Multimodal, scalable and affordable neurocognitive biomarkers

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Background: Alzheimer's disease (AD) biomarkers targeting Aβ, Tau, and Neurodegeneration are creating unprecedented opportunities for its early detection. Adhering to the A/T/N biomarker framework though comes with several challenges, mainly due to high costs. The Joint Program for Neurodegenerative Diseases (JPND) suggested that efforts should also be directed to harmonise promising cognitive tests. The group recommended the Short-Term Memory Binding (STMB) and Selective Reminding Tests (SRT). To that aim, we need to explore if such memory markers hold differential sensitivity to the AD continuum (Aim1). Whether such deficits are observable in preclinical and prodromal stages of AD regardless of the disease variants (sporadic and familial) is also unclear (Aim2). Moreover, whether combining these cognitive makers with EEG and Eye-Tracking (ET) would yield neurocognitive biomarkers for AD (Aim3) needs further research.

Methods: Memory tests recommended by the JPND and standard neuropsychological assessments entered harmonised research protocols supporting three large international collaborations. Aim1: Project 1 (UK based) involved 150 participants (HC=70, MCI=80) and Project 2, ran in collaboration with GERO, Chile, involved 264 participants (HC=37, SCC=117, MCI=79, ADD=31). Aim2: Project 3: ran in collaboration with the Neuroscience Group, University of Antioquia, Colombia involved 334 participants (HC=210, AC=124). Aim3: The STMBT combined with EEG was recorded from 20 participants and combined with Eye-tracking from 71 participants all from Project 3.

Results: Aim1: STMB deficits are detectable from the very early stages of AD (HC>SCC>(MCI=ADD)) before associative memory deficits (SRT) become apparent ((HC=SCC)>MCI>ADD). Aim2: Such deficits are also prominent in AC when their associative memory abilities remain intact. Aim3: When combined with EEG, STMB differentiated AC from HC with 89% accuracy while with ET classification accuracy reached 98%.

Conclusion: The collaborative efforts here presented suggest that AD can be detected with appropriate, affordable, culture-free and scalable neurocognitive biomarkers recently recommended by the JPND before clinical manifestations of the disease become apparent.

Glossary**:** AC = Asymptomatic Carriers of the mutation E280A-PSEN1; ADD = Alzheimer's disease Dementia; GERO = The Geroscience Center for Brain Health and Metabolism; HC = Healthy Controls; MCI = Mild Cognitive Impairment; SCC = Subjective Cognitive Complaint; STMBT: Short-Term Memory Binding Test.

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