Neural mechanisms of brain plasticity with cognitive training in healthy seniors

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Introduction: Extensive evidence has documented continuous age-related cognitive declines, even in the absence of a diagnosed dementia. A growing trend suggests that <u>cognitive training</u> may have a beneficial impact on preventing and potentially reversing age-related functional decline. However, neurobiological basis of this improvement is still poorly understood. In this study, we utilized three MRI-based measurements, i.e. pseudo-continuous arterial spin labeling (pCASL) MRI, resting state functional connectivity MRI (fcMRI), and diffusion tensor imaging (DTI), to examine brain changes across 3 time points pre, mid, and post training (12 weeks) in a randomized sample (n=37) who received cognitive training versus a control group.

Methods: A total of 37 cognitively normal older adults (mean age=62.9±3.6) were randomized to two different groups: cognitive training (CT) and control (CN). The training group underwent an evidenced-based, manualized cognitive training program referred to as gist reasoning for 3 hours per week for 12 weeks (Anand et al., 2011). The participants' MRI scans (i.e. pCASL, fcMRI, DTI) were performed on a 3T Philips scanner at three time points: Baseline (T1), mid-training at 6 weeks (T2), and post-training at 12 weeks (T3). The pCASL data underwent typical preprocessing and absolute CBF (aCBF) maps were estimated (Aslan et al., 2010). Then, the global CBF value and regional CBF (via VBA) were compared between the groups. fcMRI data were also routinely preprocessed and two major networks (seed-based) were characterized: default mode network (DMN) and central executive network (CEN). An ROI analysis of the networks was performed, DMN: posterior cingulate (PCC) and middle frontal (MFC) cortices and CEN: dorsolateral prefrontal (DLPFC) and inferior parietal (IPC) cortices. DTI images were processed in DTIstudio and left uncinate fasciculus (UF) was delineated both manually (Wakana et al., 2006) and automatically (by importing significant CBF clusters from VBA). Last, a battery of neurocognitive measures was administered at each time point, i.e. T1, T2, and T3, to assess abstract reasoning, executive function, memory and complex attention. Statistical Analysis involved a "Group x Time" Interaction with two orthogonal polynomial contrasts: Linear (increase from T1 to T3) and Quadratic (maximal increase at T2) for imaging and neurocognitive measures.

Results: <u>Cognition</u>: The CT group also showed monotonic improvements in strategic reasoning (p=.002) and executive function domains (p=.05). <u>Global CBF</u>: The global CBF at T1 for both CN and CT groups were similar; 47.2 and 47.0 ml/100g/min, respectively (p=0.98). The CT group's global CBF increased by 7.9% from T1 to T2 and remained elevated (7.9%) at T3 (p=.002). The control group showed no such changes. <u>Regional CBF</u>: To evaluate which brain regions may have contributed to the CBF increase, we conducted a voxel-wise analysis (VBA). Figure 1 shows the VBA results CT>CN. The cognitive training group showed a significant increase in blood flow at T3 in left middle temporal, left superior medial, left inferior frontal gyri compared with the control group. Additionally, the cognitive training group showed a peak increase at T2 in the inferior temporal gyrus, precuneus, and posterior cingulate gyrus compared with the control group. The control group did not show any significant increases at T2 or T3 in CBF. <u>Functional connectivity:</u> Since most of the increased rCBF findings involved two distinct brain networks: default mode network (DMN) and central executive network (CEN), we focused on these two networks in the fcMRI examination. Figure 2A shows the average functional connectivity maps (i.e. z-score maps) in the DMN and CEN for the CT group, in which is seen qualitatively that functional connectivity increases over the training sessions—linearly (T1-to-T3) in the DMN (p=.04) and with a maximum increase at T2 in the CEN (p=.03). Moreover, it is important to point out that temporal characteristics of functional connectivity changes mirrored those of the blood flow. Specifically, DMN's functional connectivity and CBF both increased monotonically (T1-to-T3) (Figure 2B top panel), whereas CEN's functional connectivity and CBF both showed peak increases at T2 (Figure 2B bottom panel). <u>DTI:</u> Because blood flow increased in left middle temporal and left superior medial frontal gyri, we hypothesize that the white matter structure that connects the two regions (Figure 3), i.e. uncinate fasciculus (UF), would most likely show a structural change. Consistent with our expectation, the FA of left UF showed a monotonic increase from T1 to T3 compared to the control group (p=.003), which signals better white matter integrity following cognitive training. <u>Relationship between imaging marker and cognition</u>: Changes in strategic reasoning and executive function domains were found to be correlated with changes in CBF. Specifically, change in TOSL (a test reflecting strategic reasoning ability) and WAIS-III Similarities (a test reflecting executive function) were found to correspond to changes between groups in brain blood flow in several brain regions.

Discussions: Our principal finding was that strategy-based cognitive training has the potential to reverse some of the negative consequences of age-related functional and structural brain losses. Specifically, we found that the training positively altered the intrinsic activity of the brain at rest as well as its structural connectivity. To our knowledge, this work provides the first convergent evidence of significant positive neurophysiological and neuroanatomical changes across 3 brain measures at rest, namely: CBF, functional, and structural connectivity. These results provide preliminary evidence that neural plasticity can be harnessed to mitigate brain losses with cognitive training in seniors.
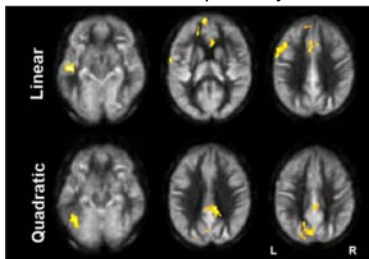

Fig 1. Results of CBF VBA superimposed on an average CBF map for linear and quadratic interaction contrasts at p<0.05 (FWE corrected) and $k \geq 1904$ mm^3.
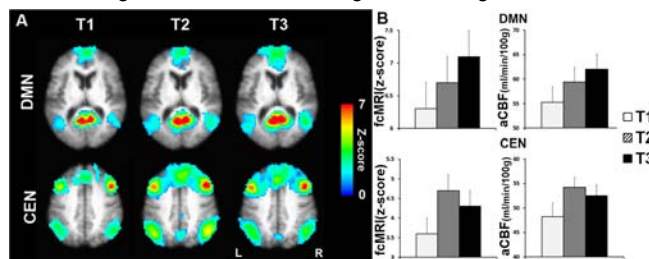

Fig 2. A. The average functional connectivity maps (i.e. DMN and CEN) of the CTgroup are overlaid on their average T1-weighted image. **B.** Mean change in fcMRI z-scores (left column) and mean change in aCBF (right column) are shown for DMN (linear) and CEN (quadratic) across time periods.
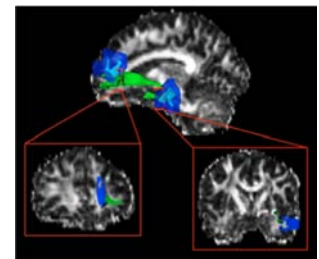

Fig 3. A representative participant's uncinate fasciculus (green) is overlaid on his fractional anisotropy map. The frontal and temporal ROIs (light blue) were expanded twice (dark blue) to ensure expansion into white matter.