

# **Interventional programmes to improve cognition during healthy and pathological ageing: Cortical modulations and evidence for brain plasticity**

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## **Research highlights:**

Non-pharmacological interventions promote neuroplasticity at advanced stages of life

The neuroplasticity mechanisms differ according to the type of intervention

Cognitive reserve level may be crucial to select specific multimodal interventions

**Conflicts of Interest:** None

## **Abstract**

A growing body of evidence suggests that healthy elderly individuals and patients with Alzheimer's disease retain an important potential for neuroplasticity. This review summarizes studies investigating the modulation of neural activity and structural brain integrity in response to interventions involving cognitive training, physical exercise and non-invasive brain stimulation in healthy elderly and cognitively impaired subjects (including patients with mild cognitive impairment (MCI) and Alzheimer's disease). Moreover, given the clinical relevance of neuroplasticity, we discuss how evidence for neuroplasticity can be inferred from the functional and structural brain changes observed after implementing these interventions. We emphasize that multimodal programmes, which combine several types of interventions, improve cognitive function to a greater extent than programmes that use a single interventional approach. We suggest specific methods for weighting the relative importance of cognitive training, physical exercise and non-invasive brain stimulation according to the functional and structural state of the brain of the targeted subject to maximize the cognitive improvements induced by multimodal programmes.

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## **1. Introduction**

The progressive ageing of the global population is leading to an increased prevalence of age-related disorders, such as Alzheimer's disease (AD) (Sosa-Ortiz et al., 2012). Nevertheless, the efficacy of current pharmacological treatments in patients with AD is among the lowest of any therapeutic area (Hay et al., 2014). In this context, the lack of tools for effective AD treatment creates a burden for patients and caregivers and affects the sustainability of public health systems (Dorsey et al., 2013). Studies of changes in cognition and the brain related to ageing and cognitive decline and investigations into residual plasticity mechanisms in the brains of individuals at advanced stages of life are important research activities that will assist in the diversification of pharmacological targets (Cummings et al., 2014) and the development of non-pharmacological interventions to treat and/or prevent cognitive deficits related to AD and other forms of dementia.

Cognitive interventions (CI), physical exercise (PE) and non-invasive brain stimulation (NIBS) are gaining popularity in the scientific community as promising approaches to improve cognition during healthy and pathological ageing. These interventions are thought to improve cognition by promoting neuroplasticity mechanisms. Neuroplasticity may be defined as the capability of the brain to undertake long-lasting structural and functional modifications in response to environmental demands. Structural neuroplasticity includes a set of processes that range from neurogenesis and synaptogenesis to the expression of neurotrophic and angiogenesis factors, whereas functional neuroplasticity involves a set of processes including long-term potentiation (LTP) and long-term depression (LTD) that do not involve changes in the brain structure (Bruehl-Jungerman et al., 2007; Huang et al., 2014). However, it is important to highlight that brain processes related to functional neuroplasticity and brain processes related to structural neuroplasticity interact between them, as already argued by previous studies (Bruehl-Jungerman et al., 2007). Therefore, both types of neuroplasticity (i.e., structural and functional neuroplasticity) cannot be considered as categorical concepts and/or independent processes. In human studies,

functional and structural neuroplasticity are typically investigated using electroencephalogram (EEG) and magnetic resonance imaging (MRI) techniques.

Evidence for structural changes in the brain after an interventional programme may be interpreted as evidence for neuroplasticity. In contrast, functional changes do not have a straightforward interpretation because they not only reflect neuroplasticity but also brain flexibility, which is defined as the capacity to optimize the brain's performance within the limits of the current brain state (for a comprehensive review of the brain flexibility concept, see Lövdén et al., 2010). In other words, the brain is a flexible organ, and functional changes do not necessarily involve modifications such as neurogenesis/synaptogenesis (i.e., structural neuroplasticity) or LTP/LTD (i.e., functional neuroplasticity). In this regard, brain flexibility involves an increased efficiency for processing information and/or managing environmental demands, which does not require brain modifications but rather the use of available alternative circuits that allow the brain to manage environmental or cognitive demands more efficiently. Therefore, increased neuroplasticity conveys increased brain flexibility; however, increased brain flexibility does not necessarily indicate increased neuroplasticity.

In this review, we briefly outline the main cognitive and neural changes observed in healthy elderly individuals and patients with AD. Next, we provide an overview of the CT, PE, and NIBS tools that have been used to improve cognitive functions and outline the underlying physiological mechanisms of action. Then, we summarize the main findings related to neurophysiological changes observed after applying these tools in samples of healthy elderly participants and patients with cognitive decline (i.e., MCI or AD). Considering the reviewed studies, we discuss relationships between brain changes and neuroplasticity (section 4) and propose a rationale to improve the efficacy of multimodal interventions (section 5).

## **2. Cognitive and brain changes related to healthy and pathological ageing**

According to numerous studies, patterns of cognitive decline related to ageing are specific to each cognitive ability. Some cognitive processes, such as processing speed, begin to decline at early stages of the adult lifespan; however, other cognitive abilities (in general, abilities related to crystallized intelligence, such as vocabulary size) may be preserved or even improved until advanced stages of life (Salthouse et al., 2009). This heterogeneous pattern of cognitive decline suggests that brain regions are differentially affected by ageing. In fact, structural imaging mainly shows age-related decreases in volume within anterior brain regions (i.e., the lateral prefrontal cortex), the hippocampus and basal ganglia, whereas neural loss is rarely observed in the occipital regions (Fjell et al, 2010; Raz et al., 2005). These structural changes are accompanied by a shift in activation, as revealed by neuroimaging studies, from posterior to anterior areas and reduced asymmetry in brain activity (Dennis and Cabeza, 2008). These modifications in neuronal activity, which positively correlate with performance (Davis et al., 2012), have been interpreted as compensatory frontal mechanisms for managing the abovementioned structural changes related to ageing (e.g., Park and Reuter-Lorenz, 2009).

Increased age is related to an increased probability of exhibiting cognitive deficits related to AD. In the early stages, AD manifests as an amnesic syndrome, which subsequently extends to other cognitive domains, such as language, visuospatial attention and executive functions (Weintraub et al., 2012). Beta-amyloid deposits and intracellular neurofibrillary tangles constitute the pathophysiological hallmarks of this neurodegenerative disease (Mattson, 2004; Walsh and Selkoe, 2004). Furthermore, patients with AD exhibit reduced cortical volumes in the frontal, temporal and parietal cortices. At the functional level, AD is mainly characterized by neural hyperexcitability (Busche et al., 2012; Cantone et al., 2014), which correlates with the degree of brain atrophy and impaired learning ability (List et al., 2013). Likewise, studies have reported a loss of age-related compensatory activation (Clément and Belleville, 2010; Friston and Price, 2003), which was related to reduced brain plasticity mechanisms (Heuninckx et al., 2008).

The healthy elderly brain shows an important potential for deploying neuroplasticity mechanisms (Feldman, 2009), which are considerably reduced after the onset of pathophysiological processes related to AD (Battaglia et al., 2007; Shao et al., 2011). Nevertheless, structural damage in AD is not always accompanied by an equivalent degree of cognitive impairment (Arenaza-Urquijo et al., 2015). In fact, different clinical severities are frequently reported for similar degrees of neural damage (Ewers et al., 2013). These findings suggest that AD patients show differences in their ability to deploy brain compensatory mechanisms, which might be related to individual differences in residual brain plasticity.

The cognitive reserve hypothesis was formulated to explain the mismatch between cognitive functioning and neural integrity in cognitively declined patients (Stern, 2009). This hypothesis assumes that persons with high cognitive reserve exhibit more resistance to AD pathology due to a more efficient deployment of functional compensatory mechanisms (for a schematic representation of the differences in ability to deploy compensatory mechanisms between patients with high and low cognitive reserve, see Figure 1). Cognitive reserve is usually estimated using proxy variables for lifetime exposure and cognitive activity, such as years of education, crystallized intelligence measures, number of intellectually stimulating leisure activities, degree of occupational complexity and socioeconomic status (Barulli and Stern, 2013).

According to recent neuroimaging studies, a higher degree of cognitive reserve is related to increased functional connectivity in elderly subjects (Marques et al., 2016; Stern et al., 2005; Stern et al., 2008; for a review, see Steffener and Stern, 2012) and patients with AD (Bozzali et al., 2015). Thus, these studies reveal the existence of differences in brain functional connectivity according to the degree of cognitive reserve. Notably, increased connectivity, a neural mechanism underlying the maintenance of cognitive function in high cognitive reserve subjects with AD pathology, is consistent with the definition of AD as a disconnection syndrome (Delbeuck et al., 2007). Increased functional connectivity and higher deployment of functional compensatory mechanisms would explain why a more advanced pathology is needed to give rise to clinical symptoms in individuals

with high cognitive reserve (Arenaza-Urquijo et al. 2015; Stern, 2009) and why some people are affected by AD pathology in the absence of symptoms of cognitive decline (Jansen et al., 2015).

Even if the proxy variables mentioned above (e.g., years of education and occupational complexity) constitute the classical approach to estimating the cognitive reserve (see Nucci et al., 2012), they have a noteworthy limitation. Specifically, these variables correlate not only with cognitive reserve but also with other variables that contaminate the measurement of cognitive reserve. For instance, a high education level correlates with other variables predicting a better general health outcome, such as income, access to health care, and healthy lifestyles and habits (Grossman and Kaester, 1997), which introduces multiple confounding factors into the interpretation of the relationship between the degree of cognitive reserve and brain functional optimization. Other proxy variables, such as occupational complexity (Andel et al., 2006; Potter et al., 2008) and intellectual activities during leisure time (Wilson et al., 2002; Verghese et al., 2003), strongly correlate with education and thus present the same methodological problems with respect to obtaining a pure measure of cognitive reserve.

Recent studies have developed a strategy based on a latent variable model to estimate cognitive reserve as the difference between the expected cognitive performance based on the neural state and socio-demographic variables and the observed cognitive performance. This model quantifies cognitive reserve as the variance in neuropsychological scores that is not explained by socio-demographic (e.g., years of education and occupational status) and brain integrity (e.g., grey matter volume and white matter hyperintensities) variables (Reed et al., 2010; Marques et al., 2016; Zahodne et al., 2013). A pioneering study decomposed scores from episodic memory tests into three components (variance explained by demographic variables, variance explained by brain integrity variables, and residual variance) and observed that the residual variance correlated with longitudinal cognitive decline and a modified rate of conversion from mild cognitive impairment (MCI) to AD (Reed et al., 2010). Interestingly, the authors reported a stronger association between brain atrophy and cognitive decline in persons with low cognitive reserve (i.e., a low score for residual variance)



than in persons with high cognitive reserve. A subsequent study replicated and extended these findings by decomposing the variance from episodic memory and executive control tests (Zahodne et al., 2013). In addition, a recent study using this model reported differences in several functional connectivity indices between subjects with high and low cognitive reserve (Marques et al., 2016). In detail, higher cognitive reserve was related with a greater functional connectivity, local efficiency and local clustering within occipital regions, greater strength and centrality values within the inferior temporal gyrus, and higher global efficiency, which represents a measure of functional integration and was related to more efficient use of the brain's resources. Overall, Marques et al (2016) concluded that higher cognitive reserve is associated with increased ability of the brain to form segregated groups of brain regions (clusters or modules), providing evidence for a relationship between high cognitive reserve and greater specialisation of the neural processing.

Because different degrees of cognitive reserve are linked to differing abilities to deploy compensatory mechanisms in response to structural brain damage related to physiological and pathological ageing, the onset and progression of the clinical symptoms may considerably differ between patients with high and low cognitive reserve. Specifically, patients with high cognitive reserve are able to compensate for structural damage for a longer time period and thus symptoms are not manifested at low/moderate degrees of neural damage. However, after achieving a critical threshold at which compensatory mechanisms are not able to be successfully deployed, clinical impairment progresses quickly (Figure 1). In contrast, in patients with low cognitive reserve, slight brain damage is sufficient to produce clinical symptoms due to weak deployment of functional compensatory mechanisms. Consequently, patients with low cognitive reserve exhibit clinical symptoms at earlier stages of the disease, and these clinical symptoms slowly progress as neural alterations evolve (Figure 1). Paradoxically, the period of time that elapses between the onset of clinical symptoms and the advanced stages of cognitive impairment is shorter in patients with high cognitive reserve than in patients with low cognitive reserve because patients with high cognitive reserve remain asymptomatic during stages prior to the collapse of compensatory mechanisms, but

patients with low cognitive reserve already show clinical symptoms during those stages (Arenaza-Urquijo et al., 2015; Jansen et al., 2015). According to this pattern of clinical progression, empirical studies have usually reported higher rates of cognitive decline in patients with high cognitive reserve than in patients with low cognitive reserve (Helzner et al., 2007; Scarmeas et al., 2006; Wilson et al., 2004 but see also Amieva et al., 2014), which is reflected in the current theoretical models of AD progression (Arenaza-Urquijo et al., 2015; Gehres et al., 2016). Hence, the time between clinical AD onset and severe clinical AD is longer for patients with low cognitive reserve than for patients with high cognitive reserve (Figure 1).

Insert Figure 1 here

The findings mentioned in this section very briefly summarize the changes related to healthy and pathological ageing and suggest the potential of the brain to undergo neuroplasticity changes throughout the adult lifespan as a result of enriched cognitive environments. These changes may modify the brain's ability to deploy compensatory mechanisms in response to major pathological conditions, such as AD, which led to the formulation of the cognitive reserve hypothesis.

### **3. Non-pharmacological interventions to improve cognition in healthy elderly individuals and patients with Alzheimer's disease**

During the last few years, a growing number of studies has provided evidence for cognitive improvements during healthy and pathological ageing after applying non-pharmacological interventions. These interventions are thought to promote residual brain plasticity mechanisms, as reported by research using animal models and human studies employing neuroimaging measures. These mentioned interventions, which are schematically summarized in Figure 2, are mainly based on CIs, PE (for a review of both types of intervention, see Bamidis et al., 2014), and NIBS (for a review, see Tatti et al., 2016).

Insert Figure 2 here

### *3.1. Cognitive and physical exercise interventions*

CIs may be considered the more classical approach to improve cognitive function or slow the progression of cognitive deficits. Two main types of CIs have been distinguished: cognitive training (CT) and cognitive rehabilitation (CR) (Clare and Woods, 2004). CT refers to a general intervention that may be implemented in healthy persons and in patients with cognitive deficits. This type of intervention includes a set of procedures used to improve general cognitive function and social skills. The complexity of the cognitive tasks is adjusted to the baseline performance and progression of each participant. This adaptive training is particularly feasible when applying computerized CT (Lampit et al., 2014) because the difficulty level may be computationally adapted on a trial-by-trial basis (Kueider et al., 2012; Lampit et al., 2014). CT may also be implemented at the group level. In this case, the intervention is usually designated as cognitive stimulation (Clare and Woods, 2004; Huntley et al., 2015). Diverse CT programmes have been implemented to improve a variety of cognitive domains, such as memory (Richmond et al., 2011), learning (Bailey et al., 2010), attention (Mozolic et al., 2011), and executive function (Basak et al., 2008). For example, Brhmer et al. (2011) implemented 25 sessions of CT in a sample of healthy elderly participants who performed a working memory task (n-back task). The difficulty level of the task increased as the participants improved their performance. Also, a healthy elderly control group was trained on the same type of working memory task at a relatively low fixed demand. fMRI was performed before and after training while the participants performed working memory tasks with a low and a high demand. After the training period, a larger decrease in brain activity was observed in participants whose training involved a progressive increase in the task difficulty level. The authors interpreted these results according to the neural efficiency account, which states that individuals with higher capacity show less brain activation at the same subjective difficulty level because they need to allocate fewer

brain resources to perform the task at the same level (Dunst et al., 2014; Haier et al., 1992). CR refers to interventions used to improve specific cognitive and/or motor dysfunctions in a patient to improve her/his quality of life. For example, Vermeij et al. (2016) implemented an adaptive training programme in working memory – an ability that is usually declined in patients with MCI – for five weeks by using n-back tasks in a sample of participants with MCI. The authors reported improved performance at a low difficulty level after the training period. Overall, current research on CIs is focusing on identifying more effective training parameters (Brehmer et al., 2011; Styliaidis et al., 2015), maintaining long-term persistence of the obtained benefits (Boyke et al., 2008; Lövdén et al., 2012), and studying transfer effects to untrained abilities (Anguera et al., 2013; Berry et al., 2010; Dahlin et al., 2008; Tusch et al., 2016; Wolf et al., 2014).

PE represents another intervention that has been used to improve cognition. The Institute of Medicine and the American College of Sports Medicine distinguish between physical activity (PA) and PE. PA refers to bodily movement produced by the contraction of skeletal muscles that increases energy expenditure. PE is defined as planned, structured, and repetitive movement to improve or maintain one or more components of physical fitness. Thus, PE is a subcategory of PA that is planned, structured and oriented to improve specific physical skills or physical fitness (Bherer et al., 2013). PE may be divided into three main categories: aerobic exercise (e.g., walking, running, and cycling), resistance training (e.g., lifting weights), and stretching and balance (e.g., yoga and Pilates). This last type of PE is considered less effective and is usually implemented in the control group to match possible benefits from social interaction (Brinke et al., 2015; Chapman et al., 2013; Erickson et al., 2011; Liu-Ambrose et al., 2012; Voss et al., 2013 but see also Mortimer et al., 2012, who reported greater cognitive improvement after toning and balance exercises (tai chi) than after aerobic training (walking) and Voss et al., 2010, who demonstrated that stretching and toning exercises improved functional brain connectivity in the default mode network after 6 months of training and in a frontal parietal network after 12 months of training. An example of an intervention using PE was implemented in a study conducted by Brinke et al (2014). In this study,

39 participants with MCI were randomly assigned to one of three groups: PE based on an aerobic training programme, PE based on a resistance training programme and a toning and balance control group. The authors reported an increased hippocampal volume in the brains of the aerobic training group after six months of training. Current research in this field is mainly devoted to investigating the parameters that maximize the cognitive benefits induced by these types of interventions (Bherer et al., 2013). Overall, several reviews about PE interventions have reported that the PE programmes improve executive function to a greater extent than other cognitive domains (Hillman et al., 2008).

### *3.1.1. Neurophysiological changes after cognitive and physical exercise interventions*

An emerging area of research is focusing on neural changes that underlie the cognitive improvement observed after interventional programmes based on CI during healthy and pathological ageing (Table 1). Modulations of event-related brain potentials (ERPs) were reported in healthy elderly who performed a working memory task (O'Brien et al., 2013) and a visual search task (Berry et al., 2010) that had implemented specific CT protocols in other cognitive domains (see Table 1 for the specific ERP modulations and other relevant details of the abovementioned studies). These results revealed neural modulations related to the transfer of learning, a concept that references the ability to apply knowledge learned in a specific context (e.g., improved performance after training on a specific cognitive task) to a different context (e.g., improved performance on a task differing from the previously taught or trained task). This concept is important because the main aim of the interventional programmes is to promote a generalized cognitive improvement in addition to the improvement in the tasks trained during the experimental sessions. Likewise, patients with AD who performed a lexical recognition task exhibited a larger N2 component (which was related to an ERP related to recognition processes) after receiving CT in several cognitive domains (Spironelli et al., 2013). Additionally, neuroimaging studies showed reduced cortical activity in healthy elderly subjects after training in working memory tasks. This result was related to greater neural efficiency (Brehmer et al., 2011; Heinzel et al., 2014), although other studies failed to

observe correlations between reduced neural activity and cognitive improvement (Forster et al., 2011); for details on these studies, see Table 1. Moreover, evidence for connectivity changes related to improved cognition after CT were reported in samples of healthy elderly individuals (Anguera et al., 2013) and patients with cognitive decline (Hampstead et al., 2011). Specifically, Anguera et al. (2013) conducted an EEG study in which healthy elderly subjects were randomly assigned to one of three different groups. The multitask training (MTT) group received training in two tasks: a visuospatial task consisting of a driving video game and a perceptual discrimination task. Another group received only the visuospatial training. Finally, a third group of participants were assigned to the inactive control group. After the participants were trained for one hour per day three times a week for four weeks, untrained executive skills were improved in the MTT group but not in the other groups. This improvement was related to higher midline frontal theta power and fronto-parietal connectivity (coherence), a circuit involved in executive function. In the fMRI study conducted by Hampstead et al. (2011) in a sample of patients with MCI, higher effective connectivity was observed within the middle temporal cortex, occipital cortex and precuneus during a face-name associative task after the participants completed three sessions of training in encoding strategies.

Insert Table 1 here

Some studies have focused on neurophysiological changes after PE (Table 2). Aerobic exercise shortened the P300 latency (an ERP component that is usually related to memory and working memory processes (Polich, 2007)) in a variety of cognitive tasks performed by healthy elderly subjects, such as an auditory oddball task (Cetin et al., 2010) and a Flanker task (Kamijo et al., 2009). Neuroimaging studies in healthy elderly subjects showed improved executive functions and related neural changes after the application of diverse PE modalities such as aerobic training (Colcombe et al., 2004; Voss et al., 2010), resistance training (Liu-Ambrose et al., 2012) and

stretching and toning (Voss et al., 2010) programmes. Moreover, aerobic training modulates the neural state at rest, as revealed by higher hippocampal activity and modulations in hippocampal-anterior cingulate cortical connectivity (Burdette et al., 2010). Additionally, in participants with MCI, aerobic exercise is related to improved performance and reduced activity in several regions within the frontal, temporal and parietal lobes during a famous-name discrimination task (Smith et al., 2013) and reduced activity in the anterior cingulate cortex during a visuospatial/attentional task (Porto et al., 2015).

Insert Table 2 here

Both CI and PE have also been shown to induce structural modifications in the brain. A memory training programme improved memory function in healthy elderly subjects, which correlated with the volumes of the right fusiform and orbitofrontal cortices (Envig et al., 2010). Additionally, spatial navigation training was related to the maintenance of hippocampal volume during the training period compared to the age-related decrease in the volume of this tissue observed in non-trained participants (Lövdén et al., 2012). Another study conducted in healthy elderly participants reported that juggling training increased the volume of the visual and temporal cortices (Boyke et al., 2008). Aerobic exercise is also related to increased volumes within the prefrontal and temporal cortices (Colcombe et al., 2006), prefrontal and cingulate cortex (Ruscheweyh et al., 2011), and hippocampus (Erickson et al., 2011) in healthy elderly participants. Notably, the increased hippocampal volume observed after aerobic training has also been observed in participants with MCI (Brinke et al., 2015). However, improved cognition in the absence of structural changes has been reported in healthy elderly subjects after aerobic exercise (Jonasson et al., 2017; Voss et al., 2013). Nevertheless, in those studies, correlations were reported between higher aerobic skills, white matter integrity within the frontal and temporal lobes, and greater memory improvement after the training period (Voss et al., 2013) and between the thickness of the

dorsolateral prefrontal cortex (DLPFC) and cognitive function (Jonasson et al., 2017). Aerobic exercise is considered the PE modality that provides the greatest benefits for cognition and brain preservation (Bherer et al., 2013; Hillman et al., 2008), although some studies also reported an increased brain volume in healthy elderly subjects after implementing programmes based on balance and toning exercises (Liu-Ambrose et al., 2010; Mortimer et al., 2012). In summary, cognitive and PE interventions have generally been successfully used to improve cognitive performance and produce concomitant functional and structural brain modulations, although the optimal parameters and the potential of these tools to promote long-term cognitive improvements and neurophysiological changes are still unclear.

### *3.2. Non-invasive brain stimulation*

NIBS techniques (transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES)) represent more recent approaches to improve and/or rehabilitate cognitive and motor functions.

TMS delivers magnetic fields (using a coil device) that interact with neural activity and induce action potentials (Barker et al., 1985). TMS pulses may be applied at low ( $\leq 1$  Hz) or high (5-20 Hz) frequencies, leading to decreased or increased neural excitability, respectively (Pascual-Leone et al., 1994). Paired associative stimulation (PAS) is a type of TMS protocol that pairs median nerve electrical stimulation with a TMS pulse applied to the contralateral cortex at specific time intervals (Stefan et al., 2000). For PAS protocols, the delivery of a TMS pulse over the cortical area at 25 ms (PAS<sub>25</sub>) or 10 ms (PAS<sub>10</sub>) after the peripheral electrical stimulus leads to excitatory and inhibitory neurophysiological effects, respectively. Another TMS protocol is theta burst stimulation (TBS), which consists of delivering bursts of 3 pulses at 50 Hz every 200 ms (i.e., at theta frequency - 5 Hz) (Huang et al., 2005). For TBS protocols, the bursts of TMS pulses can be intermittently (intermittent TBS - iTBS) or continuously (continuous TBS - cTBS) delivered, leading to excitatory and inhibitory neurophysiological effects, respectively.



Transcranial direct current stimulation (tDCS) is by far the most frequently used tES modality. tDCS consists of applying a flow of current between two electrodes at a low intensity (1-2 mA) for a long period (5-30 min). This current modulates cortical excitability by modifying spontaneous neural activity (Nitsche and Paulus, 2000). Specifically, anodal stimulation increases spontaneous neuronal firing rates, whereas cathodal stimulation reduces spontaneous neuronal firing rates. More recent tES protocols include transcranial alternating stimulation (tACS) and transcranial random noise stimulation (tRNS). tACS consists of delivering an alternating current at a given frequency, which “entrains” ongoing brain activity and thus modulates the neural firing frequency. In contrast, tRNS consists of delivering a current over the cortex at random frequencies (0.1-1000 Hz). The random neural noise added by tRNS modulates the firing rate pattern within a specific brain region or network (for a review of tES techniques, see Fertonani and Miniussi, 2016).

Studies on NIBS focus on establishing relationships between specific NIBS parameters and behavioural/neurophysiological changes. Recent theoretical developments (Miniussi et al., 2013; Rahman et al., 2015) and meta-analyses (Hsu et al., 2015; Summers et al., 2016) have suggested the absence of simple and linear relationships between the type of stimulation (excitatory/inhibitory) and physiological and cognitive-behavioural effects. In fact, the effects of NIBS are mediated by an extensive set of variables, such as the stimulation intensity, which modulates TMS (Thut and Pascual-Leone, 2010) and tDCS (Jamil et al., 2016) after-effects, and the use of offline (i.e., stimulation at rest) or online (i.e., stimulation while performing a task) modalities. Offline protocols induce changes in excitability that affect subsequent synaptic efficacy, whereas online protocols act by reinforcing activated brain circuits involved in task performance (Luft et al., 2014; Siebner et al., 2009). Additionally, individual variables, such as the ability to perform a given task, modify the effects of NIBS. For instance, Dockery et al. (2009) reported opposite effects of anodal and cathodal tDCS, according to the level of practice on a planning task. Specifically, cathodal tDCS improved performance at the initial stages of training in a motor planning task; however, when participants became relatively skilled at performing the task, anodal tDCS led to additional

improvements, whereas cathodal tDCS led to impaired performance (Dockery et al., 2009). In addition to these mentioned variables, intrinsic characteristics of healthy and pathological ageing alter the effects of NIBS in several ways. For example, brain hyper-excitability related to healthy and pathological ageing (Backer et al., 2012; Pellicciari et al., 2009) might alter the effects induced by a specific type of stimulation on cognitive improvement (Backer et al., 2012; Simkin et al., 2015). Furthermore, brain atrophy increases the distance between a stimulation hotspot and a targeted region, altering the current density distribution (Wagner et al., 2008) and thus the effect of the current on the targeted neural populations.

### *3.2.1. Neurophysiological changes after non-invasive brain stimulation*

Several investigations have provided neurophysiological evidence for modified cortical activity in healthy elderly subjects and patients with AD after applying NIBS (Table 3). Regarding TMS protocols, neurophysiological changes, namely, increased somatosensory evoked potentials, have been observed after a PAS protocol was applied over sensorimotor cortex in healthy elderly subjects (Pellicciari et al., 2009). Additionally, repetitive TMS (rTMS) applied at a frequency of 5 Hz over the left DLPFC improved face-name associative memory and increased neural activity within the posterior and right prefrontal areas in elderly subjects with a memory deficit (Solé-Padullés et al., 2006). Likewise, a high frequency rTMS treatment applied over bilateral DLPFC improved naming task performance in patients with AD, which was related to greater activity in Broca's area and a general neuropsychological improvement (Devi et al., 2014).

For tES studies, repeated sessions of both anodal and cathodal tDCS over the left dorsolateral prefrontal cortex of patients with AD improved their cognitive functions and reduced the latency of auditory P300 ERPs, which represents a correlate of memory processes (Khedr et al., 2014). Additionally, cortical EEG activity of patients with AD was modulated in a polarity-specific manner by tDCS, leading to an improvement in working memory functions (Marceglia et al., 2016). In this latter study, the authors also reported that anodal tDCS increased the high-frequency power

in temporo-parietal areas and the connectivity (coherence analysis) between temporo-parieto-occipital areas. In fMRI studies, anodal tDCS applied over the left inferior frontal cortex during a picture-name associative task (Holland et al., 2011) and over the left ventral inferior frontal gyrus during a word recognition task (Meinzer et al., 2013) improved performance in healthy elderly subjects, which correlated with neural changes in specific regions involved in performing the mentioned tasks. In a subsequent study, anodal tDCS applied unilaterally and bilaterally over the motor cortex of healthy elderly adults improved their word-retrieval ability and reduced underlying brain activity (Meinzer et al., 2014). A similar reduction in task-related prefrontal hyperactivity (which was accompanied by improved performance in a semantic word retrieval task) was observed in participants with MCI during the application of anodal tDCS over the left inferior frontal gyrus, which also resulted in the normalization of an abnormal network configuration (Meinzer et al., 2015). These results show a trend that is opposite that predicted by the stimulation-dependent model; specifically, anodal tDCS is usually related to greater cortical depolarization and increased brain activity. However, as suggested by the network activity-dependent model (Fertonani and Miniussi 2017), the tDCS is able to modulate behaviour and underlying brain activity according to the endogenous brain activity induced by the task performed during the stimulation period (e.g., Bortoletto et. al., 2015; Dockery et al., 2009). In a tDCS-fMRI study implemented in healthy elderly adults, dual (bihemispheric) tDCS yielded stronger activation of bilateral M1 when the participants used the left or the right hand during a choice reaction time task. Additionally, the application of dual tDCS at rest decreased the right hippocampal-M1 connectivity and increased connectivity in the left prefrontal cortex and the dorsal posterior cingulate cortex. These results suggested that dual tDCS effects can be mediated by complex network modulations involving interhemispheric interactions and areas related to motor control (Lindenberg et al., 2013).

Insert Table 3 here

### *3.3. Evidence for neuroplasticity from animal models*

A better understanding of the cellular and molecular mechanisms underlying brain plasticity observed after interventional programmes is obtained from studies employing animal models. The involvement of key molecular and cellular mediators involved in neuroplasticity, both at the single neuron and neural network levels, has been validated using animal studies that adopt interventional programmes based on an enriched environment. In these studies, cellular and molecular changes observed in response to enriched environments influence brain plasticity by increasing synaptic density, enhancing the expression of molecules involved in neuronal signalling and strengthening neuronal circuits (Nithianantharajah and Hannan, 2006; Sale et al., 2014).

Likewise, using physical exercise-induced neuroplasticity, evidence from animal studies has highlighted a cascade of functional and structural changes in the nervous system linked to aerobic exercise (for a review, see Kandola et al., 2016). Both micro- and macro-scale brain changes have been observed after aerobic exercise, indicating that exercise improves cognitive functions in domains dependent on the hippocampus, such as spatial or relational learning and memory, by modulating the neuroplasticity of the hippocampal dentate gyrus (for a review, see Stillman et al. 2016). More specifically, the enhancement of neurogenesis, synaptogenesis, angiogenesis (particularly vascular endothelial growth factor), synaptic plasticity and the release of neurotrophins, including growth factors such as brain-derived neurotrophic factor and insulin-like growth factor-1, have been identified as neural mechanisms mediating the beneficial effects of physical exercise on cognition, which are also paralleled by increases in grey matter volume, global white matter integrity and hippocampal changes (Ahlskog, 2011; Alkadhi, 2017; Cassilhas et al., 2015; Chieffi et al., 2017; Hamilton and Rhodes, 2015; Hotting and Roder, 2013).

For NIBS (i.e., TMS and tES), specific molecular and cellular mechanisms underlying both short- and long-term changes in synaptic plasticity have been revealed by recent findings obtained from *in vitro* experiments and *in vivo* animal studies (Cirillo et al., 2017). LTP and LTD phenomena are not the only neurobiological mechanisms used to explain the effects of NIBS. A

more complex scenario has been defined, including gene activation/regulation, protein expression, modulation of neurotransmission, morphological changes, changes in neurotrophic secretion, changes in intrinsic firing properties, modifications to network properties resulting from changes in inhibitory and homeostatic processes, and modulation of glial function (for a review, see Antal and Herrmann, 2016; Cirillo et al., 2017; Fritsch et al., 2010). In summary, studies using animal models provide evidence for the implementation of specific neuroplasticity mechanisms following the application of non-pharmacological interventions (for a schematic recap, see Figure 3).

Insert Figure 3 here

#### *3.4. Multimodal interventional approaches to maximize neural and cognitive benefits*

Multimodal interventions combining CI and PE (Kraft, 2012; Linde and Alfermann, 2013) or CI and NIBS (Bentwich et al., 2011; Cotelli et al., 2014; Gill et al., 2015; Park et al., 2014; Rabey et al., 2013) have recently been shown to lead to greater cognitive improvements than the separate application of these interventions. Studies combining CI and PE (Frantzidis et al., 2014; Klados et al., 2016; Styliadis et al., 2015) or implementing tasks that simultaneously demand CT and PE, such as juggling (Boyke et al., 2008) or performing a visual search while walking in a virtual environment (Lövdén et al., 2012), are detailed in Table 4. Multimodal interventions based on CT and NIBS are reported in Table 3 as an “online modality”. Increased benefits observed after implementing multimodal interventions have been hypothesized to occur due to the promotion of complementary neuroplasticity mechanisms (Figure 3), which may act in a synergistic manner. For instance, according to a recent review by Bamidis et al. (2014), PE increases neurogenesis and synaptogenesis, whereas CI activates and integrates neurons and synapses into pre-existing neural networks.

Insert Table 4 here

A discussion about the high complexity of designing appropriate control groups in non-pharmacological randomized controlled trials is worthwhile. This complexity is even greater in multimodal programmes studying the separate contributions of the different tools comprising the programme (e.g., Styliadis et al., 2015). Some CT studies used both an inactive and an active control group (e.g., Anguera et al., 2013), which is appropriate to control for effects related to the placebo and social interactions. Similarly, PE interventions usually employ an inactive control group (Ruscheweyh et al., 2011) or an active control group based on stretching, toning, and balance exercises (Jonasson et al., 2017), which were used to match benefits from social interactions and control for placebo effects. However, some studies have reported cognitive benefits (Mortimer et al., 2012) and optimised neural connectivity patterns (Voss et al., 2010) from these types of exercises. Thus, benefits from PE may be underestimated if balance and toning are considered as an ineffective control group. NIBS studies using cortical measures usually conduct a single intervention session to assess the effects of the application of specific NIBS protocols. An additional session that includes sham stimulation is usually implemented to control for placebo and learning-related effects. Crucially, for studying modulations of specific brain regions that mediate the hypothesized cognitive improvements, recent studies have highlighted the convenience of using another experimental session consisting of delivering a real stimulation to an area located outside the brain circuits involved in the studied cognitive function (Rossini et al., 2015). This session allows researchers to determine whether the cognitive improvements and associated neural changes are mediated by the stimulation of a specific brain area or are related to the nonspecific increase in arousal levels.

Finally, other non-pharmacological approaches have been adopted as preventive strategies to ameliorate cognitive ageing and delay the onset of cognitive deficits. Specifically, adherence to specific dietary habits has been associated with a lower risk of developing MCI and AD (Scarmeas et al., 2009). Different diets, such as dietary restriction, a low-fat diet and resveratrol consumption,

were reported to have key roles in cognitive function and brain integrity by affecting several mechanisms of plasticity, including neurogenesis, synaptic plasticity, neurotrophin release and hippocampal neuroprotection (for a review, see Greenwood and Parasuraman, 2010).

#### **4. Relationships among cognitive improvement, neural changes and the promotion of neuroplasticity**

Considering the strong therapeutic implications, in this section, we discuss to what extent the relationships between improved cognition and neural changes provide evidence for brain plasticity mechanisms. Next, we discuss how the type of intervention and degree of cognitive reserve may mediate nonlinear relationships between cognitive improvement and neural changes.

The modulation of neural activity after applying CI, PE, and NIBS was taken as evidence for neuroplasticity in most of the reviewed studies. In fact, interventional programmes based on CI and PE frequently last from several months to one year, which would be a time period more than sufficient to promote the activation of neuroplasticity mechanisms. Nevertheless, neural activity changes have also been observed after one or only a few sessions of CT in healthy elderly subjects (Belleville et al., 2011; Kirchoff et al., 2012; Miotto et al., 2014; Nyberg et al., 2003) and cognitively impaired patients (Belleville et al., 2011; Hampstead et al., 2011; Hampstead et al., 2012a). Likewise, neural activity changes have been observed after a single session or only a few sessions of TMS or tES in healthy elderly subjects (Holland et al., 2011; Lindenberg et al., 2013; Sole-Padulles et al., 2006) and cognitively impaired patients (Devi et al., 2014; Khedr et al., 2014; Meinzer et al., 2014). These results may be also related to brain flexibility, which was previously defined as the capacity to optimize the brain's performance within the limits of the current state (Lövdén et al., 2010). Therefore, considering the brief duration of the mentioned interventions, the promotion of brain flexibility might be a more straightforward explanation for the reported cognitive improvements and associated neural activity changes than brain plasticity although the deployment of brain plasticity mechanisms after a very brief period of time have been also reported

(Elvsåshagen et al., 2017; May et al., 2007). For instance, May et al (2007) demonstrated that application of repetitive TMS over the superior temporal cortex during five consecutive days caused macroscopic cortical changes in the gray matter of the auditory cortex and, interestingly, these changes gave rise to brain activity modulations. As discussed in previous research, structural changes can be more reliably attributed to brain plasticity than functional changes (Will et al., 2008). Nevertheless, in addition to the long-term maintenance of cognitive benefits and associated structural changes, the transfer effects on untrained tasks may be also investigated to provide evidence for brain plasticity.

Some studies have reported long-term maintenance of cognitive benefits after interventional programmes (Mahnke et al., 2006; Zelinski et al., 2011). However, the disappearance of cognitive improvement and/or neural changes after intervention cessation is not uncommon. For instance, in the study by Boyke et al. (2008), juggling training for three months led to functional and structural changes in elderly subjects; however, a follow-up assessment conducted three months after completion of the intervention showed that the previously observed neural changes had disappeared. According to the notion of “use it or lose it”, LTD mechanisms may accompany intervention cessation in the same manner as participation in an interventional programme promotes LTP. Based on this evidence, a maintenance programme appears to be appropriate to avoid the loss of the obtained benefits. Additionally, interventions based on CT consider transfer effects on untrained tasks as evidence for neuroplasticity (Lövdén et al., 2010), since improved performance on an untrained task suggests strengthening of the brain network underlying the executed task rather than an improvement related to task repetition effects. Nevertheless, the potential ability of cognitive interventions to exert transfer effects on untrained tasks and/or daily life activities is still unclear. Recent reviews have reported promising results (Gates and Sachdev, 2014), whereas others highlighted limited transfer effects on untrained tasks/abilities (Huntley et al., 2015). In general, the existence of transfer effects after cognitive interventions is widely influenced by the parameters of the specific experimental design (Lampit et al., 2014). In fact, a main focus of research is



identifying the training parameters (Anguera et al., 2013; Brehmer et al., 2011) and the neurophysiological variables (Dahlin et al., 2008; Filmer et al., 2013; Wolf et al., 2014) that are related to training efficacy and transfer effects. Notably, neural changes observed at rest may be considered a specific type of transfer effect (e.g., from the network involved in performing a given task to the default network). In this context, transfer effects on resting-state activity have been observed after CT (Bozzali et al., 2015; Chapman et al., 2015), PE (Chapman et al., 2013; Voss et al., 2010) and NIBS (Lindenberg et al., 2013; Meinzer et al., 2013).

Recent studies have investigated both functional and structural changes after interventional programmes to obtain a deeper understanding of the relationships among cognitive improvements, neural changes, and brain plasticity mechanisms. This strategy represents an interesting approach considering the reported relationship between cognitive performance and brain activity (Eyler et al., 2011), as well as the relationship between cognitive performance and the structural state of the brain (Kaup et al., 2011). For instance, Chapman et al. (2015) applied a CT programme for 12 weeks. Functional changes were observed in week six, whereas both functional and structural changes were observed in week 12. In another study, 8 weeks of CT improved performance and modulated functional activity, but failed to promote structural changes (Mozolic et al., 2010), which might be explained by the shorter duration of the intervention. Additionally, some studies investigated functional and structural modulations induced by PE programmes. Chapman et al. (2015) reported improved cognitive and functional changes after three months of aerobic exercise but failed to show structural changes, which may be related to the brief duration of the intervention programme. However, no NIBS studies have combined both functional and structural cortical modulations (for a recent review, see Tatti et al 2016). Indeed, only two NIBS studies used multiple sessions to investigate neural changes during advanced stages of life (Devi et al., 2014; Kehdr et al., 2014). In general, studies about the relationship between functional and structural changes in the cortex promoted by interventional programmes appear consistent with the hypothesis that structural changes result from functional changes that are maintained for a defined time period (Bruel-

Jungerman et al., 2007; Chapman et al., 2015), which is consistent with the interpretation of these changes as evidence for brain plasticity.

Nevertheless, some paradoxical results must be cited to illustrate the complex relationships between cognitive improvement and structural and functional changes in the cortex. For example, a resistance training (RT) programme improved executive function compared to the effects of a balance and toning (BAT) intervention (Liu-Ambrose et al., 2010). Nevertheless, after the training period, the brain volume was greater in the BAT group than in the RT group. Another study reported increased hippocampal volume in patients with MCI after 6 months of PE training; however, a larger left hippocampal volume was significantly correlated with cognitive decline and cortical shrinkage (see Greenwood and Parasuraman, 2010). Thus, relationships between functional/structural changes in the cortex and cognitive function are frequently nonlinear. Next, we explain how the type of intervention and individual differences in cognitive reserve represent two variables that, among others, might improve our understanding of the complex relationships between cognitive improvements and functional/structural changes in the brain.

The type of intervention must be considered as an important variable when studying relationships between improved performance and functional/structural changes due to different brain mechanisms promoted by each type of intervention (Figure 3). For this reason, multimodal interventional programmes were suggested to yield synergistic improvements (section 3.4). Specifically, PE mainly promotes the release of neurotrophic factors that increase neurogenesis and synaptogenesis (Huang et al., 2014). Thus, the hypothesis that PE interventions principally modulate brain structure is reasonable. Instead, CI improves brain connectivity within specific brain networks (Marques et al., 2016). Therefore, CI mainly results in a functional neural reorganization. Additionally, brain mechanisms promoted by TMS and tES differ according to the protocol and modality used, as presented in Figure 3. According to the neuroplasticity mechanisms promoted by every type of intervention, we hypothesize the existence of diverse time sequences for the occurrence of functional and structural changes in the brain. CI and online NIBS would initially

induce functional changes, whereas structural changes would be promoted during later stages, as argued in previous studies (Buel-Jungerman et al., 2007; Chapman et al., 2015). Instead, the timing of functional and structural changes would overlap after applying PE because neurotrophic factors reverse structural changes in volume and the improved brain structure would involve the partial restoration of damaged brain networks. Multiple follow-up assessments of interventional programmes monitoring functional and structural changes would directly allow researchers to test these hypotheses. Nevertheless, we should bear in mind that some interventions have elements that induce both functional and structural plasticity, which adds a degree of complexity for understanding the relationship between structural and functional plasticity. An illustrative example may be the study conducted by Voss et al (2010), who related the improved brain connectivity patterns observed in healthy elderly after the application of a PE intervention based on stretching and toning exercises to the cognitive component that these exercises involve (for example, their intervention required to imitate instructor's movements while learning the exercises).

Cognitive reserve is another important variable that should be considered when investigating the relationship between performance and functional/structural changes. As previously stated, the cognitive reserve hypothesis interconnects cognitive performance, brain function and brain structure, and it was formulated to explain the mismatch between cognitive function and the structural integrity of the brain (Arenaza-Urquijo et al., 2015; Ewers et al., 2013). Although people with high cognitive reserve exhibit more resistance to AD pathology due to the more efficient deployment of functional compensatory mechanisms (Steffener and Stern, 2012; Marques et al., 2016) and a higher degree of pathology is needed to give rise to clinical symptoms (Arenaza-Urquijo et al. 2015; Stern, 2009), people with low cognitive reserve begin to show clinical symptoms at very low levels of neural damage. These differences between subjects with high and low cognitive reserve are relevant because, regardless of the type of intervention, patients with high cognitive reserve will exhibit a narrow margin of functional improvement because this parameter has already been optimized. At most, functional modulations in patients with high cognitive reserve

rely on improvements in brain structure. However, patients with low cognitive reserve show a relatively well-preserved structure (the margin to modulate brain structure will be more limited in these patients), but their brain function is far from optimal. Therefore, these patients have a greater margin for optimizing brain function, which is supported by the relatively preserved brain structure. As explained in the next section, the differences observed between patients with high and low cognitive reserves might have important implications for the design of individualized interventions to ameliorate cognitive deficits.

In summary, the long-term maintenance of cognitive improvements associated to structural changes, transfer effects on untrained tasks and resting-state activity provide strong clues to interpret cognitive benefits from interventional programmes due to brain plasticity mechanisms. Nevertheless, a maintenance programme appears to be required to preserve the obtained benefits. Finally, we have hypothesized that diverse plasticity mechanisms promoted by specific interventions and the degree of cognitive reserve (high or low) of the targeted subjects or patients may determine the relationships among cognitive improvement, functional and structural changes in the brain and, as discussed below, the optimal strategy to optimize brain preservation.

## **5. A rationale for weighting the subcomponents of multimodal programmes**

Differences in the onset and progression of AD symptoms between patients with high and low cognitive reserve are the result from the diverse capabilities of individuals to deploy functional compensatory mechanisms. In this section, we propose that the efficacy of multimodal approaches can be maximized by weighting the importance of the interventions related to the promotion of functional and structural neuroplasticity mechanisms according to the degree of cognitive reserve, which may be used as an indicator of the neural and cognitive states of the treated patient.

The importance of implementing multimodal interventions is supported by the greater cognitive improvements observed after applying multimodal interventional programmes than after applying any type of intervention separately. Considering the existing differences in the brain states

of people with high and low cognitive reserve and the diverse brain plasticity mechanisms promoted by different interventions, we propose to weight the relative importance of different rehabilitative tools associated with the multimodal intervention according to the neural and functional states of the targeted patient. Specifically, we suggest that patients with low cognitive reserve may achieve greater cognitive improvements from interventions that strengthen functional processes (Figure 4, top chart), whereas patients with high cognitive reserve may achieve greater cognitive improvements from multimodal programmes that primarily focus on interventions promoting structural restoration (Figure 4, bottom chart), even if both groups of participants obtain greater benefits from multimodal programmes than from any single interventional approach.

Insert Figure 4 here

Considering the weakness of the compensatory mechanisms in the brain and the relatively well-preserved brain structure in patients with low cognitive reserve during early stages of disease, the implementation of multimodal programmes emphasizing interventions to strengthen functional processes (i.e., CIs and online NIBS) may enhance the efficiency of compensatory mechanisms in the brain and expand the asymptomatic period. The foundation for improving the functionality of compensatory mechanisms in the brain relies on a relatively well-preserved brain structure. Therefore, if the implementation of the mentioned interventions during advanced stages of life promotes brain plasticity mechanisms similar to positive life experiences (Lenehan et al., 2016), then brain connectivity patterns will be optimized in a similar manner (Steffener and Stern, 2012; Marques et al., 2016), subsequently improving cognitive function. Factors related to cognitive training, such as learning a second language, have exhibited greater utility in preserving brain functioning in elderly subjects with low cognitive reserve than in subjects with high cognitive reserve (Alladi et al., 2013; Chertkow et al., 2010; Gollan et al., 2011), illustrating the greater benefits of functional interventions in subjects with low cognitive reserve than in subjects with high

cognitive reserve. A straightforward explanation is that individuals with high cognitive reserve are already functioning at an optimal level due to a set of other cognitively enriching activities. Consequently, additional cognitive activities do not further optimize the functional brain patterns because of a ceiling effect.

According to additional evidence, interventions designed to strengthen functional processes will be more beneficial for subjects with low cognitive reserve than for subjects with high cognitive reserve. NIBS techniques improve cognitive function in low performers to a greater extent than in high performers, as reported in the meta-analysis by Hsu et al. (2015). Because cognitive reserve correlates with cognitive performance in healthy populations (Cabral et al., 2016), these results are consistent with the hypothesis that individuals with low cognitive reserve will experience greater cognitive benefits from NIBS protocols than individuals with high cognitive reserve. In this context, a recent tDCS study conducted by Brosnan et al. (2017) revealed that targeting the right fronto-parietal network, which plays an important role in supporting cognitive reserve (Robertson, 2013, 2014), increased the processing speed of items appearing on the left hemifield during a visual attention task. Crucially, performance was enhanced to a greater extent in participants with low cognitive reserve than in participants with high cognitive reserve.

On the other hand, during prodromal or early clinical stages of AD, the emerging symptomatology observed in patients with high cognitive reserve is related to moderate/severe brain damage, as shown in Figure 1. For this reason, compensatory mechanisms begin to be unsuccessful at this stage. Therefore, multimodal programmes emphasizing the promotion of neurotrophic factor release (i.e., PE) might partially restore brain structures and delay the progression of cognitive deficits by prolonging the period in which efficient compensatory mechanisms can be deployed. In this regard, BDNF levels are reduced at early stages of AD (Gezen-Ak et al., 2013; Pláteníka et al., 2014; for a comprehensive review, see Budni et al., 2016), and increasing BDNF levels is associated with improved cognition (Jiao et al., 2016; Kazim and Iqbal 2016), which suggests that restored brain structure may facilitate the re-establishment of malfunctioning connections that

would have disrupted by the structural damage. Based on other scientific data, a major focus on structural restoration is needed to observe improved cognitive performance in patients with high cognitive reserve. A degree of neural integrity is required to obtain benefits from training (Engvig et al., 2010; Hampstead et al., 2012b; Jonasson et al., 2017) as well as to transfer learning to untrained tasks (Wolf et al., 2014). For instance, in the abovementioned study, the authors applied a cognitive training programme in logical reasoning and studied the transfer of learning to fluid intelligence measures in a sample of healthy elderly subjects. The integrity of the corpus callosum was a more important variable than age or general intelligence in predicting the transfer of learning to the untrained tasks.

According to recent reviews (e.g., Bamidis et al., 2014; Kraft, 2012), multimodal interventions are capable of improving cognitive function to a greater extent than single interventional approaches, regardless of the degree of cognitive reserve of the targeted patient. This finding is related to the complementary neuroplasticity mechanisms promoted by the different interventions, as shown in Figure 3. Therefore, we postulate that the “relative dose” of interventions promoting functional optimization and interventions promoting structural restoration within multimodal rehabilitation programmes might differ among subjects according to the degree of cognitive reserve. If this hypothesis is confirmed, the capability of multimodal interventions to delay the progression of cognitive deficits would be increased.

The importance of intervening at prodromal or even preclinical stages (Dubois et al (2016) to improve the efficacy of the reviewed interventions has been highlighted. However, other variables, such as pharmacological treatments that are not necessarily related to AD (Szekely and Zandi, 2010) or genetic vulnerability (Farlow, 2010), might affect the relationship between cognitive improvement and neuroplasticity changes and/or modulate the efficacy of the reviewed interventions. Finally, a limitation of the provided rationale for increasing the efficacy of the multimodal interventions is that a clear consensus on the best method to measure cognitive reserve is currently unavailable. Even if the method based on the latent variable model (Marques et al.,

2016; Reed et al., 2010; Zahodne et al., 2013) is a very promising approach to estimating cognitive reserve, additional studies are needed to clarify and standardize a procedure to quantify this construct.

## **6. Conclusions and future directions**

The reviewed studies reveal the utility of CI, PE, and NIBS to slow or reverse cognitive decline related to normal and pathological ageing. Neuroimaging studies relying on EEG and MRI/fMRI data provide evidence for functional and structural changes in the brain after implementing the mentioned interventions. Long-term maintenance of the induced cognitive improvement, concomitant neural changes, transfer effects on untrained tasks, modulations in resting-state activity and connectivity provide strong evidence that those changes are related to brain plasticity mechanisms. Moreover, neuroplasticity studies have frequently argued that functional plasticity precedes structural plasticity. Thus, observations of this temporal sequence may support the interpretation of these changes as brain modifications related to brain plasticity. Nevertheless, relationships between functional and structural brain modifications are highly complex. We hypothesize that the type of intervention and preservation of brain structure may affect the relationships between cognitive improvement and functional and structural changes, which may have substantial implications for the design of individualized multimodal interventions. Therefore, differences in the onset and progression of clinical AD symptoms for patients with high and low cognitive reserve are related to diverse compensatory capabilities (inefficient in patients with low cognitive reserve) and structural integrity (damaged in patients with high cognitive reserve). Considering the different plasticity mechanisms promoted by the reviewed interventions, we propose that multimodal programmes emphasizing the promotion of neurotrophic factor release (e.g., PE) may help restore the neural structure and slow the progression of cognitive deficits in patients with high cognitive reserve, whereas techniques that improve functional processes (e.g., CT and online NIBS) will integrate the restored neural areas within functional brain circuits.



Additionally, multimodal interventions emphasizing functional compensatory mechanisms (e.g., CT and online NIBS) may help increase the compensatory capabilities and maximize cognitive improvements in patients with low cognitive reserve, whereas techniques promoting structural mechanisms (e.g., PE) will help maintain the preserved neural structure for a longer time period. These hypotheses provide a rationale for future studies. These studies would ideally heed the methodological suggestions presented above -i.e., they would involve the study of cortical measures, transfer effects, long-term maintenance of the obtained benefits and associated structural modulations, careful control group/s design- to determine to what extent the observed changes are related to brain plasticity mechanisms.

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## Figure captions

**Figure 1. Normative pattern of changes related to normal ageing and AD in subjects with high and low cognitive reserve.** The x-axis represents the lifespan. The y-axis represents the abilities of subjects with high (solid blue line) and low (dashed blue line) cognitive reserves to deploy compensatory mechanisms as physiological and pathological changes in the brain (red line) progress. Brain changes represented by the red line include changes related to physiological ageing (e.g., brain atrophy) and AD (e.g.,  $\beta$ -amyloid plaques and neurofibrillary tangles).

**Figure 2. Non-pharmacological interventions used to improve cognition.** This figure schematically presents the main types of non-pharmacological interventions used to improve cognitive function.

**Figure 3. Neuroplasticity mechanisms related to non-pharmacological interventions.** Cognitive interventions (CI): LTP and LTD mechanisms work together to strengthen connections and refine brain connectivity patterns within specific networks that are involved in a particular cognitive function. PE interventions promote the release of neurotrophic factors (mainly during aerobic exercise interventions) related to neurogenesis, synaptogenesis, and angiogenesis. Interventions based on NIBS promote a wide range of neuroplasticity mechanisms, according to the protocol and modality used.

**Figure 4. Effects of interventions strengthening functional processes (mainly represented by CT and NIBS) and structural states (mainly represented by PE) in subjects with high and low cognitive reserve.** Compensatory mechanisms observed without (dashed grey line for low and solid grey line for high cognitive reserve) and with (dashed blue line for low and solid blue line for high cognitive reserve) the intervention; structural brain damage observed without (solid red line) and with (dashed green line) the intervention. Bidirectional arrows represent the threshold needed to

show cognitive deficits. Multimodal interventions should be applied to both subjects with high and low cognitive reserve. Nonetheless, a ceiling effect on functional optimization would lead to modest benefits of CI/NIBS in patients with high cognitive reserve, unlike the expected greater benefits in patients with low cognitive reserve. Instead, patients with high cognitive reserve would experience greater benefits from interventions related to structural preservation (e.g., PE), which would allow them to maintain an optimized compensatory ability for a longer time period.

Figure 1

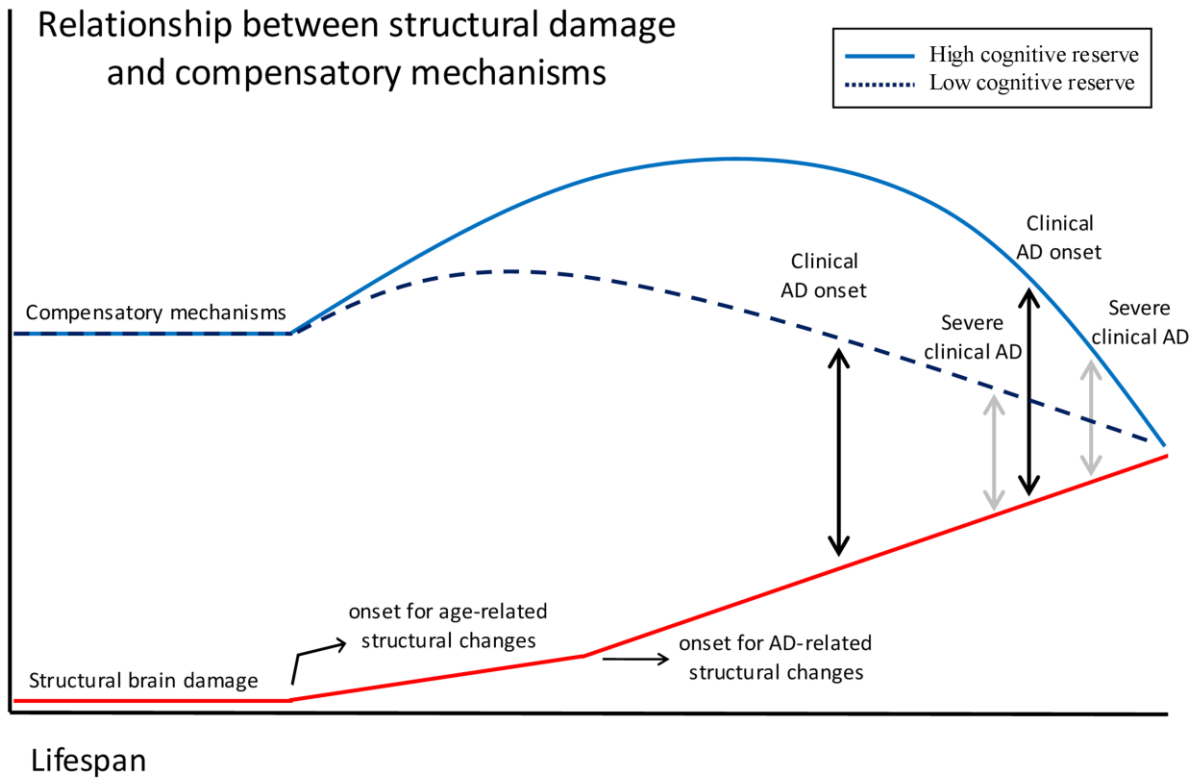


Figure 2

## Interventional approaches to improve cognitive functioning

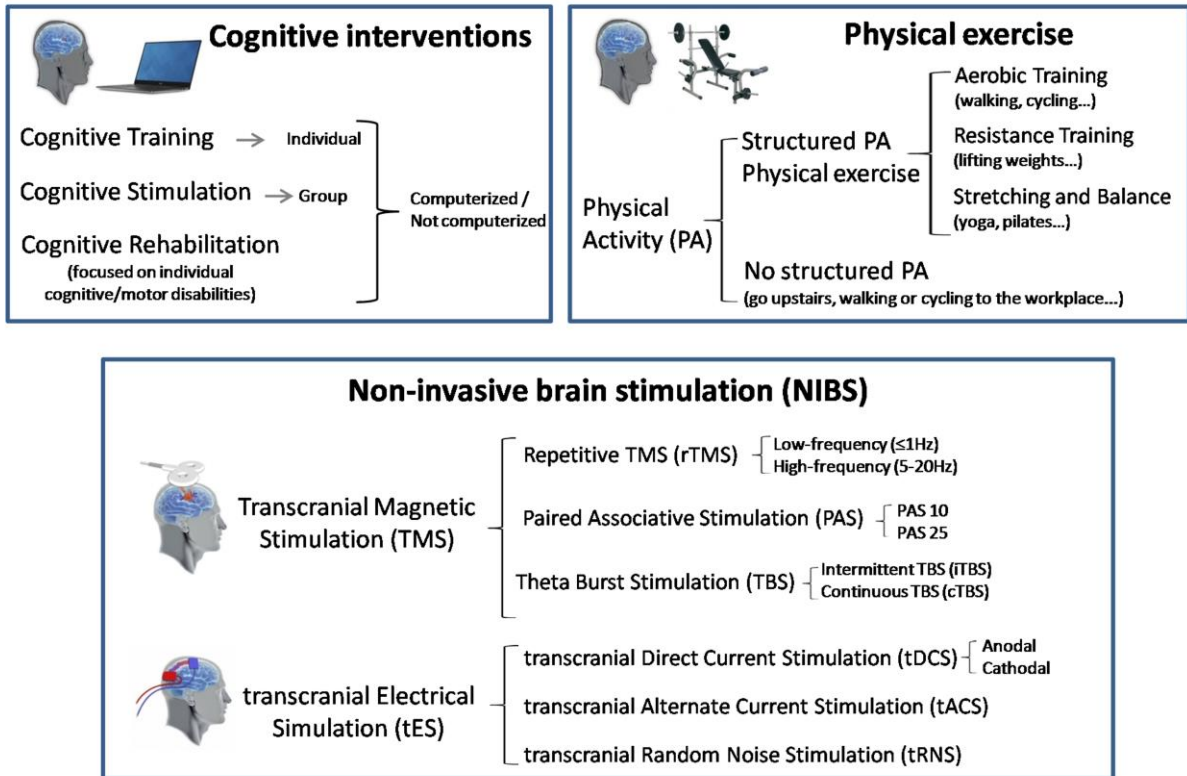


Figure 3

## Neurophysiological mechanisms underlying cognitive improvement

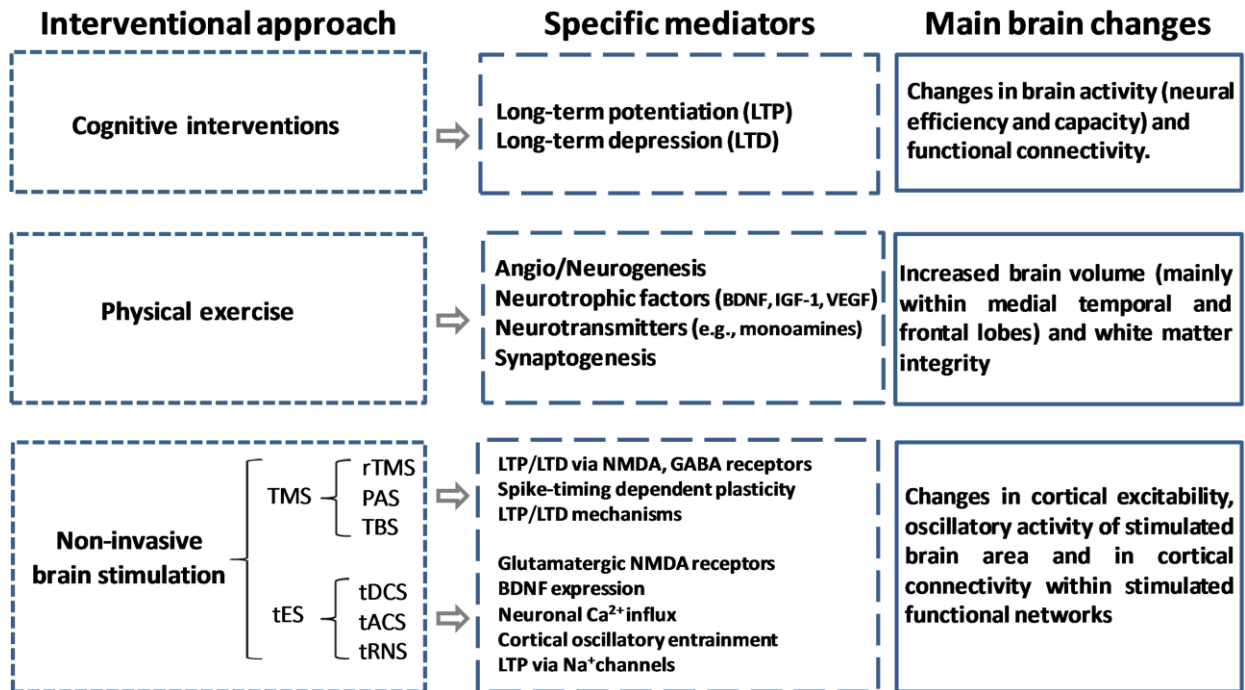
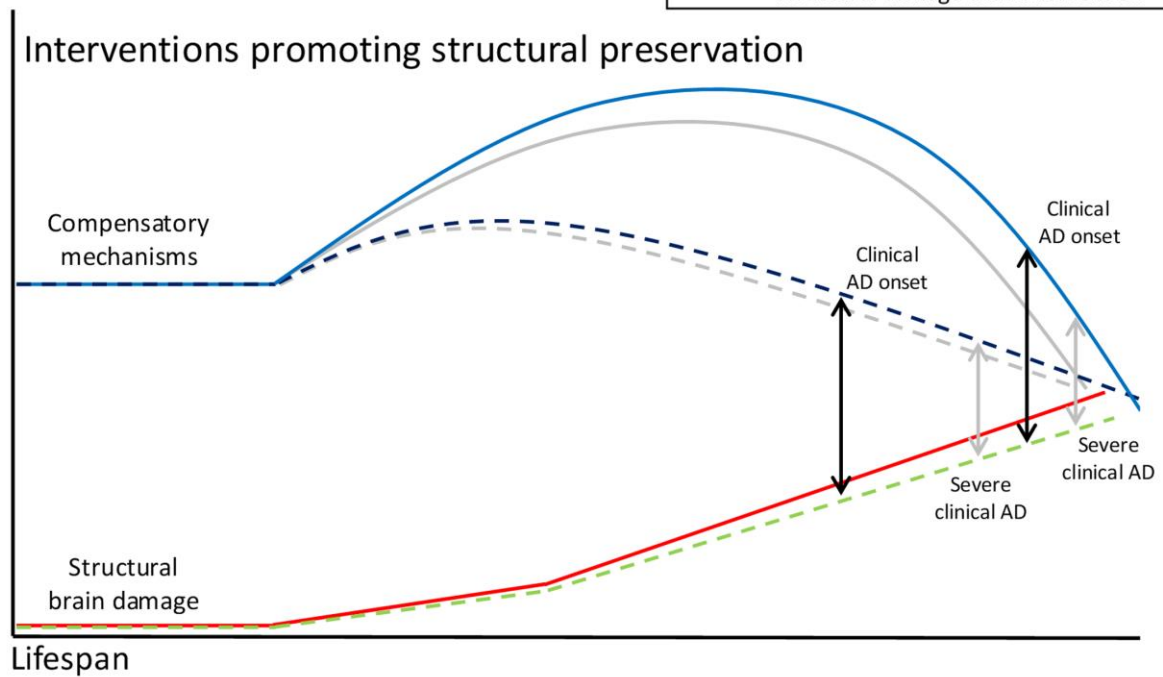
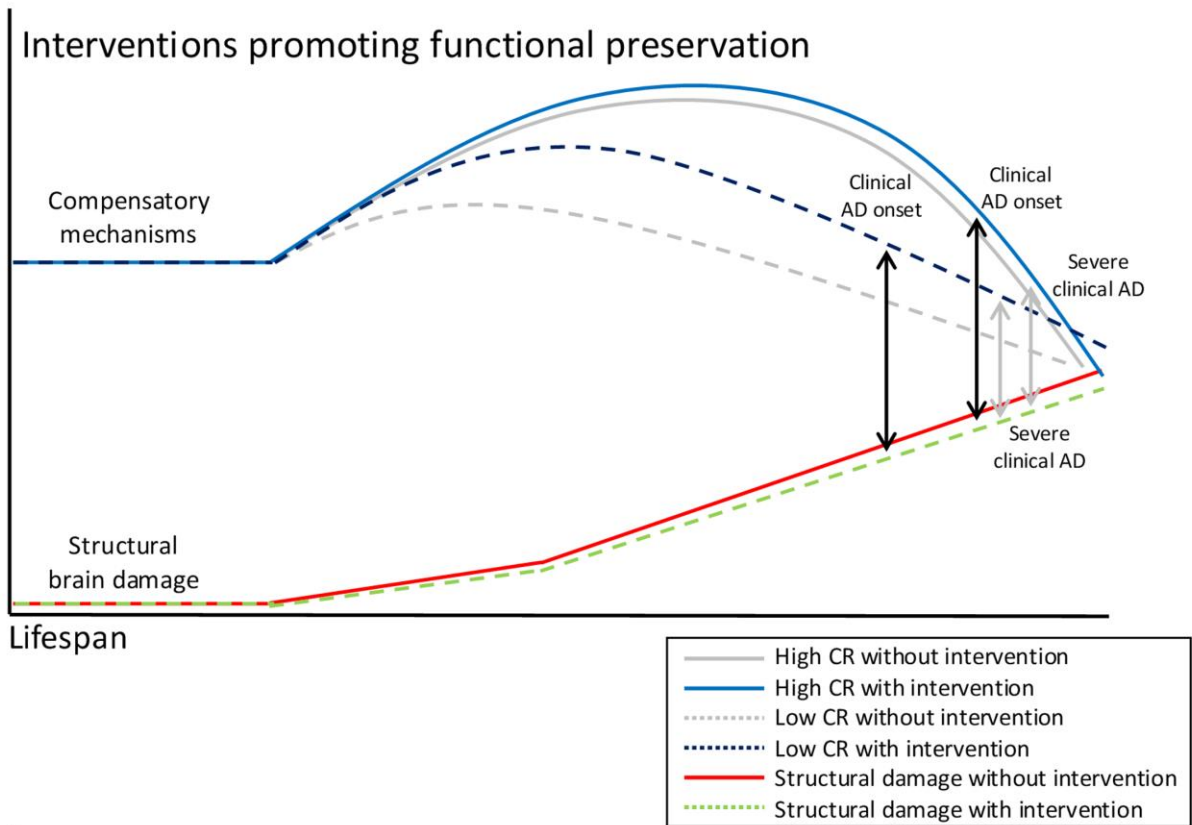


Figure 4



Study	Sample / tasks-functions	Intervention	Control Group	Cortical measures	Main findings
Anguera et al (2013) <b>EEG</b>	46HE (67). Visuospatial (driving video-game) and perceptual discrimination tasks	Multitask training (MTT) (n=16) (12 hours throughout 1 month) in both tasks	2 CG: visuospatial training (n=15) and inactive CG (n=15)	EEG and several cognitive tasks before and 1 and 6 months after training	Untrained executive skills improved only in MTT, who showed higher midline frontal theta power and fronto-parietal connectivity (coherence)
Berry et al (2010) <b>EEG</b>	32HE (72). WM task (dots movement coherence between cue and probe phases)	16HE trained in perceptual discrimination (3-5 weeks, 10h)	Inactive CG (n=16)	WM task during EEG recording was performed before and after training	Improved perceptual discrimination and transfer effect to WM in trainers. Smaller N1 after training, suggesting less effort to deploy attention
O'Brien et al (2013) <b>EEG</b>	22HE (72). Visual search task	HE (n=11) trained in speed of processing, 70', twice a week, 10 weeks	Inactive CG (n=11)	EEG was recorded while conducting the visual search before and after training	Larger N2pc and P3b after training suggested increased attentional deployment (but perform did no change, which related to baseline ceiling effect)
Spironelli et al (2013) <b>EEG</b>	11HE (76) and 11 AD (78). Lexical decision task (word/no word discrimination)	CT for 5 weeks in different cognitive domains (total, 40h of training)	HE served as CG (no AD CG)	Before and after CT, patients conducted a lexical decision task while recording EEG	AD were slower and less accurate than CG before and after training. After training, N2 Recognition Potential was larger in AD relative to CG
Tusch et al (2016) <b>EEG</b>	35HE (76). Cognitive training in visuospatial and verbal working memory tasks	Adaptive CT during 5 weeks, 5 sessions of 40' per week (n=17)	CG trained at a low fixed demands level (n=18)	ERPs were recorded before and after interventions during 0-back, 1-back and 2-back	The adaptive training group showed larger P300 after cognitive training. Overall, larger P300 correlated with better performance
Belleville et al (2011) <b>fMRI</b>	15HE (70), 15MCI (70). Word recognition task (verbal encoding and retrieval)	learning of encoding and retrieval strategies (6 weekly sessions of 120' each one)	No CG (study focused on MCI-related changes)	fMRI while performing the word recognition task before and after strategies learning	Reduced group-related differences after training; correlation between right inferior parietal activity and performance during encoding
Brehmer et al (2011) <b>fMRI</b>	23HE (64) performed 4 visuospatial and 3 verbal WM tasks	25 sessions of training with increased difficulty level (n=12)	CG trained at a fixed low difficulty level (n=11)	fMRI before and after training during WM-low and WM-high demanding tasks	Larger decrease in brain activity after training in participants increasing difficulty level, which suggested increased neural efficiency
Dahlin et al (2008) <b>fMRI</b>	22HY and 19HE (68). Retrieval of letters lists, Stroop and n-back tasks	HY (n=15) and HE (n=11) trained 5 weeks in retrieval letters. Transfer effects to n-back/Stroop tasks	Inactive CG for young (n=7) and elderly (n=8)	fMRI recording during task performance before and after training	Transfer effects to n-back only in young. It was related to common activation between both tasks in left striatum observed in young but not in elderly
Hampstead et al (2011) <b>fMRI</b>	6 MCI (73) performed a face-name associative task	Memory strategies were taught during 3 training sessions	No CG	fMRI recorded before and after training	Higher effective connectivity after training within middle temporal, occipital cortex and precuneus. Memory strategies related to brain activity patterns
Hampstead et al (2012a) <b>fMRI</b>	16HE (72), 18MCI (71). Associative memory task (object-location task)	3 training sessions in mnemonic strategies in a CG of HE (n=8) and MCI (n=9)	matched activity in a CG of HE (n=8) and MCI (n=9)	fMRI during the task before and after training. Analyses restricted to hippocampus	MCI showed lower hippocampus activity at baseline. Trained MCI showed larger hippocampus activity during encoding and retrieval stages
Heinzel et al (2014) <b>fMRI</b>	18HY, 19HE (66). n-back tasks at different load level	HE conducted 12 sessions of WM training (by using n-back tasks)	No CG (main focus on age-related changes)	fMRI scans while performing n-back tasks before and after training	Higher neural efficiency (low activity in low load tasks) and capacity (high activity in high load tasks) after training (i.e. youth-like activity pattern)
Kirchhoff et al (2012) <b>fMRI</b>	17HY, 16HE (72). Recognition memory task	2 sessions training encoding strategies to improve recognition memory	No CG (main focus on age-related changes)	fMRI recording during recognition memory task before and after training	Improved performance after training. Larger activity in superior frontal, right pre-central gyrus, left caudate during encoding. Recognition memory changes related to prefrontal/left temporal activity
Miotto et al (2014) <b>fMRI</b>	17HE (68). Words lists encoding task	Strategies to encode words by grouping words into common categories (for 30')	No CG	fMRI recording before and after training during task performance	Greater performance after training. Higher activity in prefrontal cortex, angular gyrus, cerebellum, intra-parietal sulcus and anterior cingulate
Van Paasschen et al (2013) <b>fMRI</b>	19AD (74). Recognition associative face-name task	Strategies to acquire new information (1 session a week, 8 weeks) (n=7)	2 CG: relaxation therapy (n=5) and inactive CG (n=7)	fMRI before and after training during task performance	Larger activity during recognition of face-name pairs within left middle, inferior frontal gyri, left insula, right medial parietal cortex in trained group
Vermeij et al (2016) <b>fMRI</b>	21HE (69) and 14MCI (66) performed 0-back, 1-back, 2-back, and 3-back tasks	5 weeks of adaptive working memory training (25 sessions of 45' each one)	No CG	fNIRS to assess prefrontal activity during n-back tasks before and after training	HE showed enhanced neural efficiency at high load. MCI improved performance at low load (no changes in prefrontal activation). Higher frontal recruitment at higher demands predicted larger WM gains
Förster et al (2011) <b>PET</b>	21 MCI, 15 AD (overall mean age: 73)	Multicomponent CT (6 months, weekly) for MCI (n=9) and AD (n=8)	Active CG for MCI (n=12) and AD (n=8) conducted self-studied tasks	Resting state PET and neuropsychological tests before and after intervention	Decline in glucose uptake was reduced in AD and MCI who received CT relative to CG but neural changes did not correlate with ADAS-cog/MMSE
Nyberg et al (2003) <b>PET</b>	8 HY and 16HE (68). Words lists encoding task	Training in method of loci (1 session) to improve encoding	No CG. Comparison between HE who improved and HE who did not improve	PET before and after training	After training, higher occipito-parietal and frontal activity in young. Higher occipito-parietal activity in elderly who increased performance after training
Engvig et al (2010) <b>sMRI</b>	42 middle-aged and HE (61, age range: 42-76). Memory task	HE (n=22) trained in method of loci (associate items and mental landmarks) (8 weeks)	Inactive CG (n=20)	Structural MRI and memory testing before and after training	Higher memory performance and neural volume in orbitofrontal and fusiform gyrus in trainers, which correlated with memory improvement

Hampstead et al (2012b)	21HE (73), 28 MCI (72). Object-location association task	3 training sessions in mnemonic strategies in HE (n=11) and MCI (n=14)	matched activity in a CG of HE (n=10) and MCI (n=14)	Structural MRI was taken before and after training	HE and MCI improved after training. Performance negatively correlated with inferior lateral ventricle volume in MCI
<b>sMRI</b>					
Valenzuela et al (2003)	20HE (70)	Intervention group (n=10) trained in method of loci for 5 weeks	Inactive CG (n=10)	MRI and MRS before and after training	Increased hippocampal creatine and choline after training. Higher benefits in those at risk of neural dysfunction (showed by low NAA at baseline)
<b>sMRI</b>					
Wolf et al (2014)	66HE (70)	CT group (n=41) in logical reasoning and study of transfer to fluid intelligence	Inactive CG (n=25)	Transfer effects according to neural integrity (DTI)	Transfer of learning depended on corpus callosum integrity but not on age and general intelligence.
<b>sMRI</b>					
Chapman et al (2015)	37HE (63). Cognitive tests	Strategies to improve attention and reasoning (3 times a week, 12 weeks) (n=18)	Inactive CG (n=19)	Functional/structural MRI at rest at baseline (T1), week 6 (T2) and after training (T3)	Cognitive improvement at T2/T3 and higher activity and connectivity in DMN/CEN. At T3, increased white matter integrity in left uncinated
<b>sfMRI</b>					
Erickson et al (2007)	31HY and 26HE (66). Stimulus response compatibility (SRC) tasks	HY (n=16) and HE (n=13) trained in a dual task (2 SRC tasks conducted at the same time) (5 days, 1h a day)	Inactive CG for HY (n=15) and HE (n=13)	Structural and functional MRI during single and dual task before and after training	After training, improved performance related to higher hemispheric asymmetry in ventral PFC and PFC activity was closer to "young-like pattern"
<b>sfMRI</b>					
Mozolic et al (2010)	66HE (69)	Attentional training (n=27) for 8 weeks (1h a week)	Active CG (n=31) (educational program)	Resting CBF and gray matter volume	CT increased CBF in inferior frontal cortex related to less susceptibility to distraction after training. Differences in gray matter volume were not found
<b>sfMRI</b>					

**Table 1. Summary of cognitive interventions (CI).** This table summarizes cognitive intervention approaches that have used cortical measures to evaluate cognitive intervention effects. HY: healthy young; HE: healthy elderly; MCI: mild cognitive impairment; AD: Alzheimer’s disease; fMRI: functional magnetic resonance imaging; sMRI: structural magnetic resonance imaging; sfMRI: structural and functional magnetic resonance imaging; EEG: electroencephalogram; DTI: diffusor tensor imaging; PET: Positron emission tomography; fNIRS: functional Near-Infrared Spectroscopy. DMN: default mode network; CEN: central executive network. CBF: cerebral brain flow; NAA: n-acetyl aspartate; ASL: arterial spin labelling. WM: working memory. In the “Sample” column, mean age of participants is specified within parenthesis.



Study	Sample / tasks	Intervention	Control Group	Cortical measures	Main findings
Cetin et al (2010) EEG	57HE (71). Auditory oddball task	AT (n=29) for 6 months	Inactive CG (n=28)	EEG during task performance before/after training	Faster P300 after AT. AT speeded up stimulus discrimination processes
Kamijo et al (2009) EEG	12HY and 12HE (age range: 60-74). Flanker task.	Participants undertook one session of light and moderate AT (cycling)	No CG	Event-related potentials during task performance before and after interventions	Faster reaction time after moderate exercise. Faster P3 latency after light and moderate exercise. Larger P3 after moderate exercise only in young
Burdette et al (2010) fMRI	11HE (76)	AT (n=6) for 2 months	Stretching and education CG (n=5)	Resting activity/connectivity fMRI before/after training	Higher hippocampal activity and hippocampal-anterior cingulate connectivity in AT
Colcombe et al (2004) fMRI	29HE (66). Flanker task	AT for 6 months	stretching and toning CG for 6 months	Task performance during fMRI recording before/after training	Lesser interference after AT and higher activity in middle/superior frontal gyrus and superior parietal cortex. Lesser ACC activity in AT than in CG
Liu-Ambrose et al (2012) fMRI	52HE (69). Flanker task.	2 groups: once-weekly (n=20) and two-weekly (n=15) RT and during 1 year	Two-weekly BAT CG (n=17) for 1 year	fMRI before and after training	Higher inhibitory control and higher activation in middle temporal gyrus, left anterior insula and lateral orbital cortex in RT compared to BAT.
Smith et al (2013) fMRI	18HE (76), 17 MCI (79). Name discrimination task	AT for 12 weeks	No CG (main focus on MCI-related changes)	fMRI recording during famous name discrimination task before and after interventions.	After AT, MCI improved performance. Reduced activity in a widespread of regions in both groups, suggesting greater neural efficiency during the task.
Voss et al (2010) fMRI	65HE (66).	AT (n=30) for one year	Stretching and toning CG (n=35) for 1 year	fMRI before, at month 6 and after interventions (month 12). Neuropsychological assessment	Greater improvement after AT (month 12). Improved functional connectivity patterns for AT and CG (young-like patterns), which correlated with cognitive improvement.
Porto et al (2015) PET	40 MCI (70)	AT for 24 weeks	30HE without any intervention were used as CG	Brain activity (PET) and neuropsychological tests before and after training.	AT improved cognition. Lesser anterior cingulate cortex activity was related to better visuospatial/attentional functions.
Brinke et al (2014) sMRI	39MCI (75). Verbal memory / learning tests (Rey's auditory verbal learning (RAVL))	2 interventions: AT (n=14), RT (n=12) for 6 months	BAT CG (n=13)	Hippocampal volume structural MRI before/after interventions	AT increased 5.6% left and 2.5% right hippocampus volume compared to BAT
Colcombe et al (2006) sMRI	59HE (age range: 60-79)	AT for 6 months	stretching and toning CG for 6 months	Structural MRI before/after training	Increased volume of both gray and white matter in AT, mainly within prefrontal and temporal cortices
Erickson et al (2011) sMRI	120HE (66). Spatial memory task.	AT (n=60) for 12 months	stretching and toning CG (n=60) for 12 months	Structural MRI before, at month 6 and after training.	AT increased left and right hippocampal volume increased 2.12% and 1.97%, respectively. Other studied regions (thalamus caudate) did not change
Jonasson et al (2017) sMRI	58HE (68). Episodic memory, processing speed, executive functions	AT (n=29) for 6 months	stretching and toning CG (n=29) for 6 months	Structural MRI (frontal and hippocampal volume)	Improved cognitive functioning in AT. No differences in cortical volume. Correlations between baseline DLFCP volume and improvement
Liu-Ambrose et al (2010) sMRI	155HE (70). Stroop task.	2 groups: once-weekly (N=54) and two-weekly (N=52) RT for 1 year	Two-weekly BAT CG (n=49) during 1 year	Structural MRI before and after interventions.	RT groups improved executive functioning more than BAT. However, after training, brain volume was greater in BAT compared to both RT groups
Mortimer et al (2012) sMRI	120HE (68). Neuropsychological tests	3 groups: Tai Chi (n=30), walking (n=30), social interaction (n=30) for 40 weeks	Inactive CG (n=30) for 40 weeks	MRI and neuropsychological tests at baseline, at 20 <sup>th</sup> week and at 40 <sup>th</sup> week.	Highest neuropsychological improve after Tai Chi. Increased volume after Tai Chi/social interaction. No differences between walking and CG
Ruscheweyh et al (2011) sMRI	62HE (60). Verbal learning task (episodic memory)	Low (n=21) and moderate (n=20) AT for 6 months	Inactive CG (n=21).	Structural MRI was recorded before and after intervention.	AT was related to better memory, increased gray matter volume in prefrontal/cingulate cortex, and a trend to higher BDNF.
Voss et al (2013) sMRI	70HE (65).	AT (n=35) for 1 year	Stretching and toning CG (n=35)	MRI (DTI) and neuropsychological assessment before and after interventions.	AT did not change white matter and cognitive functions but higher aerobic skills related to white matter integrity in frontal/temporal lobes and greater improve in short-term memory.
Chapman et al (2013a) sfMRI	37HE (64). Tests of executive function, memory and attention	AT (n=18) for 12 weeks	Inactive CG (n=19)	Structural and functional MRI before AT (time 1, T1), at 6 <sup>th</sup> week (T2), at 12 <sup>th</sup> week (T3)	Larger activity at rest in ACC. Improved verbal memory related to higher activity in hippocampus (no changed hippocampal volume)

**Table 2. Summary of physical exercise (PE) interventions.** This table summarizes PE programmes that have used cortical measures to evaluate intervention effects. AT: aerobic training; BAT: balance and tone training; RT: resistance training; HE: healthy elderly; MCI: mild cognitive impairment; fMRI: functional magnetic resonance imaging; sfMRI: structural and functional MRI; EEG: electroencephalogram; DTI: diffusor tensor imaging; PET: Positron emission tomography; BDNF; Brain derived neurotrophic factor; DMN: default mode network; CEN: central executive network. In the “Sample” column, mean age of participants is specified within parenthesis.

Study	Sample/task/functions	Interventions	CG/Control condition	Cortical measures	Main findings
Khedr et al (2014)	34AD (70) performed an auditory oddball task.	Offline atDCS (n=11) and ctDCS (n=12) over left DLPFC (25 min, 2mA, daily for 10 days)	CG (n=11): sham tDCS over left DLPFC	P300 ERP before and after intervention	P300 was faster after both atDCS and ctDCS. Also, both atDCS and ctDCS improved neuropsychological scores
<b>EEG/tES</b>					
Marceglia et al (2016)	7AD (75). Word recognition task (WRT)	atDCS and ctDCS over bilateral temporal-parietal lobule (15', 1.5mA)	No CG / no control condition	EEG at rest and during WRT performance before and after intervention	atDCS increased high-frequency power in temporo-parietal area and temporo-parieto-occipital connectivity (coherence)
<b>EEG/tES</b>					
Pellicciari et al (2009)	16HY and 16HE (62)	PAS20 over left somatosensory cortex (140 pairs of stimuli, 0.1Hz, 25')	No control condition / no CG (the study was mainly focused on age-related changes)	500 electric pulses before/after intervention (3Hz, 300% perceptual threshold) to right median nerve. SEPs were recorded at CP3	N20 was increased in elderly and P25 in both groups after PAS. N20-P25 was larger in elderly relative to young in somatosensory regions after intervention
<b>EEG/TMS</b>					
Holland et al (2011)	10HE (69). Picture-name task. Pictures appeared twice to study behavioural priming	Online atDCS (2 mA x 20' x 1 session) over left inferior frontal cortex	Control condition: sham tDCS over left inferior frontal cortex	fMRI recording during task performance	Faster RT during atDCS, which correlated to decreased activity in left frontal cortex regions (including Broca's area)
<b>fMRI/tES</b>					
Lindenberg et al (2013)	20HE (68). Go / no go task and resting state	Online dual tDCS (atDCS over left M1 and ctDCS over right M1) and atDCS (cathode over supraorbital region) (1 session; 1mV; 30')	Control condition: sham tDCS. The electrode setup was randomly set in order to match the "dual" or "anodal" montage"	fMRI recording during the task and at rest before and after intervention	Higher M1 activity in dual tDCS than in atDCS and greater PCC connectivity during the task. Dual and atDCS increased connectivity in left PFC and reduced it in right hippocampus and right M1 at rest
<b>fMRI/tES</b>					
Meinzer et al (2014)	20HE (68). Word generation task. 20 young recruited to study age-related changes at baseline	atDCS over left ventral inferior frontal gyrus (1 session, 1mV, 20')	Control condition: sham tDCS over left ventral inferior frontal gyrus	fMRI activity recorded during the task and at rest before and after intervention	atDCS improved performance, reduced age-related prefrontal hyperactivity during the task and reverted the age-related patterns of functional connectivity observed at rest
<b>fMRI/tES</b>					
Meinzer et al (2014)	18HE (69) and 18MCI (67)	Online dual tDCS (atDCS over left M1 and ctDCS over right M1) vs. atDCS (1 session; 1mV; 30')	Control condition: sham tDCS. The electrode setup was randomly set in order to match the "dual" or "anodal" montage"	fMRI recording. DTI and ECM (graph theory analysis) to study structural-functional changes relationships	atDCS and dual tDCS improved word-retrieval compared to stDCS. However, any brain area was not relate to the observed facilitation effect
<b>fMRI/tES</b>					
Meinzer et al (2015)	18HE (70) and 18MCI (67). Semantic word retrieval task	MCI received online atDCS over left inferior frontal cortex.	Control condition: sham over left inferior frontal cortex. HE were used as CG during sham tDCS	fMRI was recorded to study connectivity by using ECM (graph theory analysis)	Greater performance/less prefrontal hyperactivity during atDCS than during sham tDCS (reverting altered MCI resting state)
<b>fMRI/tES</b>					
Devi et al (2014)	12AD. Motor and language tasks	Offline high-frequency rTMS (90%MT) at 10Hz (n=6; total pulses per session: 1000) and at 15H (n=6; total pulses per session: 1500) (30' x 4 sessions) over the bilateral DLPFC	No CG / no control condition	fMRI was recorded at baseline, after intervention and 4 weeks after intervention ending	Naming task performance was improved immediately and 4 weeks after rTMS, which was related to higher activity in Broca's area and neuropsychological improvement
<b>fMRI/TMS</b>					
Sole-Padulles et al (2006)	40HE (69) with memory complaints. Face-name memory tasks	Offline 5Hz rTMS (80%MT) (n=20) over the left DLPFC (1 session, 5', 500 TMS pulses).	CG: sham tDCS (n=20) over the left DLPFC	fMRI was recorded during task performance before and after intervention.	rTMS improved face-name associative memory and increased bilateral posterior and right prefrontal cortex activation
<b>fMRI/TMS</b>					

**Table 3. Summary of non-invasive brain stimulation (NIBS) interventions.** This table summarizes NIBS interventions that have used cortical measures to evaluate intervention effects. HY: healthy young; HE: healthy elderly; MCI: mild cognitive impairment; AD: Alzheimer's disease; CG: control group; fMRI: functional magnetic resonance imaging; EEG: electroencephalogram; DTI: diffusor tensor imaging; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; PAS: paired-associated stimulation; ECM (eigenvector centrally mapping; DTI: diffusion tensor imaging; BA: Brodmann area; MMSE: mini-mental state examination; WAIS: Wechsler adult intelligent scale; SEPs: somatosensory evoked potentials; DLPFC: dorsolateral prefrontal cortex.

Study	Samples / tasks	Intervention	Control Group	Cortical measures	Main findings
Frantidis et al (2014)	103HE (68)	CT/PE intervention (n=66) (8 weeks): flexibility, strength / memory, attention, learning	Active CG watched documentaries for 8 weeks (n=62)	EEG resting state (closed eyes) before and after intervention	Increased synchronization between FC2-CP3, AFz-Fp2, FC6-P4 (i.e. inter-lobe and inter-hemisphere synchronization in training group)
<b>EEG</b>					
Klados et al (2016)	50MCI (69)	CT and PE (AT and RT) for 8 weeks (n=25)	Active CG (n=25) (computer skills and social interaction)	EEG resting state before and after training (cortical functional connectivity)	Increased beta band functional connectivity after intervention
<b>EEG</b>					
Styliadis et al (2015)	70MCI (71)	3 intervention groups (8 weeks): CT (n=14), PE (n=14), CT+PE (n=14),	2 CG: active CG (n=14) (watching documentaries), inactive CG (n=14)	EEG resting state was conducted before and after interventions	CT+PE was the only improved group: decreased activity of precuneus and posterior cingulate cortex in delta, theta, and beta bands, which correlated with MMSE scores
<b>EEG</b>					
Boyce et al (2008)	93HE (60). Training in juggling	64 juggled for 3 months. 25 participants reached good performance (juggling for 1') and were included into the intervention group.	25 inactive subjects was used as CG	Structural MRI before training (t1), after training (t2) and 3 months after training cessation (t3)	Increased brain volume (at T2 and T3) related to skill acquisition in right visual cortex, middle temporal area (V5). Transitory changes (at T2) in left hippocampus and bilateral accumbens
<b>sMRI</b>					
Lövdén et al (2012)	44HY and 47HE (65). Spatial navigation training	Spatial navigation training (4 months) (walking and searching animals in a virtual zoo) in HY (n=23) and HE (n=23)	Active CG (only walking) in HY (n=21) and HE (n=24)	Structural MRI before, after training, and 4 months after training cessation	Trained participants maintained hippocampus volume 4 months after intervention cessation. Contrarily, CG showed the expected age-related shrinkage during the studied time period
<b>sMRI</b>					

**Table 4. Summary of interventions involving cognitive training and physical exercise.** This table summarizes multimodal approaches that have used cortical measures to evaluate intervention effects. This table includes interventions combining cognitive and physical exercise interventions as well as those interventions that used a type of task that involves both cognitive training and physical exercise (e.g. juggling). HE: healthy elderly; MCI: mild cognitive impairment; CT: cognitive training; PE: physical exercise; CG: control group; MRI: magnetic resonance imaging; EEG: electroencephalogram; fMRI: functional magnetic resonance imaging; sMRI: structural magnetic resonance imaging; MMSE: mini mental state examination.