The neurophysiological effect of NMDA-R antagonism of frontotemporal lobar degeneration is conditional on individual GABA concentration

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Abstract

There is a pressing need to accelerate therapeutic strategies against the syndromes caused by frontotemporal lobar degeneration, including symptomatic treatments. One approach is for experimental medicine, coupling neurophysiological studies of the mechanisms of disease with pharmacological interventions aimed at restoring neurochemical deficits. Here we consider the role of glutamatergic deficits and their potential as targets for treatment. We performed a double-blind placebo-controlled crossover pharmaco-magnetoencephalography study in 20 people with symptomatic frontotemporal lobar degeneration (10 behavioral variant frontotemporal dementia, 10 progressive supranuclear palsy) and 20 healthy age- and gender- matched controls. Both magnetoencephalography sessions recorded a roving auditory oddball paradigm: on placebo or following 10mg memantine, an uncompetitive NMDA-receptor antagonist. Ultrahigh-field magnetic resonance spectroscopy confirmed lower concentrations of GABA in the right inferior frontal gyrus of people with frontotemporal lobar degeneration. There was no overall effect of memantine on the magnitude of the mismatch negativity response in right frontotemporal cortex in patients, or controls. However, the change in right auditory cortex response to memantine (vs. placebo) in patients correlated with individuals’ prefrontal GABA concentration. There was no moderating effect of glutamate concentration, or cortical atrophy. This proof-of-concept study demonstrates the potential for baseline-dependency in pharmacological restoration of neurotransmitter deficits, to influence cognitive neurophysiology in neurodegenerative disease. With changes to multiple neurotransmitters in frontotemporal lobar degeneration, we suggest that individuals’ balance of excitation and inhibition may determine drug efficacy, with implications for drug selection and patient stratification in future clinical trials.

Introduction

Frontotemporal lobar degeneration (FTLD) causes a diverse set of clinical syndromes including behavioral variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP) [1–3]. In addition to cell loss and atrophy [4, 5], bvFTD and PSP reduce the principal neurotransmitter systems that underlie cortical neurophysiology [6, 7], as measured by magnetoencephalography (MEG) [8–10]. Such neurotransmitter abnormalities are potentially remediable pharmacologically, to restore physiology and thereby cognition. Pharmacological probes may also reveal mechanisms of disease, especially when coupled with simple tasks that patients can perform, such as roving oddball paradigms that evoke “mismatch negativity” responses (MMN) in frontotemporal networks [11, 12].

The expectation and response to sensory inputs depends on hierarchical information processing, in large scale frontotemporal networks that are well suited to examine the impact of frontotemporal lobar degeneration. In oddball paradigms standard regular stimuli establish strong predictions. When these predictions are not met (e.g. on deviant trials), an error signal is generated [13–15]. The MMN has been proposed to represent the precision of this error signal [16], which in turn determines the effect on future sensory expectations and perceptual inference [17, 18]. Such predictions and error signals relay through the frontotemporal network, between the auditory and prefrontal cortex [19].
This signaling requires a critical interaction between Glutamatergic excitatory (E) and GABAergic (γ-aminobutyric acid) inhibitory (I) activity (E/I balance) [14, 20–23]. The former is dependent on N-methyl-D-aspartate receptor signaling (NMDA-R) [24], although the impact of NMDA-R treatments may be conditional on the GABA-ergic state [8, 25]. Preclinical and in vivo studies of disorders associated with frontotemporal lobar degeneration have revealed reduced GABA and glutamate, particularly in prefrontal areas [7, 26–29]. These deficits contribute to neurophysiological abnormalities observed in both bvFTD and PSP, even in areas of minimal cortical atrophy. The physiological abnormalities include loss of beta-frequency desynchronisation and connectivity, reduced gamma oscillations and connectivity, and altered network integration [30–34]. Neurochemical and neurophysiological deficits correlate with cognitive and behavioral change [8, 26, 31], making them suitable intermediate phenotypes for experimental medicine studies.

Our focus on neurochemical rather than structural change is motivated by the potential for drug treatments. For example, memantine is a moderate affinity, uncompetitive NMDA receptor antagonist. Licensed to treat Alzheimer’s disease [35, 36], it is generally well tolerated [37]. However, memantine has not been found clinically effective in two phase II studies of frontotemporal dementia [38, 39], although both were underpowered for clinical efficacy endpoints. It has also been a research tool to probe NMDA-R systems in neuropsychiatric disorders, including in Schizophrenia [40]. Although there is patient heterogeneity in drug effects (c.f. Figure 3 in [40]), memantine partially can restore frontotemporal activity and connectivity, including auditory-based paradigms measuring early-level processing and MMN responses [40–42]. Here, we use memantine in the context of frontotemporal lobar degeneration.

Drug effects often show baseline-dependency: too much or too little can both impair function. This means that group-wise tests may obscure significant effects of drugs that interact with individual differences [43, 44]. Measuring the concentration of the targeted neurotransmitter can reveal an effect of treatment in a subset of participants, and suggest stratification for future trials [8, 43, 45]. For GABA and glutamate, proton magnetic resonance spectroscopy (1H-MRS) can quantify baseline neurochemical deficits. For example, the effect of GABA reuptake-inhibition on the MMN is conditional on baseline GABA concentration in the right inferior frontal gyrus [8]. Moreover, the balance between excitatory and inhibitory innervation suggests that memantine’s influence on neurocognitive deficits may also depend on GABA concentration [46–48]. Indeed, memantine [47, 49] and the NMDA-R antagonist ketamine [25, 50, 51], are posited to act upon excitatory inputs to inhibitory interneurons. This suggests a possible interaction between glutamate and GABA, leading to GABA-dependent moderation of the effect of memantine.

We aimed to determine the effect of memantine on frontotemporal neurophysiology in people with frontotemporal lobar degeneration, and its relationship to baseline glutamate and GABA concentration. We consider bvFTD and PSP together despite molecular pathological differences, because of their clinical, neurophysiological and neurochemical commonalities [1, 6, 9, 26]. First, we test the effect of memantine on magnetoencephalographic mismatch negativity responses in PSP and bvFTD versus controls. We focused upon the responses of regions within the frontotemporal network, given their
involvement in oddball paradigms and frontotemporal lobar degeneration. Then, we test interactions between the drug effect and glutamate and GABA concentrations in the right inferior frontal cortex, exploiting the high signal-to-noise and spectral resolution of $^1$H-MRS at ultrahigh field (7T).

**Methods**

**Subjects and pharmacological design:**

24 people with probable frontotemporal lobar degeneration (12 bvFTD, 12 PSP-Richardson’s syndrome) and 20 age-/sex- matched healthy adults undertook a randomised placebo-controlled double-blind crossover study (Table 1). Participants attended two magnetoencephalography sessions two weeks apart where they received either (1) 10mg oral memantine or (2) placebo. Magnetoencephalography began 3 hours after drug administration to coincide with peak blood levels [52]. 10mg of memantine aligns with the clinically recommended starting dose in the UK [53].
Table 1
Demographic and neuropsychological information of study participants

|                  | CON   | bvFTD/PSP | CON vs bvFTD/PSP |
|------------------|-------|-----------|-------------------|
|                  | 20    | 20        | *p*-val (Bayes Factor) |
| **Sex**          | M15:F5 | M18:2     | n.s               |
| **Age**          | 66.75 (4.79) | 64.95 (8.49) | n.s (0.41)       |

**NEUROPSYCHOLOGY**

|                  | CON     | bvFTD/PSP | p-val (Bayes Factor) |
|------------------|---------|-----------|----------------------|
| **MMSE**         | 29.65 (0.49) | 26.9 (2.2) | *** (4523.27)        |
| **ACE-R**        |         |           |                      |
| Total            | 96.60 (2.48) | 80.2 (11.03) | *** (8.45e + 3)      |
| Attention        | 17.90 (0.31) | 16.95 (1.36) | ** (9.96)            |
| Memory           | 24.65 (1.46) | 21 (4.22)  | ** (38.68)           |
| Verbal Fluency   | 12.60 (1.60) | 5.7 (3.4)  | *** (1.12e + 7)      |
| Language         | 25.65 (0.81) | 23.55 (2.19) | *** (94.94)          |
| Visuospatial     | 15.80 (0.41) | 13 (3.54)  | ** (27.66)           |
| **INECO**        |         |           |                      |
| Total            | 18.22 (3.95) | 16.71 (5.4) | *** (5.27e + 4)      |
| **FAB Total**    | 14.30 (2.11) | 13.32 (3.68) | *** (334.86)         |
| **Hayling**      |         |           |                      |
| Overall Scaled score | 3.40 (2.27) | 2.65 (2.01) | *** (7.91e + 4)     |
| Graded - naming total | 25.4 (2.85) | 17.68 (5.13) | *** (1.22e + 4)     |

*, *p* < 0.05; **, *p* < 0.01; ***, *p* < 0.001, uncorrected

bvFTD, behavioral variant Frontotemporal Dementia; CON, Controls; PSP, progressive supranuclear palsy

BF, Bayes Factor; Conventional thresholds for Bayes Factors represent substantial (> 3), strong (> 10) and very strong (> 30) evidence in favour of alternate hypothesis.

ACE-R, Addenbrooke's Cognitive Examination-Revised; CBI-R, Cambridge Behavioural Inventory Revised; FAB, Frontal Assessment Battery; FRS, Frontotemporal Dementia Rating Scale; MMSE, Mini-Mental State Exam

n/a - variance in controls were equal to zero, violating assumption of equality of variances
|                          | CON          | bvFTD/PSP    | CON vs bvFTD/PSP |
|--------------------------|--------------|--------------|------------------|
| **FRS Total (Logit)**    | 4.23 (1.27)  | -0.89 (2.26) | *** (1.16e + 7)  |
| **CBI-R**                |              |              |                  |
| Total                    | 5.67 (6.03)  | 68.32 (34.29) | *** (1.35e + 6)  |
| Memory and orientation   | 2.06 (2.16)  | 10.42 (7.23) | *** (492.72)     |
| Everyday skills          | 0 (0)        | 8.74 (6.55)  | n/a              |
| Self-care                | 0 (0)        | 4.21 (4.76)  | n/a              |
| Abnormal behaviour       | 0.72 (1.02)  | 8.89 (8.18)  | *** (134.55)     |
| Mood                     | 0.67 (1.14)  | 4.05 (3.01)  | *** (269.54)     |
| Beliefs                  | 0 (0)        | 1.42 (1.8)   | n/a              |
| Eating habits            | 0.17 (0.38)  | 6.79 (4.96)  | *** (5893.82)    |
| Sleep                    | 0.89 (1.23)  | 4.11 (2.72)  | *** (331.85)     |
| Stereotypic and motor    | 0.83 (1.15)  | 8.21 (5.72)  | *** (2872.15)    |
| Motivation               | 0.33 (0.69)  | 12.11 (5.52) | *** (4.72e + 7)  |

*, p < 0.05; **, p < 0.01; ***, p < 0.001, uncorrected

CON, Controls; bvFTD, behavioral variant Frontotemporal Dementia; PSP, progressive supranuclear palsy

BF, Bayes Factor; Conventional thresholds for Bayes Factors represent substantial (> 3), strong (> 10) and very strong (> 30) evidence in favour of alternate hypothesis.

ACE-R, Addenbrooke’s Cognitive Examination-Revised; CBI-R, Cambridge Behavioural Inventory Revised; FAB, Frontal Assessment Battery; FRS, Frontotemporal Dementia Rating Scale; MMSE, Mini-Mental State Exam

n/a - variance in controls were equal to zero, violating assumption of equality of variances

Patients were recruited from tertiary referral centres with probable bvFTD, with or without parkinsonism [54] or probable PSP-Richardson’s syndrome (PSP-RS) [55], including those who had presented with “PSP-Frontal” phenotype [56]. Controls were recruited from the MRC Cognition and Brain Sciences Unit and NIHR Join Dementia Research. Participants had no history of significant neurological or psychiatric illness other than bvFTD/PSP. Written informed consent was acquired in accordance with the Declaration of Helsinki (1991). The study was approved by the local ethics committee and exempted from Clinical Trials status by the UK Medicines and Healthcare products Regulatory Agency. The International Standard Randomised Controlled Trial Number is 10616794. After quality control review, four patients were excluded from the analysis because they (i) lacked an N70 in auditory cortex (n = 1), (ii) had fewer
than half the average number of trials after artifact rejection ($n = 1$), or (iii) were unable to complete two magnetoencephalography sessions ($n = 2$).

Neuropsychological assessment included the revised Addenbrookes Cognitive Examination (ACE-R) [57], Frontal Assessment Battery (FAB) [58], Graded Naming Test [59], INECO Frontal Screening Test [60] and Hayling test [61]. A close informant completed the revised Cambridge Behavioural Inventory (CBI-R) [62] and Frontotemporal Dementia Rating Scale (FRS) [63].

Magnetoencephalography, preprocessing, and source localisation:

Magnetoencephalography was recorded during a passive roving auditory paradigm [19, 22] (Supplementary Information 1.1). In brief, participants heard a series of repeated tones ($rep_n$) at a given frequency (400-800Hz, 75ms), with stimulus-onset-asynchrony 500ms. The tone frequency changed pseudorandomly after 3–10 repetitions (approximate Poisson distribution). The first new tone is classed as deviant ($dev$). The paradigm was performed with eyes-open in three blocks of five minutes, while participants watched a silent movie. After trials rejection, participants averaged 1576 (SD = 106) stimuli per session.

Magnetoencephalography used a magnetically-shielded room (IMEDCO) and the Elekta VectorView system (Elekta Neuromag, Helsinki), with 306-channel recordings at 102 spatial locations (planar gradiometer pair and magnetometer at each site), sampled at 1000 Hz. Vertical and horizontal Electro-occulography (EOG) indicated eye movements and 5 head position indicator coils tracked head position. A 3D digitizer (Fastrak Polhemus Inc., Colchester, VA) was used to record nasion and pre-auricular fiducial point positions and > 60 scalp surface points.

Preprocessing used SPM12 (v7771), FieldTrip [64] and OSL (https://github.com/OHBA-analysis/osl-core) software in Matlab (2019a) (pipeline available at https://github.com/AlistairPerry/FTLDMEGMEM). First, MaxFilter (v2.2.12, Elekta Neuromag) was used to interpolate bad channels, remove external noisy signals (using signal source separation) and correct for head motion. The data were next downsampled (500Hz), band-pass filtered (0.1–125 Hz) and notch filtered (removing frequencies between 45–55 Hz and 95–105 Hz) [65]. Bad channels (using osl_detect_artefacts) and eye-movement related artefacts were removed with independent component analysis. Data were epoched between − 100 to 400ms relative to tone onsets, with bad trials removed (osl_detect_artefacts) and then averaged. A 125 Hz low-pass filter removed high-frequencies. Baseline correction was applied − 100 to 0ms (Supplementary Information 1.2)

Magnetoencephalography signals were source localised using all channels, in SPM12 using a single shell cortical mesh, estimated from individual T1-weighted image (co-registered using fiducial and head points). A canonical template was used for three people who did not have MRI of sufficient quality (1 patient, 2 controls). The evoked source signals were estimated for each trial type using COH inversion (sLORETA [66]). We extracted waveforms from literature specified MNI coordinates of cortical MMN sources [19, 22]. We focus on the right-hemisphere regions given right lateralized MR Spectroscopy:
auditory cortex (AUD; [46,−14, 8]), superior temporal gyrus (STG; [59,−25, 8]), and inferior frontal gyrus (IFG; [46, 20, 8]). The local peak was identified within a 7mm radius and extracted to form an average pseudo-local field potential (LFP) response. We also estimated the average event-related fields (ERFs) from all gradiometers, and frontal and temporal gradiometers (Supplementary Fig. 3B), which were baseline corrected and smoothed (moving average 20 time-points).

We focus on the deviant trial (dev) and third repetition (rep3). For both sensor and source data we calculated a difference waveform from the dev and rep3 (rep3-dev) responses, to derive the mismatch response. The mean MMN was calculated from the mean mismatch response between 125-175ms post-stimulus presentation, based on independent data [11]. This was our chosen contrast and window as prior MMN studies show electro-/magnetoencephalography peaks within this window, and a response plateau emerging by the third repetition [67, 68]. We corroborated this in an independent age-matched control cohort (mean age = 66.42) [22] (Supplementary Information 1.3, Supplementary Fig. 1). This early plateau indexes short-term plasticity and learning.

**MR imaging and spectroscopy**

Participants completed a T1-weighted MP2RAGE structural scan at 7T on a Siemens TERRA system (Siemens Healthineers, Erlangen, Germany) with 32 channel headcoil. Acquisition parameters were: 0.75mm isotropic voxels, TE = 1.99ms, TR = 4300ms, inversion times = 840ms/2370ms) (Supplementary Information 1.4). Two patients were unsuitable for 7T and underwent 3T scanning (Siemens PRIMA MPRAGE; 1.1mm isotropic voxels TE = 2.9ms, TR = 2000ms). Two controls were unsuitable for MRI.

To determine whether magnetoencephalography responses to memantine are dependent on GABA and/or glutamate concentrations, we used ultrahigh field 7T MR spectroscopy (MRS, Siemens TERRA) [26] (Supplementary Information 1.5). We focus on the association between MRS and magnetoencephalography in patients, based on disease-specific variance in neurochemistry. Three patients had incomplete scans or substantial movement artifacts. MR spectra were acquired from voxels of interest (2 x 2 x 2 cm\(^3\)) in the right inferior frontal gyrus [26] (for voxel placement see Fig. 1B); and occipital cortex as a control region. Spectra were acquired using a short-echo semi-LASER sequence [69, 70] (repetition time/echo time = 5000/26 ms, 64 repetitions). Eddy-current effects and frequency and phase shifts were corrected for using MRspa (University of Minnesota, www.cmrr.umn.edu/downloads/mrspa).

Glutamate and GABA were quantified using LCModel (Version 6.2-3) [71]. For partial volume correction, SPM12 was used for segmentation and estimation of tissue-type probabilities in each voxel. Grey matter volume was used to correct for GABA, and grey and white matter volume for glutamate. A generalized linear model controlled for the effect of age, sex and partial volume information [26]. Non-corrected MRS values are also presented.

To test whether atrophy in the right inferior frontal gyrus could account for differences in the MEG responses to drug, we estimated grey matter volume. T1 images were bias regularised (threshold of
0.0001) and tissue-segmented (SPM12 v7771), normalized to MNI space via differomorphic registration [72] and spatially smoothed (for VBM only) (8mm FWHM) (Supplementary Information 1.6). Grey matter volume (GMV) in the inferior frontal gyrus was calculated from a right-hemisphere anatomical mask of Brodmann areas 48, 49 and the frontal operculum (OP8) (github.com/inm7/jubrain-anatomy-toolbox) [73], overlapping the magnetoencephalography source region (Fig. 5A; https://neurovault.org/images/776918). We also investigated grey matter atrophy elsewhere using voxel-based morphometry (VBM) [74].

All preprocessing and analysis scripts are publicly available (https://github.com/AlistairPerry/FTLDMEGMEM).

**Statistical analysis**

Given the shared phenotypic deficits between bvFTD and PSP individuals [1, 8], principal analyses were conducted by pooling over patient groups. In auxiliary analyses, disease subgroups (PSP vs bvFTD) were compared separately. This involved a one-way ANOVA for group differences on placebo and 2x3 design for subgroup x drug interactions. For clinical and neuropsychological descriptives, we present bvFTD and PSP subgroups separately (with Tukey correction).

**Group differences in MMN responses on placebo and responses to Memantine:**

Independent t-tests assessed group differences in mean MMN on placebo for sensor and source region waveforms. Factorial 2x2 ANOVAs assessed differential group responses to memantine (group x drug interaction) in source regions, with drug session and group the within- and- between- subject factors, respectively.

Pearson correlations tested the association between patients GABA and glutamate concentrations with change in mean MMN responses to drug, relative to placebo. Stepwise linear regression was used to determine whether MRS associations with drug-dependent responses were confounded by other factors including disease subgroup, age, and placebo MMN responsivity.

Descriptive frequentist statistics were performed in MATLAB 2019a and their corresponding Bayesian analyses were conducted in JASP [75]. In contrast to frequentist t-tests or analysis of variance which may fail to reject the null hypothesis but cannot support it, the Bayesian tests can provide evidence for the null hypothesis (e.g. of no group effect or no drug effect). For sensor and source analyses involving multiple regions, Bonferroni correction (α = 0.0167 [0.05 / three source regions]) was used. For Bayesian tests, Bayes Factors (BF<sub>10</sub>) represented moderate (> 3) or strong (> 10) evidence against the null hypotheses, while < 0.33 (moderate) and < 0.10 defined (strong) evidence in favor of the null. For Bayesian ANOVAs the Bayes Inclusion Factor was calculated.

**Results**
Patients and controls did not differ in age or sex (Table 1). As expected, both bvFTD and PSP patients were impaired in the INECO, FAB, Graded Naming test, FRS, Hayling and selected subscales of the ACE-R and CBI-R. Compared to PSP, bvFTD patients performed worse on the Hayling (A+B error score) and selected CBI-R subscales, but did not differ in terms of MMSE, Hayling (overall scaled score), ACE-R subscales, FRS, or FAB (Supplementary Table 1).

Following artefact rejection, the number of deviant and rep3 trials did not differ between controls and patients, nor did the number of artifact trials removed (Supplementary Table 2). The MRS water line width did not differ across groups (Supplementary Table 2). GABA Cramer-Rao lower bounds (reflecting uncertainty in measurements) were higher in patients, but this did not survive Bonferroni correction.

Patients had bilateral atrophy in frontal, temporal, thalamic, striatal, and also left occipital regions (Fig. 1A, Supplementary Table 3; cluster-level, \( p < .05 \), FWE-corrected; height-threshold, \( p < 0.001 \), uncorrected); with reduced grey matter in bvFTD relative to controls in medial frontal, medial temporal, striatal, and insular areas. PSP demonstrated reduced grey matter in frontal, temporal, striatal, insular and hippocampal regions (Supplementary Fig. 2). bvFTD and PSP groups did not differ significantly.

Partial-volume corrected GABA concentration in the right inferior frontal gyrus was reduced in patients, but weakly at the group level (bvFTD and PSP combined; \( df = 27 \), \( p_{unc}=0.036 \), \( BF_{10} = 2.01 \)). Glutamate concentration did not differ (\( p_{unc}=0.60 \), \( BF_{10} = 0.39 \); Fig. 1B). See Supplementary Table 4 for each group separately. Uncorrected concentrations were reduced in patients for both GABA (\( p_{unc}<0.001 \), \( BF_{10} = 31.66 \)) and Glutamate (\( p_{unc}<0.001 \), \( BF_{10} = 67.13 \)).

**Group differences in physiology**

Averaged across all sensors, clear mismatch responses were observed for both groups, with average peak negative deflection (rep3-dev) at ~ 150ms (Supplementary Fig. 3A-B; see Supplementary Fig. 4 for single-condition waveforms). The groups did not differ in mean MMN (125-175ms) at any of the regional sensor groups (\( df = 38 \), \( p_{unc}>0.071 \), \( BF_{10} = 0.65-1.18 \); Supplementary Fig. 3C). The lack of a group difference was also observed in comparison to the independent control cohort (\( df = 37 \), \( p_{unc}>0.09 \), \( BF_{10} = 0.5 - 0.1 \)) (Supplementary Fig. 5).

For all source regions, we also observe no group differences in mean MMN between all-patients and controls (\( df = 38 \), \( p_{unc}>0.63 \), \( BF_{10} = 0.31-0.340 \); Fig. 2). However, across three groups (controls, bvFTD and PSP) there was a group effect in the right inferior frontal gyrus (\( df=(2,27) \), \( p_{unc}=0.009 \), \( BF_{incl}=4.89 \), Supplementary Fig. 6a, Supplementary Table 5); MMN responses were reduced in bvFTD compared to PSP (\( df = 18 \), \( p_{tukey}=0.007 \), \( BF_{10} = 10.42 \)).

We next tested whether memantine has a differential influence on source mismatch responses between controls and patients, relative to placebo. Group-wise analysis revealed that no region exhibited a group x
drug interaction ($df=(1,38), p_{unc}>0.24, BF_{incl}=0.35–1.011; \text{Fig. } 3$), even if the patient subgroups were differentiated ($df=(2,37), p_{unc}>0.14, BF_{incl}=0.20–0.85, \text{Supplementary Fig. } 7A$).

**GABA and glutamate influences on the response to Memantine**

We tested baseline-dependency of drug effects. Individual GABA concentration moderated the patients’ MMN response (dev-rep3) to memantine in the right auditory cortex (Fig. 4B, far left panel), with moderate-to-strong evidence in favor of this association ($df=15, p_{unc}=0.008, BF_{10}=7.77$): Patients with higher GABA concentration showed larger MMN responses (i.e. more negative MMN) on memantine relative to their placebo session (Fig. 4B). There was no moderating effect of Glutamate on drug-dependent mismatch responses in any region ($p_{unc}>0.41; \text{Supplementary Fig. } 8$). This association, and the non-significant relationship with glutamate, remained if using MRS concentration without partial volume correction (Supplementary Table 6). Stepwise regression with additional predictors including disease subgroup, age, and baseline (placebo) MMN responses, confirmed GABA concentration as the best predictor of patients’ MMN (rep3-dev) response to memantine ($F=9.38, p=0.0079$).

The ratio between glutamate and GABA (Glu/GABA) concentrations has been used as a proxy of cortical excitatory/inhibitory balance [48, 76]. Glu/GABA ratios in patients were negatively associated with the mean MMN change on memantine (vs. placebo) in the auditory cortex (Fig. 4D). This was not observed in controls ($df=12, r^2=0.01, p=0.90, BF_{10}=0.36$), although an interaction between group and Glu/GABA ratio on the change in MMN was non-significant (ANCOVA; df=(1,25), $p=0.23$). While comparison of Glu/GABA ratios to controls indicates no difference ($p=0.078, BF_{10}=1.20; \text{Fig. } 4C$), it does suggest patients with greater MMN responses to drug are those with relatively preserved Glu/GABA concentrations.

Atrophy of the prefrontal cortex (controlling for age and total intracranial volume) did not moderate patients’ magnetoencephalographic response to memantine in the auditory cortex ($df=15, p_{unc}=0.70, BF_{10}=0.42; \text{Fig. } 5B$), nor did cognitive (ACE-R, $df=18, p_{unc}=0.28, BF_{10}=0.48; \text{FAB, } df=17, p_{unc}=0.49, BF_{10}=0.35$) or clinical severity (FRS, $df=17, p_{unc}=0.68, BF_{10}=0.31$). Occipital GABA concentration was not associated with drug-dependent MMN changes in auditory cortex ($p=0.21, BF_{10}=0.62$).

**Discussion**

The principal finding is that in people with syndromes associated with frontotemporal lobar degeneration, the neurophysiological responses to the NMDA-R antagonist memantine is conditional on individual GABA concentration. Patients with relatively preserved GABA concentrations have greater enhancement of the mismatch responses (i.e. more negative MMN to memantine vs. placebo). This effect was not explained by regional atrophy. We suggest that in the context of future experimental medicine studies, magnetic resonance spectroscopic quantification of heterogeneity might be useful for stratification.
Otherwise, within-group neurochemical heterogeneity is liable to reduce sensitivity to treatment effects and increase type II error in clinical trials.

The selectivity of auditory cortex MMN changes to memantine is not unexpected. For example, in Schizophrenia there is both NMDA-R dysfunction and consistent abnormalities in auditory MMN [77]. Auditory regions are sensitive to memantine in Schizophrenia and controls with drug modulation of neural responses [40–42]. However, frontotemporal lobar degeneration, with bvFTD and PSP, is also associated with prefrontal cortical atrophy and GABA-ergic deficits. Neurophysiological changes can occur prior to atrophy, or in the absence of atrophy. This is in part because of the loss of synapses [78, 79] and reductions in critical neurotransmitters [6] in bvFTD, PSP [32, 33, 80, 81] and other neurodegenerative disorders [82–84]. Magnetoencephalography, or electroencephalography, may therefore provide sensitive markers of disease progression and drug response. In this study, there was a group-wise reduction in GABA concentrations in patients [8, 26], as expected from post mortem data [85], but the distribution was wide. This variation in GABA, not atrophy, correlated with the effect of memantine on the cortical MMN response.

The drug response in auditory cortex was conditional on frontal GABA status, two areas that span the hierarchical neurocognitive network for prediction and response in MMN tasks [11, 86]. The auditory cortex is relatively spared by the direct neuropathology of bvFTD and PSP, but within the hierarchical network for prediction and error signalling [87, 88], its response is conditional on backward projections from association cortex. A general feature of sensory processing hierarchies is that feedback and feedforward connections are shaped by laminar specificity in cortical units: feedforward connections project principally from superficial pyramidal cells, while feedback connections arising particularly from deep pyramidal cells and terminate on superficial layers at lower-level regions such as the auditory cortex [14, 87, 88]. Prefrontal GABA regulates the precision of the frontotemporal predictions, and the deep cortical generators of back-projecting beta-oscillations [8, 22]. Indeed, beta power and beta-connectivity are reduced in PSP and several syndromes of frontotemporal dementia [8, 9, 31, 89]. The effect of memantine on mismatch response (MMN) generation, mainly from superficial cortical layers of lower levels of the sensory hierarchy, is thereby moderated by prefrontal GABA. In other words, the mismatch between incoming deviant auditory signals with the predicted standard tone is larger on memantine in the context of (near) normal prefrontal GABA.

An alternative hypothesis is that GABA measurements in the inferior frontal gyrus index widespread GABAergic deficits. However, drug-dependent responses in the auditory cortex are independent of GABA concentrations in occipital cortex, and both occipital lobe and auditory cortex are relatively spared by the direct neuropathology.

The MMN differs across many neurological and psychiatric disorders, including Schizophrenia [77, 90], Alzheimer's disease [91], and neurodevelopmental conditions [92]. The MMN provides a robust marker of frontotemporal functioning and is well-tolerated in clinical populations. Our lack of a significant group difference in MMN response differs from previous reports of bvFTD [8–10]. The difference might arise...
from variations in MMN paradigms or heterogeneity of disease, including variance in GABA concentration, atrophy, and syndrome. Indeed, considerable variation has been reported across Schizophrenic patients [90], the canonical MMN disorder. We also note the heterogeneity in atrophy across PSP subtypes in a larger cohort [93]. Our planned comparisons pooled PSP and bvFTD patients because of their commonalities in physiology and phenotype noted in other deep phenotyping studies [1, 55], despite the clear differences in underlying molecular pathology. Consistent with the ‘frontal’ cognitive deficits in PSP, the majority of cognitive tests were similarly affected by both groups. Although the auditory MMN did not differ between groups, the supplementary analyses suggests prefrontal MMN differences with particularly blunted response in frontal cortex on placebo in bvFTD. The subgroup sample sizes ($n = 10$ each group) could be considered relatively small, but bayesian tests indicate strong evidence in favor of a group difference. The absence of a main case-control effect should be interpreted in the light of interactions, such as with the neurochemical variance to which we turn next.

Whilst memantine is an NMDA-R antagonist targeting glutamatergic functioning, the response to drug was conditional on GABA rather than glutamate concentration. There are several possible interpretations. The first is that the MRS-measured glutamate is not exclusively neuronal and available for neurotransmission, but also astrocytic as part of glutamate-glutamine cycling [94]. Second, an interaction between glutamatergic and GABAergic systems reflects a delicate balance between excitatory (E) and inhibitory (I) control of the firing of neuronal ensembles. Neurophysiological proxies of E/I functioning have found changes to this balance with ageing [95] and neurodegeneration [96]. In this study, we tested the ratio of glutamate/GABA concentrations as a proxy of an individual's E/I balance [48] and found that patients with relatively normal glutamate to GABA ratio show increased mismatch responses to memantine. Importantly, memantine and another NMDA-R antagonists, ketamine, increase pyramidal output activity through their excitatory inputs to GABA interneurons [47, 50, 51]. We speculate that this interaction between prefrontal GABA and memantine promotes coordinated pyramidal firing in response to deviant tones in the oddball paradigm. Such an effect of memantine on the E/I balance has been proposed in Schizophrenia, via influences on oscillatory dynamics [40, 46] according to the ratio of glutamine to glutamate [97].

Note that memantine's effects were moderated by a neurochemical (GABA) that is not its primary target (Glutamate receptors); and in a region (i.e. prefrontal cortex) that is non-overlapping with the dependent measure (i.e. auditory cortex). This has implications for experimental studies, in which stratification may be based on interactions between neurotransmitter systems, and interactions between connected regions. Unfortunately, spectroscopy of the auditory cortex was not available, and the frontal lobe was prioritised. Another consideration for future studies is the degree to which baseline pathology moderates a drug response. Our findings can be interpreted as relatively greater pathology (with less GABA) leading to decreased sensitivity to memantine. This is therefore not a simple restoration of function in those with more severe baseline deficits [43]. While it may be easier to show a drug effect than prove its absence, the patients’ disease severity and heterogeneity will affect the result of analyses of a drug’s group-wise main effect.
There are limitations and caveats to this study, in pharmacology, diagnosis and analysis. First, we note that memantine does not have clinical trials evidence for efficacy, and has been subject to successful (but negative) small phase II trials. We do not advocate its clinical use in either PSP or bvFTD. This study was not a clinical trial. Rather, we used the drug as a well-tolerated psychopharmacological probe of neural systems. We found no differential effect of memantine 10mg on the evoked MMN between groups. In both healthy controls and Schizophrenia a higher 20mg memantine dose changed the mismatch response [41], whereas 10mg produced no group-wise effect [40, 41]. It’s important to note their age of control (mean = 27.51) and schizophrenic participants (36.44) [41] is considerably younger than those in the current study. This precludes a direct dose comparison across the studies. Moreover, the memantine effect in schizophrenia was moderated by age [40]. Our 10mg dose was chosen to align with the clinically recommended starting dose in the UK [53].

Our patient diagnoses were clinical, not genetic or neuropathological. Clinicopathological correlations are very high for both PSP and bvFTD, although we cannot distinguish the Tau versus TDP43 pathology as the basis of the bvFTD cases. In the main analyses, we pooled PSP and bvFTD groups despite the clear differences in underlying molecular pathology, not for power considerations, but because of the commonalities in physiology and phenotype noted in deep phenotyping studies [1, 55]. Consistent with the literature on ‘frontal’ cognitive deficits in PSP, patients with PSP and bvFTD were similarly impaired on many of the same cognitive tests, with limited selectivity of deficits in bvFTD. Statistical power and precision are key considerations, especially with \( n = 20 \) per group. We used a crossover design that increases power relative to parallel groups designs for heterogeneous populations and leveraged Bayesian inference to consider the evidence in favour of the null hypothesis, as well as alternate hypotheses. For our principal finding, despite modest numbers, there was sufficient precision to draw inferences, with positive or moderate-to-strong evidence for the association between GABA concentration and change in MMN responses on memantine (BF\(_{10} > 7\)). Only a subgroup of controls completed MRS (\( n = 12 \)), so we did not attempt correlations with neurotransmitter levels within the control group. For MRS based analysis of patient effects, the ratio of glutamate/GABA concentrations as a proxy of an individual's E/I balance has recently been challenged [76], in favour of other neurophysiological measures such as the 1/f aperiodic slopes [46], but the resolution of that debate is beyond the scope of this study.

In conclusion, we have probed neurocognitive systems in two disorders associated with frontotemporal lobar degeneration, combining memantine pharmacological challenge with magnetoencephalography and ultra-high field spectroscopy. Patients' neurophysiological responses to memantine were proportionate to GABA concentration. It may be possible to de-risk the transition from experimental medicine to clinical trials of heterogeneous populations using neurophysiological outcomes and stratification by spectroscopy.

**Declarations**

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Conflict of Interest

Unrelated to this work, JBR is a non-remunerated trustee of the Guarantors of Brain, Darwin College and the PSP Association (UK). He provides consultancy to Asceneuron, UCB, Astex, Curasen, Wave, SVHealth, and has research grants from AZ-Medimmune, Janssen, and Lilly as industry partners in the Dementias Platform UK. The remaining authors have nothing to disclose.

Author Contributions

AP data analysis, interpretation of the data, and initial writing of the manuscript. LH design of the study and data acquisition. JBR concept, funding, supervision, data acquisition and interpretation, and writing of the manuscript. NA, LH, MN, MAR, DS data acquisition. EK, SJ, TEC, NA, LH analysis and interpretation. AM data acquisition and validation. All authors contributed to revision of the manuscript, and read and approved the final version of the submitted manuscript.

References

1. Murley AG, Coyle-Gilchrist I, Rouse MA, Jones PS, Li W, Wiggins J, et al. Redefining the multidimensional clinical phenotypes of frontotemporal lobar degeneration syndromes. Brain. 2020;143(5):1555–71.

2. Ramanan S, El-Omar H, Roquet D, Ahmed RM, Hodges JR, Piguet O, et al. Mapping behavioural, cognitive and affective transdiagnostic dimensions in frontotemporal dementia. medRxiv. 2021:2021.10.29.21265655.

3. Boeve BF, Boxer AL, Kumfor F, Pijnenburg Y, Rohrer JD. Advances and controversies in frontotemporal dementia: diagnosis, biomarkers, and therapeutic considerations. The Lancet Neurology. 2022;21(3):258–72.

4. Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, et al. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain. 2011;134(9):2565–81.
5. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron. 2009;62(1):42–52.

6. Murley AG, Rowe JB. Neurotransmitter deficits from frontotemporal lobar degeneration. Brain. 2018;141(5):1263–85.

7. Benussi A, Alberici A, Buratti E, Ghidoni R, Gardoni F, Di Luca M, et al. Toward a glutamate hypothesis of frontotemporal dementia. Frontiers in neuroscience. 2019;13:304.

8. Adams NE, Hughes LE, Rouse MA, Phillips HN, Shaw AD, Murley AG, et al. GABAergic cortical network physiology in frontotemporal lobar degeneration. Brain. 2021.

9. Hughes LE, Rowe JB. The impact of neurodegeneration on network connectivity: a study of change detection in frontotemporal dementia. Journal of cognitive neuroscience. 2013;25(5):802–13.

10. Shaw AD, Hughes LE, Moran R, Coyle-Gilchrist I, Rittman T, Rowe JB. In Vivo Assay of Cortical Microcircuitry in Frontotemporal Dementia: A Platform for Experimental Medicine Studies. Cereb Cortex. 2021;31(3):1837–47.

11. Garrido MI, Kilner JM, Stephan KE, Friston KJ. The mismatch negativity: a review of underlying mechanisms. Clinical neurophysiology. 2009;120(3):453–63.

12. Näätänen R, Paavilainen P, Rinne T, Alho K. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clinical neurophysiology. 2007;118(12):2544–90.

13. Rao RP, Ballard DH. Predictive coding in the visual cortex: a functional interpretation of some extraclassical receptive-field effects. Nature neuroscience. 1999;2(1):79–87.

14. Friston K. A theory of cortical responses. Philosophical transactions of the Royal Society B: Biological sciences. 2005;360(1456):815–36.

15. Fitzgerald K, Todd J. Making Sense of Mismatch Negativity. Frontiers in Psychiatry. 2020;11.

16. Moran RJ, Campo P, Symmonds M, Stephan KE, Dolan RJ, Friston KJ. Free energy, precision and learning: the role of cholinergic neuromodulation. Journal of Neuroscience. 2013;33(19):8227–36.

17. Friston K, Kiebel S. Predictive coding under the free-energy principle. Philosophical transactions of the Royal Society B: Biological sciences. 2009;364(1521):1211–21.

18. Friston K. The free-energy principle: a unified brain theory? Nature reviews neuroscience. 2010;11(2):127–38.

19. Garrido MI, Friston KJ, Kiebel SJ, Stephan KE, Baldeweg T, Kilner JM. The functional anatomy of the MMN: a DCM study of the roving paradigm. Neuroimage. 2008;42(2):936–44.

20. Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). Schizophrenia research. 2016;176(2–3):83–94.

21. Self MW, Kooijmans RN, Supèr H, Lamme VA, Roelfsema PR. Different glutamate receptors convey feedforward and recurrent processing in macaque V1. Proceedings of the National Academy of Sciences. 2012;109(27):11031-36.

22. Adams NE, Hughes LE, Phillips HN, Shaw AD, Murley AG, Nesbitt D, et al. GABA-ergic dynamics in human frontotemporal networks confirmed by pharmaco-magnetoencephalography. Journal of
23. Weber LA, Diaconescu AO, Mathys C, Schmidt A, Kometer M, Vollenweider F, et al. Ketamine affects prediction errors about statistical regularities: a computational single-trial analysis of the mismatch negativity. Journal of Neuroscience. 2020;40(8):1640–49.

24. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proceedings of the National Academy of Sciences. 1996;93(21):11962-67.

25. Rosch RE, Auksztulewicz R, Leung PD, Friston KJ, Baldeweg T. Selective prefrontal disinhibition in a roving auditory oddball paradigm under N-methyl-D-aspartate receptor blockade. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2019;4(2):140–50.

26. Murley AG, Rouse MA, Jones PS, Ye R, Hezemans FH, O’Callaghan C, et al. GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition. Brain. 2020;143(11):3449–62.

27. Procter A, Qurne M, Francis P. Neurochemical features of frontotemporal dementia. Dementia and geriatric cognitive disorders. 1999;10(Suppl. 1):80–84.

28. Gascon E, Lynch K, Ruan H, Almeida S, Verheyden JM, Seeley WW, et al. Alterations in microRNA-124 and AMPA receptors contribute to social behavioral deficits in frontotemporal dementia. Nature medicine. 2014;20(12):1444–51.

29. Gami-Patel P, van Dijken I, van Swieten JC, Pijnenburg YAL, Rozemuller AJM, Hoozemans JJM, et al. Von Economo neurons are part of a larger neuronal population that are selectively vulnerable in C9orf72 frontotemporal dementia. Neuropathology and applied neurobiology. 2019;45(7):671–80.

30. Sami S, Williams N, Hughes LE, Cope TE, Rittman T, Coyle-Gilchrist ITS, et al. Neurophysiological signatures of Alzheimer’s disease and frontotemporal lobar degeneration: pathology versus phenotype. Brain. 2018;141(8):2500–10.

31. Hughes LE, Rittman T, Robbins TW, Rowe JB. Reorganization of cortical oscillatory dynamics underlying disinhibition in frontotemporal dementia. Brain. 2018;141(8):2486–99.

32. Whiteside DJ, Jones PS, Ghosh BC, Coyle-Gilchrist I, Gerhard A, Hu MT, et al. Altered network stability in progressive supranuclear palsy. Neurobiology of Aging. 2021;107:109–17.

33. Farb NA, Grady CL, Strother S, Tang-Wai DF, Masellis M, Black S, et al. Abnormal network connectivity in frontotemporal dementia: evidence for prefrontal isolation. cortex. 2013;49(7):1856–73.

34. Cope TE, Rittman T, Borchert RJ, Jones PS, Vatansever D, Allinson K, et al. Tau burden and the functional connectome in Alzheimer’s disease and progressive supranuclear palsy. Brain. 2018;141(2):550–67.

35. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer’s disease. New England Journal of Medicine. 2003;348(14):1333–41.

36. McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, et al. Memantine for dementia. Cochrane database of systematic reviews. 2019(3).
37. Danysz W, Parsons CG. Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine—searching for the connections. British journal of pharmacology. 2012;167(2):324–52.

38. Johnson NA, Rademaker A, Weintraub S, Gitelman D, Wienecke C, Mesulam M. Pilot trial of memantine in primary progressive aphasia. Alzheimer disease and associated disorders. 2010;24(3):308.

39. Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2013;12(2):149–56.

40. Swerdlow NR, Bhakta SG, Light GA. Room to move: plasticity in early auditory information processing and auditory learning in schizophrenia revealed by acute pharmacological challenge. Schizophrenia research. 2018;199:285–91.

41. Swerdlow NR, Bhakta S, Chou H-H, Talledo JA, Balvaneda B, Light GA. Memantine effects on sensorimotor gating and mismatch negativity in patients with chronic psychosis. Neuropsychopharmacology. 2016;41(2):419–30.

42. Light GA, Zhang W, Joshi YB, Bhakta S, Talledo JA, Swerdlow NR. Single-dose memantine improves cortical oscillatory response dynamics in patients with schizophrenia. Neuropsychopharmacology. 2017;42(13):2633–39.

43. O’Callaghan C, Hezemans FH, Ye R, Rua C, Jones PS, Murley AG, et al. Locus coeruleus integrity and the effect of atomoxetine on response inhibition in Parkinson’s disease. Brain. 2021;144(8):2513–26.

44. Voon V, Pessiglione M, Brezing C, Gallea C, Fernandez HH, Dolan RJ, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. Neuron. 2010;65(1):135–42.

45. Cools R. Chemistry of the adaptive mind: lessons from dopamine. Neuron. 2019;104(1):113–31.

46. Molina JL, Voytek B, Thomas ML, Joshi YB, Bhakta SG, Talledo JA, et al. Memantine Effects on Electroencephalographic Measures of Putative Excitatory/Inhibitory Balance in Schizophrenia. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2020;5(6):562–68.

47. Povysheva NV, Johnson JW. Effects of memantine on the excitation-inhibition balance in prefrontal cortex. Neurobiology of disease. 2016;96:75–83.

48. Steel A, Mikkelsen M, Edden RA, Robertson CE. Regional balance between glutamate + glutamine and GABA + in the resting human brain. Neuroimage. 2020;220:117112.

49. Kotermanski SE, Johnson JW. Mg2 + imparts NMDA receptor subtype selectivity to the Alzheimer's drug memantine. Journal of Neuroscience. 2009;29(9):2774–79.

50. Shaw AD, Muthukumaraswamy SD, Saxena N, Sumner RL, Adams NE, Moran RJ, et al. Generative modelling of the thalamo-cortical circuit mechanisms underlying the neurophysiological effects of ketamine. NeuroImage. 2020;221:117189.

51. Murray JD, Anticevic A, Gancsos M, Ichinose M, Corlett PR, Krystal JH, et al. Linking microcircuit dysfunction to cognitive impairment: effects of disinhibition associated with schizophrenia in a cortical working memory model. Cerebral cortex. 2014;24(4):859–72.
52. Sonkusare SK, Kaul C, Ramarao P. Dementia of Alzheimer’s disease and other neurodegenerative disorders—memantine, a new hope. Pharmacological research. 2005;51(1):1–17.
53. Ables AZ. Memantine (Namenda) for moderate to severe Alzheimer’s disease. American family physician. 2004;69(6):1491.
54. Rasovsny K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain: a journal of neurology. 2011;134(Pt 9):2456–77.
55. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Movement Disorders. 2017;32(6):853–64.
56. Grimm MJ, Respondek G, Stamelou M, Arzberger T, Ferguson L, Gelpi E, et al. How to apply the movement disorder society criteria for diagnosis of progressive supranuclear palsy. Movement disorders. 2019;34(8):1228–32.
57. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke’s Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences. 2006;21(11):1078–85.
58. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology. 2000;55(11):1621–26.
59. Mckenna P, Warrington EK. Graded Naming test: manual. NFER-Nelson; 1983.
60. Torralva T, Roca M, Gleichgerrcht E, Lopez P, Manes F. INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia—CORRECTED VERSION. Journal of the International Neuropsychological Society. 2009;15(5):777–86.
61. O’Callaghan C, Naismith SL, Hodges JR, Lewis SJ, Hornberger M. Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia. Cortex. 2013;49(7):1833–43.
62. Wear HJ, Wedderburn CJ, Mioshi E, Williams-Gray CH, Mason SL, Barker RA, et al. The Cambridge behavioural inventory revised. Dementia & Neuropsychologia. 2008;2:102–07.
63. Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia. Neurology. 2010;74(20):1591–97.
64. Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Computational intelligence and neuroscience. 2011;2011.
65. Kocagoncu E, Nesbitt D, Emery T, Hughes L, Henson RN, Rowe JB. Neurophysiological and brain structural markers of cognitive frailty differ from Alzheimer’s disease. Journal of Neuroscience. 2022.
66. Pascual-Marqui RD. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods and findings in experimental and clinical pharmacology. 2002;24 Suppl D:5–12.
67. Moran RJ, Campo P, Symmonds M, Stephan KE, Dolan RJ, Friston KJ. Free Energy, Precision and Learning: The Role of Cholinergic Neuromodulation. The Journal of Neuroscience. 2013;33(19):8227–36.

68. Garrido MI, Kilner JM, Kiebel SJ, Stephan KE, Baldeweg T, Friston KJ. Repetition suppression and plasticity in the human brain. Neuroimage. 2009;48(1):269–79.

69. Öz G, Tkáč I. Short-echo, single-shot, full-intensity proton magnetic resonance spectroscopy for neurochemical profiling at 4 T: validation in the cerebellum and brainstem. Magnetic resonance in medicine. 2011;65(4):901–10.

70. Deelchand DK, Adanyeguh IM, Emir UE, Nguyen TM, Valabregue R, Henry PG, et al. Two-site reproducibility of cerebellar and brainstem neurochemical profiles with short-echo, single-voxel MRS at 3T. Magnetic resonance in medicine. 2015;73(5):1718–25.

71. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magnetic resonance in medicine. 1993;30(6):672–79.

72. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007;38(1):95–113.

73. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage. 2005;25(4):1325–35.

74. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage. 2000;11(6 Pt 1):805–21.

75. Team J. (2022).

76. Rideaux R. No balance between glutamate + glutamine and GABA + in visual or motor cortices of the human brain: A magnetic resonance spectroscopy study. Neurolmage. 2021;237:118191.

77. Adams RA, Pinotsis D, Tsirli K, Unruh L, Mahajan A, Horas AM, et al. Computational modeling of electroencephalography and functional magnetic resonance imaging paradigms indicates a consistent loss of pyramidal cell synaptic gain in schizophrenia. Biol Psychiatry. 2022;91(2):202–15.

78. Holland N, Jones PS, Savulich G, Wiggins JK, Hong YT, Fryer TD, et al. Synaptic loss in primary tauopathies revealed by [11C] UCB-J positron emission tomography. Movement disorders. 2020;35(10):1834–42.

79. Malpetti M, Jones PS, Cope TE, Holland N, Naessens M, Rouse MA, et al. Synaptic loss in behavioural variant frontotemporal dementia revealed by [<sup>11</sup>C]UCB-J PET. medRxiv. 2022:2022.01.30.22270123.

80. Tsvetanov KA, Gazzina S, Jones PS, van Swieten J, Borroni B, Sanchez-Valle R, et al. Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. Alzheimer's & Dementia. 2021;17(3):500–14.

81. Bonakdarpour B, Hurley RS, Wang AR, Fereira HR, Basu A, Chatrathi A, et al. Perturbations of language network connectivity in primary progressive aphasia. Cortex. 2019;121:468–80.
82. Passamonti L, Tsvetanov KA, Jones P, Bevan-Jones W, Arnold R, Borchert R, et al. Neuroinflammation and functional connectivity in Alzheimer's disease: interactive influences on cognitive performance. Journal of Neuroscience. 2019;39(36):7218–26.

83. Matar E, Shine JM, Halliday GM, Lewis SJ. Cognitive fluctuations in Lewy body dementia: towards a pathophysiological framework. Brain. 2020;143(1):31–46.

84. Proudfoot M, Rohenkohl G, Quinn A, Colclough GL, Wuu J, Talbot K, et al. Altered cortical beta-band oscillations reflect motor system degeneration in amyotrophic lateral sclerosis. Hum Brain Mapp. 2017;38(1):237–54.

85. Ferrer I. Neurons and their dendrites in frontotemporal dementia. Dementia and geriatric cognitive disorders. 1999;10(Suppl. 1):55–60.

86. Phillips HN, Blenkmann A, Hughes LE, Bekinschtein TA, Rowe JB. Hierarchical organization of frontotemporal networks for the prediction of stimuli across multiple dimensions. Journal of Neuroscience. 2015;35(25):9255–64.

87. Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ. Canonical microcircuits for predictive coding. Neuron. 2012;76(4):695–711.

88. Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. Cerebral cortex (New York, NY: 1991). 1991;1(1):1–47.

89. Cope TE, Sohoglu E, Sedley W, Patterson K, Jones P, Wiggins J, et al. Evidence for causal top-down frontal contributions to predictive processes in speech perception. Nature Communications. 2017;8(1):1–16.

90. Erickson MA, Ruffle A, Gold JM. A Meta-Analysis of Mismatch Negativity in Schizophrenia: From Clinical Risk to Disease Specificity and Progression. Biol Psychiatry. 2016;79(12):980–87.

91. Kocagoncu E, Klimovich-Gray A, Hughes LE, Rowe JB. Evidence and implications of abnormal predictive coding in dementia. Brain. 2021;144(11):3311–21.

92. Näätänen R. Mismatch negativity: clinical research and possible applications. International Journal of Psychophysiology. 2003;48(2):179–88.

93. Whitwell JL, Tosakulwong N, Botha H, Ali F, Clark HM, Duffy JR, et al. Brain volume and flortaucipir analysis of progressive supranuclear palsy clinical variants. NeuroImage: Clinical. 2020;25:102152.

94. Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. Journal of neural transmission. 2014;121(8):799–817.

95. Legon W, Punzell S, Dowlati E, Adams SE, Stiles AB, Moran RJ. Altered prefrontal excitation/inhibition balance and prefrontal output: markers of aging in human memory networks. Cerebral Cortex. 2016;26(11):4315–26.

96. Lauterborn JC, Scaduto P, Cox CD, Schulmann A, Lynch G, Gall CM, et al. Increased excitatory to inhibitory synaptic ratio in parietal cortex samples from individuals with Alzheimer's disease. Nature communications. 2021;12(1):1–15.
97. Rowland LM, Summerfelt A, Wijtenburg SA, Du X, Chiappelli JJ, Krishna N, et al. Frontal glutamate and γ-aminobutyric acid levels and their associations with mismatch negativity and digit sequencing task performance in schizophrenia. JAMA psychiatry. 2016;73(2):166–74.

Figures

Figure 1

**Neuroanatomical and neurochemical differences across controls and persons with bvFTD/PSP.** (A) Group-wise voxel-based morphometry comparisons between controls and patients (cluster-level, \( p < .05 \), FWE-corrected; height-threshold, \( p < 0.001 \), uncorrected). Unthresholded SPM maps are available at https://neurovault.org/collections/12279. (B) MRS concentrations of GABA (left panel) and Glutamate (right) in the right inferior frontal gyrus for both controls and patients (bvFTD, squares; PSP, triangles) corrected for age, sex and partial volume information (grey and white matter for glutamate, grey matter for GABA). Heat voxel image (far left panel) represents sum of all participants MRS voxel placement in the frontal cortex. Anatomical images are the mean brain extracted structural image across all controls and patients.
Figure 2

Mismatch responses of source regions across controls and bvFTD/PSP patients on placebo. (A) Group average mismatch responses across peri-stimulus window for controls (blue line) and bvFTD/PSP (red), derived from each individual by the difference of the rep3 and dev waveforms. Thick lines and shading represent group average and its standard error at each time point, respectively. (B) Mean MMN responses (average of mismatch waveform between 125-175ms) in controls and patients, with middle line
indicating the group mean. Boxes represent interquartile range of 25% and 75% percentile, with whiskers indicating 95% probability density.

R IFG, Right Inferior Frontal Gyrus; R STG, Right Superior Temporal Gyrus; R AUD, Right Auditory Cortex; bvFTD, behavioral variant Frontotemporal Dementia; PSP, progressive supranuclear palsy
Figure 3

**Group responses to memantine across controls and persons with PSP and bvFTD.** Mean MMN response across placebo (PLA) and memantine (MEM) drug sessions for controls (blue circles and lines) and FTLD (red). Mean group responses at each drug session are indicated by bold circles, with error bars representing 95% confidence intervals. Group average change in mean MMN across drug session indicated by solid lines, with each participants slope illustrated by opaque lines.

R IFG, Right Inferior Frontal Gyrus; R STG, Right Superior Temporal Gyrus; R AUD, Right Auditory Cortex. bvFTD, behavioral variant Frontotemporal Dementia; PSP, progressive supranuclear palsy

Figure 4

**GABA influences on the response to memantine in patients across source regions.** (A) Association between corrected GABA concentrations in the R IFG and change in MMN to memantine (vs. placebo) across bvFTD (squares) and PSP patients (triangles). (B) For the right auditory cortex, mean MMN as a function of drug session (Drug, red line and circles; Placebo, blue) and GABA concentration. (C) Glu/GABA ratios in controls and bvFTD/PSP, with middle line indicating group mean. Boxes represent interquartile range of 25% and 75% percentile, and whiskers the 95% probability density. (D) Association between the ratio of Glutamate and GABA (Glu/GABA) and change in MMN to memantine (vs. placebo) in the right auditory cortex. Data points are coloured according to baseline GABA levels.
bvFTD, behavioral variant Frontotemporal Dementia; PSP, progressive supranuclear palsy

R IFG, Right Inferior Frontal Gyrus; R STG, Right Superior Temporal Gyrus; R AUD, Right Auditory Cortex. = PLA, placebo; MEM, memantine. GABA and Glutamate concentrations corrected for age, sex, and partial volume information

Figure 5

Association between prefrontal cortical atrophy and changes in MMN response to memantine in auditory cortex. (A) Anatomical mask (blue areas) representing right inferior frontal gyrus (rIFG) region used for calculating GM volume, as visualised from axial and coronal views. Mask is available at https://neurovault.org/images/776918. Green sphere (7mm radius) indicates magnetoencephalography (MEG) source region-of-interest (ROI) used in MMN analysis. (B) Association between residual GM volume (adjusted for age and total intracranial volume) in rIFG and change in MMN to memantine (vs. placebo) (PLA-MEM) across bvFTD (squares) and PSP patients (triangles).

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Table1SI.docx
- SupplementaryInformationTP.docx