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Understanding how increasing some of the brain's chemicals can help thinking and behaviour in people with frontotemporal dementia and progressive supranuclear palsy

Submission date
15/06/2018

Recruitment status
No longer recruiting

Registration date
28/06/2018

Overall study status
Completed

Last Edited
08/07/2025

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Some brain illnesses in later life lead to a change in personality and behaviour. We are looking at two such illnesses, called frontotemporal dementia (FTD, also known as Pick's disease) and progressive supranuclear palsy (PSP). PSP is most well-known for its effect on movement and balance, but it can also change behaviour. By using a brain scanning technique called magnetoencephalography (MEG) we hope to better understand these related illnesses. A MEG scan looks at brain waves so we can study how the brain works when thinking, resting and moving. In this study, we are looking at the effects of commonly used medications. One is called ‘tiagabine’, one is called ‘zolpidem’ and the other is ‘memantine’. We are looking at how these medications may help the brain work more effectively in making decisions and directing actions in patients. We are also asking healthy volunteers to take the medications, so we can compare and separate out the effects of each medication from the effects of illness.

Who can participate?
Patients with frontotemporal dementia or progressive supranuclear palsy can take part if they have been assessed at a hospital specialist clinic. We are also including healthy volunteers between the ages of 50 and 75 years, if they are right-handed and have normal vision (with glasses or contact lenses if needed) and hearing. We are not including people who have had a history of brain injury, or who weigh less than 50 kg. Some medications cannot be taken at the same time as the drugs we are using, so some people may not be able to take part. The brain scan is also very sensitive to metal, so we do not include people who have a lot of metal inside them, such as pacemakers or some prosthetics, or those who have had a lot of dental work. Dentures are usually OK. The study team would discuss these criteria for taking part in the study before joining up.

What does the study involve?
People taking part in the study will have two MEG brain scans, on two separate days approximately two weeks apart. On one day the real drug is taken (a tablet taken by mouth),

which will be either tiagabine, zolpidem, or memantine. On the other day, a dummy tablet is given (placebo). Volunteers are told if they are in the tiagabine, zolpidem or memantine arm of the study, but not which day is the drug or placebo day.

On each visit, volunteers come to Addenbrooke's Hospital in the morning where they will complete some short thinking and memory tasks, take the tablet, and have lunch (provided). After lunch, the team accompanies them to the MEG scanner. Just before the scan, participants give a small blood sample to measure the amount of the drug in the body. During the scan, participants are asked to listen to some sounds, watch a short movie, use a joystick to move a car on a computer screen, or press buttons in response to arrows presented on a computer screen. The visit lasts approximately 5 hours and includes rest breaks for lunch, tea, coffee etc. To help us understand more about dementia, we also ask participants to have an up-to-date MRI scan. The MRI scan is optional, but helps us look at the shape of the brain, and can also measure the natural levels of brain chemicals. This can be done on a different day if preferred.

What are the possible benefits and risks of participating?
Benefits:
There will be no direct benefits to taking part in this study but you will have the pleasure of knowing that you have made a contribution to our understanding of brain illnesses, and the progress towards potential new treatments. We will reimburse travel expenses for you and a companion or escort if required.
Risks:
The dose of tiagabine we use is 10 mg, zolpidem is 5mg, and for memantine it is 10 mg. These doses are normally used to treat patients with other illnesses on a daily basis but for this study, it will only be given once. This means that the risk of side effects is low. However, as with all drugs, there is some risk of side effects. If side effects do occur, they are likely to be mild and short-lived. Any side effects of the drugs in this study would be experienced soon after taking the drugs, and we would expect these to go away within a few hours. A doctor will be available throughout the day just in case. You will be given a 24-hour contact number to call if you have any concerns after you take part in the study.

The more common side effects for people taking regular daily doses of tiagabine and zolpidem include dizziness or light-headedness, loss of strength or energy, drowsiness, nausea, nervousness or irritability, tremor, stomach pain, problems with concentrating or attention, and abnormal thinking. The more common side effects for people taking regular daily doses of memantine include dizziness, headaches, tiredness, raised blood pressure and constipation. Allergic reactions can also occur as for any medication. The likelihood of you developing these symptoms from a single dose is small, and symptoms improve within the day. As you will not know if you have taken the drug or a dummy pill on the day, as a precaution, you should not drive or operate dangerous machinery later in the day after testing.

Where is the study run from?
The study is run from the University of Cambridge, Department of Clinical Neurosciences and the MRC Cognition and Brain Sciences Unit.

When is study starting and how long is it expected to run for?
The study commenced in 2016 and will finish in December 2025.

Who is funding the study?
The Wellcome Trust

Who is the main contact?
The main contact is Dr Laura Hughes, laura.hughes@mrc-cbu.cam.ac.uk.
The principal investigator is Professor James Rowe, james.rowe@mrc-cbu.cam.ac.uk

Contact information

Type(s)
Public

Contact name
Dr Laura Hughes

Contact details
Cambridge Centre for Frontotemporal Dementia and Related Disorders
Department of Clinical Neurosciences
University of Cambridge
Herchel Smith Building, Forvie Site
Robinson Way, Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0SZ

Type(s)
Scientific

Contact name
Prof James Rowe

ORCID ID
https://orcid.org/0000-0001-7216-8679

Contact details
Cambridge Centre for Frontotemporal Dementia and Related Disorders
Department of Clinical Neurosciences
University of Cambridge
Herchel Smith Building, Forvie Site
Robinson Way, Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0SZ

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
55856

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
10/H0310/59, IRAS 55856

Study information

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

Acronym
UCAPD

Study objectives
Current study hypothesis as of 19/06/2024:
Neurodegenerative diseases are major cause of worldwide morbidity and mortality and 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, and often affects younger cohorts. FTD has very limited treatment options and no available treatment for disease modification.
There are several types of FTD, including the behavioural variant FTD (bvFTD), semantic variant (also called semantic dementia) and progressive non-fluent aphasia (PNFA). Several neurodegenerative disorders overlap with FTD and are included in the spectrum of neuropathological disorders called frontotemporal lobar degeneration (FTLD). These include progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD).
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 FTD 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), acetylcholine (ACh) as well as dopamine (DA).
The cognitive phenotypes of FTD have features in common with frontal lobe injury affecting attentional control (working memory, planning, and rule-switching) and reward-based behaviours. The impact of FTD on these cognitive and motor processes is less well understood, although they are manifest in the core diagnostic features of FTD such as disinhibition, poor social conduct, emotional blunting, mental rigidity, and utilisation.
In addition to impulsivity and disinhibition, many patients also show marked apathy. This is also part of the dysregulation of behaviour in FTD. The relationship of apathy to the other problems of FTD is poorly understood, and this has slowed down the development for ways to treat apathy.
Abnormalities of the brain's neurotransmitter chemicals underlie some of the behavioural disturbance seen with neurodegenerative diseases including FTD. For example, the levels of GABA and glutamate may be reduced, and these provide a tractable target for future treatments. However, not all neurotransmitters are affected, for example, FTD largely spares noradrenergic and dopaminergic neurotransmitter systems.
• GABA function can be modulated by using established drugs such as tiagabine, a GABA reuptake inhibitor, or Zolpidem a GABAA receptor agonist
• Glutamate function can be manipulated using the NMDA antagonist memantine, which has already been licensed for use in Alzheimer's disease.

We therefore propose to study the ability of these selective drugs to enhance the neurophysiological processes related to cognition. We focus on these drugs (zolpidem, tiagabine and memantine) in the context of the spectrum of FTLD.
Primary outcome measures are neurophysiological not clinical. The neurophysiological correlates of specific cognitive processes will be measured with MEG and electroencephalography (EEG). MRI scans will be acquired, partly for inversion of M/EEG data to source (brain) space, and partly for cross correlation to behavioural and physiological responses. In addition, we assess participants using a neuropsychological battery. We hypothesise that patients will show altered cortical oscillations in frontal and temporal cortex and that acute facilitation of GABA transmission (by tiagabine/zolpidem) or NMDA transmission (by memantine) will positively enhance oscillations towards a more 'normal' spectrum seen in healthy controls.

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Ethics approval required
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Ethics approval(s)
approved 28/09/2021, East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (The Old Chapel Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)2071048096, (0)207 104 8061, (0)207 104 8269; cambsandherts.rec@hra.nhs.uk), ref: 10 /H0310/59

Health Research Authority (HRA) East of England – Cambridgeshire and Hertfordshire Research Ethics Committee, 05/01/2011, 10/H0310/59. This approval related to the first arm of the study, which investigated citalopram in patients with FTD.
An amendment covering the application of the same protocol to tiagabine and memantine received ethics committee approval in 2015.
Version 6 was amended and approved on 30/01/2017.
Version 7 was amended and approved on 29/03/2021.

Study design
Double-blinded randomized crossover placebo-controlled study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Frontotemporal lobar degeneration, including behavioural variant of frontotemporal dementia (bvFTD), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS)/corticobasal degeneration (CBD)

Interventions
The protocol includes several experiments investigating different drugs and patient groups, however for the purpose of ISRCTN registration we describe the two experiments (experiments A and B) using the drugs tiagabine and memantine. The participants enrolled in the study include patients with FTLD and healthy controls, and each participant attends twice on separate days – once taking an oral preparation of the drug (Experiment A: oral tiagabine 10mg or Experiment B: oral memantine 10mg), and once taking an oral placebo.
On each day of assessment, the drug or placebo is taken in the morning and a short neuropsychological test battery is completed. In the afternoon, participants undergo magnetoencephalography (MEG) scanning while performing some cognitive tasks such as a computerized motor learning task (moving a visual stimulus using a joystick to a target on screen), and during a resting state (in which the participant sits still with eyes open or closed for

5 minutes, with no specific stimuli to attend to) and auditory oddball paradigm (in which participants hear a series of tones, in which the same tone is repeated several times and then changes to a different frequency). A blood sample is taken shortly before the MEG scan starts, in order to assess blood plasma levels for the drug taken. Each participant also has an MRI scan, either on the same day before the drug/placebo is taken or at a different convenient day within a month of the MEG sessions.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tiagabine, memantine, zolpidem

Primary outcome(s)
Current primary outcome measures as of 19/06/2024:
1. Motor learning assessed using combined magnetoencephalography (MEG) /electroencephalogram (EEG) and behavioural responses, approx. 2 hours after the drug or placebo is taken.
2. Cortical responses to an auditory oddball paradigm assessed using combined MEG/EEG approx. 2 hours after the drug or placebo is taken.
3. Resting state brain responses assessed using combined MEG/EEG approx. 2 hours after the drug or placebo is taken.
4. Reaction times and response inhibition using combined magnetoencephalography (MEG) /electroencephalogram (EEG) and behavioural responses, approx. 2 hours after the drug or placebo is taken.

Previous primary outcome measures:
1. Motor learning assessed using combined magnetoencephalography (MEG) /electroencephalogram (EEG) and behavioural responses after a change in condition on the afternoon after the morning when the drug or placebo is taken
2. Cortical responses to an auditory oddball paradigm assessed using combined MEG/EEG on the afternoon after the morning when the drug or placebo is taken
3. Resting state brain responses assessed using combined MEG/EEG on the afternoon after the morning when the drug or placebo is taken

Key secondary outcome(s))
1. γ-aminobutyric acid (GABA) levels assessed using magnetic resonance imaging (MRI) scanning. This is an MRI scan with structural MRPAGE, DWI, T2, PD sequences, arterial spina labelling, resting BOLD-sensitive echo-planar imaging and a magnetic resonance spectroscopy sequence for GABA. Shorter scans are possible, to obtain just a structural MRI, based on discussion between participants, their carers, and the study team. This scan is conducted at baseline and can take 60-90 minutes; however, participants can opt for a shorter 15-min scan only
2. General background data on the distribution and severity of cognitive deficits assessed using a neuropsychological testing battery. These tests can be carried out on clinic or home visits, or on the study days and are obtained just once as a measure of severity of deficit, or on both days as a measure of drug effect. The battery includes:
2.1. Addenbrooke’s Cognitive Exam- revised (ACE-r)
2.2. INECO Frontal Screening (IFS).

2.3. Frontal Assessment Battery (FAB).
2.4. Dimensional Apathy Scale (DAS)
2.5. Hayling Sentence Completion Test
2.6. Cambridge Questionnaire for Apathy and Impulsivity (CAM-QUAIT)
2.7. Carers Behavioural Inventory (CBI, can also be done at home by the carer)
3. Wellbeing, alertness and fatigue related symptoms assessed using a Visual Analogue Scale and completed completed before the drug/placebo and at the end of the day before going home, i.e. twice a day on study days

Completion date
12/12/2019

Eligibility

Key inclusion criteria
Patients in the principal study:
1. Frontotemporal dementia including subtypes diagnosed by current consensus criteria for behavioural variant or language variants

Patients in secondary studies:
2. Motor neuron disease with or without associated FTD or FTLD-related tau disorders (progressive supranuclear palsy or corticobasal degeneration, by consensus clinical diagnostic criteria)

Healthy controls:
3. No major neurological or psychiatric disorder
4. Aged 20-80 years
5. English-speaking

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
204

Key exclusion criteria
Current participant exclusion criteria as of 19/06/2024:
Participant exclusion criteria
1. Clinically significant current depression
2. Contraindications to MRI or MEG
3. Contraindications to pharmacological challenges, including:

3.1. Ischemic heart disease or significant cardiac rhythm abnormalities,
3.2. Current epilepsy
3.3. Pregnancy
3.4. Adverse drug reactions to citalopram, memantine, tiagabine, zolpidem or closely related drugs (according to experiment)
3.5. Other major psychiatric disorders including mania or schizophrenia
3.6. Known hepatic or renal failure (moderate or severe)

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3.6. Known hepatic or renal failure (moderate or severe)

Date of first enrolment
01/08/2016

Date of final enrolment
12/12/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Cambridge
Cambridge Centre for Frontotemporal Dementia and Related Disorders
Department of Clinical Neurosciences
University of Cambridge
Herchel Smith Building, Forvie Site
Robinson Way, Cambridge Biomedical Campus
Cambridge
United Kingdom
CB2 0SZ

Study participating centre
Addenbrooke's Clinical Research Centre NIHR/Wellcome Trust Clinical Research Facility & NIHR Clinical Investigation Ward

Addenbrooke's Clinical Research Centre NIHR/Wellcome Trust Clinical Research Facility & NIHR Clinical Investigation Ward. Cambridge Biomedical Campus. Hills Road.
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
MRC Cognition and Brain Sciences Unit (CBU)
MRC Cognition and Brain Sciences Unit (CBU)
University of Cambridge
15 Chaucer Road
Cambridge
United Kingdom
CB2 7EF

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust and University of Cambridge

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Not defined

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Anonymised datasets generated during and/or analysed during the current study will be available upon request from qualified academic researchers, for non-commercial purposes, following the publication of the principal reports from the study (expected by 2021). We anticipate using MEG-BIDS format and anonymised meta-data. A material transfer agreement may be required, depending on the location of the receiving part and purposes of the sharing, to ensure adequate data confidentiality measures, limit third party sharing, commercial exploitation and de-anonymization of participants. Anonymised datasets generated and/or analysed during the current study during this study may be included in the subsequent results publication. The detailed procedures for data curation and sharing are in development and will be made available at a later date. In the meantime, researchers are asked to contact the study team at the above addresses.

IPD sharing plan summary

Available on request, Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Tiagabine in healthy volunteers	19/02/2020	18/01/2021	Yes	No
Results article	Tiagabine in patients and healthy volunteers	19/02/2025	08/07/2025	Yes	No
Results article	Tiagabine in patients with bvFTD, PSP	12/03/2021	08/07/2025	Yes	No
Participant information sheet	version v6	30/01/2017	02/04/2019	No	Yes
Protocol file	version 7	29/03/2021	12/08/2022	No	No