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Objective: Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease that results in progressive decline in motor function in all patients and cognitive impairment in a subset of patients. Evidence suggests that cognitive reserve (CR) may protect against cognitive and motor decline in ALS, but less is known about the impact of specific occupational skills and requirements on clinical outcomes in ALS. We expected that a history of working jobs with more complex cognitive demands would protect against cognitive decline, while jobs that require fine and complex motor skills would protect against motor dysfunction.

Participants and Methods: Participants were 150 ALS patients recruited from the University of Pennsylvania's Comprehensive ALS Center. Participants underwent clinical and neuropsychological evaluations within 1 year of ALS diagnosis. Cognitive performance was measured using the Edinburgh Cognitive and Behavioral ALS Screen (ECAS), which includes ALS-Specific (e.g., verbal fluency, executive functions, language, social cognition) and Non-Specific (e.g., memory, visuospatial functions) composite scores. Motor functioning was measured using the Penn Upper Motor Neuron (UMN) scale and the ALS Functional Rating Scale (ALS-FRS). Occupational skills and requirements for each participant were assessed using data from the Occupational Information Network (O*NET) Database. O*NET data were assessed using principal components analysis, and 17 factor scores were derived representing distinct worker characteristics (n=5), occupational requirements (n=7), and worker requirements (n=5). These scores were entered as independent variables in multiple linear regression models using ECAS, UMN, and ALS-FRS scores as dependent variables covarying for education.

Results: Preserved ECAS ALS-Specific performance was associated with jobs that involve greater reasoning abilities (β=2.03, S.E.=0.79, p<.05), analytic skills (β=3.08, S.E.=0.91, p<.001), and humanities knowledge (β=1.20, S.E.=0.58, p<.05), as well as less exposure to environmental hazards (β=-2.42, S.E.=0.76, p<.01) and fewer demands on visual-perceptual (β=-1.75, S.E.=0.73, p<.05) and technical skills (β=-1.62, S.E.=0.63, p<.05). Preserved ECAS Non-Specific performance was associated with jobs that involve greater exposure to conflict (β=0.82, S.E.=0.33, p<.05) and social abilities (β=0.65, S.E.=0.29, p<.05). Jobs involving greater precision skills (β=1.92, S.E.=0.79, p<.05) and reasoning ability (β=2.10, S.E.=0.95, p<.05) were associated with greater disease severity on the UMN, while jobs involving more health services knowledge were associated with worse motor functioning on the ALS-FRS (β=-1.30, S.E.=0.60, p<.05).

Conclusions: Specific occupational skills and requirements show protective effects on cognitive functioning in ALS, while others confer risk for cognitive and motor dysfunction. Preserved cognitive functioning was linked to a history of employment in jobs requiring strong reasoning abilities, social skills, and humanities knowledge, while poorer cognitive functioning was linked to jobs involving a high risk of exposure to environmental hazards and high visuo-perceptual and technical demands. In contrast, we did not find evidence of motor reserve, as no protective effects of occupational skills and requirements were found for motor symptoms, and jobs involving greater precision skills, reasoning abilities, and health services knowledge were linked to worse motor functioning. Our findings offer new insights into how occupational history may protect against cognitive impairment or confer elevated risk for cognitive and motor dysfunction in ALS.

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6 Remote Smartphone Cognitive and Motor Testing in Frontotemporal Dementia Research: Feasibility, Reliability, and Validity

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Objective: Therapeutics targeting frontotemporal dementia (FTD) are entering clinical trials. There are challenges to conducting these studies, including the relative rarity of the disease. Remote assessment tools could increase access to clinical research and pave the way for decentralized clinical trials. We developed the ALLFTD Mobile App, a smartphone application that includes assessments of cognition, speech/language, and motor functioning. The objectives were to determine the feasibility and acceptability of collecting remote smartphone data in a multicenter FTD research study and evaluate the reliability and validity of the smartphone cognitive and motor measures.

Participants and Methods: A diagnostically mixed sample of 207 participants with FTD or from familial FTD kindreds (CDR®+NACC-FTLD=0 [n=91]; CDR®+NACC-FTLD=0.5 [n=39]; CDR®+NACC-FTLD≥1 [n=39]; unknown [n=38]) were asked to remotely complete a battery of tests on their smartphones three times over two weeks. Measures included five executive functioning (EF) tests, an adaptive memory test, and participant experience surveys. A subset completed smartphone tests of balance at home (n=31) and a finger tapping test (FTT) in the clinic (n=11). We analyzed adherence (percentage of available measures that were completed) and user experience. We evaluated Spearman-Brown split-half reliability (100 iterations) using the first available assessment for each participant. We assessed test-retest reliability across all available assessments by estimating intraclass correlation coefficients (ICC). To investigate construct validity, we fit regression models testing the association of the smartphone measures with gold-standard neuropsychological outcomes (UDS3-EF composite [Staffaroni et al., 2021], CVLT3-Brief Form [CVLT3-BF] Immediate Recall, mechanical FTT), measures of disease severity (CDR®+NACC-FTLD Box Score & Progressive Supranuclear Palsy Rating Scale [PSPRS]), and regional gray matter volumes (cognitive tests only).

Results: Participants completed 70% of tasks. Most reported that the instructions were understandable (93%), considered the time commitment acceptable (97%), and were willing to complete additional assessments (98%). Split-half reliability was excellent for the executive functioning (r's=0.93-0.99) and good for the memory test (r=0.78). Test-retest reliabilities ranged from acceptable to excellent for cognitive tasks (ICC: 0.70–0.96) and were excellent for the balance (ICC=0.97) and good for FTT (ICC=0.89). Smartphone EF measures were strongly associated with the UDS3-EF composite (ß's=0.6–0.8, all p<.001), and the memory test was strongly correlated with total immediate recall on the CVLT3-BF (ß=0.7, p<.001). Smartphone FTT was associated with mechanical FTT (ß=0.9, p=.02), and greater acceleration on the balance test was associated with more motor features (ß=0.6, p=0.02). Worse performance on all cognitive tests was associated with greater disease severity (ß's=0.5–0.7, all p<.001). Poorer performance on the smartphone EF tasks was associated with smaller frontoparietal/subcortical volume (ß's=0.4–0.6, all p<.015) and worse memory scores with smaller hippocampal volume (ß=0.5, p<.001).

Conclusions: These results suggest remote digital data collection of cognitive and motor functioning in FTD research is feasible and acceptable. These findings also support the reliability and validity of unsupervised ALLFTD Mobile App cognitive tests and provide preliminary support for the motor measures, although further study in larger samples is required.

Paper Session 13: Neuroanatomy | Neuroimaging topics