Early Detection of FTD & MND (EDoF):

A Digital Biomarker Study

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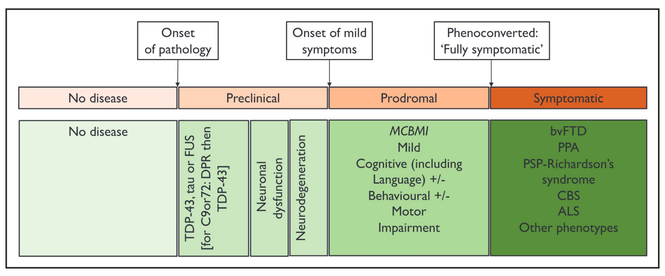
Background

The subtle and heterogeneous changes that emerge in the prodromal stages of FTD and MND are encompassed by the label **'Mild Cognitive, Behaviour and Motor Impairment' (MCBMI)**. This disease stage is of increasing interest as trials look to enrol participants earlier. My ABN fellowship uses digital technologies to sensitively detect and quantify changes across these domains.



Three cohorts are being studied:

1) **EDoF-N**: a control cohort from the general population aged 20-80 years
2) **EDoF-P**: a presymptomatic cohort of C9orf72, GRN and MAPT mutation carriers from the Genetic FTD Initiative (GENFI)
3) **EDoF-S**: a symptomatic cohort including those with behavioural variant FTD (bvFTD) and MND

Participants complete the EDoF protocol consisting of 4 weeks of testing using 2 wearable devices, 2 computerised tests, and 2 non-invasive muscle tests.

- **Wearables:** Fitbit Charge device, AX6 Inertial Measurement Unit (IMU)
- **Computerised tests:** *Ignite*, an iPad based cognitive test, and the BRAIN keyboard tapping test
- **Muscle tests:** Muscle ultrasound and surface EMG

The EDoF Protocol

Muscle Ultrasound (US) and High Density Surface EMG (HDSEMG)



- HDSEMG – collaboration with Dr James Bashford (KCL) – biceps brachii, first dorsal interosseous (FDI) and tibialis anterior (TA) on dominant side at rest (5 mins) and with voluntary activity (1 min)
- Muscle US – collaboration with Prof Emma Hodson-Tole (MMU) – 1 min recordings of the tongue and bilateral T5 paraspinals, biceps brachii, FDI, TA and medial gastrocnemius
- Outcomes include fasciculation frequency and amplitude
- Other measures include echointensity and echovariance (using US), and estimated motor unit number index (HDSEMG)

BRAIN keyboard tapping

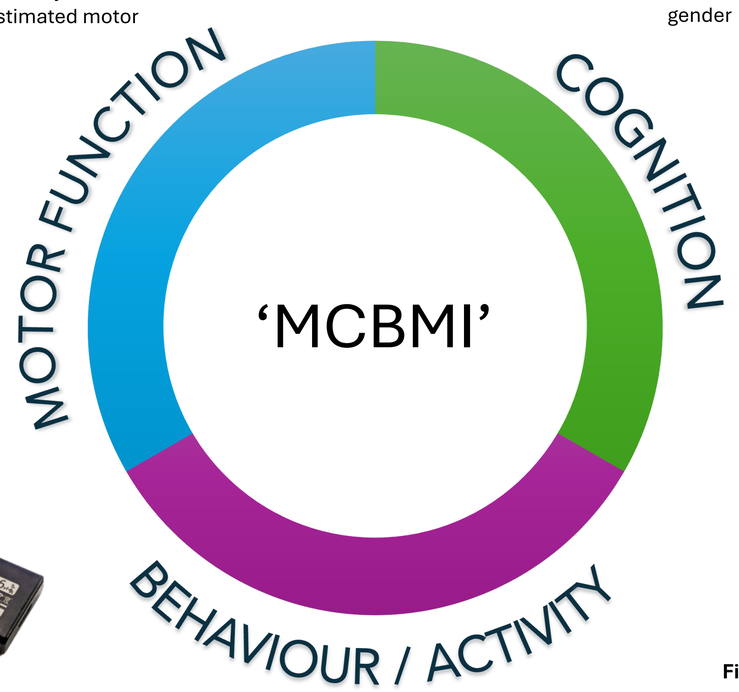


- Collaboration with Prof Alastair Noyce (QMUL)
- Performed 4 x over 4 weeks
- Outputs include measures of speed of tapping, decrement and accuracy of key presses

Inertial Measurement Unit (IMU)



- Axivity AX6 worn for 7 days on the lower back
- Outputs include:
  - Macro gait characteristics
    - Volume, pattern and variability e.g. total walking time per day, mean walking bout length, variability of bout length
  - Micro gait characteristics
    - Measures of rhythm, asymmetry, pace, variability, and postural control



***Ignite*, an iPad based cognitive app**



- 20-25 min test of cognitive function
- Repeated 4 x over 4 weeks to examine practice effects
- 7 tests of executive function, 4 of processing speed, 2 of social cognition, 1 test of visuospatial function, 1 of semantic knowledge, and 1 of calculation
- Speed-accuracy trade off scores are calculated by dividing the total correct by average response time
- Outcomes are converted to z-scores using normative data from >2000 individuals, adjusting for age, sex and gender

Fitbit Charge



- Worn for 28 days
- Outputs include:
  - Mean and standard deviation of total daily step count
  - Peak 1 min and 30 min cadence
  - Measures of circadian rhythm e.g. interdaily stability and intraday variability

Methods: *Ignite* analysis

- 73 GENFI participants with available plasma neurofilament light chain (NfL) data were included in this preliminary *Ignite* analysis.
- 47 were mutation carriers (29 C9orf72, 16 MAPT, 2 GRN), and 26 were mutation negative controls.
- Carriers were split into 3 groups:
  - **SCs (Symptomatic Carriers):** 7 carriers met bvFTD diagnostic criteria.
  - **PCs (Prodromal Carriers):** 10 were deemed prodromal on the basis of a CDR® plus NACC FTLD global score of 0.5 and raised plasma NfL. Raised NfL was defined as ≥ 13.6pg/ml, as this level is associated with increased risk of phenoconversion over 2 years (Rojas et al 2021).
  - **ACs (Asymptomatic Carriers):** The remaining 30 mutation carriers.
- Outcome metrics were generated and converted to z-scores, adjusting for age, sex and gender.
- A mixed model for repeated measures (MMRM) analysis was performed in Stata/MP v17.0 to examine change scores over time.

Results: Prodromal carriers show altered practice effects in a burst testing protocol using *Ignite*

	Controls	ACs	PCs	SCs
Number at baseline	26	30	10	7
Age in years, mean (sd)	49.7 (13.9)	40.7 (9.2)	53.4 (9.2)	63.7 (3.5)
Female, n (%)	13 (50%)	14 (47%)	6 (60%)	2 (29%)
Education in years, mean (sd)	16 (2.3)	15.5 (2.1)	15 (2.6)	12.9 (3.0)
Plasma NfL in pg/ml, mean (sd)	11.8 (8.3)	8.9 (2.7)	24.9 (9.1)	26.4 (16.0)
Completed all 4 assessments	77% (20)	77% (23)	80% (8)	57% (4)
Completed ≥ 3 assessments	92% (24)	93% (28)	90% (9)	86% (6)
Completed ≥ 2 assessments	100% (26)	100% (30)	90% (9)	100% (7)

Table 1: Baseline characteristics of the four groups

- Controls and ACs both showed statistically significant improvements ($p<0.05$) across all 16 tests between timepoint 1 and 4. Controls tended to improve the most between the 1st and 2nd timepoints, with diminishing benefit of further timepoints thereafter. ACs had a flatter trajectory of change and benefitted from a 4th timepoint.
- PCs showed significant improvements across 10/16 tests. SCs showed significant improvements on only 2/16 tests. PCs and SCs tended to have maximal improvement between the 2nd and 3rd timepoint and did not benefit from a 4th timepoint.
- Because of these varying trajectories of change, maximal differences between groups were observed in a cross-sectional analysis at timepoint 2.

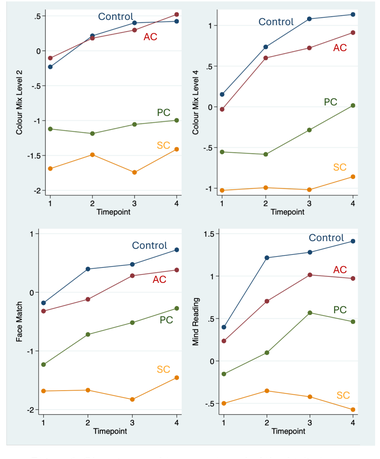


Figure 1: Change over 4 timepoints in 4 of the *Ignite* tests: Colour Mix Level 2 and 4 *(processing speed and executive function)*, and Face Match and Mind Reading *(social cognition)*.

Results: The *Ignite* composite cognitive score negatively correlates with plasma NfL

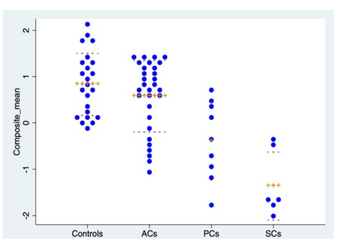


Figure 2: Dotplot of composite *Ignite* score by group at timepoint 2

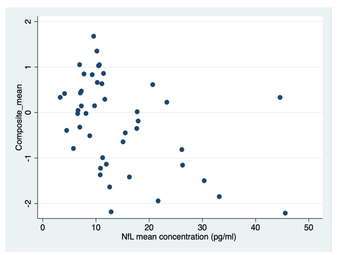


Figure 3: Scatter plot of composite *Ignite* score against plasma NfL concentration

- A composite cognitive score was generated by averaging the z-scored outcomes of the 16 *Ignite* tests.
- Significant differences in the composite cognitive score were observed between PCs and Controls, and between SCs and Controls, at every timepoint.
- There were no significant differences when comparing ACs with Controls, but a trend towards worse performance was observed in a subset of ACs (Fig 2).
- These 6 ACs had a significantly raised plasma NfL compared to ACs with a higher cognitive composite score (mean 11.0 (sd 3.12) vs 8.3 (sd 2.4), $p=0.02$), suggesting that *Ignite* is capturing early cognitive change.
- Plasma NfL was found to negatively correlate with the composite cognitive score (Spearman's rho = -0.55, $p<0.001$) (Fig 3).

Conclusions

- Early data from the EDoF-P (GENFI) cohort demonstrates significant differences in cognition in the prodromal FTD mutation carriers compared to controls, detected using the iPad test *Ignite*.
- Analysis of IMU and Fitbit data is underway to explore gait and activity, including circadian rhythm and sleep. Muscle ultrasound and high-density surface EMG quantify muscle changes including fasciculations.
- Outcomes will be correlated with clinical scales, structural imaging, and fluid biomarkers, with results contributing to a multi-stage and subtype-specific model of genetic FTD and MND.
- These digital biomarkers may be used in clinical trials: as screening criteria to identify prodromal participants, and as outcome measures that are sensitive to early clinical change.

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GENFI GENETIC FTD INITIATIVE
BLUEFIELD PROJECT Curing FTD
Patrick Berthoud Charitable Trust
ABN Clinical Research Training Fellowship