Better Memory with Literacy Acquisition Later in Life

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Study protocol

Participants: We aim to recruit a total of 120 participants (60 for the intervention and 60 as a control group).
Inclusion criteria include any gender, age between 40 and 89 years old, illiteracy (TOFHLA score <53) and availability to participate in the study for at least 12 months.
Exclusion criteria will be: A) Presence of remarkable cognitive complains and/or decompensated psychiatric illness (depression and anxiety) and/or current substance abuse such as alcohol and illicit drugs use. B) Objective cognitive impairment: 2 standard deviations or less for age and education on the Mini-Mental State Evaluation (MMSE) and/or 6 or less points on the delayed recall task from the Brief Cognitive Battery. C) History of previously diagnosed dyslexia D) Formal MRI contraindications including metal or claustrophobia. E) Severe structural lesions detected by MRI.
Informed consent will be written in accessible language and collected using the approach "teach-to-goal developed for vulnerable populations.

First, we will do pair matching with the 120 participants dividing them into two clusters paired for age, sex and baseline non-verbal intelligence and literacy level (by TOFLHA). Next, within each pair, one cluster is randomized to receive the intervention (n=60), and the other cluster receives the placebo (n=60). Based on our pilot project and historical data, we calculate an attrition rate of 20%. Thus, the final sample is expected to have 96 individuals. We will reassess the participants' cognition and neuroimaging after 6 months.

Literacy and cognitive reserve assessment: Reading comprehension and numeracy skills will be evaluated using the Test of Functional Health Literacy in Adults (TOFHLA) that has been validated for Brazilian Portuguese. A score of or lower 53 defines illiteracy. Global cognitive reserve will be assessed with a structured questionnaire available in Portuguese, that includes years of education, leisure activities and occupational attainment. Sociodemographic features, the level of physical exercise, smoking, and alcohol habits, as well as the presence of psychiatric illness, will be addressed with specific questionnaires.

Cognitive evaluation: Includes the MMSE, the Brief Cognitive Battery, and the Free and Cued Selective Reminding with Immediate Recall (FCSR-IR). The first two tests will assess global cognition and will be used as a screening for the presence of baseline cognitive impairment. The FCSR-IR includes a controlled learning phase, which provides the basis for encoding specificity and effective cued recall. The FCSR-IR Free Recall sum-of-attempts will be the proxy for episodic memory. We will also test other cognitive abilities than episodic memory such as non-verbal intelligence (Beta-3 test), attention (digit span), reading abilities (Human Frontier Science Program reading test), words and sentence repetition, rapid naming of colors, letters, numbers, and objects and verbal comprehension (Token test). Although scores for all tests described are known to be affected by literacy level, this effect will be accounted for because our participants will all have a low literacy level.

Neuroimaging acquisition and analysis: We will use the ADNI-3 protocol to acquire Diffusion tensor Imaging (DTI), resting-state functional MRI (rsfMRI), Fluid Attenuation Recovery and 3D-T1 images pre-and post-intervention in a 3T Siemens Verio scanner. For the rsfMRI analysis, a filter will be applied to attenuate noise frequencies of raw signal. We will then place a seed in the right and left hippocampus (HC) with an automated atlas that will be used to assess coherent blood oxygen level-dependent activity (BOLD) between this region and the ventral medial prefrontal cortex, corresponding to the HC-VMPFC intrinsic

functional connectivity (iFC). Both HC and VMPFC will be used in the region of interest (ROI) analyses, and ROI-averaged values for iFC and gray matter values will be calculated pre - and post-intervention.

Literacy training (intervention): The basic-literacy training will be given for 6 months. At baseline, participants will be randomized into four classes of 30. Co-I Maciel, who is an expert in adult education, will oversee the classes and meet the teachers periodically, and each class will count with a certified and experienced lead teacher and teacher aid. Two of the classes of 30 each will be the intervention group. They will receive literacy training based on analytical and phonemic methods for enabling reading and writing. The two other classes of 30 each will be the placebo group. The placebo group will have access to non-literacy classes offered at the adult school, including geography, history, informatics, and sciences, but no literacy-training.
Both the intervention and the placebo groups will attend classes of two hours/day for four days/week. The teachers will record attendance. The follow-up neuroimaging and neuropsychology testing will be done at the 6 months mark. The informed consent will have a session explaining that participants will be randomly assigned to participate in the intervention or placebo group in the first 6 months so that they will be blind to which group they were assigned for at baseline. Based on the literacy-program experience, we expect a dropout rate of 20%. Thus, we expect to have 96 participants concluding the study. Participants who drop out will be monitored by phone calls every three months and will be also reassessed after 6 months, if interested. We will compare the dropout group with the groups that kept the training to see whether there were differences in intelligence or sociodemographic aspects.

Blood samples: At the baseline, we will collect blood samples of participants to assess the apolipoprotein E genotype. Upon participant consent, plasma and serum samples will be stored for future analysis of potential peripherical markers associated with cognitive reserve.