doi:10.1093/brain/awaa305 BRAIN 2020: 143; 3449–3462 | 3449

BRAIN
A JOURNAL OF NEUROLOGY

GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition

Alexander G. Murley,[1,2] Matthew A. Rouse,[1] P. Simon Jones,[1] Rong Ye,[1] Frank H. Hezemans,[1,3] Claire O'Callaghan,[4] Polytimi Frangou,[5] Zoe Kourtzi,[5] Catarina Rua,[6] T. Adrian Carpenter,[6] Christopher T. Rodgers[6] and James B. Rowe[1,2,3]

Behavioural disinhibition is a common feature of the syndromes associated with frontotemporal lobar degeneration (FTLD). It is associated with high morbidity and lacks proven symptomatic treatments. A potential therapeutic strategy is to correct the neurotransmitter deficits associated with FTLD, thereby improving behaviour. Reductions in the neurotransmitters glutamate and GABA correlate with impulsive behaviour in several neuropsychiatric diseases and there is post-mortem evidence of their deficit in FTLD. Here, we tested the hypothesis that prefrontal glutamate and GABA levels are reduced by FTLD *in vivo*, and that their deficit is associated with impaired response inhibition. Thirty-three participants with a syndrome associated with FTLD (15 patients with behavioural variant frontotemporal dementia and 18 with progressive supranuclear palsy, including both Richardson's syndrome and progressive supranuclear palsy-frontal subtypes) and 20 healthy control subjects were included. Participants undertook ultra-high field (7 T) magnetic resonance spectroscopy and a stop-signal task of response inhibition. We measured glutamate and GABA levels using semi-LASER magnetic resonance spectroscopy in the right inferior frontal gyrus, because of its strong association with response inhibition, and in the primary visual cortex, as a control region. The stop-signal reaction time was calculated using an ex-Gaussian Bayesian model. Participants with frontotemporal dementia and progressive supranuclear palsy had impaired response inhibition, with longer stop-signal reaction times compared with controls. GABA concentration was reduced in patients versus controls in the right inferior frontal gyrus, but not the occipital lobe. There was no group-wise difference in partial volume corrected glutamate concentration between patients and controls. Both GABA and glutamate concentrations in the inferior frontal gyrus correlated inversely with stop-signal reaction time, indicating greater impulsivity in proportion to the loss of each neurotransmitter. We conclude that the glutamatergic and GABAergic deficits in the frontal lobe are potential targets for symptomatic drug treatment of frontotemporal dementia and progressive supranuclear palsy.

1 Department of Clinical Neurosciences, University of Cambridge, UK
2 Cambridge University Hospitals NHS Foundation Trust, UK
3 MRC Cognition and Brain Sciences Unit, University of Cambridge, UK
4 Department of Psychiatry, University of Cambridge, UK
5 Department of Psychology, University of Cambridge, UK
6 Wolfson Brain Imaging Centre, University of Cambridge, UK

Correspondence to: Alexander G. Murley
Herchel Smith Building, Robinson Way, Cambridge CB2 0SZ, UK
E-mail: am2505@medschl.cam.ac.uk

Keywords: frontotemporal dementia; progressive supranuclear palsy; GABA; glutamate; impulsivity

Abbreviation: bvFTD = behavioural variant frontotemporal dementia; FTLD = frontotemporal lobar degeneration; ^{1}H-MRS = proton magnetic resonance spectroscopy; HDI = high density interval; PSP = progressive supranuclear palsy; SSRT = stop-signal reaction time

Received May 24, 2020. Revised July 11, 2020. Accepted July 22, 2020. Advance access publication November 3, 2020

Introduction

Behavioural change is a common feature of the syndromes associated with frontotemporal lobar degeneration (FTLD) pathology, including behavioural variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP) (Gerstenecker *et al.*, 2013; Bang *et al.*, 2015; Lansdall *et al.*, 2017; Murley *et al.*, 2020*a*). This is associated with loss of functional independence (Agarwal *et al.*, 2019; Murley *et al.*, 2020*b*) and increased mortality (Lansdall *et al.*, 2019) in both disorders. Better treatment of behavioural symptoms might therefore improve both functionally independent survival and quality of life for patients and their families. A potential treatment strategy is to reverse neurotransmitter deficits, which has been effective in other neurodegenerative and neuropsychiatric disorders (Barone, 2010; Kandimalla and Reddy, 2017). There is evidence of neurotransmitter deficits in FTLD, but limited evidence of a relationship with phenotype (Huey *et al.*, 2006; Murley and Rowe, 2018).

The behavioural disturbance caused by FTLD syndromes comprises many neurocognitive processes with distinct anatomical and neurochemical alterations (Ranasinghe *et al.*, 2016; Passamonti *et al.*, 2018). An inability to inhibit inappropriate actions is seen in both bvFTD (O'Callaghan *et al.*, 2013*a*; Hughes *et al.*, 2018) and PSP (Gerstenecker *et al.*, 2013; Zhang *et al.*, 2016*a*). This phenotypic overlap between bvFTD and PSP is reflected in the MDS-2017 criteria for the PSP-F subtype (Höglinger *et al.*, 2017), along with frequent parkinsonism in bvFTD (Rowe, 2019). In this study, we therefore used a transdiagnostic approach to behavioural disinhibition (Husain, 2017), with 'FTLD syndromes' encompassing bvFTD, PSP-Richardson's syndrome and PSP-Frontal syndrome. We measured glutamate and GABA concentrations *in vivo*, before testing the association of these neurotransmitter deficits with behavioural disinhibition.

The neurotransmitters glutamate and γ-aminobutyric acid (GABA) are associated with behavioural variability in health and neurological and psychiatric diseases. For example, GABA concentrations in CSF (Lee *et al.*, 2009) and prefrontal cortex (Boy *et al.*, 2011; Silveri *et al.*, 2013; Hermans *et al.*, 2018) inversely correlate with impulsivity and risky decision-making (Fujihara *et al.*, 2015). Proton magnetic resonance spectroscopy (^{1}H-MRS) enables *in vivo* non-invasive measurement of glutamate and GABA, and has identified deficits in diseases associated with impulsivity (Ende, 2015; Yasen *et al.*, 2017). GABA deficits are seen in drug and alcohol addiction (Prisciandaro *et al.*, 2017; Li *et al.*, 2020), attention deficit hyperactivity disorder (Edden *et al.*, 2012; Ende *et al.*, 2016) and obsessive compulsive disorder (Zhang *et al.*, 2016*b*). There is also an association between glutamate, measured *in vivo* with MRS, and self-reported impulsivity in healthy adults (Schmaal *et al.*, 2012*a*; Coccaro *et al.*, 2013), personality disorders (Hoerst *et al.*, 2010), attention deficit hyperactivity disorder (Naaijen *et al.*, 2015; Ende *et al.*, 2016) and addiction (Schmaal *et al.*, 2012*b*). The direction of the relationship between glutamate, GABA and impulsive behaviour is complex and may depend on disease state (Ende, 2015), brain region (Dharmadhikari *et al.*, 2015; Naaijen *et al.*, 2015) and receptor subtype (Lee *et al.*, 2011; Hermans *et al.*, 2018).

There is preclinical and clinical evidence of GABA and glutamate deficits in FTLD (Murley and Rowe, 2018). For example, in transgenic tauopathy mouse models, there is impairment of both glutamatergic (Gascon *et al.*, 2014; Warmus *et al.*, 2014; Decker *et al.*, 2016) and GABAergic (Levenga *et al.*, 2014; Li *et al.*, 2017; Jiang *et al.*, 2018) neuron function. In post-mortem human studies of FTLD, glutamatergic pyramidal neurons (Ferrer, 1999; Henderson *et al.*, 2000) and receptors (Francis *et al.*, 1993; Procter *et al.*, 1999; Bowen *et al.*, 2008; Gascon *et al.*, 2014) are reduced. GABAergic neurons are markedly reduced in FTD (Ferrer, 1999) and PSP (Levy *et al.*, 1995), with loss of $GABA_A$ receptors in some brain regions (Landwehrmeyer and Palacios, 1994; Suzuki *et al.*, 2002). Post-mortem GABA concentrations are decreased in the basal ganglia in bvFTD (Kanazawa *et al.*, 1988). There is also emerging evidence of *in vivo* glutamate deficits (Benussi *et al.*, 2019). MRS in bvFTD shows reduced glutamate/glutamine levels in the frontal and temporal lobes (Ernst *et al.*, 1997; Sarac *et al.*, 2008), and there is an inverse correlation between CSF glutamate levels and verbal agitation (Vermeiren *et al.*, 2013). PET studies have also shown loss of glutamate and GABA receptors (Foster *et al.*, 2000; Leuzy *et al.*, 2016).

In this study we use ultra-high field (7 T) ^{1}H-MRS to measure glutamate and GABA *in vivo*. This method requires the target region (voxel) to be selected before each scan. We chose the right inferior frontal gyrus as our experimental region of interest. This region is critical for response inhibition (Aron *et al.*, 2004, 2014), as shown in structural (Aron *et al.*, 2003) and functional studies (Swann *et al.*, 2009; Levy and Wagner, 2011; Ye *et al.*, 2014; Rae *et al.*, 2015). In bvFTD, abnormal functional connectivity of the inferior frontal gyrus is associated with impulsivity (Hughes *et al.*, 2015, 2018). We also measured glutamate and GABA in a control region, the right occipital lobe, which is minimally affected by FTLD pathologies (Riedl *et al.*, 2014).

We tested two specific hypotheses: (i) GABA and glutamate levels are reduced in the frontal but not occipital cortex in subjects with bvFTD/PSP compared with controls, even after correction for atrophy; and (ii) the GABA and glutamate deficits in the frontal lobe of patients are associated with failure of response inhibition.

Materials and methods

Participant recruitment

Forty-four patients with bvFTD or PSP were recruited from the Cambridge Centre for Frontotemporal Dementia, the

Cambridge Centre for Parkinson-Plus and the 'Join Dementia Research' patient register. All patients had a clinical assessment to confirm they met the diagnostic criteria for bvFTD (Rascovsky *et al.*, 2011), PSP-Richardson's syndrome or PSP-Frontal syndrome (Höglinger *et al.*, 2017). Disease severity was assessed with the Clinical Dementia Rating scale modified for FTLD (Knopman *et al.*, 2008, 2011) and Progressive Supranuclear Palsy Rating Scale (Golbe and Ohman-Strickland, 2007). Twenty age- and sex-matched controls with no history of a neurological or psychiatric illness were recruited from the 'Join Dementia Research' database. Participants were asked to abstain from alcohol and PRN benzodiazepines or 'Z-drugs' for 24 h prior to the scan but continue their regular medications. No participants in the study were taking regular 'Z-drugs' or benzodiazepines. All participants gave written informed consent. The study had ethical approval from the Cambridge Central Research Ethics Committee (16/EE/0351; 16/EE/0084).

Neuropsychology

Participants underwent cognitive and neuropsychological assessments including the Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi *et al.*, 2006), Frontal Assessment Battery (FAB) (Royall, 2001), Hayling Sentence Completion test (Burgess and Shallice, 1997) and INECO Frontal Screening test (Torralva *et al.*, 2009). Each participant's closest relative completed the Cambridge Behavioural Inventory-Revised (CBI-R) (Wear *et al.*, 2008) and Frontotemporal Dementia Rating Scale (FRS) (Mioshi *et al.*, 2010). We report the Hayling A + B score instead of total score (O'Callaghan *et al.*, 2013*b*; Martyr *et al.*, 2019).

Stop-signal task

A stop-signal type response inhibition task was used to measure response inhibition (Ye *et al.*, 2014; Tsvetanov *et al.*, 2018) (Supplementary material and Supplementary Fig. 1). Participants were presented with a series of trials consisting of either go, no-go or stop trials and responded using a manual two-button box. On go trials, participants pressed the left button when shown a left-pointing black arrow and pressed the right button when shown a right-pointing black arrow. On stop trials, after a short and variable 'stop-signal' delay (SSD), the black arrow changed colour from black to red and a tone sounded at the same time (the stop signal). On stop trials, the SSD was varied using a staircase method to target a cumulative stop accuracy of 50% in each participant (see Tsvetanov *et al.*, 2018 for details). The starting SSD was calculated from 20 go trials at the start of each block. These trials were omitted from further analysis. On no-go trials, the SSD was set to zero. Participants were instructed to not respond if the arrow became red, suppressing their imminent response. Participants were given standardized instructions and asked to respond as quickly and accurately as possible. Participants were told neither to slow down on go trials, nor to wait for a possible stop signal (Verbruggen *et al.*, 2019). The task consisted of five blocks of 120 trials (go $n = 450$, no-go $n = 51$, stop $n = 99$). Participants undertook a practice session of 20 trials prior to the first block.

We used the Dynamic Models of Choice toolbox in R (Version 3.6.1) to perform parametric Bayesian hierarchical analysis of the stop-signal task (Matzke *et al.*, 2013; Heathcote *et al.*, 2019). This method is described in detail elsewhere (Heathcote *et al.*, 2019). In brief, the model assumes a race between three independent processes: one corresponding to the stop process and two corresponding to go processes that match or mismatch the choice stimulus. A correct go response occurs when the matching go process finishes before the mismatching go process. Successful stop trials occur when the stop process finishes before either of the go processes. The model assumes that the finishing times of these processes follow an ex-Gaussian skewed distribution, which is typical for reaction time data (Heathcote *et al.*, 1991). We estimated the mean (μ), standard deviation (σ) and exponential decay (τ) of the ex-Gaussian distribution separately for each process. We included two attentional failure parameters that represent the probability that the go and stop processes fail to start ('trigger failure'). We estimated these parameters hierarchically, so that parameters for individual participants were considered to be samples from corresponding group-level distributions. We fitted this hierarchical model separately for the patient and control groups. The Dynamic Models of Choice model has several advantages over other methods of calculating stop-signal reaction time (SSRT). First, it provides a distribution of plausible SSRT values, rather than a point estimate of SSRT, which may better reflect disease-related disinhibition (Matzke *et al.*, 2013). Second, the model accounts for attentional failures on go and stop trials, which occur when a participant fails to react to a go or stop signal. These 'trigger failures' are common in health (Matzke *et al.*, 2017) and diseases such as schizophrenia (Matzke *et al.*, 2017) and, if not modelled, may cause overestimation of the SSRT (Matzke *et al.*, 2019; Skippen *et al.*, 2019). Third, the model can accommodate choice errors by including two Go runners, which yields more accurate parameter estimates for the stop process (Heathcote *et al.*, 2019; Matzke *et al.*, 2019). Lastly, hierarchical Bayesian methods regularize participant-level estimates according to group statistics, which enables reliable group-level inference and produces, on average, more accurate participant-level estimates (Gelman *et al.*, 2013).

We used Markov chain Monte Carlo sampling to approximate the posterior distributions of parameters simultaneously at the level of the group and individual participants. The prior distributions for the group-level parameters were the same as used by the model developers (Heathcote *et al.*, 2019), except for slightly higher prior mean values for $\mu_{\text{go-match}}$ (1.5 s), $\mu_{\text{go-mismatch}}$ (1.5 s) and μ_{stop} (1 s), to account for slower reaction times in older age and neurodegenerative disease. We initially ran the model using 33 chains (i.e. three times the number of parameters), with thinning of every 10th sample and a 5% probability of migration for both the group and participant levels. We assessed convergence of the Markov chain Monte Carlo chains by visual inspection of the trace plots and confirmed that the potential scale reduction statistic $\hat{R}$ was <1.1 for all parameters. After this, we obtained an additional 500 iterations for each chain to create a final posterior distribution of each parameter, for further analyses. We compared the observed and simulated data (generated from the model's posterior predictive distribution), to ensure that the model adequately captures the data-generating process. The primary outcome of interest, SSRT, now without the potential confound of attentional failure, was computed as the sum of μ_{stop} and τ_{stop} (Matzke *et al.*, 2019).

Magnetic resonance spectroscopy

Participants underwent scanning with a MAGNETOM Terra scanner (Siemens Healthineers) with a 32-channel receiver and single channel transmit head coil (Nova Medical). A T_1-weighted MP2RAGE structural sequence [repetition time = 4300 ms, echo time = 1.99 ms, resolution = 99 ms, bandwidth = 250 Hz/px, voxel size = 0.75 mm^3, field of view = 240 × 240 × 157 mm, acceleration factor (A ≫ P) = 3, flip-angle = 5/6° and inversion times = 840/2370 ms] was acquired for voxel placement and partial volume correction. The default settings for tissue probability parameters (six tissue classes) in the standard SPM12 pipeline were used for tissue segmentation and voxel-based morphometry (Supplementary material).

Magnetic resonance spectra were acquired serially from one region of interest, the right inferior frontal gyrus, and one control region, the right primary visual cortex. Voxel order was randomized between participants. Both voxels (2 × 2 × 2 cm^3) were placed manually by the same operator (A.G.M.) using anatomical landmarks. To confirm that spectroscopy voxel placement was consistent across participants in both brain regions, we retrospectively overlaid the co-registered voxels on a T_1 study-wise template. (Fig. 1A and B). Spectra were acquired using a short-echo semi-LASER sequence (Öz and Tkáč, 2011; Deelchand *et al.*, 2015) (repetition time/echo time = 5000/26 ms, 64 repetitions) using the recommended pre-scan protocol of FASTESTMAP shimming (Gruetter and Tkáč, 2000) semi-LASER water-peak flip angle and VAPOR water suppression calibration (Tkac *et al.*, 1999). This spectroscopy sequence gives reliable and reproducible GABA and glutamate measurements in the human brain *in vivo* (Barron *et al.*, 2016; Kolasinski *et al.*, 2017; Joers *et al.*, 2018; Frangou *et al.*, 2019; Hong *et al.*, 2019; Ip *et al.*, 2019).

Each of the 64 individual spectral transients from each participant were saved separately. These were then corrected for effects of eddy currents and for frequency and phase shifts using MRspa (Dinesh Deelchand, University of Minnesota, www.cmrr.umn.edu/downloads/mrspa). Two patient participants had inadequate data for further analysis and were excluded, due to incomplete scans and movement artefacts.

Neurochemicals between 0.5 and 4.2 ppm, including glutamate and GABA, were quantified using LCModel (Version 6.2-3) (Provencher, 1993), with water scaling and a simulated basis set that included experimentally-acquired macromolecule spectra (Fig. 1C). For partial volume correction, fractions of grey matter, white matter and CSF were obtained from segmentation of the MP2RAGE images using SPM12. A generalized linear model was used to remove the effect of age, sex and partial volume and the residual glutamate and GABA values were used for further analysis (Supplementary material).

Statistical analysis

Analysis of variance was used to compare GABA and glutamate levels between groups, with region of interest as a within subject factor and diagnosis as a between subject factor. All *P*-values were corrected for multiple comparisons using Tukey's test. We tested the association between the right inferior frontal gyrus GABA and glutamate concentrations and behavioural disinhibition, as measured by the SSRT and carer questionnaires, in participants with bvFTD/PSP. For each value in the individual-level posterior distributions of SSRT, a Spearman's correlation coefficient was calculated with the residual glutamate and GABA values after partial volume, age and sex correction. This results in a posterior distribution of plausible correlation values (Ly *et al.*, 2018). The region of practical equivalence was defined as a Spearman's R between –0.1 and 0.1, corresponding to a small effect size (Cohen, 1992; Kruschke, 2018). The null hypotheses was rejected if the 95% highest density interval (HDI) of the 'R' correlation values did not overlap with the region of practical equivalence (Kruschke, 2018). Analysis was performed in MATLAB 2018b (MathWorks, USA) and JASP (Version 0.11).

Data availability

Anonymized data are available on reasonable request for academic purposes.

Results

Forty-four patients with bvFTD/PSP participated in the study. The primary clinical diagnoses were evenly split between bvFTD ($n = 22$) and PSP ($n = 22$), but if MAX-rules and mutual exclusivity criteria were set aside (Grimm *et al.*, 2019), many patients met more than one set of diagnostic criteria for bvFTD, PSP-Frontal syndrome and PSP-Richardson's syndrome. Thirty-six patients met the diagnostic criteria for probable bvFTD (with or without parkinsonism and oculomotor deficits), 19 met the criteria for PSP-Frontal syndrome and 23 met the criteria for PSP-Richardson's syndrome (with or without cognitive and behavioural change). Fifteen patients exhibited clinical and radiological features consistent with all three conditions. Three patients with bvFTD had parkinsonism but did not meet the diagnostic criteria for PSP. Therefore, we use a transdiagnostic approach when reporting these results and refer to all patients with bvFTD or PSP as an 'FTLD' group, noting the high, but not perfect, clinical pathological correlations between clinically probable and possible bvFTD, PSP and the pathologies of FTLD (Perry *et al.*, 2017; Gazzina *et al.*, 2019).

Patient demographics and neuropsychology results are shown in Table 1. Statistical comparisons of the FTLD subgroups (bvFTD versus PSP) are included in the Supplementary material, noting that both groups were impulsive, as expected.

First, we compared grey and white matter volumes between FTLD syndromes and healthy controls using voxel-based morphometry. Participants with FTLD had reduced grey matter volume in the frontal and temporal lobes, basal ganglia, thalamus and cerebellum, with corresponding white matter volume loss in the frontostriatal and corticospinal tracts and brainstem. Brain volume was relatively preserved in the occipital lobe (Supplementary Fig. 2). Participants with bvFTD and those with PSP had reduced grey matter in the right orbitofrontal and anterior cingulate cortex, bilateral inferior frontal gyri, insula and motor cortices, as shown by a conjunction analysis (Nichols *et al.*, 2005). This also

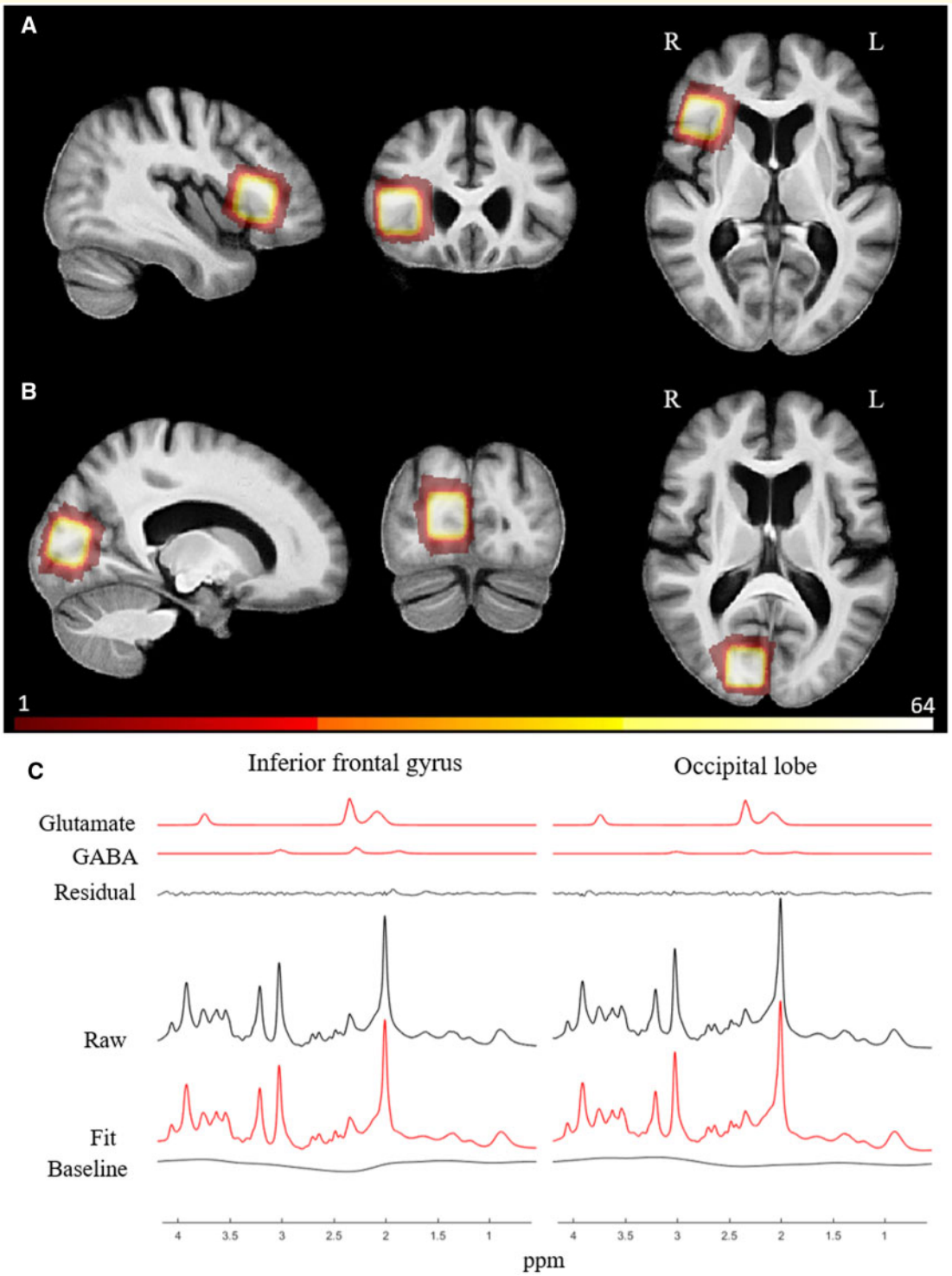

Figure 1 Spectroscopy voxel location and composition. (**A**) Frontal voxel (sum of all participants) superimposed on a mean structural image of all participants. (**B**) Occipital voxel location. (**C**) Mean spectra from all participants showing the raw data, LCModel fit, baseline, residual (fit-raw data), glutamate and GABA fits.

revealed volume loss in subcortical structures including the caudate, putamen and globus pallidus and superior cerebellum. White matter volume loss was seen in frontostriatal pathways (Supplementary Fig. 3).

Second, we used ^{1}H-MRS to measure glutamate and GABA concentrations in the right inferior frontal gyrus and occipital lobe. The spectral quality was adequate for neurotransmitter quantification in both brain regions (Table 2 and

Table 1 Demographics and neuropsychology results of the study cohort

	Control mean (SD)	bvFTD/PSP mean (SD)	*t*-statistic	*P*-value
n	20	44		
Age, years	67.1 (5.6)	66.2 (8.4)	0.47	NS
Sex, %male	65	72	0.263[a]	NS
Disease onset to study, years (SD)	NA	5.84 (11.32)	NA	NA
Diagnosis to study, years (SD)	NA	1.08 (1.48)	NA	NA
CDR® plus NACC FTLD	0 (0)	9.81 (5.19)	–8.42	<0.001
PSPRS Total	0.1 (0.31)	23.1 (17.81)	–5.75	<0.001
ACER Total	96.2 (2.71)	68 (24.11)	5.20	<0.001
FAB	17.45 (0.83)	11.14 (5.14)	5.62	<0.001
Hayling (A + B score)	4.3 (7.12)	24.31 (19.58)	–4.08	<0.001
Hayling Total	18.45 (2.28)	11.26 (4.83)	5.86	<0.001
INECO	25.78 (2.83)	14.2 (7.53)	6.63	<0.001
CBIR Total	6.35 (6.13)	64.62 (36.52)	–6.61	<0.001
FRS Total (Logit)	0.86 (0.3)	0.37 (0.28)	9.23	<0.001

ACER = Addenbrooke's Cognitive Examination-Revised; CBIR = Cambridge Behavioural Inventory-Revised; CDR® plus NACC FTLD = Clinical Dementia Rating Scale plus NACC FTLD behaviour and language domains, sum of boxes; FAB = Frontal Assessment Battery; FRS = Frontotemporal Dementia Rating Scale; NA = not applicable; PSPRS = Progressive Supranuclear Palsy Rating Scale; SD = standard deviation.
[a]Chi-squared, NS (not significant) = $P > 0.05$

Table 2 Spectral quality measurements

	Control mean (SD)	bvFTD/PSP mean (SD)	*t*-statistic	*P*-value
Water line width, Hz				
Right inferior frontal gyrus	13.9 (1.3)	13.0 (2.7)	1.86	0.18
Right occipital lobe	13.9 (1.0)	13.34 (1.7)	2.11	0.15
Signal-to-noise ratio				
Right inferior frontal gyrus	54.8 (5.3)	44.8 (8.7)	22.25	<0.001
Right occipital lobe	67.4 (15.38)	57.8 (14.1)	5.39	0.02
Glutamate CRLB				
Right inferior frontal gyrus	2.1 (0.3)	2.4 (0.5)	4.7	0.034
Right occipital lobe	2.3 (0.7)	2.4 (1.1)	0.22	0.65
GABA CRLB				
Right inferior frontal gyrus	9.4 (1.1)	12.3 (4.4)	8.21	0.006
Right occipital lobe	19.2 (17.3[a])	19.4 (9.3)	0.005	0.946

Values are presented as mean and standard deviation for each group. CRLB = Cramér Rao Lower Bound.
[a]There was one outlier in the control group (CRLB 84).

Fig. 1C). The mean correlation coefficients between all metabolites and both GABA and glutamate were less negative than –0.3, suggesting both were accurately distinguished from other metabolites (Provencher, 1993). GABA and glutamate measurements were water scaled, then corrected for partial volume, age, sex and measurement accuracy (Supplementary material). Water-scaled values without correction are shown in the Supplementary material. There was no difference between groups in glutamate concentration in either voxel [simple main effects: right inferior frontal gyrus $F(1) = 0.34$, $P = 0.56$; right occipital lobe $F(1) = 0.73$, $P = 0.40$] (Fig. 2). GABA was reduced in bvFTD/PSP compared to controls in the right inferior frontal gyrus [$F(1) = 8.67$, $P = 0.005$] but not occipital lobe [$F(1) = 0.06$, $P = 0.81$] (Fig. 2). Including white matter volume in the regression analysis for GABA concentrations did not change this finding. The GABA deficit in the right inferior frontal gyrus was present in both bvFTD [$t(38) = 2.93$, $P = 0.006$] and PSP [$t(40) = 2.36$ $P = 0.023$] subgroups compared with the healthy controls. Removing the one outlier (Grubb's test $P < 0.05$) in the occipital lobe region in the patient group did not change these results.

Third, we used Bayesian hierarchical modelling of a stop-signal task to estimate the SSRT as the measure of response inhibition. Data from nine participants with bvFTD/PSP were excluded, due to low number of trials (<50 stop trials) or inability to complete the task. These excluded participants did not have significantly different neurotransmitter concentrations from the group that completed the task [right inferior frontal gyrus GABA $t(40) = 0.47$, $P = 0.64$; glutamate $t(40) = 0.56$, $P = 0.58$]. The remaining bvFTD/PSP (bvFTD $n = 17$, PSP $n = 18$) and control participants completed a similar total number of trials (mean 663 versus 670 trials, Mann-Whitney U-test = 300, $P = 0.228$) but participants

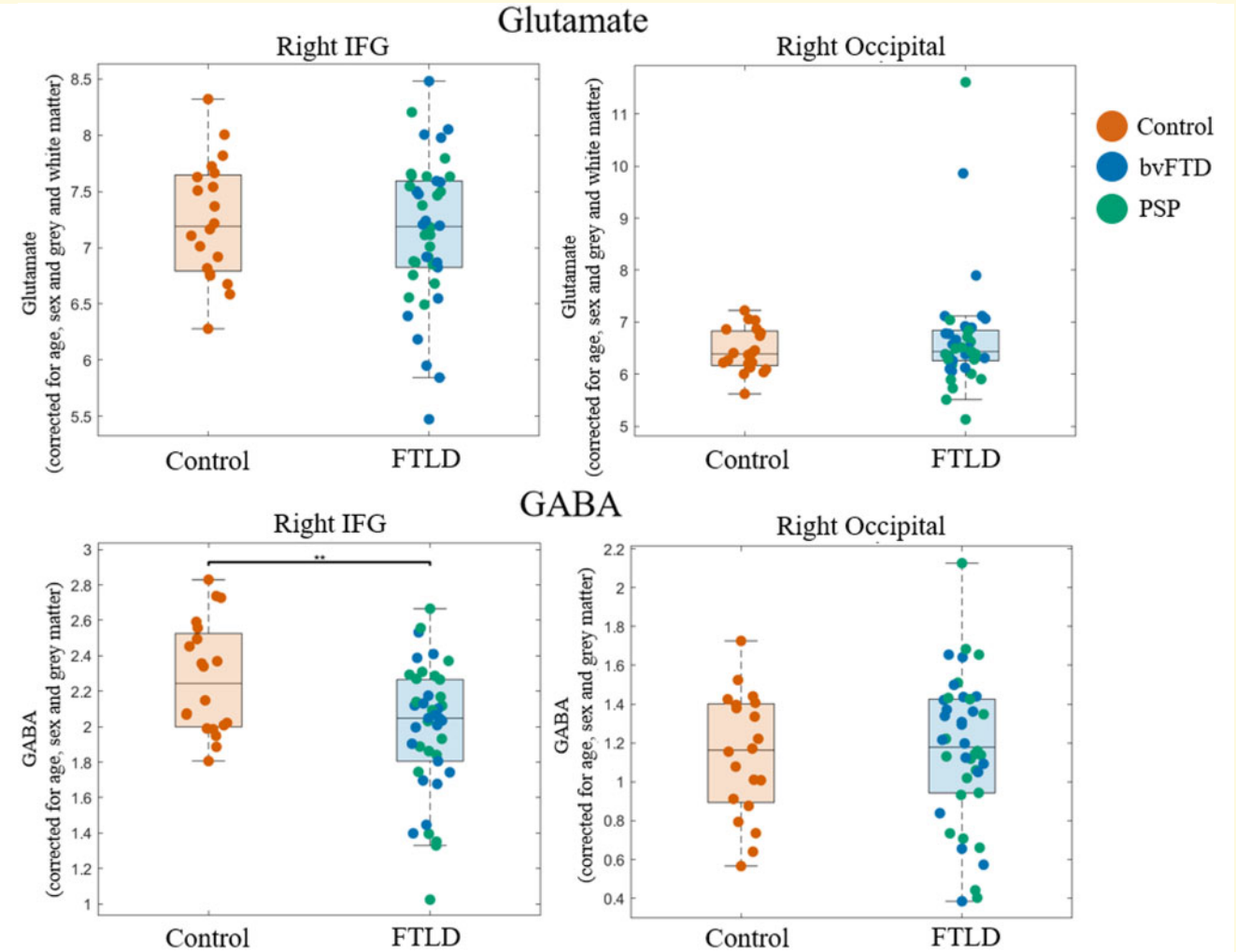

Figure 2 Glutamate and GABA concentrations in the FTLD syndromes of bvFTD and PSP. Values are corrected for age, sex and partial volume (grey and white matter for glutamate, grey matter for GABA). $^{**}P = 0.005$. IFG = inferior frontal gyrus.

with bvFTD/PSP made more go errors (Mann-Whitney U-test = 185.5, $P = 0.003$) and omissions (Mann-Whitney U-test = 231.5, $P = 0.005$). Further details regarding behavioural performance are provided in the Supplementary material.

The stop-signal task performance descriptive results, Markov chain Monte Carlo trace plots and prior and posterior density plots are shown in the Supplementary material. The posterior estimates for the group and individual level go and stop reaction time distributions for bvFTD/PSP syndromes and controls are shown in Fig. 3. All control individual-level reaction times were similar to the group-level distribution, with no evidence of strategic slowing. In bvFTD/PSP, individual go reaction time distributions varied widely; some overlapped with the control distributions, but many were markedly longer (Fig. 3A). There was also similar variability in bvFTD/PSP stop reaction time distributions (Fig. 3C).

There was a group-level difference in SSRT between the participants with bvFTD/PSP and controls, with clear separation of the ex-Gaussian distributions and no overlap in the 95% HDIs of the mean reaction time (Fig. 3D). The go reaction time did not differ significantly between groups, as evidenced by the overlapping HDI boundaries (Fig. 3B).

Next, we tested the hypothesis that GABA and glutamate deficits in the right inferior frontal gyrus are associated with impulsivity in patients who underwent MRS and completed the stop signal task (bvFTD $n = 15$, PSP $n = 18$). Both GABA and glutamate concentrations in the right inferior frontal gyrus were inversely correlated with the SSRT (Fig. 4). This association with impaired response inhibition was stronger for glutamate (95% HDI: –0.56, –0.38) than GABA (95% HDI: –0.35, –0.13), but both these credible intervals were outside the prespecified region of practical equivalence (–0.1, 0.1). The corrected glutamate and GABA concentrations did not correlate (Spearman's R = 0.06, $P = 0.70$).

Finally, we tested the specificity of the association between GABA and glutamate concentrations in the right inferior frontal gyrus and SSRT. Trigger failure probability, a measure

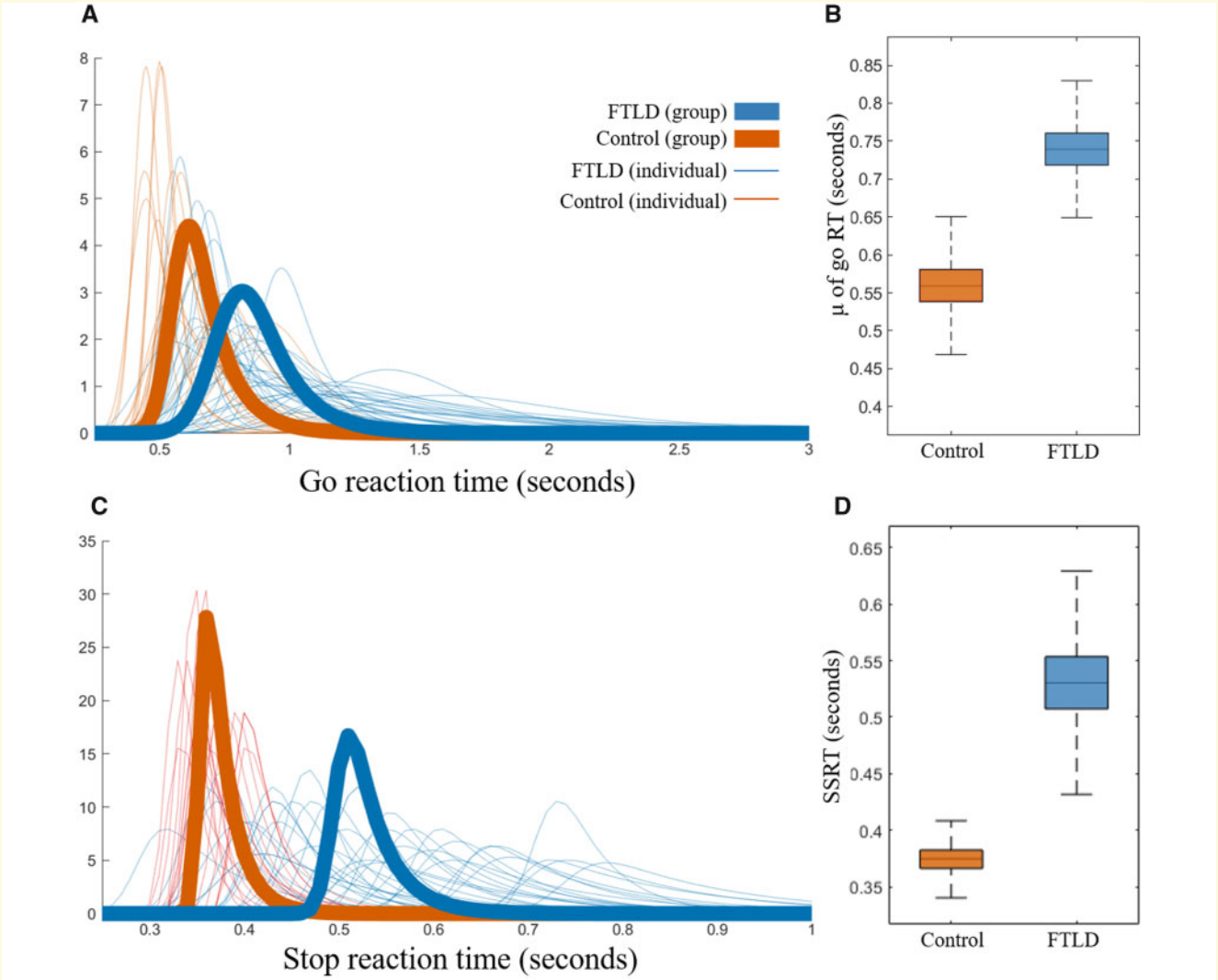

Figure 3 Reaction time distributions for patients with bvFTD/PSP and healthy controls. The group-level result is shown by the thick line and individual-level results are shown by the thinner lines. (**A**) Go reaction time distributions. (**B**) Box plot of 95% highest density interval for the μ of the go reaction time. bvFTD/PSP = blue; healthy controls = red.

of inattention derived by the Dynamic Models of Choice model, was not associated with either the GABA (95% HDI: –0.13, 0.18) or glutamate (95% HDI: –0.01, 0.31) concentration in the inferior frontal gyrus (Supplementary Fig. 9). There was no association between SSRT and other MRS-visible metabolites, including *N*-acetylaspartate (95% HDI –0.25, –0.05), creatine/phosphocreatine (95% HDI –0.03, –0.19), glycerophosphocholine/phosphocholine (95% HDI –0.01, 0.23), myo-inositol (95% HDI –0.25, –0.03), glutamine (95% HDI –0.01, 0.11) and glutathione (95% HDI –0.10, 0.11). Occipital lobe GABA and glutamate concentrations were not associated with SSRT in either group. There was no association between neurotransmitter concentrations in any region and carer ratings of challenging behaviour (Supplementary material). There was no association between neurotransmitter concentration and SSRT or trigger failure probability in healthy volunteers.

Discussion

This study has two main findings. First, GABA and glutamate levels are reduced in the right inferior frontal gyrus in patients with bvFTD and PSP, with the GABA deficit persisting after correction for age, sex and atrophy. Second, glutamate and GABA concentrations in the inferior frontal gyrus correlate with disinhibition, as measured by the SSRT.

This finding of a frontal lobe GABA deficit, as measured using ^{1}H-MRS, is supported by other *in vivo* and post-mortem evidence of GABAergic neuron loss in bvFTD and PSP (Ferrer, 1999; Levenga *et al.*, 2014). A GABAergic deficit may contribute to the abnormal functional connectivity associated with cognitive impairment in FTLD syndromes. GABAergic interneurons have widespread functions beyond simple inhibition of excitatory neurons and have a key role in the regulation of oscillatory dynamics (Owens and

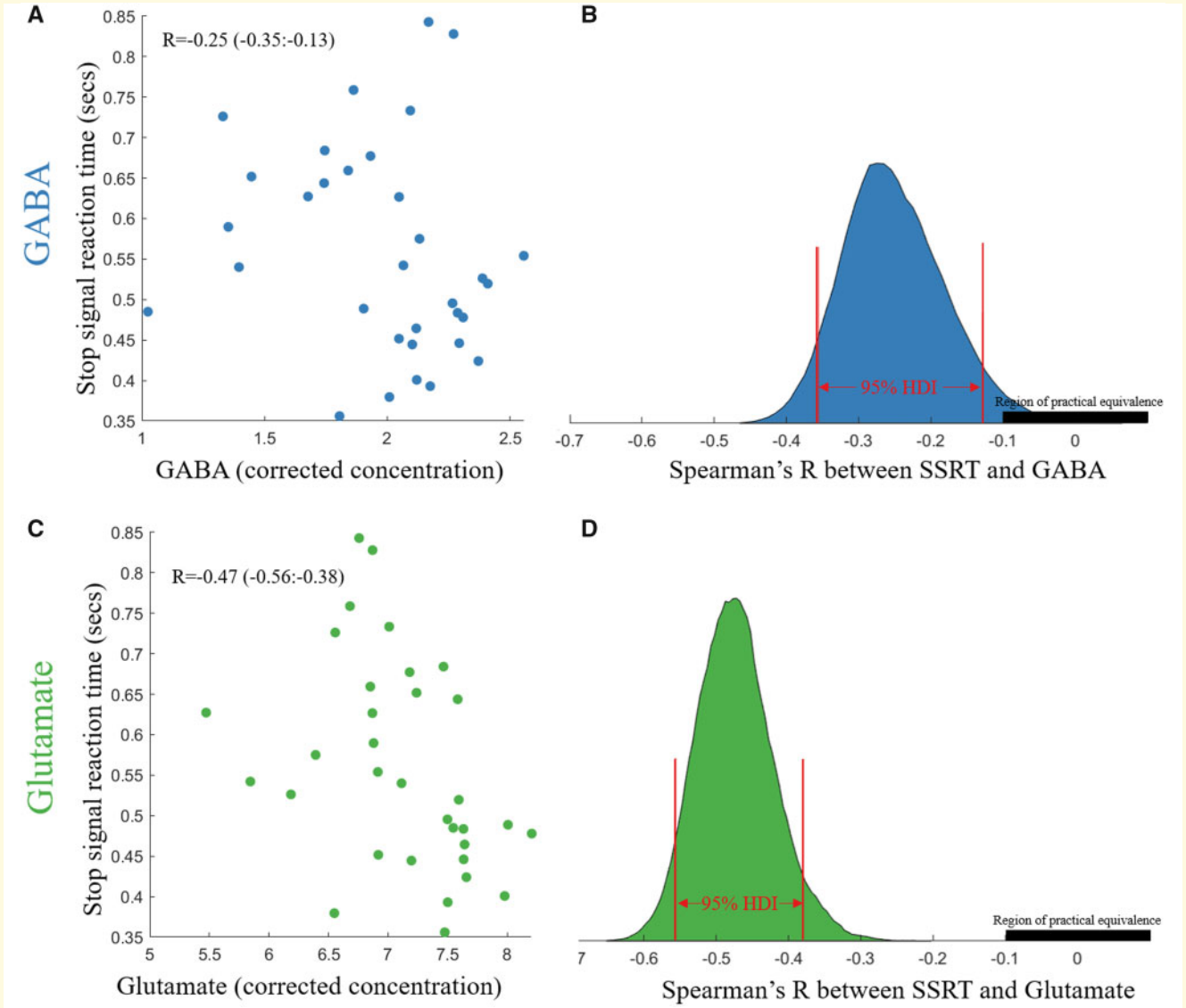

Figure 4 Correlation between neurotransmitters (GABA and glutamate) and SSRT. Results from bvFTD/PSP patients only. (**A**) Scatter plot of mean SSRT and corrected GABA, values in brackets are 95% HDI. (**B**) Histogram of Spearman's correlation values between glutamate (corrected for grey matter, age and sex) and SSRT. Red lines show 95% HDI. Black bar shows region of practical equivalence (–0.1, 0.1). (**C**) Histogram of Spearman's correlation values between glutamate and SSRT. (**D**) Scatter plot of mean SSRT and corrected glutamate.

Kriegstein, 2002; Mann and Paulsen, 2007; Buzsáki and Wang, 2012). Gamma and beta oscillation frequency correlates with cortical GABA concentration (Muthukumaraswamy *et al.*, 2009; Gaetz *et al.*, 2011; Kujala *et al.*, 2015; Baumgarten *et al.*, 2016) and $GABA_A$ receptor density (Kujala *et al.*, 2015), while inhibition of GABAergic receptors reduces oscillatory power and impairs inhibition and working memory (Hines *et al.*, 2013). Beta-power correlates with behavioural disturbance in bvFTD (Hughes *et al.*, 2018), and bvFTD reduces frontotemporal beta-coherence (Hughes and Rowe, 2013). Brain network connectivity of the inferior frontal gyrus is altered in FTLD, during response inhibition (Hughes *et al.*, 2015, 2018) and at rest (Seeley *et al.*, 2009; Sami *et al.*, 2018). These altered oscillations and frequency-bound connectivities in bvFTD may be caused partially by GABAergic deficits. This raises the possibility that correcting GABAergic deficits may restore neurophysiological function and improve cognition and behaviour.

There was no difference in glutamate concentration between patients with bvFTD/PSP and controls after correction for grey and white matter volume loss. However, it would be misleading to conclude that there is no glutamatergic abnormality in FTLD syndromes. Given the high density of glutamatergic neurons in the neocortex, grey matter atrophy typically correlates with the number of glutamatergic neurons in the remaining brain tissue (Harding, 1998; Zarow *et al.*, 2005). Unlike GABA, glutamate has many functions

in the CNS beyond neurotransmission including neuron and glia metabolism and protein synthesis (Hertz, 2013; Zhou and Danbolt, 2014). Only a small proportion of total glutamate acts as a neurotransmitter (Danbolt, 2001). Therefore, it is possible that MRS of glutamate is an indirect measure of glutamatergic neuron density. Correcting MRS measures of glutamate for atrophy would, in this case, have removed a difference between the results obtained from the participants with bvFTD/PSP and controls.

In the right inferior frontal gyrus voxel, both GABA and glutamate concentrations inversely correlated with disinhibited behaviour (impaired response inhibition, as measured by the SSRT). This complements results obtained with other functional imaging modalities, including functional MRI and electrophysiology, that show activation of the right inferior gyrus during the stop-signal task in healthy volunteers (Chambers *et al.*, 2006, 2009; Levy and Wagner, 2011; Aron *et al.*, 2014; Ye *et al.*, 2014; Rae *et al.*, 2015). The right inferior gyrus forms part of a cognitive control network, which is activated during response inhibition and also includes the presupplementary motor area and subthalamic nucleus (Rae *et al.*, 2015). GABA levels in this network, specifically the presupplementary motor area, inversely correlate with SSRT in healthy older adults (Hermans *et al.*, 2018), although Hermans *et al.* used an edited MRS sequence at 3 T and did not measure glutamate levels. One strength of our 7 T MRS study is that both glutamate and GABA can be measured at the same time in the same brain region to study whether both contribute to response inhibition in FTLD syndromes.

There was no association between GABA and glutamate concentrations in the right inferior gyrus and carer ratings of global behavioural impairment. This might be because the right inferior gyrus is just one of many regions associated with the socially disinhibited and challenging behaviours reported by carers. It cannot be assumed that GABA and glutamate concentrations in the right inferior gyrus are representative of the whole frontal lobe. Global behavioural impairment results from pathology in multiple brain regions and impairment in diverse cognitive processes. New sequences measuring glutamate and GABA across the whole brain may show correlation with other behavioural impairments in FTLD syndromes and are a promising area for future research (Moser *et al.*, 2019). In addition, deficits in other neurotransmitter pathways, including serotonin, dopamine, noradrenaline and acetylcholine also contribute to behavioural impairment in FTLD syndromes (Huey *et al.*, 2006; Hughes *et al.*, 2015; Murley and Rowe, 2018). Ultimately, an effective treatment for behavioural symptoms in FTLD may need to restore multiple neurotransmitter pathways.

This study has several limitations. First, MRS measurement accuracy is limited by scan quality (Wilson *et al.*, 2019). To mitigate this, we used a validated sequence, with automated shimming and water and outer volume suppression, that is recommended by recent consensus guidelines (Öz *et al.*, 2020). Our measures of MRS quality, including water linewidth, signal-to-noise ratio and Cramér-Rao lower bounds, were within standard limits for ultra-high field ^{1}H-MRS (Wilson *et al.*, 2019; Öz *et al.*, 2020). In addition, the absence of a group difference in the control region (occipital lobe) suggests the results in the inferior frontal gyrus reflect a true neurotransmitter deficit and not an artefact of movement or another patient-related bias. Second, the spectroscopy regions of interest may have varied between individuals, particularly in the proportion of brain included, because participants had different total brain volumes, but their MRS voxels remained the same size. This was necessary to avoid a confound of varying signal-to-noise but means that the region of interest covers a slightly different proportion of the brain between participants. Third, brain volume within the MRS voxel was lower in the groups of patients with bvFTD/PSP. The GABA and glutamate concentrations of CSF are not high enough to be MRS-visible; therefore, this partial volume effect must be considered when reporting MRS results (Quadrelli *et al.*, 2016; Porges *et al.*, 2017). One approach is to report the relative concentration of the metabolite of interest to an internal standard, using another metabolite such as creatine. However, this was not appropriate in our patient group, where the creatine level is likely also to be abnormal, because of impaired metabolism (Foster *et al.*, 1988; Diehl-Schmid *et al.*, 2007; Pathak *et al.*, 2013). Absolute metabolite correction uses tissue water concentration to 'water scale' metabolite results and some studies enter the voxel fraction of CSF at this stage of analysis. This does not account for voxel differences in grey and white matter volume, which have different GABA and glutamate concentrations (Choi *et al.*, 2006; Gasparovic *et al.*, 2009; Bhattacharyya *et al.*, 2011). We used a generalized linear model, weighted for Cramér-Rao lower bound, to remove the effects of age, sex, grey and white matter from the results. This approach may still bias results if tissue volume closely correlates with metabolite concentration but, if anything, is likely to cause a type II error. Finally, nine patients were unable to complete the stop signal task, due to greater cognitive or motor impairment. This limits the applicability of these results to patients at the later stages of FTLD syndromes.

In conclusion, MRS has potential as an imaging biomarker of degeneration in bvFTD and PSP and possibly other syndromes associated with FTLD. In early bvFTD, there is selective vulnerability of glutamatergic von Economo neurons in the anterior cingulate and frontoinsular cortex (Seeley *et al.*, 2006; Kim *et al.*, 2012). MRS could enable *in vivo* quantification of this glutamatergic deficit, as an adjunct to studies of presymptomatic carriers of causative mutations (Rohrer *et al.*, 2015). Moreover, the association with neurotransmitter deficits and impaired response inhibition leads to the hypothesis that GABA reuptake inhibitors might be used to restore function (Adams *et al.*, 2020). Since behavioural disinhibition is associated with carer stress and poor patient outcome, symptom-oriented clinical trials are required for affected patients within the spectrum of disorders associated with FTLD.

Acknowledgements

We thank the patients and their families and carers, Professor Heathcote, University of Tasmania, for his help with implementing the DMC toolbox, Dr Dinesh Deelchand, University of Minnesota, for his advice and the basis set for 7 T MRS analysis, the radiographers at the Wolfson Brain Imaging Centre, University of Cambridge, and all the staff at the Cambridge Centre for Frontotemporal Dementia and Related Disorders, University of Cambridge. The MRS package was developed by Gülin Öz and Dinesh Deelchand and provided by the University of Minnesota under a C2P agreement. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Funding

This work was funded by the Holt Fellowship (A.G.M.), Wellcome Trust (J.B.R., 103838), a Sir Henry Dale Fellowship from the Wellcome Trust and the Royal Society (C.T.R., 098436/Z/12/B] the Cambridge Trust and Fitzwilliam College, Cambridge (F.H.H.), the Medical Research Council (MR/M008983/1, SUAG/051 G101400), the National Institute for Health Research Cambridge Biomedical Research Centre and Cambridge Brain Bank (146281) and the Cambridge Centre for Parkinson Plus.

Competing interests

J.B.R. serves as an associate editor to *Brain* and is a non-remunerated trustee of the Guarantors of Brain, Darwin College Cambridge, and the PSP Association (UK). He has provided consultancy to Asceneuron, Biogen, UCB and has research grants from AZ-Medimmune, Janssen, Lilly and WAVE as industry partners in the Dementias Platform UK.

Supplementary material

Supplementary material is available at *Brain* online.

References

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. J Neurosci 2020; 40: 1640–9.

Agarwal S, Ahmed RM, D'Mello M, Foxe D, Kaizik C, Kiernan MC, et al. Predictors of survival and progression in behavioural variant frontotemporal dementia. Eur J Neurol 2019; 26: 774–9.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003; 6: 115–6.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004; 8: 170–7.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci 2014; 18: 177–85.

Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet 2015; 386: 1672–82.

Barone P. Neurotransmission in Parkinson's disease: beyond dopamine. Eur J Neurol 2010; 17: 364–76.

Barron HC, Vogels TP, Emir UE, Makin TR, O'Shea J, Clare S, et al. Unmasking latent inhibitory connections in human cortex to reveal dormant cortical memories. Neuron 2016; 90: 191–203.

Baumgarten TJ, Oeltzschner G, Hoogenboom N, Wittsack HJ, Schnitzler A, Lange J. Beta peak frequencies at rest correlate with endogenous GABA+/Cr concentrations in sensorimotor cortex areas. PLoS One 2016; 11: 1–15.

Benussi A, Alberici A, Buratti E, Ghidoni R, Gardoni F, Di Luca M, et al. Toward a glutamate hypothesis of frontotemporal dementia. Front Neurosci 2019; 13: 1–9.

Bhattacharyya PK, Phillips MD, Stone LA, Lowe MJ. In vivo magnetic resonance spectroscopy measurement of gray-matter and white-matter gamma-aminobutyric acid concentration in sensorimotor cortex using a motion-controlled MEGA point-resolved spectroscopy sequence. Magn Reson Imaging 2011; 29: 374–9.

Bowen DM, Procter AW, Mann DMA, Snowden JS, Esiri MM, Neary D, et al. Imbalance of a serotonergic system in frontotemporal dementia: implication for pharmacotherapy. Psychopharmacology (Berl) 2008; 196: 603–10.

Boy F, Evans CJ, Edden RAE, Lawrence AD, Singh KD, Husain M, et al. Dorsolateral prefrontal γ-aminobutyric acid in men predicts individual differences in rash impulsivity. Biol Psychiatry 2011; 70: 866–72.

Burgess PW, Shallice T. The Hayling and Brixton Tests: Thames Valley Test Company: Bury St. Edmonds, UK; 1997.

Buzsáki G, Wang X-J. Mechanisms of gamma oscillations. Annu Rev Neurosci 2012; 35: 203–25.

Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, et al. Executive 'brake failure' following deactivation of human frontal lobe. J Cogn Neurosci 2006; 18: 444–55.

Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 2009; 33: 631–46.

Choi IY, Lee SP, Merkle H, Shen J. In vivo detection of gray and white matter differences in GABA concentration in the human brain. Neuroimage 2006; 33: 85–93.

Coccaro EF, Lee R, Vezina P. Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects. J Psychiatr Res 2013; 47: 1247–53.

Cohen J. A power primer. Psychol Bull 1992; 112: 155–9.

Danbolt NC. Glutamate uptake. Prog Neurobiol 2001; 65: 1–105.

Decker JM, Krüger L, Sydow A, Dennissen FJ, Siskova Z, Mandelkow E, et al. The Tau/A152T mutation, a risk factor for frontotemporal-spectrum disorders, leads to NR 2B receptor-mediated excitotoxicity. EMBO Rep 2016; 17: 552–69.

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. Magn Reson Med 2015; 73: 1718–25.

Dharmadhikari S, Ma R, Yeh CL, Stock AK, Snyder S, Zauber SE, et al. Striatal and thalamic GABA level concentrations play differential roles for the modulation of response selection processes by proprioceptive information. Neuroimage 2015; 120: 36–42.

Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Förstl H, et al. Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. Neurobiol Aging 2007; 28: 42–50.

Edden RAE, Crocetti D, Zhu H, Gilbert DL, Mostofsky SH. Reduced GABA concentration in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2012; 69: 750–3.

Ende G. Proton magnetic resonance spectroscopy: relevance of glutamate and GABA to neuropsychology. Neuropsychol Rev 2015; 25: 315–25.

Ende G, Cackowski S, Van Eijk J, Sack M, Demirakca T, Kleindienst N, et al. Impulsivity and aggression in female BPD and ADHD patients: association with ACC glutamate and GABA concentrations. Neuropsychopharmacology 2016; 41: 410–8.

Ernst T, Chang L, Melchor R, Mark Mehringer C. Frontotemporal dementia and early Alzheimer disease: differentiation with frontal lobe H-1 MR spectroscopy. Radiology 1997; 203: 829–36.

Ferrer I. Neurons and their dendrites in frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10: 55–60.

Foster NL, Gilman S, Berent S, Morin EM, Brown MB, Koeppe RA. Cerebral hypometabolism in progressive supranuclear palsy studied with positron emission tomography. Ann Neurol 1988; 24: 399–406.

Foster NL, Minoshima S, Johanns J, Little R, Heumann ML, Kuhl DE, et al. PET measures of benzodiazepine receptors in progressive supranuclear palsy. Neurology 2000; 54: 1768–73.

Francis PT, Holmes C, Webster MT, Stratmann GC, Procter AW, Bowen DM. Preliminary neurochemical findings in non-Alzheimer dementia due to lobar atrophy. Dementia 1993; 4: 172–7.

Frangou P, Emir UE, Karlaftis VM, Nettekoven C, Hinson EL, Larcombe S, et al. Learning to optimize perceptual decisions through suppressive interactions in the human brain. Nat Commun 2019; 10: 1–12.

Fujihara K, Narita K, Suzuki Y, Takei Y, Suda M, Tagawa M, et al. Relationship of γ-aminobutyric acid and glutamate + glutamine concentrations in the perigenual anterior cingulate cortex with performance of Cambridge Gambling Task. Neuroimage 2015; 109: 102–8.

Gaetz W, Edgar JC, Wang DJ, Roberts TPL. Relating MEG measured motor cortical oscillations to resting γ-Aminobutyric acid (GABA) concentration. Neuroimage 2011; 55: 616–21.

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. Nat Med 2014; 20: 1444–51.

Gasparovic C, Yeo R, Mannell M, Ling J, Elgie R, Phillips J, et al. Neurometabolite concentrations in gray and white matter in mild traumatic brain injury: an 1H-magnetic resonance spectroscopy study. J Neurotrauma 2009; 26: 1635–43.

Gazzina S, Respondek G, Compta Y, Allinson KS, Spillantini MG, Molina-Porcel L, et al. Neuropathological validation of the MDS-PSP criteria with PSP and other frontotemporal lobar degeneration. bioRxiv 2019: 520510. doi: 10.1101/520510.

Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis. Bota Racon, FL: CRC Press; 2013.

Gerstenecker A, Duff K, Mast B, Litvan I. Behavioral abnormalities in progressive supranuclear palsy. Psychiatry Res 2013; 210: 1205–10.

Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007; 130: 1552–65.

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. Mov Disord 2019; 34: 1228–32.

Gruetter R, Tkáč I. Field mapping without reference scan using asymmetric echo-planar techniques. Magn Reson Med 2000; 43: 319–23.

Harding A. Variation in hippocampal neuron number with age and brain volume. Cereb Cortex 1998; 8: 710–8.

Heathcote A, Lin YS, Reynolds A, Strickland L, Gretton M, Matzke D. Dynamic models of choice. Behav Res Methods 2019; 51: 961–85.

Heathcote A, Popiel SJ, Mewhort DJK. Analysis of response time distributions: an example using the stroop task. Psychol Bull 1991; 109: 340–7.

Henderson JM, Carpenter K, Cartwright H, Halliday GM. Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications. Brain 2000; 123: 1410–21.

Hermans L, Leunissen I, Pauwels L, Cuypers K, Peeters R, Puts NAJ, et al. Brain GABA levels are associated with inhibitory control deficits in older adults. J Neurosci 2018; 38: 7844–51.

Hertz L. The glutamate-glutamine (GABA) cycle: importance of late postnatal development and potential reciprocal interactions between biosynthesis and degradation. Front Endocrinol (Lausanne) 2013; 4: 1–16.

Hines RM, Hines DJ, Houston CM, Mukherjee J, Haydon PG, Tretter V, et al. Disrupting the clustering of GABAA receptor? 2 subunits in the frontal cortex leads to reduced?-power and cognitive deficits. Proc Natl Acad Sci USA 2013; 110: 16628–33.

Hoerst M, Weber-Fahr W, Tunc-Skarka N, Ruf M, Bohus M, Schmahl C, et al. Correlation of glutamate levels in the anterior cingulate cortex with self-reported impulsivity in patients with borderline personality disorder and healthy controls. Arch Gen Psychiatry 2010; 67: 946–54.

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. Mov Disord 2017; 32: 853–64.

Hong D, Rohani Rankouhi S, Thielen J, van Asten JJA, Norris DG. A comparison of sLASER and MEGA-sLASER using simultaneous interleaved acquisition for measuring GABA in the human brain at 7T. PLoS One 2019; 14: e0223702.

Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. Neurology 2006; 66: 17–22.

Hughes L E, Rowe J B.The impact of neurodegeneration on network connectivity: a study of change detection in frontotemporal dementia. J Cognitive Neurosci 2013; 25: 802–13. doi: 10.1162/jocn_a_00356.

Hughes LE, Rittman T, Regenthal R, Robbins TW, Rowe JB. Improving response inhibition systems in frontotemporal dementia with citalopram. Brain 2015; 138: 1961–75.

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

Husain M. Transdiagnostic neurology: neuropsychiatric symptoms in neurodegenerative diseases. Brain 2017; 140: 1535–6.

Ip IB, Emir UE, Parker AJ, Campbell J, Bridge H. Comparison of neurochemical and BOLD signal contrast response functions in the human visual cortex. J Neurosci 2019; 39: 7968–75.

Jiang S, Wen N, Li Z, Dube U, Del Aguila J, Budde J, et al. Integrative system biology analyses of CRISPR-edited iPSC-derived neurons and human brains reveal deficiencies of presynaptic signaling in FTLD and PSP. Transl Psychiatry 2018; 8: 265. doi: 10.1038/s41398-018-0319-z.

Joers JM, Deelchand DK, Lyu T, Emir UE, Hutter D, Gomez CM, et al. Neurochemical abnormalities in premanifest and early spinocerebellar ataxias. Ann Neurol 2018; 83: 816–29.

Kanazawa I, Kwak S, Sasaki H, Muramoto O, Mizutani T, Hori A, et al. Studies on neurotransmitter markers of the basal ganglia in Pick's disease, with special reference to dopamine reduction. J Neurol Sci 1988; 83: 63–74.

Kandimalla R, Reddy PH. Therapeutics of Neurotransmitters in Alzheimer's Disease. J Alzheimers Dis 2017; 57: 1049–69.

Kim EJ, Sidhu M, Gaus SE, Huang EJ, Hof PR, Miller BL, et al. Selective frontoinsular von economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. Cereb Cortex 2012; 22: 251–9.

Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008; 131: 2957–68.

Knopman DS, Weintraub S, Pankratz VS. Language and behavior domains enhance the value of the clinical dementia rating scale. Alzheimers Dement 2011; 7: 293–9.

Kolasinski J, Logan JP, Hinson EL, Manners D, Divanbeighi Zand AP, Makin TR, et al. A mechanistic link from GABA to cortical architecture and perception. Curr Biol 2017; 27: 1685–91.e3.

Kruschke JK. Rejecting or accepting parameter values in Bayesian estimation. Adv Methods Pract Psychol Sci 2018; 1: 270–80.

Kujala J, Jung J, Bouvard S, Lecaignard F, Lothe A, Bouet R, et al. Gamma oscillations in V1 are correlated with GABAA receptor density: a multi-modal MEG and Flumazenil-PET study. Sci Rep 2015; 5: 16347.

Landwehrmeyer B, Palacios JM. Alterations of neurotransmitter receptors and neurotransmitter transporters in progressive supranuclear palsy. J Neural Transm Suppl 1994; 42: 229–46.

Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, Rodríguez PV, Wilcox A, Wehmann E, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. Brain 2017; 140: 1792–807.

Lansdall CJ, Coyle-Gilchrist ITS, Vázquez Rodríguez P, Wilcox A, Wehmann E, Robbins TW, et al. Prognostic importance of apathy in syndromes associated with frontotemporal lobar degeneration. Neurology 2019; 92: E1547–E1557.

Lee R, Chong B, Coccaro E. Growth hormone responses to GABAB receptor challenge with baclofen and impulsivity in healthy control and personality disorder subjects. Psychopharmacology (Berl) 2011; 215: 41–8.

Lee R, Petty F, Coccaro EF. Cerebrospinal fluid GABA concentration: relationship with impulsivity and history of suicidal behavior, but not aggression, in human subjects. J Psychiatr Res 2009; 43: 353–9.

Leuzy A, Zimmer ER, Dubois J, Pruessner J, Cooperman C, Soucy JP, et al. In vivo characterization of metabotropic glutamate receptor type 5 abnormalities in behavioral variant FTD. Brain Struct Funct 2016; 221: 1387–402.

Levenga J, Krishnamurthy P, Rajamohamedsait H, Wong H, Franke TF, Cain P, et al. Tau pathology induces loss of GABAergic interneurons leading to altered synaptic plasticity and behavioral impairments. Acta Neuropathol Commun 2014; 2: 34.

Levy BJ, Wagner AD. Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. Ann N Y Acad Sci 2011; 1224: 40–62.

Levy R, Ruberg M, Herrero MT, Villares J, Javoy-Agid F, Agid Y, et al. Alterations of GABAergic neurons in the basal ganglia of patients with progressive supranuclear palsy: an in situ hybridization study of GAD67 messenger RNA. Neurology 1995; 45: 127–34.

Li JN, Liu XL, Li L. Prefrontal GABA and glutamate levels correlate with impulsivity and cognitive function of prescription opioid addicts: a 1H-magnetic resonance spectroscopy study. Psychiatry Clin Neurosci 2020; 74: 77–83.

Li X, Wang Z, Tan L, Wang Y, Lu C, Chen R, et al. Correcting miR92a-vGAT-mediated GABAergic dysfunctions rescues human tau-induced anxiety in mice. Mol Ther 2017; 25: 140–52.

Ly A, Boehm U, Heathcote A, Turner BM, Forstmann B, Marsman M, et al. A flexible and efficient hierarchical Bayesian approach to the exploration of individual differences in cognitive-model-based neuroscience. In: Moustafa AA, editor. Computational models of brain and behavior. Chichester, UK: John Wiley & Sons, Ltd; 2018. p. 467–479.

Mann EO, Paulsen O. Role of GABAergic inhibition in hippocampal network oscillations. Trends Neurosci 2007; 30: 343–9.

Martyr A, Boycheva E, Kudlicka A. Assessing inhibitory control in early-stage Alzheimer's and Parkinson's disease using the Hayling Sentence Completion Test. J Neuropsychol 2019; 13: 67–81.

Matzke D, Curley S, Gong CQ, Heathcote A. Inhibiting responses to difficult choices. J Exp Psychol Gen 2019; 148: 124–42.

Matzke D, Dolan CV, Logan GD, Brown SD, Wagenmakers EJ. Bayesian parametric estimation of stop-signal reaction time distributions. J Exp Psychol Gen 2013; 142: 1047–73.

Matzke D, Hughes M, Badcock JC, Michie P, Heathcote A. Failures of cognitive control or attention? The case of stop-signal deficits in schizophrenia. Atten Percept Psychophys 2017; 79: 1078–86.

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. Int J Geriat Psychiatry 2006; 21: 1078–85.

Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia. Neurology 2010; 74: 1591–7.

Moser P, Hingerl L, Strasser B, Považan M, Hangel G, Andronesi OC, et al. Whole-slice mapping of GABA and GABA + at 7T via adiabatic MEGA-editing, real-time instability correction, and concentric circle readout. Neuroimage 2019; 184: 475–89.

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 2020a; 143: 1555–71.

Murley AG, Rouse MA, Coyle-Gilchrist I, Simon P, Li W, Wiggins J, et al. Predicting loss of independence and mortality in frontotemporal lobar degeneration syndromes. medRxiv. 2020b: 02.11.20022061. doi: 10.1101/2020.02.11.20022061.

Murley AG, Rowe JB. Neurotransmitter deficits from fronto temporal lobar degeneration. Brain 2018; 141: 1263–85.

Muthukumaraswamy SD, Edden R A E, Jones DK, Swettenham JB, Singh KD. Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc Natl Acad Sci USA 2009; 106: 8356–61.

Naaijen J, Lythgoe DJ, Amiri H, Buitelaar JK, Glennon JC. Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: a review of magnetic resonance spectroscopy studies. Neurosci Biobehav Rev 2015; 52: 74–88.

Nichols T, Brett M, Andersson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. Neuroimage 2005; 25: 653–60.

O'Callaghan C, Hodges JR, Hornberger M. Inhibitory dysfunction in frontotemporal dementia: a review. Alzheimer Dis Assoc Disord 2013a; 27: 102–8.

O'Callaghan C, Naismith SL, Hodges JR, Lewis SJG, Hornberger M. Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia. Cortex 2013b; 49: 1833–43.

Owens DF, Kriegstein AR. Is there more to GABA than synaptic inhibition? Nat Rev Neurosci 2002; 3: 715–27.

Öz G, Deelchand DK, Wijnen JP, Mlynárik V, Xin L, Mekle R, et al. Advanced single voxel 1 H magnetic resonance spectroscopy techniques in humans: experts' consensus recommendations. NMR Biomed 2020; 65: e4236. doi: 10.1002/nbm.4236.

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. Magn Reson Med 2011; 65: 901–10.

Passamonti L, Lansdall CJ, Rowe JB. The neuroanatomical and neurochemical basis of apathy and impulsivity in frontotemporal lobar degeneration. Curr Opin Behav Sci 2018; 22: 14–20.

Pathak D, Berthet A, Nakamura K. Energy failure: does it contribute to neurodegeneration? Ann Neurol 2013; 74: 506–16.

Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. Brain 2017; 140: 3329–45.

Porges EC, Woods AJ, Lamb DG, Williamson JB, Cohen RA, Edden RAE, et al. Impact of tissue correction strategy on GABA-edited MRS findings. Neuroimage 2017; 162: 249–56.

Prisciandaro JJ, Tolliver BK, Prescot AP, Brenner HM, Renshaw PF, Brown TR, et al. Unique prefrontal GABA and glutamate disturbances in co-occurring bipolar disorder and alcohol dependence. Transl Psychiatry 2017; 7: 1–8.

Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10: 80–4.

Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993; 30: 672–9.

Quadrelli S, Mountford C, Ramadan S. Hitchhiker's guide to voxel segmentation for partial volume correction of in vivo magnetic resonance spectroscopy. Magn Reson Insights 2016; 9: MRI.S32903.

Rae CL, Hughes LE, Anderson MC, Rowe JB. The prefrontal cortex achieves inhibitory control by facilitating subcortical motor pathway connectivity. J Neurosci 2015; 35: 786–94.

Ranasinghe KG, Rankin KP, Pressman PS, Perry DC, Lobach IV, Seeley WW, et al. Distinct subtypes of behavioral variant frontotemporal dementia based on patterns of network degeneration. JAMA Neurol 2016; 73: 1078–88.

Rascovsky 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 2011; 134: 2456–77.

Riedl L, Mackenzie IR, Förstl H, Kurz A, Diehl-Schmid J. Frontotemporal lobar degeneration: current perspectives. Neuropsychiatr Dis Treat 2014; 10: 297–310.

Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 2015; 14: 253–62.

Rowe JB. Parkinsonism in frontotemporal dementias. Int Rev Neurobiol 2019; 149: 249–75.

Royall DR. The FAB: a frontal assessment battery at bedside [1]. Neurology 2001; 57: 565.

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: 2500–10.

Sarac H, Zagar M, Davorka V, Henigsberg N, Bilic E, Pavlisa G, et al. Magnetic resonance imaging and magnetic resonance spectroscopy in a patient with amyotrophic lateral sclerosis and frontotemporal dementia. Coll Antropol 2008; 32: 205–10.

Schmaal L, Goudriaan AE, van der Meer J, van den Brink W, Veltman DJ. The association between cingulate cortex glutamate concentration and delay discounting is mediated by resting state functional connectivity. Brain Behav 2012a; 2: 553–62.

Schmaal L, Veltman DJ, Nederveen A, Van Den Brink W, Goudriaan AE. N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: a randomized crossover magnetic resonance spectroscopy study. Neuropsychopharmacology 2012b; 37: 2143–52.

Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 2006; 60: 660–7.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009; 62: 42–52.

Silveri MM, Sneider JT, Crowley DJ, Covell MJ, Acharya D, Rosso IM, et al. Frontal lobe γ-aminobutyric acid levels during adolescence: associations with impulsivity and response inhibition. Biol Psychiatry 2013; 74: 296–304.

Skippen P, Matzke D, Heathcote A, Fulham WR, Michie P, Karayanidis F. Reliability of triggering inhibitory process is a better predictor of impulsivity than SSRT. Acta Psychol (Amst) 2019; 192: 104–17.

Suzuki M, Desmond TJ, Albin RL, Frey K. A. Cholinergic vesicular transporters in progressive supranuclear palsy. Neurology 2002; 58: 1013–8.

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, et al. Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 2009; 29: 12675–85.

Tkac I, Starcuk Z, Choi I-Y, Gruetter R. In vivo1H NMR spectroscopy of rat brain at 1 ms echo time. Magn Reson Med 1999; 41: 649–56.

Torralva T, Roca M, Gleichgerrcht E, López P, Manes F. INECO Frontal Screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia. J Int Neuropsychol Soc 2009; 15: 777–86.

Tsvetanov KA, Ye Z, Hughes L, Samu D, Treder MS, Wolpe N, et al. Activity and connectivity differences underlying inhibitory control across the adult life span. J Neurosci 2018; 38: 7887–900.

Verbruggen F, Aron AR, Band GPH, Beste C, Bissett PG, Brockett AT, et al. A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. Elife 2019; 8: 1–26.

Vermeiren Y, Le Bastard N, Van Hemelrijck A, Drinkenburg WH, Engelborghs S, De Deyn PP. Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia. Alzheimer's Dement 2013; 9: 488–98.

Warmus BA, Sekar DR, McCutchen E, Schellenberg GD, Roberts RC, McMahon LL, et al. Tau-mediated NMDA receptor impairment underlies dysfunction of a selectively vulnerable network in a mouse model of frontotemporal dementia. J Neurosci 2014; 34: 16482–95.

Wear HJ, Wedderburn CJ, Mioshi E, Williams-Gray CH, Mason SL, Barker R. A, et al. The Cambridge behavioural inventory revised. Dement Neuropsychol 2008; 2: 102–7.

Wilson M, Andronesi O, Barker PB, Bartha R, Bizzi A, Bolan PJ, et al. Methodological consensus on clinical proton MRS of the brain: review and recommendations. Magn Reson Med 2019; 82: 527–50.

Yasen AL, Smith J, Christie AD. Reliability of glutamate and GABA quantification using proton magnetic resonance spectroscopy. Neurosci Lett 2017; 643: 121–4.

Ye Z, Altena E, Nombela C, Housden CR, Maxwell H, Rittman T, et al. Selective serotonin reuptake inhibition modulates response inhibition in Parkinson's disease. Brain 2014; 137: 1145–55.

Zarow C, Vinters HV, Ellis WG, Weiner MW, Mungas D, White L, et al. Correlates of hippocampal neuron number in Alzheimer's disease and ischemic vascular dementia. Ann Neurol 2005; 57: 896–903.

Zhang J, Rittman T, Nombela C, Fois A, Coyle-Gilchrist I, Barker RA, et al. Different decision deficits impair response inhibition in progressive supranuclear palsy and Parkinson's disease. Brain 2016a; 139: 161–73.

Zhang Z, Fan Q, Bai Y, Wang Z, Zhang H, Xiao Z. Brain gamma-aminobutyric acid (GABA) concentration of the prefrontal lobe in unmedicated patients with Obsessivecompulsive disorder: a research of magnetic resonance spectroscopy. Shanghai Arch Psychiatry 2016b; 28: 263–70.

Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. J Neural Transm 2014; 121: 799–817.