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

Jesús Cespón[a,b,*], Carlo Miniussi[a,c], Maria Concetta Pellicciari[a]

[a] Cognitive Neuroscience Section, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[b] BCBL, Basque Center on Cognition, Brain and Language, Spain
[c] Center for Mind/Brain Sciences – CIMeC, University of Trento, Rovereto, TN, Italy

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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.

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 (Bruel-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 (Bruel-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

* Corresponding author at: Cognitive Neuroscience Section, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Via Pilastroni, 4, 25125, Brescia, Italy.
E-mail address: jesus.cespon@cognitiveneuroscience.it (J. Cespón).

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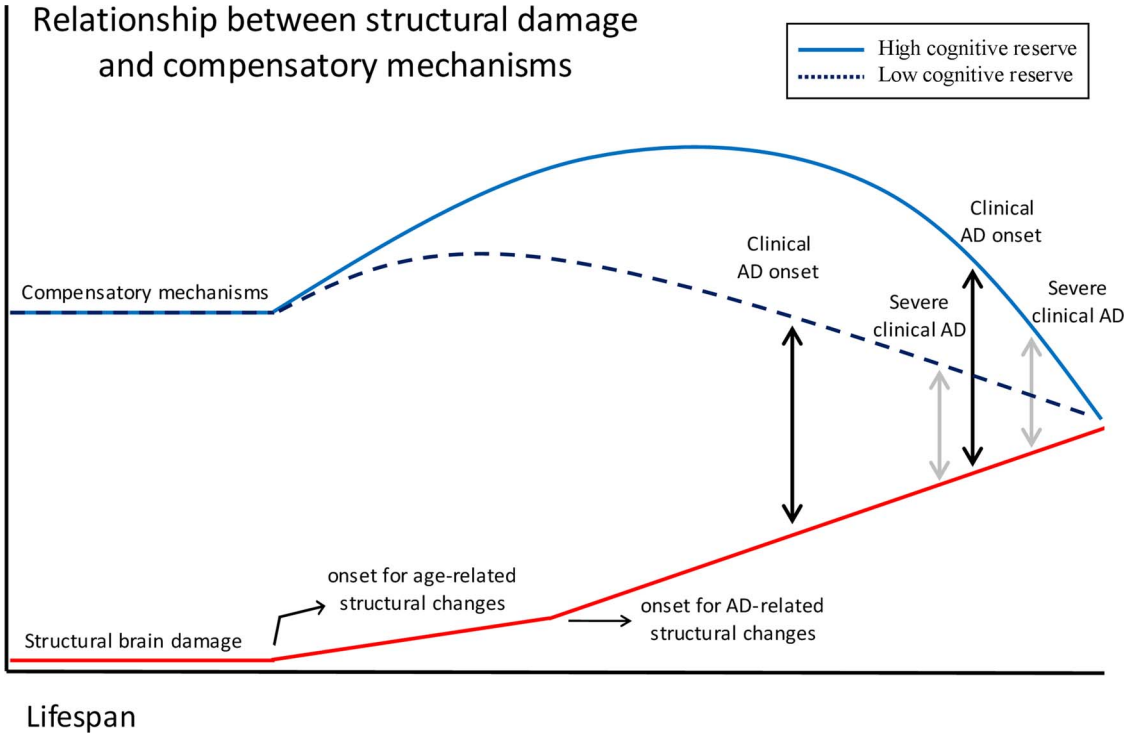

Fig. 1. Normative pattern of changes related to normal ageing and AD in subjects with high and low cognitive reserve. The x-axis represents the lifespan. The y-axis represents the abilities of subjects with high (solid blue line) and low (dashed blue line) cognitive reserves to deploy compensatory mechanisms 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., β-amyloid plaques and neurofibrillary tangles).

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 crystalized intelligence, such as vocabulary size) may be preserved or even improved until advanced stages of life (Salthouse, 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 hyper-excitability (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