using such complex paradigms in MEG clearly indicate its suitability to study rule and response inhibition. We may supplement the MEG data with EEG using easy-fit caps. Data are pre-processed with Neuromag software continuous head position information to correct all data to a standard head position; with automatic and manual detection of bad channels; then in SPM (Statistical Parametrical Modelling software) and Matlab, band pass filtered (0.1 to 48 Hz); corrected with PCA for eye-blinks and other artefacts; and averaged into epochs with reference to stimulus and response events of interest and baseline time windows. Although the

topography of gradiometer, magnetometer and EEG channels is reviewed, our primary interest is in the analysis and comparison of cortical source activity. Subject specific structural MRI scans will be used in SPM to construct scalp, skull and cortical meshes, for optimised source localisation.

Additional cognitive and behavioural tests

These fall into two categories. First, those tests undertaken in the clinic or home visits, or study days, to provide general background data on the distribution and severity of cognitive deficits in FTLD. Many of these are used as standard in the clinic, but might be added for research purposes in a given patient. Second, specific targeted tests related to inhibition or serotonergic functions will be performed while on the drug, immediately before or after the MEG scanning. These will provide supplementary information about the effects of serotonin on cognitive endophenotypes in the context of FTLD.

The supplementary cognitive testing requires participants to sit using a computer or paper and pencil and thus could potentially cause fatigue. Participants will perform the cognitive testing battery for no more than 2 hours. Breaks will be included throughout the session, and participants will be reminded that they can take a break at any time by asking the researcher. The procedures used in this experiment will neither be physically stressful nor impinge on the safety of the participants. The images and feedback that are presented are also not emotional and have not caused any distress in related studies of patients or healthy controls. Testing will stop if a patient reports excessive frustration or appears tired. Tests will be drawn from the following battery:

a. visual and auditory acuity
b. Addenbrookes cognitive examination ACE (usually done in NHS clinic)
c. MMSE (Included within the ACE)
d. Beck depression inventory (can be completed at home)
e. Apathy questionnaire
f. Kirby temporal discounting test
g. national adult reading test or Spot the Word
h. Cambridge behavioural Inventory (CBI, usually done in the NHS clinic)
i. Digit-symbol test
j. Picture naming (eg. Graded naming Test, famous faces naming), picture association tasks (eg. Camels and Cactus test) and picture copying (Benson or Rey figure copy) (standard in the NHS clinic).
k. Selected tests from the standardised Cantab computerised battery of cognitive function may be used, for example of reaction times, short term memory span, attention and attentional shift test. These are each short (5-15 minute) computer based tests using simple pictures and button press responses, testing attention, decision making and motor reactions.
l. Visual analogue tests of fatigue, arousal, mood.
m. Measurement of eye-movements (saccades and saccade inhibition), using a standard lightweight head mounted saccadometer.
n. INECO and Frontal assessment battery (usually done in NHS clinic)
o. Hayling Test of executive function.

General procedures: safety and comfort

The safety of our participants is paramount. Participants undergoing MRI will have no contraindications to MRI, and for the pharmacological studies, they will also have no contraindications to the appropriate drug. MEG is non-invasive and extremely safe, within SOPs. A preliminary checklist for contraindications will be used at the recruitment stage, with further secondary safety checks immediately prior to drug administration and scanning. The screening checklists are provided separately with this application. Some participants may require an ECG, and this is made clear in the PIS.

Volunteers will be screened via questionnaire to ensure they have no history of relevant medical problems (e.g. significant cardiac disease, uncontrolled hypertension, adverse drug reactions to these or closely related drugs, and relevant psychiatric disorders), and are not taking other medications which might interact adversely.

Pharmacological challenges.

For the pharmacological studies of patients, we are using oral preparations of commonly used drugs, taken once on the morning of the assessment day. These are typically used in the NHS out-patient setting for adults and children, without supervision of first dose effects. It is therefore not necessary that a doctor be present with the participant throughout the assessment period and scanning. However, a named qualified doctor will be available on the same research site throughout each session, and contactable by telephone or bleep.

The medical supervisor would however meet all participants prior to drug challenges, to ensure safety procedures have been correctly followed, and to answer any medical questions that may arise. By default, this will be Professor James Rowe (consultant neurologist and CI) but the medical supervisory role may delegated to an appropriately qualified clinical research fellow or registrar attached to the study in the future. An out of hours 24 hour telephone contact number will be provided in case of any symptoms following participation.

Citalopram is one of the most widely used antidepressant medications. In comparable research studies, it has been used extensively in oral and intravenous preparations in healthy volunteers. We propose to use oral 30 mg, the standard starting dose in most out-patient neuropsychiatric settings (clinical range 20-60 mg). Although citalopram is only contraindicated in patients with mania, we would as a precaution also exclude patients with current epilepsy or significant cardiac disease. Some patients will already be treated with citalopram or related Selective serotonin re-uptake inhibitors.

We propose a partial withdrawal from serotonergic (SSRI) medication, akin to the routine dopamine withdrawal schedules used to study Parkinson's disease. To study withdrawal effects on behaviour and neurophysiology, we would randomise to withdrawal or usual treatment for the two MEG sessions. The duration of withdrawal would vary according to the half-life of the medication, but approximating 1 to 1.5 half-lives. Cessation of SSRIs can induce a withdrawal syndrome. This is discussed in the PIS. Despite this possibility, episodic non-compliance rates are >50% in other disorders treated with SSRIs (anxiety, depression, obsessive-compulsive disorders). We would interview patients and carers about previous

omissions of SSRIs. If they had no significant symptoms, I would plan to delay medication for approxiamtely1.5 x the half-life of the SSRI.

Tiagabine is a licenced, widely used treatment for epilepsy (clinical range 4-56mg per day). It has been used in research studies of healthy volunteers, often up to 15mg [66]. We are proposing to use an oral 10mg dose. It is contraindicated in patients taking some types of antiviral and antifungal tablets, and these patients would be excluded.

Memantine is a common treatment for some types of dementia (for example, Alzhimer's Disease), with a clinical dose range of 5-28mg per day, and used in research studies up to 20mg. For patients with frontotemporal dementias, neither tiagabine or memantine are used regularly in our clinical practice (although memantine is commonly used in FTLD in overseas centres), so we do not include a withdrawal study.

Zolpidem is a licenced, widely used treatment for insomnia with a starting dose of 5mg, and used in research studies up to 10mg. We are proposing to use an oral 5mg dose. For patients with FTLD zolpidem is not regularly prescribed. It is contraindicated in patients with severe hepatic impairment, respiratory impairment, and in patients with complex sleep behaviours (for example frequent sleep walking) and these patients would be excluded.

Cardiac safety.

An ECG is not part of routine clinical use of these drugs proposed in the described studies, even when higher doses than above are used. Given the range of participants in the study a routine ECG is not required. We propose to review the ECG only in individual cases as advised by the study physician. This would include for example to confirm benign begeminy or benign sparse ectopics if the pulse were felt to be irregular. An ECG would be performed if required and reviewed by a supervising physician.

Blood tests.

For pharmacological studies of patients, a blood test will be performed prior to scanning. This is to measure drug levels, to ensure correct randomisation and for post-hoc analysis using drug levels as covariates. Up to 10 ml (two teaspoons) will be taken, and the PIS refers to this and the associated minor discomfort. Blood will be taken by a qualified doctor, nurse or phlebotomist. Blood will be processed for storage of serum, not whole blood. Patients refusing a blood test would nonetheless be able to continue with other parts of the study.

Experimental details.

Experiment 1 – preliminary open label investigation (completed)

Experiments 2-4 use a standard dose of citalopram 30 mg, based on optimal doses and behavioural effects in studies of inhibition and cognitive flexibility in healthy adults. One issue that has been discussed extensively in the development of this protocol is the difference between acute and chronic

SSRI therapies, due in part to the acute effects of 5HT-1A inhibitory autoreceptors. In animal studies using SSRIs, short-term elevation of 5-HT in the midbrain raphe nuclei (the site of the 5-HT cell bodies) stimulates the 5-HT_{1A} autoreceptor and thus may in principal attenuate further 5-HT release.

In experiment 1 therefore, we propose a behavioural study at the CRF, using the combination of Pindolol 10 mg and Citalopram 30 mg. This drug is well tolerated, and does not exacerbate depression - indeed, it may attenuate depression and anxiety in patients treated concurrently with SSRIs [81, 82].

In this open label pilot study we will study six patients with FTD, with no contraindications to beta-blockers (asthma, heart failure, bradyarrhythmias, hypotension, heart block). The neurophysiological and behavioural tests will be those proposed below for the principal experiment 2. Three would be treated with citalopram alone, three with citalopram plus Pindolol.

Experiment 2 - randomised controlled crossover investigation of serotoninergic modulation of the neurophysiology of inhibition in FTD (completed)

This will focus on Inhibition and cognitive flexibility, including the failure to adjust behaviour on post-error trials. Hypothesis 1: patients show diminished source currents in inferior frontal cortical sources; and Hypothesis 2**:** acute facilitation of serotonin transmission by the SSRI citalopram enhances the activity of the inferior frontal gyrus enabling better behavioural restraint. No-go-stimuli elicit a frontal complex in EEG/MEG studies with an early N2/m140 response localised to the inferior frontal sulci [83] and a later P3/m300 ms localised to cingulate cortex. These responses are attenuated in impulsive conditions such as Huntington's Disease (HD), PD and personality disorder [84-87] These are therefore candidates for the maximal effects of bvFTD and serotonergic intervention.

Drugs: A pharmacological MEG study using(a) placebo vs citalopram 30 mg in 16 patients with bvFTD or (b) normal medication vs SSRI short term withdrawal in up to 16 patients with bvFTD on concurrent SSRIs and (c) and 18 controls. The order of medication will be randomised (see general methods) and crossover within patient.

Patients not already taking an SSRI will be randomly permuted to receive a single dose of citalopram 30mg or placebo 3 hours before scanning (the time to serum-peak for oral citalopram, corroborated by changes in cortisol and/or prolactin). Subjects already taking SSRIs will be randomly permuted to take normal medication or to delay their SSRI (see general methods above).

Participants will be scanned twice, approximately two weeks apart (minimum 1 week). All subjects will undergo structural MRI scanning with MRPAGE and diffusion weighted sequences on one occasion.

Tasks: Subjects will undergo MEG scanning during three tasks:

(a) Go-No-go task, with button presses or inhibition to shapes/beeps. Reaction times, omission and commission errors recorded.

(b) Stop signal task, with button presses to shapes and occasionally countermanded by shape/beep. Reaction times, omission and commission errors recorded, with estimation of the time needed to stop an initiated action.

(c) A simplified reversal learning paradigm [57] using visual stimuli and button press responses. They learn by trial and error with visual feedback which stimulus is correct. Trials are classified *post hoc* as correct trials, error trials following a change of rule, error trials immediately preceding successful reversal and trials immediately after successful reversal.

Analysis: MEG will use the MRC-CBU 306 channel Neuromag scanner, with active shielding and "easy-fit" EEG electrode caps. The three tasks will be divided over 90 minutes scanning to give sufficient signal to noise after correction or rejection of trials affected by artefacts or error. MEG and EEG channel data would be pre-processed according to general methods above. The effect of group (patient vs control) and intervention (patient on vs off SSRI) on source activation over peri-stimulus time will be tested for equivalent sources, using randomisation-permutation tests. Behavioural data of error rates and reciprocal-latencies will be compared with ANOVAs. Secondary analyses of MEG data will include time frequency analysis and analysis of coherence between inferior frontal cortex and premotor cortex.

Predictions: (1) bvFTD is associated with severe reductions of m140 and m300 responses on inhibition trials, correlated with clinical impulsivity scales; (2) citalopram acutely will enhance the m140 response, and to a lesser extent the m300 on NoGo trials, but not improve the SSRT; (3) the improvement in neurophysiological indices will correlate with reduced commission errors.

Experiment 3 - serotonergic modulation in FTD variants (completed)

In this subsidiary experiment, the effects of citalopram on the neurophysiological processes underlying response inhibition and rule reversal will be extended to patients with two variants of the behavioural phenotype that resembles FTD. The first is those who appear non-progressive and have normal structural brain imaging. These patients have a 'mimic' or 'phenocopy' of FTD. The underlying systems of behavioural control are deregulated, but from a different mechanism. Nonetheless, persistent disabling behavioural symptoms and signs occur, warranting further investigation.

In experiment 3 therefore, we would repeat the experimental design from experiment 2, but apply to patients with a phenocopy of bvFTD, as defined clinically by their consultant neurologist or psychiatrist. Further control data would not be acquired, unless significant changes in the scanner facilities had occurred, requiring new control data. In such a case, 18 new control subjects would also be investigated.

Depending on the comparison of EEG and MEG data in experiment 2, and the sensitivity to the effects of neurodegeneration and citalopram modulation, we may opt to use EEG facilities on the Addenbrooke's campus. These are available at both the Herchel-Smith Building (University of Cambridge) and the Clinical Research facility (Addenbrooke's Hospital).

Experiment 4 - serotonergic modulation of non-FTD tauopathies (completed)

In this subsidiary experiment, the effects of citalopram on the neurophysiological processes underlying response inhibition and rule reversal will be extended to patients with Progressive Supranuclear Palsy (PSP) and Corticobasal degeneration. Like FTD, these patients have an underlying tau neuropathology, causing a behavioural syndrome with poor performance on tests of frontal lobe function, including inhibition.

In experiment 3 therefore, we would repeat the experimental design from experiment 1, but apply to 16 patients with PSP and 16 with CBD, as defined clinically by their consultant neurologist or psychiatrist. Further control data would not be acquired, unless significant changes in the scanner facilities had occurred, requiring new control data. In such a case, 18 new control subjects would also be investigated.

In PSP and CBD, the experimental protocol would be supplemented by simple tests of movement, because of the movement disorder (parkinsonism) associated with PSP and CBD. For these tests, participants would press buttons with their right and left hand in response to visual cues, every few seconds, for up to 10 minutes.

Experiment 5 – supplementary neuropsychological studies of FTD and related disorders.

As noted above, the core behavioural tests undertaken in the scanner will be supplemented by behavioural and cognitive tests. For many of these tests, we are not seeking the effects of citalopram, but rather baseline performance in the context of FTD (or health). These may be undertaken in clinic, or on the scanning study day (time and fatigue permitting). However, they may also be completed at a separate visit to the clinic suite (Herchel-smith building) or at home with an agreed home visit by a member of the study team.

For patients unable or unwilling to participate in the scanning experiments, we would nonetheless invite participation in behavioural testing. This amounts to a separate experiment (experiment 5), establishing a larger database of the effects of FTD effects on behavioural tests without drugs or scanning.

The cognitive testing requires subjects to sit using a computer or paper and pencil and thus could potentially cause fatigue. Subjects will perform the cognitive testing battery for no more than 2 hours. Breaks will be included throughout the session, and subjects will be reminded that they can take a break at any time by asking the researcher. The procedures used in this experiment will neither be physically stressful nor impinge on the safety of the participants. The images and feedback that are presented are also not emotional and have not caused any distress in related studies of patients or healthy controls. Testing will stop if a patient reports excessive frustration or appears tired.

Tests included are listed above in the section Additional cognitive and behavioural tests

Experiment 6 - Randomised controlled crossover investigation of GABA modulation of the neurophysiology of action control and inhibition in FTLD syndromes

This experiment will focus on actions, inhibition and cognitive flexibility, including the failure to adjust behaviour on post-error trials. Hypothesis 1: patients show diminished frequency specific power in frontotemporal and motor cortical sources; and Hypothesis 2**:** acute facilitation of GABA transmission by the reuptake inhibiter tiagabine will enhance gamma power enabling better behavioural control. Previous research has demonstrated that peak gamma frequency is determined by GABA concentration[63], and that an increase in GABA, after administration of Tiagabine, is associated with enhanced gamma power during cognitive inhibition [88]. The effect of FTD and related disorders on high frequency gamma oscillations (30-100Hz) is not yet established but my recent data shows reduced frontotemporal gamma power with age suggesting a contribution to age-related neurocognitive inefficiency.

Drugs: A pharmacological MEG study using (a) placebo vs tiagabine 10 mg in 20 patients with FTLD and (b) 20 controls. The order of medication will be randomised (see general methods) and crossover within participant. Participants will be scanned twice, approximately two weeks apart (minimum 1 week). All subjects will undergo MRI scanning with structural MRPAGE, functional resting state fMRI, MR-spectroscopy and diffusion weighted sequences on one occasion.

Tasks: Participants will undergo MEG scanning during three active tasks and rest:

(a) A response inhibition task, with button presses to shapes/beeps. Reaction times, omission and commission errors recorded.

(b) A simplified motor learning paradigm using visual stimuli and manual joystick responses. Participants learn by trial and error with visual feedback for correct responses. Trials are classified *post hoc* as correct trials and error trials following or preceding a change of condition.

(c) Simple auditory, visual and sensorimotor paradigms.

(d) Participants will also undergo ‘resting state’ MEG where data are recorded during a passive state with eye’s open or closed, but with no specific visual or auditory stimulation.

Analysis: will be similar to Experiment 2.

Predictions: (1) FTLD is associated with diminished power in the gamma band, and loss of coupling between gamma and alpha/beta bands in frontal and motor cortical sources; and (2) acute facilitation of GABA transmission by the reuptake inhibiter tiagabine enhances gamma power enhancing motor responses. (3) The improvement in neurophysiological indices will correlate with reduced errors and better motor control, (4) MEG data modelling will confirm the changes in inferred GABA receptor function.

Experiment 7 - Randomised controlled crossover investigation of NMDA modulation of the neurophysiology of action control and inhibition in FTD

This experiment will focus on the role of NMDA in cortical circuits underlying cognition Hypothesis 1: patients show diminished frequency specific power in frontotemporal and motor cortical sources; and Hypothesis 2**:** acute facilitation of NMDA transmission by the reuptake inhibiter memantine enhances gamma power enabling better behavioural control. Previous research using NMDA receptor antagonists, such as memantine, have been demonstrated in animal models to increase the power of gamma oscillations [67, 68]. NMDA intervention (including memantine [69]), is widely used to treat dementia, including Alzheimer's disease.

Drugs: A pharmacological MEG study using (a) placebo vs memantine 10mg in 20 patients with FTLD and (b) 20 controls. The order of medication will be randomised (see general methods) and crossover within participant. Participants will be scanned twice, approximately two weeks apart (minimum 1 week). All subjects will undergo MRI scanning on one occasion as in experiment 6.

Tasks: Participants will undergo MEG scanning during three active tasks:

(a) Response inhibition, with button presses to visual stimuli. Reaction times, omission and commission errors recorded.

(b) A simplified motor learning paradigm using visual stimuli and manual joystick responses. Participants learn by trial and error with visual feedback for correct responses. Trials are classified *post hoc* as correct trials and error trials following or preceding a change of condition.

(c) Simple auditory, visual and sensorimotor paradigms.

Participants will also undergo 'resting state' MEG where data are recorded during a passive state with eye's open or closed, but with no specific visual or auditory stimulation.

Analysis: analysis pipelines will be similar to Experiment 2.

Predictions: (1) FTLD is associated with diminished power in the gamma band, and loss of coupling between gamma and alpha/beta bands in frontal and motor cortical sources; and (2)**:** acute facilitation of NMDA transmission by the reuptake inhibiter memantine enhances the gamma power enabling better motor responses. (3) The improvement in neurophysiological indices will correlate with reduced errors and better motor control. (4) MEG data modelling will confirm the changes in inferred NMDA receptor function.

Experiment 8 - Randomised controlled crossover investigation of GABA modulation of the neurophysiology of action control and inhibition in FTLD

This experiment will focus on the role of GABA in cortical circuits underlying actions and

cognition, including the ability to flexibly initiate and inhibit actions. Hypothesis 1: patients show modulated frequency specific power in frontotemporal and motor cortical sources; and Hypothesis 2**:** acute facilitation of GABA transmission by the GABAa receptor agonist Zolpidem modulates low frequency power enabling improved behavioural control. Previous research using Zolpidem has demonstrated in patients with PSP, PD and brain injury a dose dependent increase in beta power and a decrease in alpha power, and concomitant improvements in motor function, including speech and eye movements.

Drugs: A pharmacological MEG study using (a) placebo vs Zolpidem 5mg in up to 48 patients with FTLD (including bvFTD, PSP and CBD) and (b) up to 48 age-matched controls. The order of medication will be randomised (see general methods) and crossover within participant. Participants will be scanned twice, approximately two weeks apart (minimum 1 week). All subjects will undergo MRI scanning with structural MRPAGE, functional resting state fMRI, MR-spectroscopy and diffusion weighted sequences on one occasion.

Tasks: Participants will undergo MEG scanning during three active tasks:

(a) Response initiation and inhibition, with button presses to visual stimuli and visual feedback. Reaction times, omission and commission errors recorded.

(b) Simple auditory, visual and sensorimotor paradigms.

(c) Participants will also undergo 'resting state' MEG where data are recorded during a passive state with eye's open or closed, but with no specific visual or auditory stimulation.

Analysis: analysis pipelines will be similar to Experiment 2.

Predictions: (1) FTLD is associated with diminished power in the beta and alpha bands, and loss of coupling between frontal and motor cortical sources; and (2)**:** acute facilitation of GABA transmission by zolpidem enhances low frequency power enabling better motor responses. (3) The improvement in neurophysiological indices will correlate with reduced errors and better motor control. (4) MEG data modelling will confirm the changes in inferred GABA receptor function.

Experiment 9 – Follow-up measure of cognitive decline and related neurophysiological changes.

This experiment will focus on change in cognition, behaviour and cortical circuits, after 12 months progression, compared to the placebo session in Experiment 8. Hypothesis 1: Disease progression will cause changes in cognition and behaviour, and neurophysiology. Hypothesis 2: Baseline scores will predict disease relevant changes at 12 months.

Tasks: All participants who have participated in Experiment 8, including the healthy controls, will be invited back for a single follow-up visit approximately 12 months after the placebo MEG scan. The

session will be completed as for the experimental sessions in Experiment 8. Participants will also be invited for a follow-up MRI scanning as in Experiment 8, which may take place on a separate day if preferred by the participant.

In this Experiment participants will be given a placebo tablet, in order to match the experimental conditions with the baseline measures in Experiment 8. Participants will be advised in advance, as in Experiment 8 that it could either be the Zolpidem or the placebo, even though only a placebo is given. We acknowledge that this involves a degree of temporary deception, and participants will be debriefed after completing the study.

Tasks: As in Experiment 8. With additional debriefing after the session completes to explain the placebo deception.

Analysis: analysis pipelines will be similar to Experiment 2. With a direct comparison of the placebo session in Experiment 8 with the session in Experiment 9.

Predictions (1) Patients cognitive scores will decline over time, and behavioural measures are predicted to show a change from baseline indicating a progression of disease. (2) cognitive and behavioural changes will relate to changes in neurophysiology: cortical oscillations will be altered. (3) Neurophysiological indices from the placebo session in Experiment 8 will predict the change in cognitive/behavioural decline in Experiment 9.

6 STUDY SETTING

Recruitment and screening will be undertaken through the specialist neurology clinics. For study days, patients and carers, or healthy controls, will attend the Clinical Research facility (CRF) and/or the Herchel-Smith Building for Brain and Mind Sciences (HSB), clinical suite on the Addenbrooke's campus. They will undergo:

1. Greeting and reassurance
2. Review of screening and safety
3. Consent
4. ECG if required. Blood pressure and Pulse check
5. Administration of drug
6. Rest
7. Pretraining on relevant tasks and supplementary neuropsychological testing
8. Refreshments and toilet breaks

Then, for MEG, they will be transferred by car/taxi to the MRC-Cognition and Brain Sciences Unit where the MEG is placed. Here they will undergo:

9. Familiarisation with MEG suite
10. MEG checks

11. Easy-fit electrode cap fitting
12. Blood test if required
13. MEG scanning with breaks
14. Refreshments and toilet break.
15. Debriefing.
16. Return to Addenbrooke's campus for rest and MRI (WBIC) if required.
17. Home

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Recruitment. Patients with frontotemporal lobar degeneration syndromes (FTD, PSP, CBS by consensus criteria) will be recruited via the Outpatient clinics of the Cambridge University Department of Clinical Neurosciences, Addenbrookes Hospital (including the Memory clinic, Early Dementia Clinic and clinic for disorders of movement and cognition). If adopted by the DENDRON and local clinical research networks, other recruitment sites may be added including "JDR" (Join Dementia Research) but investigations would remain based in Cambridge. Healthy control participants will be recruited initially from the MRC-CBU volunteer panel, Join Dementia Research (JDR), or other healthy volunteers presenting themselves to the study team. The Cambridge BioResource managers may be approached for future healthy controls if separate ongoing studies indicate a need for genotypic matching of patients to controls, in terms of common polymorphisms. Racial background will not be used for inclusion or exclusion criteria.

Participant age will be between 20 and 80 years old. The age cut off at 80 years is precautionary on two fronts. (1) the risk of side effects in pharmacological studies may increase with advanced age, and (2) the risk of latent cerebrovascular disease or severe atrophy alongside FTLD increases with advanced age. The proposed threshold at 80 years is a compromise that should allow our sample to be representative of the general FTLD population, while at the same time reducing the frequency of significant latent comorbidities.

7.1.1 Inclusion criteria

Diagnostic category

- Principal studies:
  - Frontotemporal dementia including subtypes diagnosed by current consensus criteria for behavioural variant or language variants [89, 90].
  - Progressive Supranuclear Palsy (an FTLD related tau-disorder) including Richardson syndrome and PSP frontal syndrome and other presentations of PSP. Diagnosed by current consensus criteria: MDS-PSP 2017 criteria for PSP–Richardson's syndrome [91].
  - Corticobasal syndrome by consensus clinical diagnostic criteria, [92].
- Secondary studies:

  - Motor neuron disease with or without associated FTD
  - phenocopy (non-degenerative) FTD
- Healthy control (no major neurological or psychiatric disorder)
  - Age 20-80
  - English speaking

7.1.2 Exclusion criteria

Clinically significant current depression

Contraindications to MRI or MEG

Contraindication to pharmacological challenges:

Ischemic heart disease or significant cardiac rhythm abnormalities,

Current epilepsy

Pregnancy

Myasthenia gravis

Adverse drug reactions to Citalopram, Memantine, Tiagabine, Zolpidem or closely related drugs (according to experiment)

Other major psychiatric disorders including mania or schizophrenia

Known hepatic or renal failure (moderate or severe)

Zolpidem is also contraindicated in people with respiratory impairment (sleep apnoea), and people with complex sleep behaviours (frequent sleep walking).

We will refer to the STOPP/START Screening Tool of Older Person's Prescriptions in the evaluations of the drug suitability for individuals [93, 94], but note that we propose a single stat dose not regular treatment.

7.2 Sampling

7.2.1 Size of sample

Patients

We will study up to 48 patients per experiment with FTD, PSP, and CBD, (up to 16 with each diagnosis) per study in this protocol. We will primarily recruit patients from long established clinics for each disease led by Prof Rowe and colleagues at Cambridge University Hospitals NHS Trust.

This number in patient recruitment will facilitate: 1) the inclusion of the different clinical groups, 2) further increase the power of group-comparisons as previously documented, 3) allow for the identification of individual differences in brain function from MRI and MEG in relation to clinical and behavioural measures, further allowing for the individual stratification of patients and, 4) further replicate and validate key results from the first studies under this protocol, and elsewhere. 5) It also allows for attrition of study numbers, especially at the 12 month follow-up.

Controls

Up to 48 control participants will be recruited per experiment. Historical control data can be useful, but contemporary control data are required if there are modifications to the tasks and to ensure that changes in hardware (eg MEG scanner replacement 2020) and acquisition protocols do not confound group effects.

Power. For MEG studies, we base our power estimates for n~16 for each study on data from smaller but experimentally comparable studies of Huntington's disease and PD [84, 86]. Power calculations (Gpower, Kiel) show that if citalopram reduces the disease related abnormality of m300 by 25%, we would have >95% power to detect that effect at α=0.05. We would have 60% power to detect a 25% reduction of the disease effect on the m140 response, and 97% power to detect a 50% reduction at α=0.05. In experiments, 1-7, these power calculations have been supported, with evidence for the effects of disease, and revealing the effect of respective drug interventions.

Attrition may arise from participant dropout during or between scanning, or from technical problems. Death or change of consent capacity is not likely during the short period of participation by any one subject. Based on previous neuroimaging of clinical populations, we estimate 20% attrition within each study. At 12 month follow up we estimate further 10% attrition due to the progression of disease which may prevent participants attending the second session, but with increased power through the within-subject nature of longitudinal data.

7.2.2 Sampling technique

Patients will be diagnosed according to consensus criteria, or be patients with a clinical overlap syndrome that has features of these disease but without specificity. Up to 48 controls will also be studied to develop the test protocols per experiment, and as a comparison for disease groups. Patients are selected according to their principal diagnosis.

7.3 Recruitment

7.3.1 Sample identification

Diagnosis of dementia follows the international consensus diagnostic criteria, used in specialist clinics to establish the diagnoses. For PSP we used the criteria from Litvan et al., (1994), but switched to the current MDS-PSP 2017 criteria for PSP–Richardson's syndrome. For CBS we used the classifications suggested by Matthew and Hodges (2012), but switched to using the new Armstrong et al (2013) criteria; for FTD until 2011 we used the Manchester-Lund 2001 criteria but then adopted the evidence-based criteria from Rascovsky et al., (2011). These consensus criteria for FTD have been adopted worldwide by FTD researchers and clinicians alike. These criteria are the same as those used by the NHS clinical doctors. All of these diagnostic criteria rely on a set of symptoms, signs, and tests that are implemented in the clinics as standard. Importantly, no research specific tests are required before recruitment because the investigations are made during the patient's ordinary NHS clinical care.

Patients will be actively recruited through the Disorders of Movement and Cognition Clinic, the FTD clinic and the Memory clinics run by Prof James Rowe, and in collaboration with Prof Roger Barker at the PD research clinic. Referrals for research would be considered from other sources e.g. other consultants in the department and Join Dementia Research

Up to 48 healthy control participants will be recruited initially from the MRC-CBU volunteer panel, Join Dementia Research (JDR), or other healthy volunteers presenting themselves to the study team. The Cambridge BioResource managers may be approached for future healthy controls if separate ongoing studies indicate a need for genotypic matching of patients to controls, in terms of common polymorphisms.

7.2.2 Consent

A written information sheet is given ahead of time (by letter or in person) and the project discussed in person by Rowe or Hughes or supervised research assistant. Initial interest is assessed, before discussing further details of the study and questions from the patients and carers. A screening form is used (Appendix 11.4) to assess suitability if interest is expressed in the study. Patients are consented in the presence of their next of kin, spouse, carer or advocate.

Many patients will have cognitive disorders or dementia. This does not necessarily mean that they cannot consent. Consent pertains to the decision in front of them, the information required to understand and decide, the assessment of risk/benefits and the communication of a decision or revised decision. For this type of study, many of our patients would have sufficient capacity to make a decision to participate or refuse. All would have the ability to communicate their wishes (we will not include patients with severe language problems or mutism).

However, in case the capacity to consent is borderline, intermittent, transient or liable to question either now or in the future, we have developed safeguards within our consent procedures. Whereas patients will be asked for their consent, this will be done in consultation with, and in the presence of, their spouse, close relative, principal carer, or advocate. Such a patient's signature of consent will be countersigned by the witnessing spouse, close relative, carer, or advocate. Therefore, the patients consent (or refusal) is paramount, but supported by a level of protection that would be applicable to someone with impaired consent.

To achieve this, we are mindful of the Mental Capacity Act Code of Practice (issued by the Lord Chancellor 2007 in accordance with sections 42 and 43 of the Act) chapter 11. In particular: we assume that a person has capacity, unless there is evidence that they lack capacity to make the specific decision, but that the person must also receive support to try to help them make their own decision. The person whose capacity is in question has the right to make decisions that others might not agree with, and in particular they have the right not to take part in research: a decision not to participate would not be challenged. b. In accordance with section 11.11 of the guidelines we note that FTD can be an impairing condition that affects the person who lacks capacity, and our protocol may affect (even temporarily) their treatment of that condition (for example, in those patients who withdraw from medication for a short period) c. there are reasonable grounds for believing that the research would be less effective if only people with capacity are involved, and the research project will make arrangements to consult carers and to follow the other requirements of the Act. d. In accordance with 11.12 of the guidelines, we are clear that the aim of the research is to provide knowledge about the cause of, or treatment or care of people with FTD and similar conditions. We do not intend with this study to directly benefit the person who lacks capacity. e. In addition, the risk to the person who lacks capacity would be negligible; there is no significant interference with the freedom of action or privacy of the person who lacks capacity; and nothing will be done to or in relation to the person who lacks capacity which is unduly invasive or restrictive.

In addition, GPs will be notified of a patient's participation, although patients will make the decision to participate themselves. The GP letter will include a copy of the PIS.

Note regarding the PIS: We have written a 'modular' PIS, that clearly explains the proposed research to any given participant. The PIS includes two front pages with general information about the study, and summary information on the number of sessions and medication, together with a summary of medico-legal issues. Each potential participant would also be given the relevant supplementary sheets, regarding medication and study details (B to H) and a full statement regarding confidentiality, complaints and insurance (sheet I). We believe that this modular approach is most easily accessible for lay participants, allowing them to locate and focus on the relevant information necessary to provide informed consent. All PIS forms include the name and contact details as principal investigator. A second contact person may also be included, where that person is a clinical research fellow or post-doctoral research fellow closely associated with the study and likely to have direct contact with the participant during their screening or assessment sessions.

Psychiatric state. Some of our participants will have known dementia. However, during the course of the study, participants will undertake screening tests such as the MMSE and the BDI. If a participant scores unexpectedly and significantly outside the normal range, we would treat this as any other abnormal finding, and inform the GP (with the subjects consent). However, the MMSE is not a diagnostic tool for dementia, and there are many reasons why a participant might score low on a given day. Clinical judgment from an experienced cognitive neurologist (Dr Rowe) would be used in deciding the appropriate response to a low MMSE score.

Regarding the BDI, it is unlikely that suicidal patients would be selected. If an unexpectedly suicidal patient were to be assessed, and complete question 9 with a rating of 2 or 3, this would be counted as an abnormal result, and with the subject's permission, the GP or specialty consultant would be notified. It should be noted that the BDI is not a diagnostic tool for depression, and does not replace a clinical diagnostic approach by the patient's NHS doctors (GP and neurologist), nor does it replace the clinical diagnostic criteria for depression. Furthermore, the standard cut-off values for research ratings of depression using the BDI are based on physically fit depressed patients and are not necessarily applicable to patients with neurodegenerative disease. This is because the BDI, like many questionnaire assessments of depression symptoms, includes physical symptoms (eg. fatigue, sexual interest and sleep change) that may inflate the score in the absence of depression. The BDI is used in our study as an index of our case mix. It is not a clinical outcome measure or diagnostic tool.

Reimbursement to subjects. Healthy participants will be reimbursed at standard rates for behavioural and imaging studies at the CBU and WBIC (currently £6 per hour for behavioural tests, 10 per hour for MRI or MEG studies, plus travel expenses). We have spoken with the Pension Credit Support line and the Benefits Enquiry Line regarding the issue of benefits entitlements. Pension Credit would not be affected by a single reimbursement from this study. The reimbursement would not be considered as income (as a single payments related to research study participation). A similar response was given for Housing Benefit and Council Tax benefit. Attendance allowance and Disability Living Allowance are not means tested, and would not be affected by study reimbursement. We mention this in the PIS. For patient participants, full travel costs would be reimbursed.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

Standard Operating Procedures (SOPs) govern MEG and MRI investigations at the CBU, including clear guidance on all matters relevant to safety of research participants and researchers. Neither immediate nor delayed adverse effects are to be expected. A contact number is provided, including for out of hours problems following participation, whether or not a problem is directly related to participation. Prior to MEG or MRI scanning a safety questionnaire is performed, for MEG this is essentially to prevent the MEG scanner from damage by metallic objects nearby, and for MRI to screen for any risk to participants by metal about their person.

Regarding safeguarding the MRC CBU has a safeguarding policy in place to prevent or reduce harm to vulnerable groups, with a Designated Safeguarding Person (DSP) onsite. All MRC CBU researchers who work with vulnerable groups (including patients) are required to be aware of and

conform to this safeguarding policy. The MRC-CBU safeguarding policy abides by accepted practice on the limitations of confidentiality when a safeguarding issue arises.

If undertaking a home visit the MRC CBU's safeguarding policy will apply as above. Additionally, the MRC CBU has in place a 'Before You Go' guide for safe home visiting based on the MRC's Health and Safety Policy. All researchers undertaking home visits as part of this study will adhere to the safeguarding guidelines.

8.2 Research Ethics Committee (REC) review & reports

Before the start of the study, approval will be sought from the REC and local NHS R&D department for the study protocol, informed consent forms, participant information leaflet and other relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (along with acceptance by the local R&D departments if applicable, or through other research governance mechanisms, before being implemented in practice at the research sites). All correspondence with the REC will be retained. The Chief Investigator's will produce annual progress reports as required and will notify the REC of the end of the study.

Note that this document, protocol v7, is a substantial re-writing from a longstanding approved protocol.

8.3 Peer review

The imaging management committee (IMC) oversees all MEG and MRI research at the CBU. The IMC ensures that specific studies have been subjected to peer review through including the Imaging Interest Group (IIG). They ensure that safe standard procedures are followed. They have established a process of MEG operators, who are independant of the MEG researchers, to ensure adherence to the SOPs. The onsite MRI facility is staffed by qualified radiographers and trained MRI operators. All research staff undertakting an imaging study are required to undertake a MRI safety course and/or MEG researcher training course prior to starting data collection. Any problems, including adverse events, are reported to the IMC and appropriate investigation and action would be taken by the IMC. Following completion of individual studies, researchers also report back to the Imaging Interst Group – including scientific outcomes, technical issues and if relevant any adverse events whether or not harm resulted from them.

The program of research set out in the protcol implements research proposals that have been subject to rigorous external international blinded independent peer review, arranged by the Wellcome Trust and MRC, during the highly competitive applications for grant funding.

8.4 Patient & Public Involvement

Patients and carers affected by the reference diseases are involved in discussion of our research program in advance and by interval feedback, through (i) our carer meetings for patients attending

clinic (ii) newsletter updates (iii) patient and family days organised by the FTD-support group and PSP Association.

8.5 Regulatory Compliance

Before a site can enrol patients into this study, the Chief Investigator/ Principal Investigator will apply for NHS permission from the site management organisation, HEI or NHS Research & Development (R&D). For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/Principal Investigator will confirm with that site's R&D department that NHS permission is ongoing.

Note that version 6 of this protocol has been approved and received such permissions. They will be re-sought if version 7 is approved by the research ethics committee.

8.6 Protocol compliance

Accidental protocol deviations can happen at any time. Any deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable and will prompt immediate action and if appropriate will be classified as a serious breach.

8.7 Data protection and patient confidentiality

Please see the statements on these issues in the Participant Information Sheet and IRAS submission documents. In brief, data will be stored for a minimum of ten years and possibly longer, within confidential and secure systems at the CBSU and University Department of Clinical Neurosciences. Cambridge University Hospitals, the Department of Clinical Neurosciences and the Cognition and brain Sciences Unit each comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and are committed to upholding the Act's core Data Protection Principles. Data will be identified by a code number. The records of participation in the study may include personal information including name, date of birth and reference number. Members of the Cambridge University Department of Clinical neurosciences and the MRC Cognition and Brain Sciences Unit (CBU) will have access to relevant data. Anonymised data will be shared with collaborating researchers working with the CBU and Department of Clinical Neurosciences and Psychiatry. Where data are transferred the same standards of confidentiality will apply for receiving parties. We anticipate added value from sharing anonymised data within and beyond the UK, ensuring that participants' contributions and efforts in research yield most benefit. The regulations and laws may differ in other countries, but the research team would maintain up to date with guidelines on maintenance of confidentiality and privacy (even of anonymised data), and impose restrictions as necessary on receiving parties as part of material transfer agreements. The consent

form acknowledges these differences and invites specific consent. Note that from April 2017, the CBU becomes formally part of the University of Cambridge, and that data acquired before and after the integration will move with the CBU.

8.8 Indemnity

Comprehensive insurance for different types of claim (negligent and non-negligent), and against different study team members (clinical and non-clinical) and organisations (CBSU and University and NHS) has been established through the University Insurance Office and MRC CBSU.

For negligent harm arising from the management and design of the research provision will be:

1. For the chief investigator, his own Medical Protection Society Insurance has been extended to include clinical negligence during research based private practice, whether of NHS patients or non−NHS participants.
2. Following approval from the R&D office of Cambridge University NHS Trust (Addenbrooke's), patients will be covered by the NHS indemnity scheme
3. Following approval by R&D office and REC, no−fault compensation insurance will be purchased via the University Insurance Office.

For negligent harm arising from the conduct of the research provision will be:

1. Patients will be recruited from NHS sites and NHS indemnity will apply for them.
2. Control Participants may not be recruited from NHS sites. Subject to R&D approval, no−fault insurance will be purchased via the University Insurance office.
3. For claims against MRC employees, relating to harm on MRC property unrelated to participation in the research project, indemnity will be provided by the Medical Research Council. The Medical Research Council provides no insurance cover for non−negligent harm, but will give 'sympathetic hearing' to claims.

Regarding arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises:

1. The CI will purchase insurance on a no−fault basis. This will be arranged with the administrative assistance of the University Insurance Office following REC and R&D offices approval of the project. The project is 'low risk' and no obstacles are anticipated for getting this insurance.
2. The Medical Research Council provides no insurance cover for non−negligent harm, but will give 'sympathetic hearing' to claims, if it is unrelated to participation in this research.

8.9 Amendments

Any amendments made to this study protocol will first be assessed by the CI to determine whether they are substantial or non-substantial. Following this determination the relevant bodies will be informed of the amendment as per HRA recommended procedures, including submit a valid notice of amendment to the REC for consideration. All amendments will be generated and submitted electronically via the IRAS system as detailed on the HRA website (http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/preparing-amendments/). The sponsor and relevant R&D departments will be informed at the time of this submission to ensure they are aware of the changes to the protocol. On receiving approval from the REC this will be immediately communicated to the sponsor and R&D department prior to implementation of the amendment. All amendments and protocol version changes will be recorded in the most recent protocol version appendix (see below), including date and version number to ensure the most recent protocol is easily identifiable. Electronic versions of all historical amendment applications and protocols will be stored for further reference if required.

8.10 Access to the final study dataset

Access will be permitted to those outlined in the consent procedure and research protocol. The chief investigator is employed until 2035. Anonymised data may be used for secondary analyses, and sharing with researchers as set out in the PIS and consent.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The results of this study will be disseminated through conference presentations, peer reviewed scientific journals and regular internal reports and presentations at relevant departmental scientific meetings including for example the local dementia interest group (DIG). Access to raw data and the right to publish freely by all investigators in this study will also be implemented by an Independent steering committee on behalf of all investigators.

Feedback is made regularly to the PSP Association about PSP and CBD research going on through the Clinic. Similar feedback is intended to the FTD society and its local branch.

The data are owned by the CBU, which becomes integrated with the University of Cambridge from 2017. Ownership then passes to the University. The funding of the research will be acknowledged but the funders do not have rights to preview, alter or publish the results.

Metadata are reported monthly, quarterly and yearly to relevant organisations including the Clinical Research Networks, the Research Ethics Committee and the Biomedical Research Centre. Derived

data (but not PiD) are also presented to researcher meetings, the Dementias Platform UK, potential funders and current regulatory bodies as required. Anonymity is preserved and metadata and derived data cannot be used to identify individuals.

9.2 Authorship eligibility guidelines and any intended use of professional writers

As per guidelines from the International Committee of Medical Journal Editors, overseen by the Chief Investigator.

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11. APPENDICIES

11.1 Appendix 1- Required documentation

Completed Amendment Tool
Participant information sheet
Participant consent form
CVs of the three new members in the research team

Letters *of invitation to participants.*

11.2 Appendix 2 – Schedule of Procedures

Procedures	**Visits - Neuropsychological tests will not be repeated if already completed as part of previous clinical assessment. MRI may not be undertaken again if done previously and within 6 months.**			
	Clinic review	**Session 1 Placebo/drug**	**Session 2 Placebo/drug**	**Session 3 Follow up**
Informed consent	x	x	x	x
Demographics	x	x		
Medical history	x	x		x
Cognitive assessments	x	x	x	x
Supplementary neuropsychological assessment		x	x	x
MEG (with EEG) scan		x	x	x
MRI scan			x	x

11.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
3rd Amendment	V6	30/01/2017	James Rowe	One main change: 1. Include an MRI spectroscopy sequence. Total imaging time will be typically up to 60 minutes (but possibly up to 90 minutes).
2nd Amendment	V5	27th August 2015	James Rowe	Three main changes: 1. End date extended to December 2019 due to renewed funding by the Wellcome Trust and new staff added to the project, namely Ms Julie Wiggins, Research Nurse, Dr Saber Sami, Research Associate and Dr David Nesbitt, Clinical Research Associate. All have honorary contracts in place with the Cambridge University Hospitals NHS Trust. 2. Include up to 100 additional patients and 100 additional controls (bringing the total to 202 patients and 160 controls) in order to: (i) to increase the power of the main comparisons, following successful preliminary studies, enabling the exploration of individual differences in brain function in relation to clinical and behavioral differences, (ii) to include two additional drugs (described in detail below) and (iii) to enable replication of key results, an important step in validation of scientific advances. 3. We extended the pharmacological probes to include two additional drugs: Tiagabine a licenced and widely used treatment for epilepsy. We proposed to use a 10mg dose (equivalent to the usual clinical starting dose, and

				appropriate for older adults). The second drug is Memantine, a licensed and widely used treatment for dementia (Alzheimer's Disease). We proposed to use a single and relatively low dose 10mg. Both the design and of the additional experiments will mirror the current design, with placebo-controlled blinded cross over design and physiological not clinical endpoints.
1st Amendment	V4	1st Sept 2011	James Rowe	Minor changes to the protocol including removing pindolol from Experiment 1 and extending the end data to 2014.

11. 4 Appendix 4 – Screening Form

Screening Form (by telephone, then checked before medication)

"Have you had an opportunity to read the volunteer information sheet that I sent to you? Do you have any questions about the study? We need to ask you a few questions to see if you would be suitable for the experiment. Your answers will be treated confidentially. You don't have to answer any questions if you do not wish to."

Volunteer Name ……..

Date of Birth …… Age…… Approximate Weight: ……

Handedness……

Contact phone numbers……..

Availability. Do you work at the moment? What hours do you work? Do you have access to transport to get into Cambridge? We advise that you do not drive on the test days.

…… ……..

Health & Safety screening

If participant answers 'yes' to any of the following questions, details will be collected and a physician will be consulted to determine whether it is safe to include the participant in the study.

Your Health:

Which medications do you take regularly?

……..…….

……..

……

Do you take other medications on an "as needed" basis? Y N

……..……

Have you taken other medications in the last 14 days?

……..……

Have you ever taken antidepressant medication? Y N if so which ……when……

Do you have any allergies? Y N ……

Do you have a history of fainting or collapse? Y N ……

Do you have a history of sleep walking? Y N ……if yes how often:……

Do you have sleep apnoea? Y N ……

Do you have any of the following?

heart conditions Y N ……

slow/irregular heart beat Y N ……

high blood pressure Y N ……

asthma or emphysema or chronic bronchitis

Y N ……

migraine Y N ……

epilepsy or fits Y N ……

depression or anxiety Y N ……

diabetes Y N ……...

glaucoma Y N ……

stomach ulcers Y N ……

liver/kidney failure Y N ……

myasthenia gravis Y N ……

other significant illness Y N……

Family History:

As far as you know, has any family member suffered from the following?

heart disease, angina? Y N ……

anxiety or depression Y N ……

……

Blood sample (if relevant):

Would you mind giving a small blood sample? Y N

……..

Drugs & Alcohol:

How much alcohol do you drink if at all? ……

Do you smoke? Y N ……/day

MRI contraindications (if applicable):

Do you have any metal in your body eg.

Bone pins or plates Y N ……

Or a heart pacemaker? Y N

False teeth, braces, bridges Y N ……

Metal splinters or shrapnel Y N ……

Have you ever done any metal- or lathe- work? Y N

Do you suffer from claustrophobia? Y N ……

…….. ……..

With glasses (if needed) can you read normally? Y N

If you need glasses, please bring them with you on the day.

If volunteer answers 'no' to all questions (except glasses), volunteer may proceed with the study.

If volunteer answers 'yes' to any question, a physician will be consulted before volunteer may proceed with the study.

Suitable for inclusion in study? Y N

Is a ECG required? Y N

(Hypertension, Diabetes or Personal or family history of heart disease)

Physician consulted (where applicable):

Date:

Signature: