Cognitive interventions in Alzheimer’s and Parkinson’s diseases: emerging mechanisms and role of imaging

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Purpose of review
There has been recent debate about the lack of compelling scientific evidence on the efficacy of cognitive interventions. The goal of this study is to review the current state of cognitive interventions in Alzheimer’s disease and Parkinson’s disease, present emerging mechanisms, and discuss the role of imaging in designing effective intervention strategies.

Recent findings
Cognitive interventions appear to be promising in Alzheimer’s disease and Parkinson’s disease. Although feasibility has been shown in mild cognitive impairment, early Alzheimer’s disease, and mild to moderate Parkinson’s disease, studies to investigate long-term efficacy and mechanisms underlying these interventions are still needed.

Summary
There is a need to conduct scientifically rigorous studies to validate the efficacy of cognitive intervention trials. Future studies will greatly benefit from including longitudinal imaging in their study design. Imaging can be used to demonstrate the efficacy and mechanisms by measuring brain changes over the intervention period. Imaging can also be used to determine biological and disease-related factors that may influence the treatment response, that is, the effect modifiers. Consideration of effect modifiers will allow us to measure the treatment response in biomarkers and cognition with greater sensitivity and also aid in designing trials that will lead to better patient outcomes.

Keywords
Alzheimer’s disease, cognitive training, imaging, neuroplasticity, Parkinson’s disease

INTRODUCTION
The world population is aging at an accelerated rate. With increasing life expectancy, more people will be diagnosed with neurodegenerative disorders such as Alzheimer’s disease and Parkinson’s disease. These diseases are characterized by the deposition of abnormal proteins in the brain that are tied into specific clinical symptoms and cognitive deficits. Cognitive deficits in Alzheimer’s disease: the primary pathological causes of Alzheimer’s disease are neuritic plaques composed of β-amyloid fibrils and neurofibrillary tangles composed of hyperphosphorylated tau [1]. These disorders cause neurodegeneration typically but not always beginning in the medial temporal lobes. Though early cognitive deficits are related to memory; decline is seen in all cognitive domains as the disease progresses [2–4]. Cognitive deficits in Parkinson’s disease: the primary pathological causes of Parkinson’s disease are Lewy bodies, which are mainly composed of α-synuclein [5]. Though Parkinson’s disease is primarily characterized by progressive worsening of motor symptoms, cognitive impairment, and executive dysfunction, in particular, is a common aspect [6–8]. In those with Parkinson’s disease progressing to mild cognitive impairment (MCI) (typically multidomain nonamnestic) and dementia, visuospatial, working
memory, language, and learning and recall deficits are additionally observed [9].

Observational studies in Alzheimer’s disease and Parkinson’s disease have provided evidence that non-pharmacological or behavioral changes are associated with better disease courses [10]. Although there is emerging evidence that cognitive interventions may provide neuroprotective, neurorestorative, and secondary prevention benefits, there has been debate about the lack of compelling scientific evidence backing their effectiveness [11–15]. The goal of this work is to review the current state of cognitive interventions in Alzheimer’s disease and Parkinson’s disease, present emerging mechanisms, and discuss the role of imaging in designing intervention trials.

Cognitive interventions can be divided into cognitive stimulation, cognitive training, and cognitive rehabilitation. Cognitive stimulation engages participants in a range of general activities and discussions, and is commonly conducted in groups. It aims at general enhancement of cognitive and social functioning. Cognitive training focuses on guided practice on a set of tasks that reflect particular cognitive functions, such as memory, attention or problem solving or offers instruction, and practice of mnemonic approaches such as the method of loci or visual imagery (i.e., strategy training). Cognitive rehabilitation intends to identify and address the individual’s needs and goals, which may require strategies for taking in new information or compensatory methods such as using memory aids [13].

This section reviews the existing literature on cognitive interventions in Alzheimer’s disease and Parkinson’s disease and possible mechanisms. In addition to cognitive intervention studies, we have included literature from the field of cognitive reserve which is often used to explain the intersubject variability in cognitive performance in the face of brain pathology [16]. Cognitive intervention is suggested to increase an individual’s cognitive reserve [16] and, therefore, mechanistic interpretations associated with higher vs. lower cognitive reserve are generalizable to mechanisms invoked through cognitive interventions.

COGNITIVE INTERVENTIONS IN ALZHEIMER’S DISEASE

Cognitive stimulation consistently improves global cognition, primarily in individuals with mild-to-moderate dementia [15,17]. These benefits appear to be over and above any medication effects and remained evident at 3 months follow-up. Significant benefits were also noted for quality of life and well being, and on clinical staff ratings of communication and social interaction. No effects were found for mood, activities of daily living or challenging behavior [15,17] (Table 1). However, cognitive training did not result in any statistically significant effects in any domain for early stages of Alzheimer’s disease [12,13]. Cognitive rehabilitation may be promising for self-rated competence and satisfaction in performing meaningful personal goals, memory capacity, and general quality of life in Alzheimer’s disease patients [12]. For general quality of life, these effects persisted 6 months after the intervention [12]. However, the authors stated that more studies are required to obtain definitive evidence (Table 1). In MCI, cognitive training resulted in small benefits for episodic memory and other cognitive functions [18,19], although there is debate about these effects [14]. A recent review concluded that computerized-cognitive training (CCT) may be promising for improving attention and executive functions, and reducing depressive symptoms and anxiety [20*]. Yet, another recent review concluded that there is not enough evidence to support CCT alone for improvement or maintenance of cognitive function in MCI or Alzheimer’s disease [21*]. Cognitive stimulation has been less intensively studied in MCI. Wenisch et al. [22] found small benefits for an associative memory paradigm but more studies are needed for definite evidence. Cognitive rehabilitation [14] may be beneficial for subjective measures of cognition and neuropsychiatric symptoms [23], whereas a current review suggested that objective effects on specific cognitive domains were inconsistent across studies (Table 1) [24].

Underlying mechanisms

In Alzheimer’s disease, studies in transgenic mice with environmental enrichment have found
alteration in behavioral, cellular, and molecular aspects of pathogenesis [25]. Mice raised with social, physical, and cognitive stimulation showed protection against cognitive impairment, decreased brain β-amyloid deposition, and increased hippocampal synaptic immunoreactivity [26]. However, the literature in humans based on cognitive reserve studies is inconsistent. No effect of cognitive reserve has been found on the underlying Alzheimer’s disease pathology [27–29] and cognitive reserve is also suggested to lower the degree of Alzheimer’s disease pathologies [30–32]. Though the effect of cognitive intervention on Alzheimer’s disease pathology may be minimal, measuring amyloid and tau levels using CSF and PET imaging during the course of the cognitive interventions will be important in answering this debated question.

There is sufficient evidence to support that brain structure and function differ with cognitive reserve [33–35]. As plasticity is fundamental to the pathophysiology of Alzheimer’s disease [36], the possible mechanisms invoked by cognitive interventions may be through brain structure and function [37]. Though there is some evidence of transient increase in gray matter with cognitive interventions, there are no studies that have shown the long-term maintenance of these neuronal increases [38,39]. Change in neural activity is more common than volumetric increases after cognitive training [39–41]. This change can be either activation of new regions, or decreases/increases in neural activity in task-related structures [39,42]. Alterations of activity following cognitive training may reflect flexibility in deployment of resources because of strategy change rather than a manifestation of plasticity resulting in an increase in intrinsic neural or cognitive capacity [43]. To provide compelling scientific evidence for efficacy of cognitive interventions, measuring brain changes is fundamental in long-term trials [44].

### COGNITIVE INTERVENTIONS IN PARKINSON’S DISEASE

Despite their clinical efficacy for motor symptoms, antiparkinsonian medications can negatively impact cognition and behavior [45]. Cognitive interventions that provide clinical benefit without detrimental side-effects are therefore needed to mitigate disabling nonmotor symptoms. Few studies have examined the effects of cognitive intervention on Parkinson’s disease and have primarily used cognitive training (Table 1). The combination of cognitive interventions with physical therapies for Parkinson’s disease makes it hard to discern the effect of cognitive intervention alone. Cognitive performance was improved on tests of attention, information processing speed, executive functions, semantic verbal fluency, and visuospatial abilities in Parkinson’s disease patients who received CCT [46,47] compared with Parkinson’s disease control patients, and in some cases changes were maintained at 6-month follow-up [47]. Another study examining the effects of CCT focusing on processing speed in individuals with different subtypes of MCI [48] found that the single domain, nonamnestic MCI subtype (common in Parkinson’s disease)
showed the greatest improvement compared with other subtypes or controls and these changes were maintained over 5 years. A recent meta-analysis of randomized-controlled trials of cognitive training in patients with mild-to-moderate Parkinson’s disease [49] found only seven studies using repeated practice on cognitively challenging tasks of computerized or paper-and-pencil approaches for at least 4 h. Large and statistically significant effect sizes were found for working memory, processing speed, and executive functioning, but effect sizes were small to negligible and nonsignificant for memory, attention, visuospatial abilities, depression, quality of life, and activities of daily living.

**Underlying mechanisms**

Similar to Alzheimer’s disease, the mechanism of action maybe through brain structure and function. A recent study by Nombela et al. [50] compared the performance of Parkinson’s disease patients and healthy controls on a measure of attention and executive functioning during functional MRI (fMRI) and found that performance during ‘posttreatment’ scanning showed that only the Parkinson’s disease patients who received training showed improvement on the task (vs. untrained Parkinson’s disease and controls), and there were corresponding alterations in brain activation in primarily frontal and parietal areas.

In addition, dopamine levels probably play an important role in Parkinson’s disease. Variations in the dopamine transporter gene (DAT1) appear to be the key in regulating striatal dopamine availability [51]. Some investigators have assessed performance gains across several sessions of working memory training to examine the influence of the DAT1 polymorphism on plasticity [52]. Young adults were assessed with a cognitive test battery before receiving 20–25 sessions of CCT over 4 weeks on seven working memory tasks and were found to have improved performance, with larger gains observed in DAT1 9/10-repeat carriers than DAT1 10-repeat carriers. Given the above assumption, larger training gains in DAT 9/10-repeat carriers may be related to lower striatal DAT availability resulting in higher extracellular dopamine and more active dopaminergic pathways. In normal aging, age-related differences in presynaptic binding potential for the dopamine transporter as well as postsynaptic receptor densities account for significant portions of the age-related variation in executive functioning, episodic memory, and information processing speed [53–55], and these associations are seen in striatal as well as extrastriatal dopamine markers [56,57]. Studies have demonstrated that cognitive training may enhance performance on tasks demanding executive functioning in healthy older adults [58,59] and that executive plasticity is associated with striatal increases of neural activity [60]. Working memory underlies executive functioning [61] (i.e., higher-order abilities that underlie skills necessary for performing daily activities and commonly affected in Parkinson’s disease). Changes in the basal ganglia and executive-control network, that is, dorsolateral frontal and parietal neocortices, as well as changes in dopamine receptor density, have been noted following cognitive intervention in non-Parkinson’s disease individuals [62].

**ROLE OF IMAGING IN COGNITIVE INTERVENTION TRIALS**

**Demonstrating efficacy and mechanisms**

The key mechanisms of action and efficacy may be demonstrated by measuring the slower rate of brain shrinkage (because of pathology) in individuals undergoing cognitive training vs. those who are not. Additionally, positive neuroplasticity changes in the structural and functional connectivity of the brain (i.e., increased synaptic strengths and synaptogenesis [63]) have been suggested and are supported by cognitive reserve imaging studies. Several MRI acquisitions can be useful in measuring intervention-related brain structural and functional changes: structural MRI: recently published methodologies utilize high dimensional normalization between serial MRI scans and require smaller sample sizes to see trajectory changes [64–67]. We hypothesize that an effective cognitive intervention may slow the progression of age and pathology-related atrophy in disease-specific signature regions. Diffusion tensor imaging: white matter plasticity because of long-term practice effects (e.g., professional musicians, early blindness, and car racing) [68–71] has been demonstrated using diffusion tensor imaging. We hypothesize that cognitive interventions may be successful in attenuating the rapid decline in fractional anisotropy and diffusivity increases seen in Alzheimer’s disease and Parkinson’s disease patients [72,73]. fMRI: exercise-induced functional plasticity in large-scale systems in the aging brain over 12 months has been measured [74]. In addition to task fMRI, task-free MRI can aid in measuring local and global functional plasticity changes [75,76]. However, the relatively high variability of the method needs to be considered [77]. Arterial spin labeling: arterial spin labeling, a perfusion imaging technique, can detect changes in cerebral perfusion with good accuracy [78,79] and will be useful in capturing intervention-related neuronal changes [80–82].
Effect modifiers: sample enrichment, stratification, and intervention optimization

Effect modifiers are the main biological and disease-related factors that may influence the treatment response in cognitive intervention trials. Therefore, determining the effect modifiers using molecular, structural, and functional imaging before the start of the intervention would greatly improve the intervention practicability. Increasing age and baseline cognitive status significantly influences the response to cognitive interventions [83,84]. Education levels may also have a significant impact on the response [34]. The recent emergence of amyloid imaging in Alzheimer’s disease has shown that individuals with higher levels of amyloid show diminished practice effects [85,86], suggesting greater strength of trials in amyloid positive individuals. Another study in individuals with subjective memory impairment predicted response to cognitive training by hippocampal volume [87]. They found that larger pretraining hippocampal volumes were related to better verbal delayed recall 1 week after cognitive training. Further, hippocampal subfield volumetry suggested that the effects on long-term verbal memory change were selective for the left CA2/3 and CA4/dentate gyrus, which both play a role in episodic memory [87]. Effect modifiers impact the overall learning seen in individuals undergoing cognitive training.

Imaging biomarkers can facilitate stratification of patients and/or intervention optimization based on phenotype or genotype. Moreover, enrichment strategies for recruitment to the intervention (i.e., including only those most likely to benefit) can improve the response rate. A classic example is the A4 trial where only amyloid positive individuals are recruited to the antiamyloid treatment trial [88]. An example in the context of cognitive intervention is the idea that targeting different memory systems (e.g., episodic memory vs. working memory) will optimize effects for different memory subtypes and in different patient groups. There is definitely a link between a treatment-induced change in the biomarker and the desired clinical outcome measure, as well as a link between the treatment-induced changes in the biomarker and disease process. Therefore, accounting for effect modifiers will aid in measuring the treatment response in biomarkers and cognition with greater sensitivity and designing trials that will lead to better patient outcomes.

CONCLUSION

There is a need to conduct scientifically rigorous studies to validate the efficacy of cognitive intervention trials. The availability of imaging technologies for evaluating molecular, structural, and functional imaging changes in the brain has provided us with a unique opportunity to design rigorous cognitive intervention trials. Imaging can play a key role in demonstrating the efficacy and mechanisms underlying cognitive intervention trials. Additionally, imaging can be used to determine effect modifiers and thus improve treatment response through sample enrichment, stratification, and intervention optimization.

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Conflicts of interest

There are no conflicts of interest.

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