Randomized controlled trials of non-pharmacological interventions for healthy seniors: Effects on cognitive decline, brain plasticity and activities of daily living-A 23-year scoping review

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Supplementary Table 2 - MULTI-DOMAIN COGNITIVE INTERVENTIONS - for abbreviations we refer to Table 1						
Author/year & Research question	**Population & Design**	**Nature and duration of intervention(s)**	**MRI measures/derivates; behavioral variables**	**Main findings: brain plasticity**	**Main findings: behavior & relation to brain changes**	**Conclusions/ remarks**
Bubbico et al., 2019 Can second language learning in HE over 4 months induce functional reorganization of the brain?	26 HE (59-79y, M=68y) RCT: EG - CON Unbalanced gender partition: M/F: EG 2/12, CON 5/7 and age EG M=70y > CON M=66y	**Second language learning** EG: English course for beginners CON: none EG – 1.5h/wk + 30min homework/wk - 4 months (total: 2h/16wks)	Whole-brain Seed-based RS-fMRI/FC; Seed: Posterior Cingulate Cortex (PCgC) of the Default Mode Network (DMN) T0 – T1 (post-training) BEHAVIOR: global cognition (MMSE), short- and long-term episodic memory, attention (trail making tests), verbal fluency and EF (frontal assessment battery).	EG *vs.* CON, T1 *vs.* T0: FC increase of the PCgC with R IFG, R SFG, L SPL	The increase in FC was associated with an improvement in overall cognitive performance (MMSE; far transfer). In fact, the CON group showed superior MMSE performance at T0 and decreased in performance at T1, whereas the EG group remained stable. No significant differences occurred for the other cognitive tests.	✓A 4-month second language training course starting at beginner level in HE induced increased FC of the DMN (PCgC) with the R IFG, R SFG and L superior parietal lobule. ✓This FC increase correlated to improved global cognition. Such an intervention may thus contribute to healthy aging.
Carlson et al., 2009 Can participating in "Experience Corps" (EC), a social service program, improve age-vulnerable executive function, and change functional brain activity during a flanker test in a high-risk population of HE?	17 HE (>60y, M=68) Community dwelling African-American women with low education, low income, and marginally low MMSE scores EG - CON No genuine RCT, groups matched for all sociodemographic variables	**Real-life social intervention** EG: Multimodal experience corps (EC) activity program (a social service program designed to help elementary school children with reading achievement, library support, and classroom behavior) CON: none (waiting list) EG: 15h/wk – 6 months within the academic year	Task fMRI: /event related design: flanker task (interference control) ROI analyses: ACC and L & R dorsal and ventral PFC T0 – T1 (post-training) BEHAVIOR: Eriksen flanker task (during fMRI); interference: RT to inconsistent trials minus RT consistent trials	EG *vs.* CON, T1 *vs.* T0 BOLD activity increase in L vlPFC, L dlPFC & ACC correlating to improved interference reduction	EG *vs.* CON, T1 *vs.* T0: enhanced interference reduction EG: The activation pattern modification correlated with behavioral improvement	✓Participating in a social service program over 6 months, induced gains in EF and increased prefrontal cortical activations during a flanker test in HE with an elevated risk for cognitive impairment. ✓Postretirement lifestyle behavior implicating cognitive and physical activities within a social setting can confer important cognitive and brain benefits for older adults.
Chapman et al., 2015 Can complex cognitive reasoning training over 3 months induce improvements in general cognitive and brain function and WM integrity in HE?	Original and behavioral (M=sample 37 HE (57-71y, M=63); final DTI sample 31 HE (M=63) RCT: EG - CON	**Non-computerized gist-reasoning intervention** EG: complex cognitive training "gist reasoning" (strategy based) in small groups (n≤5). Involves 1) strategic attention, 2) integrated reasoning, and 3) innovation	DTI/FA (structural) 1) ASL, RS-fMRI (functional) i. CBF ii. whole-brain functional connectivity 2) ROI analyses in PCgC and middle frontal cx (part	STRUCTURAL: EG, T0 *vs.* T1 *vs.* T2: monotonic increase of FA in L uncinate fasciculus (= increased WM integrity) FUNCTIONAL: EG *vs.* CON, T2 *vs.* T0: enhanced FC in DMN and CEN,	Behavior EG *vs.* CON, T2 *vs.* T0: improved strategic reasoning and EF performance Increased CBF correlated to improved strategic reasoning and EF performance	✓Complex cognitive gist reasoning increased white matter integrity in the left uncinate fasciculus that normally shows age-related decline. ✓The gist reasoning increased resting-state neural activity and connectivity in the DMN and CEN in combination with increased CBF in these networks.

		CON: none EG: 1h/wk, supervised + 2×1h homework/wk – 3 months	of DMN) & dlPFC and IPC (part of CEN) T0, T1 (6 weeks), T2 post-training 3 months *NB T0 is called T1 in this study and so forth* BEHAVIOR: neuropsychological battery (strategic reasoning, EF, memory (CVLT), complex attention)	mirrored by increased CBF in the same regions Increased CBF in 1) L MTG, L superior medial & L inferior frontal gyri (linear increase = DMN) 2) L ITG, L precuneus and posterior cingulate gyrus (quadratic pattern = CEN)		✓CBF increase correlated with improved strategic reasoning and EF performance. ✓This work provides the first convergent evidence of significant positive neurophysiological and neuroanatomical changes across 3 brain measures: CBF, functional, and structural connectivity, associated with improved gist reasoning.
Hardcastle et al., 2022	58 HE (65-89y, M=71) RCT EG -CON	**Computerized multidomain cognitive training** EG: web-based platform, 8 tasks: 4 attention/speed, 4 working memory; adaptive Active CON: education (watching videos answering questions) 5*40min/wk – 12-week	RS-fMRI 4 RS networks Frontoparietal Control, Dorsal Attention, DMN, Cingulo-Opercular T0, T1 (12 weeks) BEHAVIOR Trained tasks	EG *vs.* CON, T1 *vs.* T0: no group interactions over time EG, T1 *vs.* T0: increased FC within Frontoparietal Control network	EG *vs.* CON, T1 *vs.* T0: interactions in 7/8 cognitive outcomes, in favor of EG : EG, T1 *vs.* T0: all 8 cognitive outcomes improved Double Decision task (attention and processing speed) improvement correlated positively to within-network FC increase in the Frontoparietal Control network	✓The frontoparietal control network may underpin improvements in divided attention and speed-of-processing following multidomain cognitive training ✓Results show efficacy of 12-week multimodal cognitive training to produce improvements in all tasks, specifically a large magnitude of proximal improvement in the Double Decision task
Kawata et al., 2022 Can auditory or cognitive training or their combination enhance brain plasticity and cognitive performance?	50 HE (M=68) RCT EG1-3 - CON	**Auditory and cognitive training** Adaptive training: EG1: auditory-cognitive EG2: auditory EG3: cognitive Active CON: non-adaptive low-level training 2x1h/wk – 4 weeks	VBM Regional GM volume (rGMV) FC T0 – T1 (post-training) BEHAVIOR: Digit-Cancellation (D-CAT) Logical Memory (LM) DSF/DSB Pure-Tone Audiometry (PTA)	EG1 *vs.* EG2-3 & CON, T1 *vs.* T0: GM increase in R dlPFC, L ITG, L SFG, L OFC, R Cb (lobule 7 Crus 1) EG1-2 *vs.*EG3&CON, T1 *vs.* T0*:* GM increase in L temporal pole EG1&3 *vs.* EG2&CON, T1 *vs.* T0: GM increase R inferior occipital gyrus, R Cb (lobule 7 Crus 1), R ITG	EG1 *vs.* EG2-3 & CON, T1 *vs.* T0: no auditory or cognitive improvement EG1-2 *vs.*EG3&CON, T1 *vs.* T0*:* improved PTA EG1&3 *vs.* EG2&CON, T1 *vs.* T0: improved LM and D-CAT scores No significant correlation between changes in auditory and cognitive measures over time and brain structural changes	✓Post-intervention, AC (Auditory-Cognitive) training led to neural changes but did not improve cognitive or auditory functions ✓Auditory training showed improvements in auditory performance and specific brain regions related to auditory processing. ✓Cognitive training showed improvements in cognitive measures (LM and D-CAT) and changes in brain regions involved in cognitive tasks ✓No significant correlation between changes in auditory and cognitive measures over time and brain structural changes.
Kim et al., 2015 Can robot assisted multi-domain cognitive training *vs.*	71 HE (≥60y M=67 of original sample of 85 HE); RCT1:	**Computerized robot-assisted intervention** EG-r: robot-assisted multi-domain cognitive training	SBM/CT T0 & T1 post-training (12 weeks)	EG-r & EG-t *vs.* CON T1 *vs.* T0: less cortical thinning in bilateral mPFC and R MTG EG-r *vs.* EG-t, T1 *vs.* T0: less	EG-r: positive correlation between CT changes in L temporo-parietal junction and L ITG and EFs scores EG-t: positive correlation between CT	✓Traditional and robot assisted multi-domain cognitive training induced decreased CT thinning in the frontotemporal association cortices compared to the control

traditional multi-domain training over 12 weeks alter cortical thickness in HE?	EG - CON RCT2: (double blind & stratified by age, sex, education, neuropsychological tests scores, physical activity, cardiovascular risk factors & number of APOE e4 alleles): EG1 - EG2	EG-t: traditional multi-domain cognitive training CON: None Both interventions comprised memory, calculation, language, EF and visuospatial training EG-r, EG-t & CON: pre-baseline dementia prevention courses 2h/wk – 5 days EG-r, EG-t - 5×90min/wk – 3 months	Behavior: -ADAS-cog -7 subtests of the CANTAB	cortical thinning in L & R ACC, and small areas in R inferior temporal cx CON *vs.* EG-r & EG-t greater mean CT thinning	changes in R ITG and R subgenual ACC and visual memory scores	group. Robot assisted training induced additional decreased thinning in the ACC. ✓CT changes in the robot group correlated to executive function performance. ✓Robot assisted training induced more CT changes than traditional training, but this may be also explained by the individual feedback provided to the robot group participants.
Lampit et al., 2015 What are the neural underpinnings of 3-month computerized cognitive training and their time course in HE?	12 HE (>65y, M=71), original sample n=18, 4 drop-outs) RCT (double blind): EG – CON EG: n=7, 1 male CON: n=5, 5 males	**Computerized cognitive intervention** EG: attention, processing speed, memory, EF and language (COGPACK, see Table 1) CON: watching videos and answering questions EG & CON: 3×1h/wk – 3 months	1) VBM 2) SBM/CT, small volume correction 3) DTI/TBSS 4) RS-fMRI: seed-based regions analysis (Hc + PCgG) T0, T1: at 3 weeks, T2 post-training (3 months) BEHAVIOR: composite cognitive score "global cognition" (processing speed, memory, EF)	STRUCTURAL EG *vs.* CON interaction Time × Group: GM density increase in R post-central gyrus at T1 *vs.* T0 and T2 *vs.* T0, greater increase at T2 than at T1 EG *vs.* CON, T2 *vs.* T0, increased CT in L fusiform gyrus & supra marginal and post-central gyri No significant DTI results FUNCTIONAL EG *vs.* CON, T1 *vs.* T0: FC between PCgG and R SFG decreased in the EG and increased in the CON EG *vs.* CON, T1 *vs.* T0: FC between the R Hc and the L STG increased in the EG and decreased in the CON At T2 FC changes faded	BEHAVIOR (global cognition): EG > CON, T1 *vs.* T0 & T2 *vs.* T0; greater effect size (Cohen's d) at T2 than at T1 STRUCTURAL & BEHAVIOR: EG *vs.* CON, T2 *vs.* T1 *vs.* T0: positive correlation between changes in GM density in the post-central gyrus and increase in the global cognition score FUNCTIONAL & BEHAVIOR FC changes at T1 *vs.* T0 between the CgG and R SFG correlated inversely with global cognition at T2 FC changes at T1 between R Hc and STG correlated positively with global cognition at T2	✓Computerized multi-domain cognitive training progressively increased GM density in the post-central gyrus over 3 months; this increase was positively correlated to a global cognition score. ✓About half of the GM density increase occurred at T1 after 3 weeks of 3×1h training, and the global cognition performance also increased gradually over time. ✓FC changes induced by training occurred early (T1, 3 weeks) but faded at T2 (3 months). FC changes were temporally and spatially different from structural changes and preceded brain structural and cognitive change. ✓Given the very small number of participants, reliability and validity cannot be ensured

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