

GABAergic modulation of cortical oscillations during motor learning in people with frontotemporal lobar degeneration.

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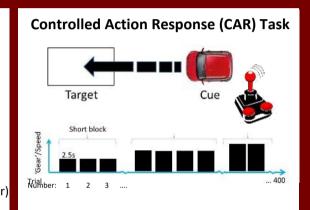
Cambridge Centre for Frontotemporal Dementia

Introduction

Patients with frontotemporal lobar degeneration (FTLD) are typically impulsive and disinhibited, with an impaired ability to adapt and update behaviours in response to a changing environment^{1,3} We use Magnetoencephalography with a novel visuo-motor learning task (CAR Task) to understand these abnormal behaviours in the context of impaired GABAergic neurotransmission, and potential restoration by GABA-reuptake inhibition using Tiagabine (TGB, GAT1 transporter inhibitor).

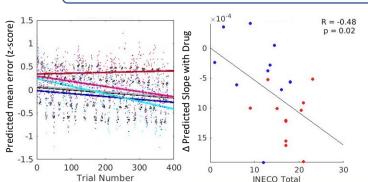
Methods

- Design: Double blind placebo controlled cross over design. 10mg Tiagabine / placebo
- Participants: 11 bvFTD, 11 PSP, 18 healthy controls (mean age 66, SD 7.5)
- MEG Sensor: Individual linear models of trial covariates. ANOVA of group and drug effects.
- MEG Source of Beta: LCMV Beamformer & connectivity (amplitude envelope correlations) using Desikan-Killiany Atlas (5000 permutations, p<0.05 corr)



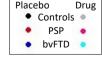
Behaviour: Linear Mixed Model

MeanError ~ 1 + TrialNumber*DrugSession + (1+Gear|Subject)', FitMethod', 'REML'



Performance over trials was improved on drug for patients.

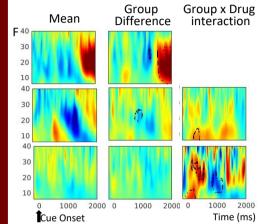
Improvement on drug correlated with INECO – patients with better cognitive performance showed more improvement on drug.



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MEG Power spectra of behavioural covariates



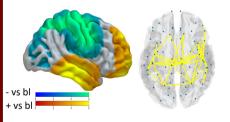
Movement time related spectra. ERD/ERS is diminished in patients vs controls

Mean Error: Better accuracy associated with greater ERD, reduced in patients. TGB increases alpha power in bvFTD but decreases it in PSP, with greater accuracy.

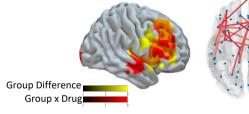
Trial No. TGB enhances ERD in PSP, but elevates Beta power in bvFTD as trials progressed.

--- p<0.001 FWE cluster corrected

LCMV Beamformer & Amplitude Envelope Correlation of beta



Group Mean: Task related beta modulation vs baseline, and mean network connectivity



Group x Drug Interaction: TGB enhances ERD in right IFG, and enhanced frontal connectivity in patients.

Discussion

GABA modulation improved motor learning in bvFTD and PSP patients, by differential enhancement of Beta power, within a primary source of right prefrontal cortex. This is a key region in a frontal network for behavioural control and inhibition, and a region known for loss of GABA neurotransmission in FTLD^{2,3}.

References

1. Hughes et al., (2018) Brain, 2. Murley et al., (2018) Brain 3. Murley et al., (2020) Brain

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Thank you to the study participants and their families and carers. This study was funded by the Wellcome Trust and the NIHR Cambridge Biomedical Research Centre.