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Frontotemporal Dementias

PB1.1 / P001

Cross-Linguistic Assessment Of Oral Production In Primary Progressive Aphasia: Insight From English, Chinese, and Italian.

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Session 01 .1 - Diversity & Epidemiology (1) - Exploring Cross-Linguistic Variations in Language and Dementia, september 19, 2024, 11:00 - 11:45

State of the Art: The diagnostic criteria of Primary Progressive Aphasia (PPA) are primarily based on English-speaking patients' studies [1]. There is a growing need to take into account the possible impact of linguistic diversity. Our study aims to: (1)describe the speech/language profile of individuals with PPA, speaking English, Chinese, and Italian; (2)identify shared and language-specific diagnostic features.
Methodology: 129 participants were included in the study, 90 PPA (30 for each language) and 39 matched healthy controls (HC; 13 for each language). Speech samples, collected using the Picnic picture [2], underwent CLAN analysis to characterize phonetic-phonological, lexico-semantic, morpho-syntactic, and discourse-pragmatic domains. To identify impaired shared (in all three languages) and language-specific (impaired only in one/two languages) features in PPA, non-parametric tests were used separately for each language. Logistic regressions were adopted to investigate whether language-specific features significantly increase the ability of shared features to distinguish between PPA and controls separately for each language.
Results: Some features were impaired in PPA vs HC in all languages: the proportion of empty pauses, the mean length of utterances, the number of words/minute, and repetitions (all $p<0.005$). Specific features, belonging to phonological and lexico-semantic domains, increased diagnostic accuracy only for Italian patients ($p=0.001$).
Conclusion: Shared language features, reflecting the core language impairment of PPA, well-differentiated PPA from controls in all three languages. Only for Italian, language-specific features significantly improved the classification, suggesting the need to further explore cross-linguistic differences and their diagnostic implications.

[1] Gorno-Tempini et al., Neurology (2011): 76 1006-1014.
[2] Kertesz (1982)

PB1.2 / P002

Bilingualism contributes to resilience in AD but not FTLD syndromes

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Session 01 .1 - Diversity & Epidemiology (1) - Exploring Cross-Linguistic Variations in Language and Dementia, september 19, 2024, 11:00 - 11:45

State of the art: Previous studies on bilingualism's effects in FTD and Alzheimer's spectrum disorders are mixed. There remains an unclear role of bilingualism in preventing the onset of disease (resistance) and in mitigating effects in the presence of aging or neuropathological changes (resilience). The effects of bilingualism may depend on the underlying neuropathology, and this remains unexplored.

Methodology: We leveraged a cohort of 484 patients (404 monolingual and 80 bilingual speakers) with FTLD CDR box scores, a measure of clinical disease severity, and plasma neurofilament light chain (NfL) levels, a marker of neurodegeneration, at one or more timepoints. The patients were classified into four groups (healthy controls, Alzheimer's disease (AD), 4-repeat (4R) tau, and TAR DNA-binding protein 43 (TDP-43)) based on autopsy-confirmed (N=302) or predicted (N=182) neuropathology. We used linear mixed-effects models to estimate the longitudinal change in FTLD CDR box scores.

Results: Bilingual speakers with AD pathology had a slower rate of change in FTLD CDR box scores compared to monolingual speakers when controlled for NfL levels as a proxy of neurodegeneration. This effect was not seen in healthy controls, tau or TDP pathology groups.

Conclusions: These results point towards a protective, disease-specific effect of bilingualism in AD, supporting a role of bilingualism in resilience. A study strength is its exploration of bilingualism's effects in a largely autopsy-confirmed cohort with distinct AD/FTLD neuropathologies. The study emphasizes the need to explore bilingualism within specific AD/FTLD subtypes to clarify the mechanism by which it contributes to cognitive and brain resilience.

PB1.3 / P003

Insights into Dyslexia Phenotypes and Hypometabolism in Spanish-Speaking Patients with Primary Progressive Aphasia

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Session 01 .1 - Diversity & Epidemiology (1) - Exploring Cross-Linguistic Variations in Language and Dementia, september 19, 2024, 11:00 - 11:45

State of the art: Surface dyslexia serves as a complementary feature in the classification of the semantic variant of Primary Progressive Aphasia (PPA). In opaque languages, tasks involving regular and irregular words and non-words are useful tools for dyslexia diagnosis. However, in transparent languages different approaches are needed. This study aims to: 1) present an alternative approach for detecting dyslexia in Spanish-speaking PPA patients, 2) identify brain FDG hypometabolism patterns in PPA subjects. Methodology: We assessed 17 PPA patients and 61 age-sex-education-matched healthy subjects with tasks of word and non-word reading, foreign word reading, and lexical decision. Employing a case series methodology with a case-control design, we conducted comparisons against controls and intra-subject analyses. To assess hypometabolism, we performed 18F-FDG PET scans on all subjects. We adjusted a prediction model of 18F-FDG signal in control subjects to determine the w-score for each patient. Results: We detected dyslexia in 94% of all PPA subjects. Specific patterns were identified: 5 cases of surface dyslexia, 2 of phonological dyslexia, 3 of mixed dyslexia, and 6 unspecified. The FDG-PET results revealed left ventral occipitotemporal, left ventral inferior parietal, and left superior temporal cortex hypometabolism. Conclusion: This study offers valuable insights into the ocurrence and types of dyslexia exhibited by PPA patients. Our findings underscore the need to employ different tasks to assess lexical reading mechanisms in Spanish-speaking contexts. Moreover, the identification of hypometabolism contributes additional insights into the deficits observed in PPA patients and is consistent with reported data about regions linked to reading.

PB1.4 / P004

The influence of cultural background on social cognition in genetic FTD

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Session 01.2 - Diversity & Epidemiology (2) - Influential factors in Frontotemporal Dementia across the world, september 19, 2024, 11:45 - 12:50

State of the art: Although many studies have demonstrated deficits in facial emotion recognition (FER) and theory of mind in progressed disease stages of frontotemporal dementia (FTD), no significant decline has been found in global multicenter cohort studies focusing on earlier (prodromal and presymptomatic) disease stages. One potential reason might be that the cross-cultural validity of traditional tests is not sufficient and prevents reliable differentiation. In this study, we examined the influence of cultural background on FER in presymptomatic and symptomatic genetic FTD.

Methods: An initial cohort of 367 presymptomatic (150 male/227 female, age 20-75) and 164 symptomatic (101 male/63 female, age 35-81) mutation carriers, and 302 mutation-negative controls (130 male/172 female, age 19-83) from the GENFI cohort (10 countries) was included. Data inclusion from the ReDLat study cohort is ongoing. Linear mixed models with age, gender, education, and country as predictors were applied to FER scores. In addition, we will perform voxel-based morphometry with T1-weighted MRI scans to investigate underlying neural correlates of FER for each country.

Results: After controlling for age, gender and education, country of origin accounted for 15% of the variability in controls and 17% in presymptomatic individuals. In the symptomatic group, only education is a significant predictor ($p<0.05$); country does not significantly contribute to the variability.

Discussion: Culture does significantly contribute to variation in performance on a social cognition task in presymptomatic individuals and controls, but this variation decreases in symptomatic individuals. Final results and imaging analyses will be presented during the conference.

PB2.1 / P005

Baseline characteristics for INFRONT-3: A Phase 3 double-blind, placebo-controlled 96-week study evaluating latozinemab in FTD-GRN

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Session 05 - Clinical (1), september 20, 2024, 09:00 - 09:45

State of the Art:
Latozinemab is a human monoclonal antibody being developed for the treatment of frontotemporal dementia (FTD) due to a heterozygous progranulin gene (GRN) mutation. Latozinemab blocks and downregulates the sortilin receptor, which regulates plasma and brain progranulin (PGRN) levels. Prior studies demonstrated that latozinemab increased PGRN to physiologic levels and slowed disease progression relative to matched controls. Herein, we describe the baseline characteristics for participants in the INFRONT-3 study.

Methodology:
INFRONT-3 (NCT04374136) is a pivotal Phase 3 multicenter, randomized, double-blind, placebo-controlled 96-week study. Participants have a baseline CDR plus NACC FTLD-SB score ≤0.5 with elevated serum NfL (At-risk Cohort), or a CDR plus NACC FTLD-SB score of >0.5 with 1 or more of 6 behavioral/cognitive symptoms required for diagnosis of possible bvFTD or PPA (Symptomatic Cohort).

Results:
A total of 119 participants (103 Symptomatic) were enrolled with global CDR score of 0 (n=15), 0.5 (n=25), 1 (n=47), or 2 (n=32). Mean age was 62 years (range: 37-85), with 51% female, and 89% Caucasian. The At-risk Cohort had a mean ±SD CDR-SB of 0.0±0.13 and a median serum NfL of 14.4 pg/mL (range 7.8-42.9). The Symptomatic Cohort had a mean ±SD CDR-SB of 6.9±4.05 and a median serum NfL of 66.9 pg/mL (range 6.5-190.0). Symptomatic participants were diagnosed with bvFTD (64), PPA (28), or both bvFTD and PPA (7).

Conclusion:
INFRONT-3 is designed to provide evidence of efficacy and safety for latozinemab, a potential first-in-class approach for treating FTD-GRN in a representative population spanning disease severity.

PB2.2 / P006

Communication Bridge 2: Results from a global randomized controlled trial (RCT) for primary progressive aphasia

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Session 05 - Clinical (1), september 20, 2024, 09:00 - 09:45

State of the art: Primary progressive aphasia (PPA) is a currently incurable language-based neurodegenerative dementia syndrome. Speech-language interventions have increased to meet the urgent need to maximize quality of life and communication participation for individuals living with PPA and their communication partners. Initial studies show promise but have lacked randomized controlled trials (RCT). Here we report outcomes for, Communication Bridge-2 (CB2), the first global telemedicine speech-language (RCT) for PPA.

Methodology: CB2 is an international, single enrollment site, Phase 2, Stage 2, parallel-group, active control, behavioral RCT delivered via video-chat to individuals with PPA and their communication partners. Interventions include use of a custom web-application. Participants were randomized 3:2 into one of two intervention arms: Communication Bridge™, a dyadic intervention based on communication participation models, or the Control intervention, a non-dyadic intervention based on impairment models. Participants completed two intervention blocks over ~12 months. Primary outcomes included communication confidence and participation measures assessed at baseline, at each intervention block, and at 12 months post-enrollment.

Results: Ninety-five PPA participants (mean enrollment age: 67.1 years, 49% female) were enrolled and randomized (n=4 countries). Dropout was <10%. Experimental arm superiority was demonstrated at Block 1 for Goal Attainment Scale measurement, a primary participation outcome. The Communicative Participation Item Bank showed positive within-group responsiveness at Block 1 exclusively for the experimental arm. Communication confidence measurement was unresponsive.

Conclusions: Results suggest feasibility and initial efficacy for a global telemedicine intervention, providing an exciting path for clinically meaningful interventions for mild-to-moderate PPA and related dementias.

PB2.3 / P007

Interim Safety and Biomarker Data From upliFT-D Trial of PBFT02 in FTD with GRN Mutations

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Session 05 - Clinical (1), september 20, 2024, 09:00 - 09:45

State of the art
Approximately 25-30% of frontotemporal dementia (FTD) is caused by autosomal dominant mutations, usually in one of three genes, C9orf72, GRN, or MAPT. There are currently no disease-modifying treatments approved for FTD, including FTD-GRN.
Methodology.
PBFT02 is an AAV1 vector that delivers a copy of the human GRN gene directly to the CSF via a single intra-cisterna magna (ICM) administration. PBFT02 is being studied in a first-in-human, dose escalation clinical trial, upliFT-D (NCT04747431 [ClinicalTrials.gov]), which will enroll two sequential FTD-GRN cohorts, with an optional third cohort. The primary objective is safety and tolerability; secondary objectives include biomarkers of target engagement (e.g., progranulin; PGRN), biological activity, and disease progression. The 2-year trial will be followed by a 3-year extension for safety and durability of effect.
Results
As of December 2023, 3 subjects received PBFT02 at a dose of 4.5 x 10e13 genome copies. PBFT02 was generally well-tolerated with a steroid regimen of 1 g IV methylprednisolone on study days 1-3, followed by 60 mg oral prednisone on days 4-60. CSF PGRN levels increased >2-3x relative to healthy adult controls in all participants at Day 30 post treatment; supraphysiological concentrations in CSF PGRN were maintained at 6 months. Following PBFT02 administration, plasma PGRN did not increase. Updated data will be included at the time of the presentation.
Conclusions
Interim safety and biomarker data from the upliFT-D trial provides initial evidence that PBFT02 has potential as a one-time therapy for FTD-GRN, thus supporting further clinical development.

PB2.4 / P400

Onset-predictive biomarker testing for clinical trial recruitment in FTD: perspectives of (potential) mutation carriers

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Session 05 - Clinical (1), september 20, 2024, 09:00 - 09:45

State of the art
Onset-predictive biomarker tests (OPBT) that predict symptom onset of genetic frontotemporal dementia (FTD) are essential to identify pre-symptomatic participants for clinical trials with potential therapeutic agents aiming to delay or prevent neurodegeneration. This interview study explores the willingness of (potential) carriers of genetic FTD to undergo OPBT for trial recruitment and the impacts they foresee of OPBT results.

Methodology
We conducted twenty-five semi-structured qualitative interviews with Dutch pre-symptomatic carriers (n=11) and individuals at 50% risk (n=14) of genetic FTD about their perspectives on OPBT. We analyzed the data using inductive thematic analysis.

Results
Both pre-symptomatic carriers and individuals at 50% risk were willing to undergo OPBT regularly (e.g. annually) for the purpose of clinical trial recruitment or as stand-alone test. The majority of individuals at 50% risk would only be willing to undergo OPBT if pre-symptomatic genetic testing were not a precondition. Foreseen impacts of OPBT results signaling imminent symptom onset were decisions on work, enjoying life, spending time with loved ones, care and end-of-life directives. Participants preferred a blood or MRI test, an estimated time to onset of either 2-5 years or 10 years, more precise estimates, and a positive predictive value of >70%-95%.

Conclusion
Both pre-symptomatic carriers and individuals at 50% risk of FTD accepted disclosure of OPBT results for trial recruitment. OPBT results signaling imminent symptom onset are expected to impact personal life planning. Ethical guidelines are needed for future OPBT, as it amounts to indirect genetic testing in individuals at 50% risk.

PB3.1 / P009

CSF/serum albumin ratio in frontotemporal lobar degeneration syndromes

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Session 07 - Neuropsychology, september 20, 2024, 14:30 - 16:00

STATE OF THE ART: The CSF/serum albumin ratio (Q-Alb) reflects the function of the blood/CSF barrier. It has been evaluated to a limited extent in neurodegenerative diseases. METHODOLOGY: We evaluated Q-Alb in a retrospective cohort of 92 patients (59 M and 33 F) with FTLD syndromes (FTLDSs) (40 bvFTD, 13 CBS/CBD, 5 PSP, 18 nfvPPA, 2 svPPA, 14 FTD-ALS) and 92 non-neurodegenerative neurological controls (CTRLs; 56 M and 36 F). RESULTS: In FTLDSs, median age was higher compared to CTRLs (68.35 y vs. 60.5 y; $p < 0.0001$). Neither in CTRLs nor in FTLDSs did Q-Alb correlate with age ($p > 0.05$). Q-Alb did not differ significantly between FTLDSs and CTRLs ($p = 0.3556$). Differently from CTRLs, in FTLDSs Q-Alb was higher in males compared to females (6,16 vs. 4,89; $p = 0.0197$), which was not due to age differences between the two groups ($p = 0.9952$). Finally, Q-Alb did not differ between categories of FTLDSs (bvFTD; CBS/CBD + PSP; nfvPPA + svPPA; FTD-ALS) ($p = 0.8443$). CONCLUSION: The blood/CSF barrier does not seem to be significantly altered in FTLDSs. Further studies are warranted in order to investigate larger cohorts of single disease entities and to analyze correlations with CSF and blood biomarkers. The sex difference of Q-Alb in FTLDSs also deserves additional study. As the blood/CSF barrier does not exactly coincide with the blood/CSF barrier (BBB), further neurochemical and neuroradiological investigations focusing on the BBB are also warranted.

PB3.2 / P010

The identification of GRN mutation carriers by a simple finger stick collection - DropAD

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Session 07 - Neuropsychology, september 20, 2024, 14:30 - 16:00

State of the art: Heterozygous mutations in the progranulin gene (GRN) are one of the most frequent causes of inherited frontotemporal dementia (FTD). Pharmacological trials in FTD targeting the pathophysiological effects of such mutations often aim to increase the reduced baseline progranulin concentrations observed in these mutation carriers.
Methodology: We aimed to evaluate whether progranulin levels can be quantified using dried blood spot collection from finger stick (DBScapillary). In total, 16 GRN mutation carriers (mean [SD] age, 55 [13] years; n [%] 12 females [75%]) and 44 non-mutation carriers (mean [SD] age, 64 [11] years; n [%] 21 females [48%]) tertiary dementia research clinic were enrolled in the study. Paired DBScapillary and EDTA samples were collected from each patient; progranulin levels were assessed using ELISA in plasma and with assay buffer-extracted DBScapillary samples.
Results: DBScapillary progranulin levels were significantly reduced in GRN mutation carriers (2.38 ng/mL [1.0]) compared to non-mutation carriers (4.37 ng/mL [0.68]; U = 42; P < 0.0001) with an area under the receiver operating characteristic curve [AUC] = 0.94 (95% CI, 0.83-1.00). Progranulin levels were highly associated between DBScapillary and EDTA plasma (R = 0.819; P < 0.001) and stable on DBS cards for at least 10-days. The extraction demonstrated high reproducibility.
Conclusions: Progranulin levels can be determined by finger-stick blood collection with high precision. This simple method may allow for the regular and remote monitoring of progranulin levels in FTD therapeutic trials and might represent a first-level screening test to identify GRN mutations

PB3.3 / P281

The Position of Sporadic FTD Cases within the Human Proteomics Neurodegenerative Disease Landscape

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Session 07 - Neuropsychology, september 20, 2024, 14:30 - 16:00

State of the Art:
Frontotemporal dementia (FTD) is a major cause of early-onset dementia. Finding a treatment is hampered by its considerable heterogeneity: it is hereditary in 30% of cases (genetic FTD), while the remaining 70% can be conceived as complex trait disorder (sporadic FTD). We aim to construct a multi-omics neurodegenerative disease framework to enable positioning of sporadic FTD cases. We investigate multiple brain regions (i.e., frontal and temporal cortex, frontal insula, anterior cingulate, and occipital cortex) from both hemispheres. Proteomic data is supplemented with snRNAseq transcriptomics and genetic screening.

Methodology:
We have gathered a wide-ranging neurodegenerative donor cohort (n>80), including cases of genetic FTD (FTD-C9, FTD-GRN, FTD-MAPT, FTD-CHMP2B), Alzheimer's Disease, Parkinson's Disease, sporadic FTD, and non-demented controls. We measured the post-mortem medial temporal gyrus proteome using a data-independent mass spectrometry-based quantitative approach. Peptide data was analysed with DIA-NN and MS-DAP. The top-100 differentially abundant proteins in each distinct disease group were used for unbiased clustering of all cases.

Results:
Clustering the neurodegenerative cohort based on proteomic profile demonstrates the presence of distinct and/or partly-overlapping disease clusters. Sporadic FTD cases divide along this framework, either overlapping with existing disease clusters or forming clusters of their own. These data indicate the presence of distinct proteomic subtypes within the sporadic FTD group.

Conclusion:
Construction of a proteomic framework for neurodegenerative disease enables characterization of sporadic FTD cases. With our efforts we can start to reveal disease mechanisms for sporadic FTD and pave the way for the development of disease subtype-specific treatments.

PB3.4 / P401

Psychoeducational program in Primary Progressive Aphasia: An innovative collaboration between the community and academic environments

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Session 07 - Neuropsychology, september 20, 2024, 14:30 - 16:00

State of the art: Accessing information about Primary Progressive Aphasia (PPA) is a challenge for patients and their caregivers. Studies assessing the efficacy of psychoeducational programs have shown clear benefits regarding knowledge of PPA, self-confidence and communication. However, specialized resources are limited, especially outside city centers. This study aimed to document the co-construction and the impact of Apprivoiser l'APP, an exportable in-person psychoeducational program offering information and support to people living with PPA and their caregivers.
Methods: A five weeks in-person program was co-developed by the Research Chair on PPA – Fondation de la famille Lemaire, Université Laval and ARTERE, a community resource for people who have suffered a stroke, including those living with aphasia. It consisted of videos created by experts in the field of PPA, covering different aspects of the disease and its evolution (i.e. communication, cognition, behavioral changes), as well as group discussions and activities to be led by the community association. Furthermore, a pilot study composed of five dyads was carried out to assess the impact of the program.
Results: Results showed that the program increased participants' knowledge about PPA and available resources. They reported feeling better prepared to face the future. Feedback also led to the spreading of the sessions over 6 weeks.
Conclusion: This study confirmed the feasibility and efficacy of Apprivoiser l'APP, an innovative program on PPA currently deployed throughout the province of Quebec via community associations, thus meeting critical needs expressed by people living with PPA and their caregivers.

PB4.1 / P127

Integrative transcriptomic analysis of the frontal cortex reveals an upregulation of S100A6 in FTLD-TDP

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Session 09.2 - Fundamental research, september 21, 2024, 11:00 - 12:00

State of the art: To date, the transcriptomic consequences of TDP-43 proteinopathies and the resulting molecular mechanisms contributing to the diversity of FTLD-ALS spectrum disorders remain largely unknown, limiting the identification of biomarkers and therapeutic targets.
Methodology: Here, we assessed a total of 150 post-mortem frontal cortex transcriptomes, leveraging short-read RNA-sequencing data from 126 TDP-43-related FTLD-ALS spectrum patients and 24 control subjects. Furthermore, long-read RNA-sequencing data from a subset of 32 specimens were generated and incorporated into our pipeline through an integrative analysis.
Results: Our differential gene expression analysis of the short-read series revealed several significant genes, with S100A6 emerging as a top hit, upregulated in FTLD-ALS spectrum patients compared to controls. Co-expression analysis disclosed genes associated with the regulation of immune system processes, cytoplasmic translation, and synaptic signaling, among others. Furthermore, specific patterns were observed for patients that appeared to be driven by FTLD rather than ALS. Deconvolution analysis uncovered a lower proportion of neurons and an increased proportion of astrocytes in FTLD (+/- ALS) compared to ALS. Importantly, our long-read data confirmed significant upregulation of S100A6 in FTLD (+/- ALS) and identified a novel differentially expressed S100A6 transcript.
Conclusion: Our data provide a detailed landscape of gene and transcript expression alterations in FTLD-ALS spectrum disorders. S100A6, encoding a ubiquitously expressed calcium-binding protein, emerged as a promising candidate in FTLD when analyzing the primary affected region, the frontal cortex, suggesting its potential as a disease-relevant biomarker.

PB4.2 / P128

UNC13A polymorphism shortens survival in behavioural variant frontotemporal dementia

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Session 09.2 - Fundamental research, september 21, 2024, 11:00 - 12:00

State of the art: Genetic studies on amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) have identified polymorphisms in UNC13A as a shared genetic risk factor. TAR-DNA binding protein 43 pathology is shown to drive the pathophysiological mechanism of UNC13A and is implicated in the majority of behavioural variant FTD (bvFTD) cases. Homozygosity for the risk allele at rs12608932 is associated with shorter survival in ALS, but this relation is unknown for (bv)FTD.
Methodology: We included 219 patients with a diagnosis of bvFTD and genetic data available from the Amsterdam Dementia Cohort (ADC). A recessive model was used to form groups for comparison. Hazard ratios for survival were determined using cox proportional hazard models, correcting for age, sex and Principal Components 1-5.
Results: The median age was 64 [IQR 59 - 69] years whilst 60% were male. Genotyping resulted in 34 (15.5%) CC, 98 (44.7%) AC, and 87 (39.7%) AA genotypes. There was no significant difference between genotypes for age, sex, age at onset and disease duration. The median survival for the bvFTD cohort was 63.3 months [IQR 42.6-93.3] from date of diagnosis. Homozygosity for the C-allele at rs12608932 is associated with a shorter survival compared to the other genotypes (HR 1.58, 95% confidence interval 1.01-2.48, $p<0.05$).
Conclusion: Homozygosity for the C-allele at rs12608932 modifies the phenotype in bvFTD in a similar manner to ALS. This further exemplifies the similarity between the two diseases and could pave the way for a common application of future therapies targeting TDP-43.

PB4.3 / P129

Genetic influences on progression of clinical, motor, fluid biomarker and MRI changes in familial FTLD

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Session 09.2 - Fundamental research, september 21, 2024, 11:00 - 12:00

State of the art
Disease progression models (DPM) of familial FTLD (f-FTLD) are useful for clinical trial endpoint selection and identifying high-risk presymptomatic participants. This study extends and refines previous models with additional participants, genetic and biomarker data, and statistical optimization.

Methodology
Bayesian repeated-measures DPM incorporated longitudinal clinical status (CDR®+NACC-FTLD-SB), neurological exam findings, ALS-FRS-R, neuropsychological scores, regional brain atrophy, and plasma neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) in 1,017 mutation carriers (GRN, MAPT, C9orf72) and 504 non-carrier controls from ALLFTD and GENFI with 3,699 visits (42% increase since publication). Timing, magnitude, and variability of change of each endpoint were analyzed, and we tested effects of genetic modifiers (TMEM106B and APOE) on rate of progression.

Results
Motor abnormalities on examination were present in 63% of symptomatic mutation carriers (CDR®+NACC-FTLD-SB ≥ 0.5) and worsened over time at a similar rate as other clinical measures. Modest presymptomatic GFAP elevations occurred in C9orf72 and MAPT, with large elevations in GRN that paralleled rises in NfL ~10 years prior to symptom onset. MRI remained a strong predictor of time to onset in all carriers. Protective effects of TMEM106B-G/G homozygosity on disease progression were observed in GRN, with a subtle effect in C9orf72. Presence of an APOE E4 allele did not alter progression rates.

Conclusion
These results suggest DPM accuracy and identification of high-risk presymptomatic participants is improved via inclusion of motor exam findings, GFAP, and specifically in carriers of mutations associated with TDP-43 pathology, TMEM106B genotype.

PB4.4 / P126

White Matter Hyperintensities are An Early Biomarker in GRN-related Frontotemporal Dementia

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Session 09.2 - Fundamental research, september 21, 2024, 11:00 - 12:00

State of the Art: Prior studies on genetic frontotemporal dementia (FTD) have noted increased white matter hyperintensities (WMHs) on T2-weighted imaging, particularly among GRN mutation carriers. However, the temporal relationship between WMHs abnormalities and other imaging and blood biomarkers remains insufficiently explored.

Methodology: T1 and T2 MRI scans from 182 GRN carriers and 298 healthy controls in the GENFI2 dataset were automatically segmented for WMHs (Dadar et al. MRM 2021; 85(4) 1881-1894). The geodesic information flow algorithm (Cardoso et al. IEEE TMI 2015; 34(9) 1976-1988) was employed for cortical and subcortical volume parcellation. Serum neurofilament light (sNfL) levels were quantified using Simoa technology. Discriminative event-based modeling (DEBM) identified the sequence of biomarker abnormalities (Venkatraghavan et al. NeuroImage 2019; 186 518-532). Longitudinal data were analyzed using a mixed-effects model to assess associations between neuroimaging biomarkers and WMHs.

Results: Findings from the DEBM analysis revealed that, when present, WMHs are among the initial observable alterations in the progression of the disease along with subcortical volume loss, preceding changes in sNfL, ventricular sizes, and cortical atrophy in frontal and temporal lobes. Longitudinal examination highlighted WMHs volumes as predictive of forthcoming neurological alterations in significant subcortical and cortical areas. The lack of an inverse association indicates that WMHs likely precede neurodegeneration and gray matter atrophy.

Conclusion: While WMHs may not be evident in every case of FTD, their presence, when observed, typically occurs during the early stages of the disease. Therefore, it is important to consider WMHs when constructing models to depict disease progression.

PB5.1 / P125

Connectomic markers of executive function in frontotemporal degeneration and typical aging

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session 11 - Clinical (2), september 21, 2024, 16:15 - 17:00

State of the art: Breakdown of brain connectivity in aging and disease may contribute to impaired executive function (EF). We hypothesized that connectomic markers of EF impairment identified from diffusion MRI would generalize to independent participants and EF measures.

Methodology: We used elastic net regression to identify associations between EF and deterministic tractography in data from the Connectomic Imaging in Familial and Sporadic Frontotemporal Degeneration study. EF was assessed using the EXAMINER executive composite in 105 training participants (27 controls; 16 individuals with sporadic frontotemporal lobar degeneration (FTLD); and 39 asymptomatic and 23 symptomatic carriers of MAPT, GRN, or C9orf72 variants). Connection strength was quantified using tractwise generalized fractional anisotropy (GFA). Model coefficients were multiplied by connectivity matrices to produce connectome-based EF scores, which we correlated with independent measures requiring EF in training participants and 128 test participants (85 controls, 9 asymptomatic and 15 symptomatic carriers, and 19 sporadic FTLD cases).

Results: The EF composite was positively associated with GFA in 60 symmetrically-distributed connections, primarily connecting the default mode, salience, and dorsal attentional networks. In training data, connectome-based EF scores were correlated (alpha=0.05) with the EXAMINER composite (R=0.672), Trails B completion time (R=0.555), lexical fluency (F-words, R=0.391; total intrusions, R=-0.214), and backward digits correct (R=0.374). These associations generalized to test data: Trails B (R=0.468); F-words (R=0.420) and total intrusions (R=-0.247); and backwards digits correct (R=0.446).

Conclusion: We identified replicable biomarkers of executive dysfunction using connectomic imaging. Results suggest white matter degeneration contributes to EF impairment in FTLD and typical aging.

PB5.2 / P275

Paying Attention - What Hallucinations reveal about FTD

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session 11 - Clinical (2), september 21, 2024, 16:15 - 17:00

State of the Art: Psychotic symptoms similar to that observed in primary psychiatric disorders are well established across the frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) spectrum, however the mechanisms for vulnerability to these symptoms is less well understood than in psychiatric and other neurodegenerative diseases. Functional MRI (fMRI) advancements have offered insights into potential symptom mechanisms across diseases.
Methodology: Leveraging a behavioural paradigm of visual misperception combined with neuropsychology and whole-brain-based functional MRI analysis in 46 patients across the ALS-FTD spectrum this study for the first time provided an impartial delineation of functional architecture underlying visual hallucinatory vulnerability in ALS-FTD.
Results: Significantly higher misperception scores were found in patients with visual hallucinations compared to those without ($p < .001$); in those carrying the C9orf72 expansion relative to noncarriers ($p = .021$); as well as in the bvFTD compared to the ALS group ($p = .003$). Misperception errors were negatively correlated with performance specific to attentional functions (all $p < .05$). Abnormal connectivity between the attentional and default mode and executive control networks were implicated in the manifestation of visual misperception in ALS-FTD (age-adjusted and FWE-corrected p of .042 with 10000 permutations; $r = .95$).
Conclusion: These results suggest a model for hallucination vulnerability related to alterations within attentional networks and converge with findings from the schizophrenia, Parkinson's disease, and dementia with Lewy bodies literature. This adds evidence for shared neurobiological underpinning of psychosis vulnerability nd provides support for a transdiagnostic model for hallucinations across primary psychiatric and neurodegenerative conditions.

PB5.3 / P276

NEUROPSYCHIATRIC SHADOWS: UNRAVELING THE DEEPER TIES OF PSYCHOTIC SYMPTOMS IN BEHAVIOURAL FRONTOTEMPORAL DEMENTIA

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session 11 - Clinical (2), september 21, 2024, 16:15 - 17:00

BACKGROUND: The behavioural variant of Frontotemporal Dementia - bvFTD - is characterized by personality changes, cognitive deficits and behavioural disorders. Psychiatric symptoms, such as delusions, hallucinations and emotional blunting, are not formally considered clinical features of bvFTD. We investigated the frequency and severity of psychotic symptoms in patients with bvFTD compared to AD patients.

METHODS: We included two groups of participants: 1) bvFTD (n = 11, 6M/5F; mean age = 65.2±6.7 years; mean schooling = 9.4±5.3; Disease Duration: 4.1±2.4; MMSE= 24.8±4.3); and 2) AD (n = 13; 4M/9F; mean age = 69.1±9.61years; mean schooling = 9.0±6.1; Disease Duration: 6.31±5.1; MMSE= 22.38±4.2). The groups were matched for age, sex, and education level. All participants underwent a comprehensive cognitive assessment. The psychotic symptoms were evaluated using PANSS (Positive and Negative Syndrome Scale).

RESULTS: bvFTD showed a higher total PANSS score than AD (p=0.001). Patients with bvFTD had more severe negative symptoms (p=0.004) and general psychopathology symptoms (p=0.005) compared to those with AD.
Among the general psychopathology symptoms, bvFTD performed worse than AD in the "tension" (p=0.014) and "preoccupation - autistic experiences” (p=0.047) scores.
Similarly, bvFTD performed worse than AD in negative symptoms, particularly in "blunt affect" (p=0.008), "poor rapport" (p=0.010), “Passive/apathetic social withdrawal” (p=0.021) and "lack of spontaneity and flow of conversation" (p=0.038).

CONCLUSIONS: Patients with bvFTD manifest more negative psychotic symptoms than AD patients. These findings should be considered in the clinical distinction between bvFTD and AD.

PB5.4 / P277

Behavioural variant frontotemporal dementia and Alzheimer's disease differ in favourite music activation profiles on fMRI

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session 11 - Clinical (2), september 21, 2024, 16:15 - 17:00

State of the art: Music processing might be relatively preserved in individuals with Alzheimer's disease (AD), while it seems affected early in behavioural variant frontotemporal dementia (bvFTD). Here, we studied if individuals with bvFTD and AD differ in activation on functional MRI when listening to their favourite music.

Methodology: We recruited 60 participants (58.3% female; mean age 65.0), of which 13 bvFTD, 22 AD, and 25 healthy controls from the Amsterdam Dementia Cohort of the memory clinic of the Alzheimer Center Amsterdam. We designed a novel fMRI paradigm based on passive listening to self-selected favourite music and pre-selected neutral musical pieces in a sparse-sampling fMRI design. Activation patterns of favourite music listening (favourite > silence), neutral music listening (neutral > silence) and favourite music more than neutral music (favourite > neutral) were calculated for each participant, and syndromic subgroup differences of each contrast were investigated.

Results: Atrophy patterns were consistent with the dementia type. Functional activation in response to favourite and neutral music occurred in similar anatomical patterns in all groups. When contrasting favourite and neutral music, we found that compared to AD and controls, patients with bvFTD showed less activation in the supplementary motor area (SMA), and AD individuals had less activation in the caudate nucleus and dorsal brain stem compared to bvFTD.

Conclusion: Our results suggest that favourite music is processed differently in patients with bvFTD and AD. Possibly, the reduced activation in the SMA may explain altered music processing in bvFTD.

PB6.1 / P278

Methylome analysis of FTLD patients with TDP-43 pathology identifies epigenetic signatures specific to pathological subtypes

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Session 12 - Clinical (3), september 21, 2024, 17:00 - 17:45

State of the art: In the last decade, the importance of DNA methylation in the functioning of the central nervous system has been highlighted, yet the genome-wide contribution of epigenetic changes to the development of FTLD remains largely unexplored.
Methodology: We performed reduced representation bisulfite sequencing of matched pairs of post-mortem tissue from frontal cortex (FCX) and cerebellum (CER) from FTLD-TDP types A, B and C, GRN mutation carriers, C9ORF72 repeat expansion carriers (N=25 pairs per group), and neurologically normal controls (N=42 pairs). Case-control differential methylation analyses were performed both at the single-CpG level and regions, either including all genomic locations or only gene promoters.
Results: Using the largest FTLD-TDP methylation dataset generated to date, we identified thousands of differentially methylated CpGs (FCX=6,877; CER=7,483) and several hundred differentially methylated regions (DMRs) in FTLD-TDP brains (FCX=151; CER=224). Of these loci, less than 10% are shared between pathological patient groups, suggesting epigenetic signatures specific to FTLD-TDP subgroups. After prioritizing loci using a custom scoring system, and interrogation of available transcriptomic data, we identified dysregulation of CAMTA1 in FTLD-TDP_A (logFC_DMR=-0.93; P=0.02); both Cadherin (P=0.0006) and Actin binding (P=0.028) pathways in FTLD-TDP_B; OTX2 (logFC_DMR=0.97; P=7.45E-03) as well as several transcription factors involved in developmental processes (P=0.022) in FTLD-TDP_C; and RASA3 as a promising candidate across FTLD-TDP pathological subtypes (strongest in FTLD-TDP_A; logFC_DMR=-0.86; P=4.25E-04).
Conclusion: Overall, our results suggest that epigenetics plays a role in FTLD-TDP pathophysiology and highlights the need for further studies to profile additional epigenetic layers within each FTLD-TDP pathological subtype.

PB6.3 / P280

Progranulin deficiency in microglia and its impact in neurodegeneration

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Session 12 - Clinical (3), september 21, 2024, 17:00 - 17:45

State of the art
Loss of function mutations in the progranulin gene (GRN), are the second most common genetic cause of frontotemporal lobar degeneration (FTLD), a disorder that accounts for 10-20% of all young-onset dementias. GRN, as other risk genes associated with dementia, is primarily expressed in microglia, the immune cells of the brain. However, the functional consequences of granulin deficiency on human microglia biology remain unknown. There are extensive differences in the transcriptomic and proteomic profiles of human and mouse microglia, hence it is essential to use human/humanized systems to understand the impact of disease-causing mutations on microglial homeostasis and their contribution to disease.

Methodology
We generated two homozygous GRN deficient induced pluripotent stem cell (iPSC) lines and differentiated them into microglia using our MIGRATE protocol. We have performed a series of in vitro experiments exploring whether GRN deficiency leads to functional alterations in the endo-lysosomal pathway. To better understand the effect of microglial GRN deficiency in vivo, we xenotransplanted the human iPSC-derived microglia progenitors into the mouse brain.

Results
GRN-deficient microglia displayed extensive endolysosomal alterations, including both structural as well as functional aspects, such as increased phagocytosis. In addition, GRN-deficient cells showed transcriptomic changes associated with cytokine activity and the HLA pathway. Xenotransplanted GRN-deficient microglia display an over-activated profile with an increased polarization into DAM state and more pronounced expression of inflammatory-related genes.

Conclusion
GRN-deficient microglia show transcriptomic and functional alterations linked to inflammation and endolysosomal dysfunction both in vitro and in vivo.

PB6.4 / P008

Detection of misfolded TDP-43 in CSF from genetic FTD and FTD/ALS patients

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Session 12 - Clinical (3), september 21, 2024, 17:00 - 17:45

State of the art: Seed amplification assays (SAAs) have shown promising results in detecting misfolded TDP-43 in cerebrospinal fluid (CSF) of patients with genetic FTD with TDP-43 pathology. However, results have yet to be replicated in other laboratories. Also, there are no data available on SAA analysis of CSF from patients at presymptomatic phase of the disease.
Methodology: We tested TDP-43 seeding activity in CSF of 15 patients carrying pathogenic GRN mutations or C9orf72 expansion, 4 presymptomatic carriers (2 GRN and 2 C9orf72 carriers) and 7 controls (subjects without neurodegenerative disorders). All subjects underwent extensive clinical and neuropsychological evaluation. Truncated recombinant TDP-43 protein has been used as a SAA reaction substrate and underwent to several incubation and shaking cycles. The aggregation was monitored by measuring thioflavin T fluorescence.
Results: We found a seeding activity in 11 out of 15 samples from FTD patients with either GRN or c9orf72 mutations (73,3% sensitivity). Two out of 4 (1 GRN and 1 C9orf72 carrier) presymptomatic subjects resulted positive (50% sensitivity). All controls resulted negative (100% specificity).
Conclusion: We confirm our previous data (Scialò et al. Brain Commun. 2020;14;2(2):fcaa142) indicating the presence of seeding activity for TDP-43 in the CSF of symptomatic patients with genetic forms of TDP-43 pathology. However, what is particularly intriguing is our demonstration that this seeding activity is also detectable in presymptomatic disease stages. While these results are highly promising, they necessitate validation in a larger sample cohort for further confirmation.

PB7.1 / P402

The Empathy Effect: Improving FTD Support, Medical Practices and Societal Awareness with an Immersive Approach

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Poster Blitz session 2, september 22, 2024, 11:00 - 11:20

State of the Art
The level of empathy and understanding of FTD profoundly impacts the action taken to support care for FTD individuals. Effective means to increase these are necessary to improve support for FTD families.

Methodology
We have conducted polls and surveys to gain an understanding of how caregivers, healthcare professionals and the public understand dementia, and how equipped they feel to provide care or support.

We have created a high impact simulation experience that immerses participants into life with dementia. This allows participants to gain firsthand experience in what it's like to live with dementia. This is followed by a customizable education session to deliver dementia health literacy, improved communication methods, brain health and other resources/management tools. Feedback forms are used to analyze the effectiveness and increase in education, empathy, and confidence to support dementia patients.

Results
Surveys indicate that few individuals grasp what FTD or dementia are, and even less feel equipped to support someone with dementia or the family. Caregivers feel isolated and "on their own." However, of our 200+ immersive workshop participants, >90% indicated an increase in empathy, understanding and/or perceived confidence. Results and participant feedback will be presented.

Conclusion
An individuals' level of empathy profoundly impacts the level of action/inaction taken to support FTD families. An immersive approach to education is an effective pathway to empathy and improvements to FTD care. Further immersive education should be utilized to promote growth in the field of FTD caregiving, medical practices, and societal awareness.

PB7.2 / P403

Transcranial Direct Current Stimulation for Primary Progressive Aphasia: Individualised Targeting Using Neuroimaging

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Poster Blitz session 2, september 22, 2024, 11:00 - 11:20

State of the art

Transcranial Direct Current Stimulation (tDCS) has been used to enhance language therapy for Primary Progressive Aphasia (PPA). Previous tDCS targeting has been guided by typical atrophy seen in PPA subtypes: non fluent (nfvPPA), logopenic (lvPPA) and semantic (svPPA). This approach does not account for variation in atrophy between individuals within these groups. We developed an imaging driven approach to personalise tDCS targeting and tested this within a PPA cohort.

Methodology

Previously obtained imaging from 35 individuals with a diagnosis of PPA from a tertiary cognitive neurology centre were obtained (10 nfvPPA; 15 lvPPA; 10 svPPA). We identified abnormal voxels representing atrophy in comparison with a group of healthy controls. Calculation of the proportion of abnormal voxels within language Brodmann Areas (BA) enabled us to assign the BA of greatest involvement (peak BA), the least atrophic contiguous BA (target BA) and closest ‘10-20’ electrode for neurostimulation (target electrode).

Results

An imaging driven targeting method had a different outcome compared to a method based upon clinical syndrome in terms of peak BA (60%) and target electrode (60%). The most frequent peak BA was the left anterior temporal lobe (57%), including participants in subgroups not typically associated with this region (nfvPPA and lvPPA).

Conclusion

An individually tailored, imaging-based approach to neurostimulation may account for variation in atrophy within PPA subtype groups. The left anterior temporal lobe was highly involved in all PPA variants within our cohort. This may inform future planning of tDCS montages to enhance language gains.

PB7.3 / P011

Spontaneous speech alterations and evolution in primary progressive aphasia variants

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Poster Blitz session 2, september 22, 2024, 11:00 - 11:20

State of the art. To identify: which features of speech, standard language and gray matter (GM) parameters most effectively distinguish primary progressive aphasia (PPA) variants from each other; how speech evolves over time, and the best combination of features predicting speech evolution.
Methodology. 95 PPA patients underwent the “Picnic Scene” test and a structural MRI. A subgroup of 34 patients underwent a follow-up.
Stepwise-regression-models were used to identify speech, standard-language tests and GM parameters that best distinguished groups. In each PPA group, linear-mixed-effect models were performed for defining speech changes over time, and the prediction analysis was conducted using variables from the best stepwise-models.
Results. The best models to differentiating PPA variants included: left temporal and frontal volumes, and syntax production features when comparing nfvPPA vs svPPA (R2=0.89); lexical contents, syntax complexity, left temporal and insular volumes in nfvPPA vs lvPPA (R2=0.81); left temporal volumes and speech production rates in svPPA vs lvPPA (R2=0.86). Over time, nfvPPA patients showed more phonological errors, which were predicted by syntax production features at baseline. SvPPA and lvPPA showed reduced naming and reduced number of words in sentences, respectively, which were predicted by left temporal volumes.
Conclusion. The speech, standard-language and GM variables that we identified as the most affected at baseline and over time by each PPA variant, may be used in the clinical practice for increasing knowledge on disease progression, prognosis and speech language therapy interventions.

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PB7.4 / P012

The dynamics of auditory working memory impairment in primary progressive aphasia and Alzheimer's disease

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Poster Blitz session 2, september 22, 2024, 11:00 - 11:20

State of the art: Impaired auditory verbal working memory is a diagnostic hallmark of logopenic variant primary progressive aphasia (lvPPA) and non-fluent/agrammatic variant primary progressive aphasia (nfvPPA). Our clinical impression is that temporal factors affect digit span and phrase repetition in patients with PPA. However, the temporal dynamics of auditory working memory in these syndromes is poorly characterised. Here we addressed this issue in lvPPA and nfvPPA.

Methodology: In eight patients with lvPPA, five with nfvPPA, 17 with typical memory-led AD and 18 healthy age-matched controls, we assessed how temporal manipulations of standard auditory verbal working memory tasks (forward digit span and phrase repetition) affected performance. We separately varied the tempo of spoken digit string delivery and the gap between successive phrase repetition trials. Participants also underwent pure tone audiometry and a comprehensive general neuropsychological assessment.

Results: Healthy controls performed consistently under different temporal conditions. However, lvPPA and tAD groups performed worse repeating more slowly presented digit strings, and this effect was particularly marked in the lvPPA group. lvPPA and nfvPPA groups performed worse repeating more rapidly presented sequential phrases.

Conclusions: Our findings open a novel physiological window on working memory in dementia syndromes, and suggest a dynamic physiological lesion of the phonological buffer that is most marked in lvPPA and varies mechanistically between syndromes. Further work is warranted to better characterise this lesion and assess how it impacts communication in patients' daily lives, with a view to developing bespoke communication interventions.

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Practice effects are reduced within prodromal and symptomatic FTD mutation carriers using the Ignite app

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State of the art: Reduced practice effects may be an early feature of genetic FTD. We used a burst testing protocol to examine this in carriers of C9orf72, MAPT, and GRN mutations.

Methodology: 73 participants (47 carriers and 26 controls) completed Ignite, an iPad app consisting of 16 cognitive tests, on 4 occasions over 4 weeks. 7 were Symptomatic Carriers (SCs) with bvFTD, 10 were Prodromal Carriers (PCs) and 30 were Asymptomatic Carriers (ACs). Outcomes were converted to z-scores adjusting for age, sex and education. Statistical analysis was performed in Stata using a mixed model for repeated measures.

Results: Control participants and ACs showed significant improvements across 16/16 tests between timepoint 1 and 4, and on the majority of tests between timepoints 1 and 3. PCs showed significant improvements across 10/16 tests, while SCs showed significant improvements on 2/16. The trajectory of change differed between groups, with Controls showing the greatest improvement between the first 2 timepoints. ACs had a more stable rate of change, while PCs and SCs improved the most between the 2nd and 3rd timepoints. Three timepoints were sufficient to explore practice effects in all groups, while two timepoints were optimal to enhance between group differences in a cross-sectional analysis.

Conclusion: Prodromal and symptomatic mutation carriers show reduced or absent practice effects across a range of computerised cognitive tests. This can be leveraged to enhance between group differences on repeated testing.