Neural Effects of Cognitive Intervention in Healthy Aging and Dementia

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Abstract: Cognitive intervention being recognized as a viable non-pharmacological approach for age-related cognitive changes and as a complementary therapy to pharmacological therapies in dementia, in recent years has been gaining substantial scientific and public attention.

Indeed, recent studies have shown promising results concerning the efficacy of cognitive intervention in the amelioration of cognitive deficits with benefits in functionality and quality of life. Despite an increasing amount of studies with neuropsychological, behavioral, functionality and quality of life outcomes, the neural bases of cognitive intervention remain comparatively less explored and understood.

In the present work we review existing evidence concerning the impact of cognitive intervention in brain functioning of healthy older adults as well as people with dementia.

Keywords: Brain aging, Cognitive aging, Cognitive intervention, Cognitive rehabilitation, Cognitive stimulation, Cognitive training, Dementia, Neuroimaging.

INTRODUCTION

Aging is considered a process of physiological deterioration and decline in cognitive function [1-3]. It is widely acknowledged that higher-order functions such as memory, executive functioning and speed of processing show a decline in later life [4, 5] with a corresponding overall volume reduction in most brain regions [6–8]. The aforementioned cognitive decay and cerebral deterioration are even more pronounced when dementing disorders are present.

Despite the latter mentioned fact, plasticity is still believed to be present throughout the entire human developmental span, although with different extent according to age, as adaptive cerebral, cognitive and behavioral changes originated by a continuous mismatch between the organism and environmental stimulations and demands [9].

In order to ameliorate and minimize cognitive changes, non-pharmacological theory-driven behavior-ral interventions for improving cognition (*i.e*. cognitive interventions) have been increasingly used in complement to medication. These interventions range from training of specific functions to general cognitive stimulation, and can be designed from a restorative or compensatory framework [10-12].

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Although evidence is not yet conclusive [13], cognitive intervention is considered a valuable approach for tackling age-related cognitive decay, with several randomized controlled trials (RCT's) showing benefits of cognitive intervention in healthy aging, pre-dementia and dementia [14-18]. Recent evidence suggests that these cognitive and functionality benefits in the elderly may last up to a decade [19].

Indeed, an increasing number of programs for cognitive enhancement are clinically available and recommended to the public with scientific data providing a basis for their utility and efficacy [18, 20]. However, the neural mechanisms involved in cognitive intervention of aging still remain to be fully elucidated. Such an advance would be an important step in the field since characterizing the changes in response to cognitive intervention could lead to the identification of target areas and mechanisms that could prove to be instrumental in advances of other therapies and cognitive interventions. Moreover, as Berlucchi [21] notes, the understanding of brain plasticity mechanisms is a requirement for attaining rehabilitation practices based on science.

There is recent evidence, from higher animal model research on normal aging and Alzheimer's disease, suggesting that behavioral enrichment can promote cortical plasticity [22]; lead to improvements in cognitive performance and cellular health, minimize oxidative damage and Aβ accumulation, and regulate

E-ISSN: 2409-3564/15

caspase pathways [23], as well as lead to amelioration of cognitive performance even without a reduction in brain beta-amyloid (A beta) deposition [24].

Additionally, as Pieramico *et al*. [25] point out, neuroimaging advances have led to an improved understanding of functional, spatiotemporal and structural aspects of the brain, as well as consolidated concepts of behavioral plasticity, structural and functional neuroplasticity in the aging brain. Indeed, converging with animal research and human clinical studies, evidence from human neuroimaging studies shows that cognitive intervention leads to neuropsychological improvements and brain changes [26-28].

Overall, these results suggest that even the older adult brain retains neuroplasticity to some extent and can benefit from continuous experiences and training which might lead to improved performance and neural modifications. These changes can be attained through several strategies [29] (*e.g*. cognitive, physical, and relaxation training).

In the present review we address the available evidence on the current state of art of the neural bases of the effects (assessed through neuroimaging) of cognitive intervention in both healthy aging and dementia. We aim to provide a brief and balanced perspective of the current knowledge and evidence for neural changes, their mechanisms and overlap with cognitive effects of cognitive intervention in these populations.

MATERIALS AND METHODS

The present work is a selective narrative review, with included articles obtained from literature known by the author and searches on PubMed/MEDLINE. Cognitive intervention studies in aging and dementia, including neuroimaging outcomes, were searched. The following terms, and their variations, were combined and used for the search: brain, magnetic resonance imaging; voxel-based; Default Mode Network (DMN); positron emission tomography (PET); functional Magnetic Resonance Imaging (fMRI); neuroimaging; aging, elder (and their variations); dementia; Alzheimer; Parkinson; Frontotemporal; Vascular dementia; and several variations of the term cognitive intervention (*e.g*. cognitive training, cognitive rehabilitation, cognitive stimulation, mental exercise, cognitive exercise, neuropsychological rehabilitation, mental fitness, brain fitness).

Relevant articles, including both reviews and clinical studies, were selected through abstract inspection.

Electrophysiological and animal studies were discarded since they were out of the scope of the present work.

RESULTS

Neuropsychological Effects of Cognitive Intervention in Aging and Dementia

Research suggests the potential and benefits of cognitive intervention and other non-pharmacological approaches in normal age-related cognitive decline and dementia (both at pre-dementia and dementia stages) [12, 25, 30], leading to hope that these approaches might assist in impeding, minimizing or delaying cognitive dysfunction associated with healthy and unhealthy trajectories of aging.

Current research shows that cognitive intervention might lead to cognitive improvements in healthy aging and that these effects can last up to 10 years with positive repercussions in instrumental daily functioning [19]. Moreover, a growing number of studies in dementia have shown that cognitive intervention might result in improved cognition, quality of life and meeting patients' goals, and also lessen both the normal and neurodegenerative age-associated neuropsychological decay [11, 12, 20, 31-35]. However, this is not a consensual position and some authors consider that current evidence is insufficient for making statements such as that cognitive intervention might promote successful aging, delay or slow progression of dementia in healthy older adults [36].

Additionally, research on the neural mechanisms correlating with the observed results is steadily increasing but still scarce. For example, Forster and colleagues [34] found that amnestic MCI (aMCI) patients show attenuated mental and cerebral decline in response to a cognitive intervention program of 6 months.

Therefore, at present time, despite technological and conceptual advances, the cerebral effects of cognitive intervention remain to be further explored and clarified.

In the following sections we review the available evidence on this topic in order to provide an evidence-based perspective on the cerebral effects of cognitive intervention.

Cerebral Effects of Cognitive Intervention in Healthy Aging

Although experience-based neuroplasticity is more prominent in critical periods of brain development where there is increased nervous system sensitivity for experience-dependent changes, motor and cognitive studies in humans and animals show that neuroplasticity is also a property of an older adult brain [37].

A considerable number of studies has been conducted assessing the neuropsychological effects of cognitive intervention in healthy aging [38]. For example, in one of the largest randomized controlled trials conducted up to date (ACTIVE study - Advanced Cognitive Training for Independent and Vital Elderly) there were within domain improvements with long-term effects persisting for 2 years, 5 years, and even at 10-year follow-ups in terms of cognition and daily functioning [19,39,40]. Specifically, reasoning and speed-of-processing interventions still displayed cognitive effects at 10 years, and all intervention groups showed less difficulty with instrumental activities of daily living than control subjects. These results are even more outstanding when we notice that interventions were relatively short since they comprised of ten training sessions for memory, reasoning, or speed of processing; and four booster sessions at 11 and 35 months.

Another large-scale trial (IMPACT - Improvement in Memory with Plasticity-based Adaptive Cognitive Training) with community dwelling seniors (65-years and older) showed benefits in memory and attention after only 8 weeks of cognitive intervention [41].

Regarding neural effects, recent research has shown that healthy older adults display increased brain activity related to improved memory performance even after a brief training of semantic strategies [42, 43]. Structural changes have been also reported with evidence of white-matter changes after 8 weeks of intensive memory training, which the authors hypothesized as being related to myelin related plasticity [44]. Convergent structural findings were also reported previously by Engvig and colleagues [45] who found that an 8 week verbal source memory training using the method of loci, led to an increase in cortical thickness in the right fusiform and lateral orbitofrontal cortex correlated with the increased performance in source memory.

In convergence with unimodal neuroimaging studies, research assessing both functional and structural brain outcomes of complex reasoning training demonstrates brain changes related to improved cognition. Specifically, this type of intervention increased regional and global cerebral blood flow, connectivity in DMN and central executive network, and increased white matter integrity in the left uncinate, with authors suggesting neurovascular coupling as putative underlying mechanism leading to both the observed functional and structural changes [26, 27].

Additionally, Mozolic and colleagues [46] assigned healthy elderly to an attention training program for 8 weeks, or to a control intervention program, while observing improved resistance to distraction and increased prefrontal cortex resting cerebral blood flow. However no gray matter volume changes were observed. It is important to consider that the existence of differential brain patterns of activation between studies can be influenced by several factors. For example, different interventions might lead to substantially different cerebral outcomes [47]. Therefore it is important to consider that intervention parameters such as type/nature, duration, intensity and frequency of training might partially contribute to discrepancies.

Recent findings [48] also show that changes in brain connectivity may be a marker for cognitive training generated improvement and for transfer effects to untrained tasks and functions. Namely, Strenziok and colleagues [48] enrolled healthy elderly to six weeks of cognitive training in one of the following domains: auditory perception, visuomotor and working memory, and strategic reasoning. While strategic reasoning led to no transfer of benefits to untrained cognitive functions, working memory and auditory perception did and were accompanied by decreased functional connectivity between superior parietal cortex and the inferior temporal lobe. Interestingly, the authors found that auditory perception training effects transferred to everyday problem solving and reasoning with a concomitant and selective change in occipito-temporal white matter integrity.

Another recent study of a 4 week cognitive training program, also suggests that long-term generalization of improvements to related cognitive domains is associated with increased structural integrity in the corpus callosum [49].

At last, it is worthwhile to mention that there is preliminary evidence regarding protective effects suggesting that cognitive intervention might lead to a diminution of brain shrinkage in the cerebellum, although not in any other brain region, as observed in the time range of 6 months after approximately a 3 month long cognitive training program [50].

Cerebral Effects of Cognitive Intervention in Dementia

With an estimated prevalence of 5%-7-% [51], dementia has considerable implications and costs for patients, caregivers and society [52].

In hopes of ameliorating cognition in neurodegenerative disorders non-pharmacological cognitive approaches have been developed and studied for their efficacy. For example, in one of the largest trials conducted up to date in people with dementia, Spector and colleagues [18] conducted a single-blind randomized controlled trial with 201 elderly showing improvements in cognition (*i.e*. MMSE and ADAS-Cog) and in quality of life. In a recent meta-analysis, Alves *et al*. [12] have also shown that cognitive intervention might lead to improvements in global cognitive status. Moreover, Alves *et al*. [35] showed that cognitive stimulation can be experientially relevant even when no cognitive benefits are observed.

Despite the encouraging palliative and preventive findings in neuropsychological, quality of life and experiential outcomes, the brain mechanisms underlying potential effects of cognitive intervention in dementia and its potential differential effects, remain even less explored than in healthy older adults.

In one of the few and first studies of its kind, Clare *et al*. [53] addressed this issue with an fMRI study of an MCI patient which, after intervention, showed improvement in a visual memory task and brain activation decrease in sensory areas and increases in regions associated with memory.

In a subsequent study the same team conducted a trial of cognitive rehabilitation for people in early stages of Alzheimer's disease in which participants were allocated to either an 8-week intervention or to control groups (relaxation, and no treatment). The authors found that patients receiving the intervention displayed comparatively higher activation than control participants in the left middle and inferior frontal gyri, the left insula, and right medial parietal cortex during recognition of face-name pairs; although performance stayed without improvement in all groups. Also, at post-intervention assessment moment, the control participants showed decreased activation in the aforementioned areas during recognition [54].

Other team used FDG-PET to explore the brain effect of cognitive intervention in amnestic MCI and Alzheimer's disease (AD) patients participating in a group-based multicomponent cognitive intervention of 6-months, with aMCI patients showing attenuation of glucose metabolism decline [34].

In respect to MCI, Belleville and colleagues [28] report the results of a 6-week memory intervention program. Namely, the authors observed a resulting increased activation in frontal, parietal and temporal regions and an approximation of activation in relation to the healthy control group. Conversely the healthy control group exhibited a pattern of decreased activation, which we could interpret as a possible increase in neural processing efficacy.

In a recent review, Hosseini and colleagues [55] summarized the current findings in pre-dementia/MCI and interpreted them as an existence of compensatory effects in prefrontal, medial temporal and posterior DMN's and frontoparietal and entorhinal regions gray matter changes for people at risk for AD.

Additional large-scale studies of non-pharmacological interventions aiming at preventing or delaying cognitive impairment in the elderly, and including neuroimaging as an outcome, are currently being conducted [56,57].

DISCUSSION

We reviewed the existing literature in order to provide the current evidence on the cerebral effects of cognitive intervention in healthy elderly, pre-dementia and people with dementia.

Our review suggests, based on several research examples that cognitive intervention may lead to functional and structural brain changes in both healthy and unhealthy aging. Nonetheless, definite conclusions are impeded by the scarcity of studies, mainly in the area of dementia.

Our findings are in accordance with previous research considering structural neuroplasticity and functional compensatory brain mechanisms throughout aging as a tangible reality [58,59]. The studies reported here, suggest that cognitive intervention can potentiate or lead to compensation of neuropsychological and brain functioning even when neuropathology is present. As Hosseini and colleagues [55] pointed out, the patterns observed in healthy aging and people at risk of developing AD suggest that cognitive intervention may potentiate a compensatory processes and lead to a partial restoration of cognitive function, at least in MCI.

Additionally, our review also supports the value of functional and structural neuroimaging techniques as a biomarker of cognitive intervention effects [60].

Some limitations should be noted when considering present findings. First, we must consider that brain functional activation changes in studies of cognitive intervention might not represent neuroplasticity and be an alternative activation/functional brain performance pattern resulting from the participants adoption of another strategy for performing the tasks (*e.g*. adopting visual memory strategies) [5]. Nonetheless, structural changes in response to intervention have been reported throughout the present review, which may support the view of the existence of neural changes related to intervention. Moreover, even considering the aforementioned change of strategy hypothesis as an underlying active principle, it could lead to cognitive and cerebral plasticity effects through continuous practice and subsequent function normalization.

Other methodological issues such as experimental fMRI task design and intra-task learning effects between pre and post-intervention assessment might also contribute to the observed results and need to be considered. Lastly, file drawer effects need to be evaluated in future systematic reviews and meta-analyses.

Therefore, there is a need for further well controlled multi-modal neuroimaging studies, to probe for convergent evidence from different individual studies, different outcomes (neuropsychological, cerebral, etc.) and techniques (fMRI, DMN, PET) in healthy aging and according to each stage of dementia. Quantitative systematic reviews are also needed to aggregate results from individual studies and clarify the extent of effects and potential sources of bias.

Moreover, studies should systematically address the possible functional and structural responses to intervention in relation to the stage of dementia.

Such steps and information would assist in:

- Clarifying whether compensation and restoration of cerebral functions is possible, at what stages of impairment can it take place if this process is viable, for which types of dementia is it viable;
- Assisting in designing and implementing interventions tailored for each neuropsychological and cerebral manifestation of the disease stage;
- Further clarifying which approach might lead to better results in each stage and type of dementia. For example, could computerized memory training generate more specific brain effects than cognitive stimulation approaches? Is cognitive training too demanding for the remaining compensatory processes in moderate Alzheimer’s disease stages?

In sum, although cognitive intervention studies suggest neural changes in response to it, claims about cerebral effects should be restricted and contextualized with individual studies, mainly due to the limited amount of available evidence.

CONCLUSION

Aging incurs alterations in neuropsychological and cerebral aspects [4, 61-63], which are influenced by a complex interaction of factors such as menopause, cognitive reserve, exercise, physical fitness and cognitive intervention, which can accelerate, compensate or protect from deleterious age-related alterations and neurodegenerative diseases [5, 64-68].

The present review shows that there is evidence of neuropsychological effects of cognitive intervention as well as some preliminary evidence for brain changes.

The determination of the precise impact of cognitive intervention in the brain, is therefore, of utmost importance for clarifying an extent of its potential effects as a preventive, remediative and perhaps restorative tool for promoting successful aging both in healthy and neurodegenerative states.

ACKNOWLEDGEMENTS

The author wishes to acknowledge Dr. Agavni Petrosyan for her assistance in English language editing.

The author declares no conflicts of interest with respect to the research, authorship, and/or publication of the present work.

No source of funding.

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Received on 16-11-2014 Accepted on 08-12-2014 Published on 14-04-2015

http://dx.doi.org/10.15379/2409-3564.2015.02.01.4