Gerontology & Geriatrics: Research

Open Access

Austin Publishing Group

Review Article

# The Neural Correlates of Physical and Cognitive Training in the Prevention of Age-Related Cognitive Decline: A Review

**Angeles Garcia*, Luedke Angela, Itorralba Justine, Fernandez-Ruiz Juan**
Department of Medicine and Neuroscience Centre, Queen's University, Canada

***Corresponding author:** Angeles Garcia, Department of Medicine and Neuroscience Centre, Queen's University, 340 Union Street, Rm1-175 Kingston, ON, Canada

**Received:** November 20, 2015; **Accepted:** February 18, 2016; **Published:** February 22, 2016

**Abstract**

Physical activity and cognitive training are heavily studied non-pharmacological interventions for the deceleration of age-related cognitive decline and the prevention of dementia. Epidemiological studies and randomized control trials have found evidence that both of these lifestyle modifications administered separately or together, may provide improvements in overall cognition. While evidence in support of physical and cognitive activity is vast, the neural underpinnings of this training-induced cognitive improvement have yet to be fully elucidated. This review will attempt to combine the most recent research regarding the neural correlates of cognitive enhancement driven by physical and cognitive training interventions. A heavy focus will be placed on structural brain volume, functional MRI, functional connectivity, and white matter integrity changes before and after physical or cognitive training interventions.

**Keywords:** Exercise interventions; Cognitive training; Healthy aging; Neural plasticity

## Introduction

Healthy cognitive aging is associated with many neurophysiological and cognitive changes. Various aspects of cognition demonstrate age-related declines, including memory, attention, and processing speed [1]. Additionally, healthy aging is associated with neuroanatomical changes in both gray and white matter, functional connectivity patterns, and functional brain activations that can all be detected using various imaging techniques. Therefore, interventions decelerating age-related declines are needed, especially at its earliest stages, to prevent or postpone subsequent conversion to early dementia and Mild Cognitive Impairment (MCI).

Of these interventions, cognitive training and physical activity have been the most heavily studied. Increased physical activity has not only been linked to health benefits [2], but also to the maintenance or enhancement of cognitive functioning [3,4]. Increasing use of technology amongst seniors combined with the rising popularity of programs like Lumosity and Brain Age, have led to heightened interest in the efficacy of these personalized cognitive training programs. Recently, research concerning physical activity and cognitive training in the elderly has focused on determining the neural underpinnings of lifestyle-induced improvements. We reviewed recent Randomized Controlled Trials (RCTs) in the healthy elderly population with a focus on the neural correlates of training-induced changes.

## Methods

We searched electronic databases (PubMed, Web of Science, and Medline) for RCTs investigating the impact of physical exercise and cognitive training on cognition and the brain. Search terms included: healthy aging, cognition, exercise, physical activity, exercise training, brain, white matter, grey matter, cognitive aging, cognitive training, cognitive stimulation, intellectual stimulation, intellectual activity, and brain games. Due to discrepancy in the way different studies define "cognitive training," search terms including the words brain games, intellectual, stimulation, and activity were used to prevent exclusion of any potentially relevant RCTs.

Since the focus of our review was on interventions in healthy aging, articles had to include cognitively normal elderly treatment and control groups with participants aged 50 and above, include both a cognitive and neurophysiological measure, and have at least 10 participants per intervention group. Additionally, each RCT had to have a clearly defined intervention protocol with outcome measures collected at least before and after the intervention administration. In the interest of novelty, RCTs conducted before 2004 were excluded.

While there were a large number of studies testing the efficacy of cognitive training and physical exercise in healthy aging, studies obtaining both behavioral and neurophysiological measures pre- and post-intervention were not as prevalent. Furthermore, the types, frequencies, and durations of these interventions were markedly variable between studies, which had the potential to introduce a fair amount of bias when comparatively analyzing these randomized control trials. Therefore, since there were so few of these types of RCTs found, we did not include any parameters quantifying or assessing the risk of bias of individual studies.

## Results

Our initial database search yielded a total of 8587 records. After eliminating irrelevant studies, duplicates, and studies that were published before 2004, we were left with 364 records. Those that were considered irrelevant or out of scope were review articles, studies that applied interventions to the clinical population (i.e. Alzheimer's




**Citation:** Garcia A, Angela L, Justine I, Fernandez-Ruiz Juan. The Neural Correlates of Physical and Cognitive Training in the Prevention of Age-Related Cognitive Decline: A Review. Gerontol & Geriatr Res. 2016; 2(1): 1006.

**Table 1:** Summary of RCTs involving physical activity and cognitive training using structural volume outcome measures.

| *Study* | *Sample Size* | *Mean Age (SD)* | *Intervention Description* | *Frequency/ Duration* | *Outcome Measures* | *Important Findings* |
|---|---|---|---|---|---|---|
| Colcombe et al., [9] | $n_E$ = 59<br>$n_{CY}$=20 | T = 65.5<br>CE = 66.9<br>CY = age range (18-30) | T1 = Aerobic<br>C = non-aerobic (stretching and toning) | 3 x 1-hr per week/ 6 months | MMSE, structural MRI, $VO_2$ | Aerobic group had increase in $VO_2$, GM volume in frontal lobes and white matter volume in ACC |
| Erickson et al., [10] | $n_{T1}$ = 60<br>$n_c$ = 60 | T1 =67.6 (5.81)<br>C =65.5 (5.44) | T1=Aerobic (walking)<br>C = Non-aerobic(stretching and toning) | 3 x 40-mins per week/ 1 year | Hippocampal volume, serum BDNF, spatial memory task, $VO_2$ | 1) Increased bilateral anterior hippocampal volume in aerobic group<br>2) Change in hippocampal volume correlated with improved memory and serum BDNF |
| Mortimer et al., [11] | $n_{T1}$= 30<br>$n_{T2}$= 30<br>$n_{T3}$= 30<br>$n_C$= 30 | $T_1$= 67.3(5.3)<br>$T_2$=67.8 (5.0)<br>$T_3$=67.9 (6.5)<br>C=68.2 (6.5) | T1 = Tai Chi<br>T2 = Walking<br>T3 = Social Interaction<br>C = no intervention | 3 x 50-60-min per week/ 40 weeks | WAIS-R DS and ST, BCT, ROCF (copying and recall), Stroop Test, CAVLT, CVFT, TMT, CDT, BNT, DRS, structural MRI | 1) Improved scores on CAVLT, TMT, CVFT, DRS in Tai chi group<br>2) Social interaction group had increased scores on CVFT<br>3) Increased whole brain volume in Tai chi and social group |
| Ruschewey et al., [12] | $n_{T1}$= 20<br>$n_{T2}$ =21<br>$n_C$= 20 | T1 = 60.1 (6.2)<br>T2 = 62.5 (6.4)<br>C= 58.1 (6.7) | T1 = Nordic Walking<br>T2 = Gymnastics<br>C= no intervention | 3-5 x 50-mins per week/6 months | Lactate step test, G-AVLT, BDI, serum levels of G-CSF, BDNF, catecholamines, structural MRI | Physical exercise associated with increased episodic memory scores, GM volume in prefrontal and cingulate regions, and a trend for increased peripheral BDNF |
| Liu et al., [13] | $n_{T1}$= 46<br>$n_{T2}$= 47<br>$n_{T3}$= 42 | T1 = 69.4 (3.0)<br>T2 = 69.5 (2.7)<br>T3 = 70.0 (3.3) | T1 = Resistance training twice per week<br>T2 = Resistance training once per week<br>T3 = Balance and tone training twice per week | 1-2 x 60 mins per week/ 1 year | Primary: Stroop test<br>Secondary: TMT, WMS forward backward verbal digit span, gait speed, muscular function, whole – brain volume | 1) Resistance training (once and twice per week) improved Stroop scores compared to balance and tone training<br>2) Resistance training twice per week resulted in improved peak muscle power<br>3) Whole – brain volume was reduced in both resistance training groups compared to balance and tone training |
| Mozolic et al., [14] | $n_T$ = 23<br>$n_C$ = 25 | 69.5<br>T = 69.5 (3.2)<br>C = 69.5 (2.5) | ***Treatment Group: Attention and Distractibility Training***<br>Laboratory-Based Auditory and Visual SA<br>***Active Control Group:***<br>Educational program | 1 x 1-hr per week/ 8 weeks | ASL, GM volume, fMRI modality distraction task | 1) Larger increases in resting CBF to the PFC<br>2) No alterations in GM volume after training<br>3) Improved distraction suppression<br><br>CBF increases correlated with reduced distraction |
| Engvig et al., [15] | $n_{TSMI}$ = 19<br>$n_{TH}$ = 22<br>$n_C$ =20 | $T_{SMI}$ = 60.9 (10.4)<br>$T_H$ = 61.3 (9.4)<br>$C_H$ = 60.3 (9.1) | ***Method of Loci (MoL) Memory Training***<br>VM | 4 x 1-hr per week/8 weeks | CVLT-II, Memory Questionnaire, ROCF, GM volume | 1) Increased CVLT-II post-training<br>2) Regional cortical volume increases in the bilateral Lateral Temporal Lobes, Left Supramarginal and Left Entorhinal gyri, and the Right Inferior Frontal and Right Lateral Orbitofrontal cortices<br>3) Increased Left Hippocampal volume<br>4) Left Hippocampal volume change correlated with improved CVLT score |

$n_t$, $n_c$: Number of Participants in Treatment or Control Group; T: Treatment; T1, T2, T*n*: Treatment Group 1, 2, *n*; C: Control Group; WAIS: Weschler Adult Intelligence Scale; WAIS-R DS and ST: Weschler Adult Intelligence Scale-Revised Digit Span and Similarities Test; CAVLT: Chinese Auditory Verbal Learning Test; CVFT: Category Verbal Fluency Test; TMT: Trail Making Test; CDT: Clock Drawing Test; BNT: Boston Naming Test; DRS: Mattis Dementia Rating Scale; CE: Control Elderly; CY: Control Young; MMSE: Mini Mental State Examination; $VO_2$: Maximal Oxygen Uptake; ACC: Anterior Cingulate Cortex; GM: Grey Matter; ACC: Anterior Cingulate Cortex; BDNF: Brain-Derived Neurotrophic Factor; G-AVLT: German Auditory Verbal Learning Test; BDNF: Brain Derived Neurotrophic Factor; BDI: Beck's Depression Inventory; WMS: Wechsler Memory Scale; WMS: Wechsler Memory Scale; G-CSF: Granulocyte Colony Stimulating Factor; SA: Selective Attention; ASL: Arterial Spin Labeling; CBF: Cerebral Blood Flow; PFC: Prefrontal Cortex; SMI: Subjective Memory Impairment

Disease, Mild Cognitive Impairment, Parkinson's Disease), and studies that contained an intervention group with a mean age below sixty. These records were then preliminarily screened on the basis of their title and abstract. This preliminary screening yielded 199 RCTs for further analysis and eliminated 165 records that did not meet the aforementioned eligibility criteria and did not contain a training intervention, neurophysiological outcome measure, or cognitive outcome measure. We then further examined 22 RCTs closely for quality, and they had to include clearly defined training intervention descriptions, and both neurophysiological and cognitive outcome measures collected at least pre- and post-intervention. This final inquiry left a total of 22 RCTs for qualitative analysis.

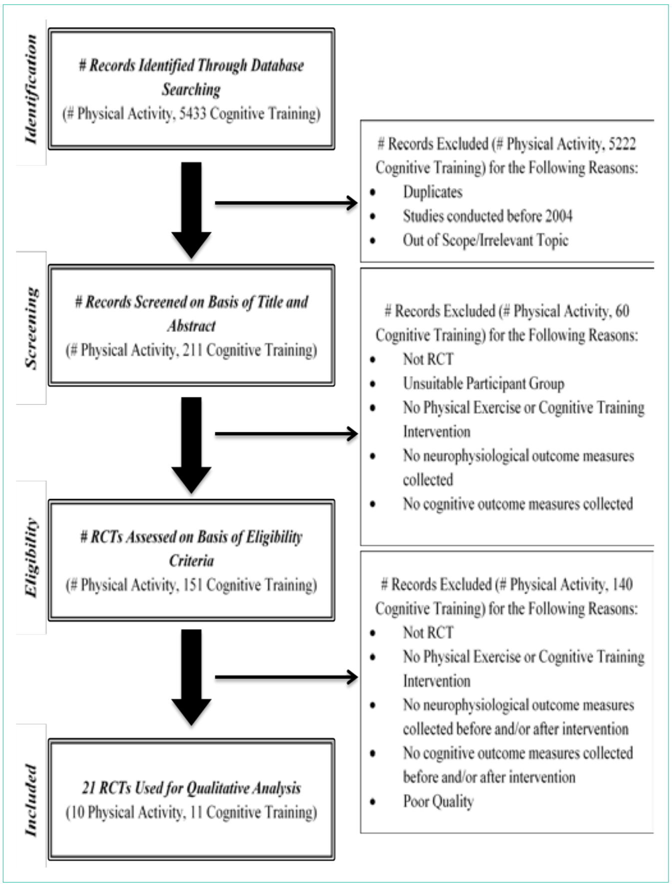
## Discussion

### Structural volume changes

**Physical exercise:** The link between grey matter volume and exercise has been studied in several RCTs, with promising results (Table 1). Higher levels of physical exercise are associated with increased grey matter volume in prefrontal areas [5,6], temporal lobes including the hippocampus [6-8], and in white matter [7]. One study of healthy adults aged 60 -79 found that aerobic exercise training for 6 months was enough to increase gray matter in areas of the frontal and temporal lobes, as well as the anterior portion of the Corpus Callosum (CC) compared to a non-aerobic control group (toning and stretching) [9]. Another RTC involving 120 sedentary adults over the age of 55 comparing an aerobic (walking) program with a stretching and toning control program, found that a year-long aerobic exercise intervention was enough to offset the normal age related shrinking of the anterior portion of the hippocampus [10]. Furthermore, despite no group differences in spatial memory post-intervention, change in hippocampal volume correlated positively with VO2, a measure of peak oxygen consumption, and spatial memory. Serum Brain Derived Neurotrophic Factor (BDNF) levels, a neurotrophin linked to plasticity also correlated with bilateral hippocampal volume changes in the exercise group [10]. However, the type of exercise may be an important factor to consider, as there is inconsistency in the literature as to the beneficial effects of aerobic versus non- aerobic exercise.

A study of adults aged 60-79 investigating whole brain volume and cognition found that 3 times weekly participation in Tai Chi and social interaction groups resulted in increased whole brain volume and improved cognitive scores compared to a walking and no intervention group after 40 weeks [11]. Although, when the walking group was stratified into fast and slow walkers, the faster walkers had slightly less brain tissue loss than slow walkers, and performed significantly better on measures of selective attention and verbal memory. Ruscheweyh et al. (2011) [12] investigated the difference between medium-intensity (Nordic walking) and low-intensity (gymnastics) exercise interventions, and a control (no intervention) group on episodic memory and grey matter volume in adults ranging from 50-72 years. Nordic walking incorporated hand held poles while walking to add upper body exercise. The gymnastic group participated in stretching, toning and flexibility training. Both the medium and low intensity groups had to participate for a minimum of three times per week, and up to five times, for 50 minutes each session. There were no group differences between medium and low intensity groups on episodic memory testing; rather it seemed that physical activity increased memory scores independently of intensity level. Similarly, increased physical activity correlated with increased grey matter volume in several prefrontal and cingulate areas including the dorsal Anterior Cingulate Cortex (ACC), the Supplementary Motor Area (SMA), and Middle Frontal Gyrus (MFG). In addition, there was a trend towards increased peripheral BDNF levels in both exercise intervention groups compared to the control group. Although, another study of healthy female adults compared once and twice per week resistance training (leg press and free weights) with twice per week balance and tone training (stretching, core-strength exercise, and Tai Chi forms), and found that after the one year intervention both resistance training groups had improved Strop scores, a measure of selective attention, compared to the balance and tone group, as well as improved muscular power in the twice per week resistance training group [13]. However, unexpectedly, both resistance training groups had significant whole-brain volume reductions compared to the balance and tone training group. The authors suggest these results be viewed with caution however, as whole-brain volume was a secondary measure and the study included exclusively females of a specific age range (65-75).

Thus, many studies suggest that physical activity in general has positive, dose-dependent effects on brain volume; however inconsistencies exist in the literature. This could partially be due to




the vast differences in types of exercise interventions (i.e. aerobic versus non-aerobic), as well as specific outcome measurements (i.e. whole - brain volume versus specific grey matter structure volume).

**Cognitive training:** Cognitive training RCTs focusing on grey matter volume changes have yielded conflicting results. A study conducted by Mozolic et al. [14] found no post-intervention grey matter volume changes, despite significant improvements in the ability to suppress multisensory distraction. In contrast, Engvig et al. [15] found after memory training, that the left hippocampus experienced significant training-related volume increase, which correlated with improved post-intervention CVLT-II (California Verbal Learning Test-II) scores. These conflicting results may provide insight into the neural mechanisms underlying cognitive improvement after intellectual stimulation. Although the studies conducted by Engvig et al. [15] and Mozolic et al. [14] had similar training frequencies and durations, the types of interventions administered differed. Verbal memory, which was emphasized by Engvig et al. [15] is strongly tied to the hippocampus, whereas attention, emphasized by Mozolic et al. [14], is more commonly associated with the coordination of numerous frontal and parietal areas constituting the attentional network. Consequently, perhaps changes in cognitive functions associated with more complex neural networks may not be as easily detectable via volumetric analysis and thus, may require additional investigation using methods like functional Magnetic Resonance Imaging (fMRI) and functional connectivity analysis.

## Functional changes

**Physical exercise:** Exercise can alter the functional

**Table 2:** Summary of RCTs involving physical activity and cognitive training using fmri and eeg outcome measures.

| ***Study*** | ***Sample Size*** | ***Mean Age (SD)*** | ***Intervention Description*** | ***Frequency/ Duration*** | ***Outcome Measures*** | ***Important Findings*** |
|---|---|---|---|---|---|---|
| Colcombe et al., [16] | n=29 | T=67.85 (6.74)<br>C=66.7 (4.56) | T1 = aerobic<br>C = non-aerobic (stretching and toning) | 3 x 40-45 mins per week/ 6 months | $VO_2$, interference related reaction times in flanker task, pre- and post-fMRI flanker task | Aerobic group showed greater level of task-related activity in MFG, SFG, and SPL, and reduced activity in ACC |
| Voelcker Rehage et al., [17] | $n_{T1}$=17<br>$n_{T2}$=16<br>$n_C$=11 | T1= 68.47<br>T2= 71.13<br>C=69.27 | T1 = Walking<br>T2 = Coordination Training<br>C = Relaxation and Stretching | 3 x 1 hr per week/ 1 year | $VO_2$, executive control (flanker task), processing speed (visual search task), fMRI | 1) Walking group had decreased activity in left SFG and MFG, bilateral medial frontal gyrus, left parahippocampal gyrus, right superior MTG compared to control group<br>2) Increased activity in IFG, SPC, thalamus, caudate body in coordination group<br>3) Accuracy on flanker task improved in walking group<br>4) Coordination group had improved accuracy and speed on visual search task and flanker task |
| Liu-Ambrose et al., [18] | $n_{RT1}$ = 20<br>$n_{RT2}$ = 15<br>$N_{c(BAT)}$ = 17 | BAT = 69.2 (3.2)<br>RT1= 69.7 (2.8)<br>RT2= 68.9 (3.2) | T1= Resistance training (RT)<br>C= Balance and Tone Training (BAT) | 1 (RT1) or 2 (RT2,BAT) sessions per week/ 1 year | RT, fMRI during Erikson flanker task | RT2 led to increased functional plasticity in the left MTG and anterior insula |
| Rosano et al., [19] | $n_T$ = 20<br>$n_C$= 10 | T=80.8 (3.95)<br>C=81.45 (2.77) | T = Walking, flexibility, strength and balance<br>C = health related classes | 150 mins per week/ 1 year | fMRI DSST, psychomotor speed using DSST, executive control | Exercise group had faster psychomotor speed on DSST and increased activation in areas related to executive control (DLPFC, ACC) |
| Berry et al., [20] | $n_T$ = 15<br>$n_C$ = 15 | 71.93 (1.33) | ***Sweep Seeker Program (Posit Science, InSight)***<br>Visual PD | 3-5 x 40-mins per week/<br>3-5 weeks | ERP during untrained WM Tasks, Trained and Untrained PD Tasks | 1) Decreased N1 amplitude<br>2) Improved WM performance<br>Correlation between improved WM accuracy and changes in N1 amplitude |
| Anguera et al., [21] | $n_{T1}$ = 16<br>$n_{T2}$ = 15<br>$n_C$ = 15 | 67.1 (4.2)<br>T1 = 64.9 (5.2)<br>T2 = 68.8 (6.8)<br>C = 66.8 (6.2) | ***NeuroRacer Video Game***<br>T1 = Multitasking training<br>T2 = Single Task Training<br>Attention and Multitasking (T1 only) | 3 x 1-hr per week/ 4 weeks | *Pre-, Post- and Post-6 month Intervention:*<br>EEG while playing Neuroracer, TOVA, Delayed-recognition WM, Dual, Useful Field of View, Filter, Change and Stimulus Detection, and Digit Symbol Tasks | 1) Only T1 improved behaviourally (diminished multitasking costs, improved sustained attention and WM)<br>2) Only T1 improved on EEG measures (enhanced midline frontal theta power and long-range theta coherence). |
| O'Brien et al., [22] | $n_T$ = 11<br>$n_C$ = 11 | 71.6 (5.06)<br>T = 71.91 (4.51)<br>C = 71.82 (5.79) | ***SOP Video Game Training***<br>Perception, SOP, Attention, Memory | 2 x 70-mins per week/<br>10 weeks | EEG during Visual Search Task | 1) Improved selective attention<br>2) Increased N2pc and P3b amplitudes, reflecting attentional allocation and capacity enhancement |
| Kirchhoff et al., [23]<br>Kirchhoff et al., [24] | $n_T$ = 16<br>$n_C$ = 17 | T = 71.9 (4.1)<br>C = 22.8 (4.0) | ***Semantic Encoding Strategy Training***<br>Elderly Group only<br>Verbal Memory | 2 sessions | Self-initiated Strategy Questionnaire, fMRI Intentional Encoding Task, fMRI Abstract/Concrete Task, fMRI Recognition Memory Task | ***Kirchhoff 2011 only***:<br>1) Improved subjective memory<br>2) Eliminated pre-training young vs old differences in Recognition Memory performance<br>3) Increased activity in the Medial SFG, Right Precentral Gyrus, and Left Caudate during Intentional Encoding Recognition Memory Improvements correlated with:<br>1) ***Kirchhoff 2011:*** Increased activity in Prefrontal and Left Lateral Temporal Regions (associated with semantic processing and strategy use in young)<br>2) ***Kirchhoff 2012:*** Increased bilateral hippocampal activity during memory retrieval |

$n_t$, $n_c$: Number of Participants in Treatment or Control Group; T: Treatment; T1, T2, T*n*: Treatment Group 1, 2, *n*; C: Control Group; $VO_2$: Maximal Oxygen Uptake; SFG: Superior Frontal Gyrus; MFG: Middle Frontal Gyrus; SFG: Superior Frontal Gyrus; SPL: Superior Parietal Lobule; ACC: Anterior Cingulate Cortex; MTG: Middle Temporal Gyrus; IFG: Inferior Frontal Gyrus; SPC: Superior Parietal Cortex; DSST: Digit Symbol Substitution Test; DLPFC: Dorsolateral Prefrontal Cortex; PD: Perceptual Discrimination; ERP: Event Related Potential; WM: Working Memory; N1: Negative Deflection 100ms; EEG: Electroencephalography; TOVA: Test of Variables of Attention; SOP: Speed of Processing; N2pc: Second Negative Deflection Posterior Contralateral; P3b: Positive Deflection 300ms Subcomponent B plasticity of the adult brain. In one RTC adults aged 58- 77 grouped into either a walking or stretching and toning condition participated in an fMRI study using the flanker task, a measure of selective attention [16]. The authors reported exercise-related activity increases in brain regions related to attention, such as the MFG, Superior Frontal Gyrus (SFG), and the Superior Parietal Lobule (SPL), and a decrease in the Anterior Cingulate Cortex (ACC), which is related to conflict detection [16]. Behaviorally, the walking group showed decreased interference-related reaction times on the flanker task compared to the control group. While another fMRI study with a similarly aged population (62-79 years) using the flanker task also found decreased activity in the ACC in the group receiving cardiovascular training (walking), the authors report a decrease in additional areas including the left superior MFG, bilateral medial frontal gyrus, left parahippocampal gyrus, and the right superior MTG, while these regions showed increased activation in the control group (no intervention), suggesting more efficient processing [17]. In addition, Voelcker-Rehage et al. [17] found that coordination training resulted in increased activity in the inferior frontal gyrus, superior parietal cortex, thalamus, and caudate body, areas related to the visual-spatial network, compared to the cardiovascular exercise and control groups. Both exercise groups showed cognitive improvement on the flanker task in terms of accuracy, however only the coordination group has significant increases in speed on the visual search task. Twice weekly resistance training (but not once weekly) has also been found to lead to changes in neural activity in an fMRI study of 52 elderly women ranging from 65-75 years of age [18]. Specifically, increased activity was found in areas relating to response inhibition as well as increased performance on the flanker task. A different study explored the possible long term benefits of exercise interventions by comparing two groups that underwent a one year lifestyle RTC: physical activity consisting of mostly walking and a control group that met for health sessions pertaining to the elderly including nutrition, medications and foot care [19]. The authors found that even two years post-exercise intervention, older adults who maintained physical activity showed increased activation in executive control areas, and faster reaction times and accuracy on a digit symbol substitution test compared to sedentary participants [19].

Overall, studies examining the effects of physical exercise on brain plasticity seem positive (see Table 2 for summary). However, variability in findings of exercise related brain areas exists despite implementing a similar task. Activity differences may therefore be attributed to the diversity of exercises and length of interventions.

**Cognitive training:** There are numerous Electroencephalography (EEG) and fMRI studies investigating the synchronous whole-brain activity required to perform complex cognitive tasks. Despite some methodological differences, seemingly disparate methods like computerized cognitive training selectively targeting one cognitive domain [20] and video games involving multiple cognitive domains [21,22] have mostly exhibited comparable, intervention-induced neural firing changes associated with improved cognitive performance. This has been chronicled in the multiple EEG studies showcased in (Table 2). Notably, Anguera et al. [21] investigated the benefits of a car-racing video game, on users who were further split into multitasking and single task training groups. Interestingly, only the multitasking group exhibited improvements on behavioral tests and EEG measures of cognitive control, both at post-intervention and 6 months after cessation of training, thereby alluding to the enhanced short- and long-term efficacy of therapies involving simultaneous overlapping cognitive control processes.

Functional MRI randomized control trials have similarly demonstrated training-induced benefits. Kirchhoff et al. [23,24] used a verbal recognition memory training paradigm and found subjective and objective cognitive improvements and increased activation in a number of frontal and temporal regions commonly associated with semantic processing in young adults. This further supports the notion that cognitive training leads to strengthening of pre-existing neural networks via training-induced neuroplasticity.

### Functional connectivity changes

**Physical exercise:** Only one study investigated the relationship between aerobic(walking) and Flexibility, Toning and Balancing (FTB) exercises, cognition, and functional connectivity in a group of adults (55- 80 years old) [25] (see Table 3 for summary). The authors found that walking and FTB exercises increased DMN (Default Mode Network) and frontal executive network functional connectivity after 12 months. Additionally, the FTB group had functional connectivity increases at 6 months. The authors suggest that the novelty of exercise, progressive difficulty, and mimicking of instructors in the FTB group may have contributed to these changes. In both exercise groups, increased functional connectivity was associated with increased executive functioning on cognitive tests. While these results fit with other research involving functional connectivity changes with age, the field is lacking study reproductions to conclude if functional connectivity changes result from exercise.

**Cognitive training:** In line with the hypothesis that the neural underpinnings of training-related improvements would involve neural networks often disrupted throughout aging, a study by Chapman et al. [26] demonstrated both increased functional connectivity and increased regional cerebral blood flow in the DMN and Central Executive Network (CEN), which further correlated with improved abstraction and reasoning skills. In contrast to the classroom-based cognitive training used by Chapman et al. [26], functional connectivity changes were also noted using home-based video game training methods. The differential efficacy and functional connectivity changes related to video games like Brain Fitness, Space Fortress, and Rise of Nations further elaborated on the aforementioned research [27]. Looking at specific components of the dorsal and ventral attentional networks, Strenziok et al. [27] determined that cognitive training of the top-down modulation of sensory processing (Brain Fitness and Space Fortress) yielded the most consistent behavioral improvements, which were specifically correlated to decreased functional connectivity between the SPC (Superior Parietal Cortex) and the ITL (Inferior Temporal Lobe). This neuroplastic change was postulated to be a reflection of reduced demands on the SPC for attentional control of auditory sensory cortices, therefore resulting in more efficient top-down attentional control mechanisms. However, with Chapman et al. [26] reporting broad increased functional connectivity amongst large-scale neural networks and Strenziok et al. [27] conversely reporting decreased training-induced regional connectivity, it is clear that further in-depth analysis is still needed.

**Table 3:** Summary of RCTs involving physical activity and cognitive training using functional connectivity outcome measures.

| Study | Sample Size | Mean Age (SD) | Intervention Description | Frequency/ Duration | Outcome Measures | Important Findings |
|---|---|---|---|---|---|---|
| Voss et al., [25] | $n_T$= 30<br>$n_{CY}$ = 32<br>$n_{CE}$ = 35 | T= 67.30 (5.80)<br>CY = 23.91 (4.44)<br>CE = 65.37 (5.24) | T = Walking<br>CE = non-aerobic group (Flexibility, toning and balancing) | 3 x 40 mins per week/ 1 year | $VO_2$, DS, spatial WM, task-switching, WCST, fMRI functional connectivity | 1) Aerobic exercise increased functional connectivity in DMN and FE network, - FTB group showed increased DMN and Fronto-parietal network connectivity<br>2) Increased functional connectivity associated with better executive function in both groups |
| Chapman et al., [26] | $n_T$ = 18<br>$n_C$ = 19 | 62.9 (3.6)<br>T = 64 (3.6)<br>C = 61.8 (3.3) | ***Gist Reasoning Training***<br>Reasoning | 1 x 1-h per week/ 12 weeks | *Pre-, Mid-, and Post-Intervention:* Test of Strategic Learning, Daneman and Carpenter Test, Trails A/B, WAIS-III , CVLT-II, Delis-Kaplan Executive Function System, Stroop, Backward Digit Span, ASL, Functional Connectivity, White matter integrity | 1) Increased DMN and CEN global and regional CBF and functional connectivity<br>2) Post-training improvements in Reasoning and Abstraction |
| Strenziok et al., [27] | $n_{BF}$ = 14<br>$n_{SF}$ = 14<br>$n_{RON}$ = 14 | BF = 69.70 (6.9) SF = 68.52 (5.6)<br>RON = 69.41 (2.3) | ***Brain Fitness (BF):*** Auditory Perception<br>***Space Fortress (SF):*** Visuomotor/Working Memory<br>***Rise of Nations (RON):*** Strategic Reasoning | ***Lab:***<br>3 x 1-h per week/ 6 weeks<br>***Home:***<br>3 x 1-h per week/ 6 weeks | WAIS-III , Everyday Problems Test, Word/Letter Series, WMS , Delayed Match-to-Sample Task, Functional Connectivity, White matter integrity | 1) BF had most consistent positive changes and RON had least consistent changes in Working memory, Reasoning, and Problem Solving<br>2) BF and SF decreased in functional connectivity between SPC and ITL, compared to RON |

$n_T$, $n_C$**:** Number of Participants in Treatment or Control Group; CY: Control Young; CE: Control Elderly; T: Treatment; T1, T2, T*n*: Treatment Group 1, 2, *n*; C: Control Group; $VO_2$: Maximal Oxygen Uptake; DS: Digit Span; WM: Working Memory; WCST: Wisconsin Card Sorting Test; DMN: Default Mode Network; FE: Frontal Executive Network; FTB: Flexibility Toning Balancing; WAIS: Weschler Adult Intelligence Scale; ASL: Arterial Spin Labeling; CEN: Central Executive Network; CBF: Cerebral Blood Flow; FA: Fractional Anisotropy; WMS: Weschler Memory Scale; AD: Axial Diffusivity; SPC: Superior Parietal Cortex; ITL: Inferior Temporal Lobe

## White matter tract changes

**Physical exercise:** One RTC has investigated the relationship between physical exercise and white matter tract changes (see Table 4). Voss et al. [28] implemented Diffusion Tensor Imaging (DTI) and cognitive measures in a walking and a stretching control group consisting of older adults aged 55 - 80. In the walking group, a greater percentage change in fitness was related to increased FA (Fractional Anisotropy) in prefrontal regions and temporal cortices following a one-year intervention. While change in aerobic fitness correlated with performance on the backwards digit span in the walking group, no group differences were found on measures of cognition post-intervention, and increases in white matter integrity measures were not associated with any cognitive measures. Again, since this is the only RTC, the relationship between exercise, cognition and white matter in healthy elderly remains unclear.

**Cognitive training:** In relation to cognitive training and healthy aging, studies have generally shown increased global [29] and regional white matter integrity in attentional network [27] and limbic areas [26]. Interestingly, the genu of the CC, which is particularly sensitive to age-related changes, plays a fascinating role in both short- and long-term retention of training-related cognitive improvements and individual susceptibility to training-induced benefits [30]. Specifically, Wolf et al. [30] demonstrated that younger elderly individuals (ages 60-70), who had comparatively superior pre-training structural integrity in the genu of the CC were not only able to retain and transfer training-related gains in cognitive function, but were also able to maintain these improvements in the long run. This relationship, unfortunately, did not persist amongst older elderly individuals (ages 70-85), who were unable to maintain initial transfer gains, regardless of initial CC integrity, therefore possibly alluding to a short window of opportunity for maximum efficacy of cognitive training in the elderly. This structure also appeared in earlier research presented by Lovden et al. [31], who demonstrated cognitive training-induced decreased MD (Mean Diffusivity) and increased FA selectively in the genu of the CC in healthy elderly (mean age = 68.9 ± 2.7). However, despite noting post-training behavioral improvements on working memory, episodic memory, and processing speed tasks, none of these improvements correlated with any of the FA and MD measures.

## Combination of physical exercise and cognitive training

Some studies have examined the efficacy of a combination, rather than separate administration, of these lifestyle modifications. Theoretically, physical exercise can provide the biological substrate needed to facilitate the structural and functional neuroplastic changes induced by cognitive training [32]. More specifically, frequent cognitive exercise during a time frame of physical exercise-induced synaptogenesis and neurogenesis could lead to the functional integration of new neurons and improve cognitive performance [33]. However, some studies that have examined separate and combined effects of cognitive training and physical exercise, have found that participation in cognitive training improves cognitive function in both single and combined methods, while mild aerobic training alone does not provide significant improvements [34,35].

## Limitations and future directions

There were some limitations in comparing the studies in this review. Many studies included a range of different outcome measures of cognitive performance, administered at varying time points, making comparison of cognitive benefits and evidence of transfer effects extremely difficult. Furthermore, the heterogeneity in the intervention type, duration, and frequency is a methodological

**Table 4:** Summary of RCTs involving physical activity and cognitive training using white matter integrity measures.

| Study | Sample Size | Mean Age (SD) | Intervention Description | Frequency/ Duration | Outcome Measures | Important Findings |
|---|---|---|---|---|---|---|
| Voss et al., [28] | $n_{T1}$= 35<br>$n_{T2}$ = 35 | T1 = 65.17 (4.40)<br>T2 = 64.57 (4.46) | T1 = walking<br>T2 = non-aerobic group (Flexibility, toning and balancing) | 3 x 40 mins per week/ 1 year | $VO_2$, DS, spatial working memory, task-switching, WCST, DTI | 1) Trend for increased FA in prefrontal white matter in aerobic group<br>2) Magnitude of change in fitness related to increases in mean FA<br>3) No group differences on cognitive tests |
| Chapman et al., [26] | $n_T$ = 18<br>$n_C$ = 19 | 62.9 (3.6)<br>T = 64 (3.6)<br>C = 61.8 (3.3) | ***Gist Reasoning Training***<br>Reasoning | 1 x 1-h per week/ 12 weeks | *Pre-, Mid-, and Post-Intervention:*<br>Test of Strategic Learning, Daneman and Carpenter Test, Trails A/B, WAIS-III , CVLT-II, Delis-Kaplan Executive Function System, Stroop, Backward Digit Span, ASL, Functional Connectivity, White matter integrity | 1) Increased FA in the left uncinate<br>2) Post-training improvements in Reasoning and Abstraction |
| Strenziok et al., [27] | $n_{BF}$ = 14<br>$n_{SF}$ = 14<br>$n_{RON}$ = 14 | BF = 69.70 (6.9) SF = 68.52 (5.6) RON = 69.41 (2.3) | ***Brain Fitness (BF):***<br>Auditory Perception<br>***Space Fortress (SF):***<br>Visuomotor/Working Memory<br>***Rise of Nations (RON):***<br>Strategic Reasoning | ***Lab:***<br>3 x 1-h per week/ 6 weeks<br>***Home:***<br>3 x 1-h per week/ 6 weeks | WAIS-III , Everyday Problems Test, Word/Letter Series, WMS , Delayed Match-to-Sample Task, Functional Connectivity, White matter integrity | 1) BF had most consistent positive changes and RON had least consistent changes in Working Memory, Reasoning, and Problem Solving<br>2) BF group increased occipito-temporal AD, which correlated with problem solving improvement |
| Engvig et al., [29] | $n_T$ = 21<br>$n_C$ = 21 | T = 61.7 (9.4)<br>C = 60.3 (9.1) | ***Method of Loci (MoL) Memory Training***<br>Verbal Memory | ***Classes:***<br>1 x 1-hr per week/ 8 weeks<br>***Homework:***<br>4 assignments per week/ 8 weeks | White matter integrity, Source Memory Task | 1) Increased frontal MD<br>2) Increased FA<br>3) Significant correlation between memory improvement and change in FA |
| Lovden et al., [31] | $n_{TY}$ = 20<br>$n_{TE}$ = 12<br>$n_{CY}$ = 10<br>$n_{CE}$ = 13 | TY = 25.1 (2.8)<br>TE = 68.9 (2.7)<br>CY = 25.1 (2.8)<br>CE = 68.9 (2.7) | ***Computerized Cognitive Training***<br>PS, EM, WM | 1-h daily/ 100 days | Practiced Tasks , Transfer Tasks, White matter integrity | 1) Increased PS, EM, and WM<br>2) Decreased MD in the CC (genu), driven by decreases in RD, but not AD<br>3) Increased FA in the CC (genu) |

$n_T$, $n_C$: Number of Participants in Treatment or Control Group; T: Treatment; T1, T2, T*n*: Treatment Group 1, 2, *n*; C: Control Group; $VO_2$: Maximal Oxygen Uptake; DS: Digit Span; WCST: Wisconsin Card Sorting Test; DTI: Diffusion Tensor Imaging; FA: Fractional Anisotropy; TY, TE: Treatment Young and Elderly; CY, CE: Control Young and Elderly; PS: Perceptual Speed; EM: Episodic Memory; WM: Working Memory; MD: Mean Diffusivity; RD: Radial Diffusivity; AD: Axial Diffusivity; CC: Corpus Callosum

constraint in determining the optimal intervention type and dose. The current literature is also limited in the number of longitudinal randomized control trials, with most studies limiting data collection to only pre- and post-intervention. Furthermore, given the relative paucity of RCTs investigating how exercise and cognitive training programs impact certain neurophysiological measures, more work needs to be done to establish the true benefits of these non-pharmacological interventions in preventing cognitive decline.

## Conclusion

This review examined the behavioral effect and underlying neural mechanisms of cognitive and physical training on age-related cognitive decline. Despite their heterogeneity, the studies presented suggest that increased cognitive or physical activity result in functional and structural brain changes, which correlate with cognitive improvements that may delay or prevent the onset of cognitive impairment. However, the exact mechanism, site, extent, and transfer effects of these improvements remain unclear.

With the global incidence of dementia on the rise, investigations into non-pharmacological strategies aimed at the prevention and delay of cognitive impairment are more important than ever. Specifically, the studies showcased in this review evaluating the efficacy of these non-invasive therapies in the healthy elderly are of extreme importance given their potential to prevent preclinical stages of dementia, such as mild cognitive impairment, for which there is currently no successful treatment. A recent RCT of older women with mild cognitive impairment suggests that aerobic training (walking) increased total hippocampal volume compared to a resistance training and balance and tone group [36].

In line with previous reviews [37], the RCTs reviewed here ultimately emphasize the need for further study of individual and combined exercise and cognitive training interventions. This need for continued study is further substantiated by the discrepant conclusions of past reviews. For instance, a recent Cochrane review [38] concluded that there was insufficient evidence to suggest that aerobic exercise interventions help improve cognition, while other reviews have reported potential positive effects [39,40]. Similarly, another Cochrane review on the effects of cognitive training interventions in the elderly found mixed results [41]. While the studies in this review generally showed significant behavioral and neurophysiological changes following both cognitive and exercise training, its underlying mechanisms and permanence remained unclear, thereby providing an exciting opportunity for future research into these potentially effective non-invasive responses to the rising significance of cognitive impairment in the elderly.

## References

1. Goh JO, Park DC. Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. Restor Neurol Neurosci. 2009; 27: 391-403.

2. Lemura LM, Von Duvillard SP, Mookerjee S. The effects of physical training of functional capacity in adults. Ages 46 to 90: a meta-analysis. J Sports Med Phys Fitness. 2000; 40: 1-10.

3. Laurin D, Verreault R, Lindsay J, Mac Pherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001; 58: 498-504.

4. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003; 14: 125-130.

5. Weinstein AM, Voss MW, Prakash RS, Chaddock L, Szabo A, White SM, et al. The Association Between Aerobic Fitness and Executive Function is Mediated by Prefrontal Cortex Volume. Brain Behav Immun. 2012; 26: 811-819.

6. Gordon BA, Rykhlevskaia EI, Brumback CR, Lee Y, Elavsky S, Konopack JF, et al. Neuroanatomical Correlates of Aging, Cardiopulmonary Fitness Level, and Education. Psychophysiology. 2008; 45: 825-838.

7. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, et al. The effects of physical activity, education, and body mass index on the aging brain. Hum Brain Mapp. 2011; 32: 1371-1382.

8. Szabo AN, McAuley E, Erickson KI, Voss M, Prakash RS, Mailey EL, et al. Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. Neuropsychology. 2011; 25: 545-553.

9. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006; 61: 1166-1170.

10. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA. 2011; 108: 3017-3022.

11. Mortimer JA, Ding D, Borenstein AR, DeCarli C, Guo Q, Wu Y, et al. Changes in Brain Volume and Cognition in a Randomized Trial of Exercise and Social Interaction in a Community-Based Sample of Non-Demented Chinese Elders. J Alzheimers Dis. 2012; 30: 757-766.

12. Ruscheweyh R, Willemer C, Kruger K, Duning T, Warnecke T, Sommer J, et al. Physical Activity and Memory Functions: An Interventional Study. Neurobiol Aging. 2011; 32: 1304-1319.

13. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance Training and Executive Functions: A 12-month Randomized Controlled Trial. Arch Intern Med. 2010; 170: 170-178.

14. Mozolic JL, Hayasaka S, Laurienti PJ. A cognitive training intervention increases resting cerebral blood flow in healthy older adults. Front Hum Neurosci. 2010; 4: 16.

15. Engvig A, Fjell AM, Westlye LT, Skaane NV, Dale AM, Holland D, et al. Effects of Cognitive Training on Gray Matter Volumes in Memory Clinic Patients with Subjective Memory Impairment. J Alzheimers Dis. 2014; 41: 779-791.

16. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci USA. 2004; 101: 3316-3321.

17. Voelcker-Rehage C, Godde B, Staudinger UM. Cardiovascular and Coordination Training Differentially Improve Cognitive Performance and Neural Processing in Older Adults. Front Hum Neurosci. 2011; 5: 26.

18. Liu-Ambrose T, Nagamatsu LS, Voss MW, Khan KM, Handy TC. Resistance Training and Functional Plasticity of the Aging Brain: A 12-Month Randomized Controlled Trial. Neurobiol Aging. 2012; 33: 1690-1698.

19. Rosano C, Venkatraman VK, Guralnik J, Newman AB, Glynn NW, Launer L, et al. Psychomotor Speed and Functional Brain MRI 2 Years After Completing a Physical Activity Treatment. J Gerontol A Biol Sci Med Sci. 2010; 65: 639-647.

20. Berry AS, Zanto TP, Clapp WC, Hardy JL, Delahunt PB, Mahncke HW, et al. The influence of perceptual training on working memory in older adults. PLoS One. 2010; 5: e11537.

21. Anguera JA, Boccanfuso J, Rintoul JL, Al-Hashimi O, Faraji F, Janowich J, et al. Video game training enhances cognitive control in older adults. Nature. 2013; 501: 97-101.

22. O'Brien JL, Edwards JD, Maxfield ND, Peronto CL, Williams VA, Lister JJ. Cognitive Training and Selective Attention in the Aging Brain: An Electrophysiological Study. Clin Neurophysiol. 2013; 124: 2198-2208.

23. Kirchhoff BA, Anderson BA, Barch DM, Jacoby LL. Cognitive and neural effects of semantic encoding strategy training in older adults. Cereb Cortex. 2012; 22: 788-799.

24. Kirchhoff BA, Anderson BA, Smith SE, Barch DM, Jacoby LL. Cognitive Training-Related Changes in Hippocampal Activity Associated with Recollection in Older Adults. Neuroimage. 2012; 62: 1956-1964.

25. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci. 2010; 2: 32.

26. Chapman SB, Aslan S, Spence JS, Hart JJ, Bartz EK, Didehbani N, et al. Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. Cereb Cortex. 2015; 25: 396-405.

27. Strenziok M, Parasuraman R, Clarke E, Cisler DS, Thompson JC, Greenwood PM. Neurocognitive Enhancement in Older Adults: Comparison of Three Cognitive Training Tasks to Test a Hypothesis of Training Transfer in Brain Connectivity. Neuroimage. 2014; 85: 1027-1039.

28. Voss MW, Heo S, Prakash RS, Erickson KI, Alves H, Chaddock L, et al. The Influence of Aerobic Fitness on Cerebral White Matter Integrity and Cognitive Function in Older Adults: Results of a One-Year Exercise Intervention. Hum Brain Mapp. 2013; 34: 2972-2985.

29. Engvig A, Fjell AM, Westlye LT, Moberget T, Sundseth O, Larsen VA, et al. Memory Training Impacts Short-Term Changes in Aging White Matter: A Longitudinal Diffusion Tensor Imaging Study. Hum Brain Mapp. 2012; 33: 2390-2406.

30. Wolf D, Fischer FU, Fesenbeckh J, Yakushev I, Lelieveld IM, Scheurich A, et al. Structural Integrity of the Corpus Callosum Predicts Long-Term Transfer of Fluid Intelligence-Related Training Gains in Normal Aging. Hum Brain Mapp. 2014; 35: 309-318.

31. Lovden M, Bodammer NC, Kuhn S, Kaufmann J, Schutze H, Tempelmann C, et al. Experience-Dependent Plasticity of White-Matter Microstructure Extends into Old Age. Neuropsychologia. 2010; 48: 3878-3883.

32. Fissler P, Kuster O, Schlee W, Kolassa IT. Novelty Interventions to Enhance Broad Cognitive Abilities and Prevent Dementia: Synergistic Approaches for the Facilitation of Positive Plastic Change. Prog Brain Res. 2013; 207: 403-434.

33. Bamidis PD, Vivas AB, Styliadis C, Frantzidis C, Klados M, Schlee W, et al. A review of physical and cognitive interventions in aging. Neurosci Biobehav Rev. 2014; 44: 206-220.

34. Gajewski PD, Falkenstein M. Training-Induced Improvement of Response Selection and Error Detection in Aging Assessed by Task Switching: Effects of Cognitive, Physical, and Relaxation Training. Front Hum Neurosci. 2012; 6: 130.

35. Shatil E. Does Combined Cognitive Training and Physical Activity Training Enhance Cognitive Abilities More Than Either Alone? A Four-Condition Randomized Controlled Trial Among Healthy Older Adults. Front Aging Neurosci. 2013; 5: 8.

36. Ten Brinke LF, Bolandzadeh N, Nagamatsu LS, Hsu CL, Davis JC, Miran-Khan K, et al. Aerobic Exercise Increases Hippocampal Volume in Older Women with Probable Mild Cognitive Impairment: A 6-month Randomised Controlled Trial. Br J Sports Med. 2015; 49: 248-254.

37. Brehmer Y, Kalpouzos G, Wenger E, Lövdén M. Plasticity of brain and cognition in older adults. Psychol Res. 2014; 78: 790-802.

38. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2015; 4: CD005381.

39. Angevaren M, Aufdemkampe G, Verhaar HJJ, Aleman A, Vanhees L. Physical Activity and Enhanced Fitness to Improve Cognitive Function in Older People Without Known Cognitive Impairment. Cochrane Database Syst Rev. 2008; 16: CD005381.

40. Carvalho A, Rea IM, Parimon T, Cusack BJ. Physical activity and cognitive function in individuals over 60 years of age: a systematic review. Clin Interv Aging. 2014; 9: 661-682.

41. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. Cochrane Database Syst Rev. 2011; 19: CD006220.

Gerontol & Geriatr Res - Volume 2 Issue 1 - 2016
**Submit your Manuscript** | www.austinpublishinggroup.com


**Citation:** Garcia A, Angela L, Justine I, Fernandez-Ruiz Juan. The Neural Correlates of Physical and Cognitive Training in the Prevention of Age-Related Cognitive Decline: A Review. Gerontol & Geriatr Res. 2016; 2(1): 1006.