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Cognitive Interventions for Neurodegenerative Disease

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Abstract

Purpose of Review To critically review recent research in the development of non-pharmacological interventions to improve cognitive functioning in individuals with Alzheimer's disease (AD) or Parkinson's disease (PD).

Recent Findings Cognitive interventions can be grouped into three categories: cognitive stimulation (CS), cognitive training (CT), and cognitive rehabilitation (CR). CS confers temporary, nonspecific benefits and might slightly reduce dementia risk for neurologically healthy individuals. CT can improve discrete cognitive functions, but durability is limited and real-world utility is unclear. CR treatments are holistic and flexible and, therefore, most promising but are difficult to simulate and study under rigorous experimental conditions.

Summary Optimally effective CR is unlikely to be found in a single approach or treatment paradigm. Clinicians must be competent in a variety of interventions and select those interventions best tolerated by the patient and most relevant to their needs and goals. The progressive nature of neurodegenerative disease necessitates that treatment be consistent, open-ended in duration, and sufficiently dynamic to meet the patient's changing needs as their disease progresses.

Keywords Neurodegenerative disease · Cognitive training · Non-pharmacological interventions · Neuropsychological rehabilitation · Multidisciplinary

Introduction

The prevalence of neurodegenerative conditions such as Alzheimer's disease (AD) and Parkinson's disease (PD) has increased in recent decades because of the continually growing population of older adults worldwide. Global rates of dementia associated with these and other diseases are estimated to reach 152 million people by 2050, with an estimated annual cost of $2 trillion by 2030 in the USA alone [1]. Despite the widening scope of this problem, there remains no curative treatment for neurodegenerative diseases nor for the progressive cognitive, behavioral, and functional impairments they cause. Cholinesterase inhibitor and N-methyl-D-aspartate (NMDA) receptor antagonist drugs have been available for approximately two decades but only provide temporary, palliative treatment of cognitive symptoms in AD [2, 3]. The disease modifying drugs aducanumab [4] and lecanemab [5] have shown promise in treating cognitive symptoms in early clinical stage AD but are associated with adverse events in some individuals. Further, data on the long-term cognitive benefits of these drugs and, most importantly, the clinical significance of their cognitive effects are still being collected.

The development of non-pharmacological cognitive interventions for individuals with neurodegenerative disease has therefore developed into an active area of clinical research, with scientifically rigorous studies proliferating substantially over the last several years. Cognitive interventions were originally developed for the rehabilitation of individuals with stroke or traumatic brain injury (TBI) and were later adapted for the treatment of those with various other conditions, including multiple sclerosis and spinal cord injuries [6, 7]. The use of cognitive interventions in individuals with neurodegenerative disease represents the newest frontier of neuropsychological rehabilitation, but the often insidious and invariably progressive course of neurological decline in these diseases poses questions and challenges arguably not encountered previously. Regardless of the patient population in which they are used, these interventions are designed to maintain or enhance cognitive abilities and

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develop compensatory skills to improve daily functioning and enhance quality of life [7, 8].

Here, we critically review current research on the development of non-pharmacological interventions designed to improve cognitive and/or functional skills in individuals with neurodegenerative disease. We divide cognitive interventions into three categories: cognitive stimulation, cognitive training, and cognitive rehabilitation, as done previously [9–13]. In addition, we concentrate on studies involving individuals with prodromal or clinical AD or individuals with PD because research has mostly focused on addressing cognitive symptoms in individuals with these diseases, and we highlight some of the most rigorous recent studies.

Cognitive Stimulation

Cognitive stimulation (CS) involves engaging individuals in various activities, either individually or in groups, that require cognitive effort. Such activities include group discussions, learning a new skill such as a craft, and puzzles or games such as crosswords, Sudoku, or chess. CS has been studied empirically and used clinically to help prevent cognitive decline in healthy older adults and to slow cognitive decline in individuals with mild to moderate dementia. Secondary analyses of a large longitudinal dataset including data used to assess education and individuals' levels of cognitive activity and social engagement at various points in the lifespan indicate that engagement in cognitively stimulating activities across the lifespan reduces dementia risk for an undetermined period [14], perhaps through a reciprocal relationship with cognitive reserve [15]. Consistent with that, structured CS interventions have been shown to modestly reduce dementia risk in non-demented older adults. Clearly, however, this association is correlational and could be explainable by a participation bias in that individuals who are physically healthier, psychologically "open," of higher socioeconomic status, and/or of a higher cognitive baseline, all of whom have been shown to be at lower dementia risk, are more likely to engage in cognitively stimulating activities and participate in research on CS interventions.

CS activities might temporarily or situationally improve mood and overall well-being by providing entertainment and engagement in a structured environment. In addition, the notion that CS improves neurological resistance to disease by inducing synaptogenesis and strengthening existing synaptic connections is reasonable. However, CS activities generally have minimal to no long-term cognitive benefit for those with even mild to moderate dementia as determined by scores on brief cognitive screening tools, such as the Mini Mental Status Examination (MMSE) [9, 12, 13]. For example, Fonte and colleagues [16•] examined the potential cognitive benefits of structured stimulation of preserved or "residual" cognitive skills through reminiscence about and practice of familiar and overlearned but cognitively demanding activities, such as playing a musical instrument or cooking, in individuals with AD. The intervention was associated with an average four-point score advantage on the MMSE at 3 months post-treatment. This represents a substantial score difference, but the scores of individuals in both the experimental and control groups were still in a range associated with impairment following treatment, and the durability of the treatment effect beyond 3 months is unknown.

Cognitive Training

Cognitive training (CT) aims to maintain or improve specific cognitive functions, such as attention, executive functioning, or memory via structured, repetitive exercises and/or training in compensatory methods and the use of assistive devices in a manner analogous to physical training, which targets improvements in mobility, strength, and coordination. CT is generally comprised of manualized interventions delivered in individual or group formats, as computer software, smartphone applications, or classroom-based programs, and consists of hierarchically organized lessons or exercises provided with repetition and reinforcement throughout the training protocol [12, 17]. For example, a CT intervention can involve repetitive cognitive exercises in which an individual practices a specific skill, such as working memory [18] or consist of training in memory skills, such as chunking and other methods of deep encoding, mnemonic techniques, and/or note-taking [7, 8].

As an example of recent work investigating the cognitive benefits of CT interventions, Kim and colleagues [19] piloted a program consisting of eight 50-min sessions delivered once weekly over 8 weeks with both cognitively normal individuals and those with amnestic MCI. Their program had both a memory skills training component (e.g., instruction in mnemonic methods, such as association and chunking) and a compensatory skill training component (e.g., instruction in the use of timers, alarms, and calendars). Neuropsychological testing administered both before and immediately after training revealed statistically significant improvements in attention, processing speed, language functions such as naming, verbal recognition memory, and nonverbal memory, all with medium effect sizes. Given that the intervention targeted memory, the range of test score improvements in those with MCI suggested transfer of trained cognitive skills to related but untrained skills. However, the study included a small number of participants, had no control group, and there was no subsequent follow-up, features common to many similar studies of CT interventions. Indeed, many studies are similarly promising, but small sample sizes and limited follow-up windows mean that larger scale RCTs are needed to better investigate durability of treatment effects and generalizability of study findings.

In a more rigorous RCT design with a much larger sample, Luo and colleagues [20] investigated the cognitive benefits of a 12-week program involving training in skills needed for visual art creation and storytelling using a videoconferencing platform in individuals with amnestic MCI. The control treatment consisted of weekly sessions that included training in memory strategies for daily activities as well as education on diet and exercise. Immediately following program completion, individuals who received the experimental treatment evidenced an average 2-point score improvement on the Montreal Cognitive Assessment (MoCA) in addition to functional connectivity (FC) increases between the ventromedial prefrontal cortex and left angular gyrus, components of the executive control network. The control group did not exhibit improvement in MoCA scores and showed decreased FC in the executive control network. Nevertheless, neither group showed significant changes in neuropsychological test scores in a pre-post analysis, and the clinical significance of improved MoCA scores in the experimental group was of uncertain but likely minimal clinical significance. Similar future studies would ideally use more sensitive neuropsychological measures and/or indicators of competence in IADLs and examine outcomes over a longer follow-up period given that individuals often live with dementia for up to a decade after diagnosis.

Many recently studied CT interventions in neurodegenerative disease have been delivered via smartphone or computer [21, 22••, 23••]. Li et al. [24] investigated the cognitive effects of an at-home, computerized, multimodal cognitive training program in individuals with MCI. Participants completed 120-min sessions of cognitive training 3 to 4 times per week for 6 months, and the control group received no treatment. The training involved repetitive cognitive exercises requiring various discrete cognitive functions, such as working memory (e.g., rapidly calculating the total numerical value of an increasingly large series of numbered playing cards) and episodic memory (e.g., viewing and later recalling visual scenes depicting various events). Findings indicated statistically significant improvements on cognitive measures at 6 months post-treatment, most strongly in attention and memory but also in executive functioning and visuospatial processing, along with findings of increased activity in neocortical and mesial temporal regions associated with memory on fMRI. However, there were no significant differences between the treatment and control groups on cognitive outcome measures at 12 months post-training, and neither mood nor daily functioning outcomes were assessed.

Cavallo and colleagues [25] investigated the cognitive effects of a similar computerized intervention program, the Brainer rehabilitation software [25], for individuals with early-stage AD. The software is a suite of cognitive exercises targeting attention, executive functioning, memory, and language that was administered to participants in three 30-min sessions over 12 weeks. The experimental group obtained statistically significantly higher scores on neuropsychological measures of attention, working memory, executive functioning, and memory for stories compared to the control group, who received a CS-type intervention comprised of activities such as reading and discussing news articles with a neuropsychologist. Training effects were seen both immediately and at 6 months post-training. However, these effects were not maintained after 12 months, with cognitive outcome scores returning to baseline levels [26]. There were no neuropsychiatric benefits observed in this study, and daily functioning outcomes were not assessed.

Similarly, evidence for the effectiveness of computerized cognitive training in PD remains limited. Van Balkom and colleagues [27] reported that their 8-week computerized cognitive training program consisting of twenty-four 45-min sessions was associated with statistically significant but small beneficial effects on measures of processing speed and some aspects of executive functioning. However, they found no significant overall, long-term effects on cognitive functioning nor improvements in subjective cognitive complaints in individuals with PD.

Following a large systematic review of RCTs, Leung and colleagues [28] reported that CT interventions were safe and yielded statistically significant improvements in working memory, processing speed, and aspects of executive functioning in individuals with mild to moderate PD. Effect sizes were medium ($g = 0.74$) for working memory but small for processing speed ($g = 0.31$) and executive functioning ($g = 0.30$), and effects on measures of global cognition, attention, memory, visuospatial processing, mood, self-reported quality of life, and instrumental activities of daily living were not statistically significant. The cognitive areas in which significant improvements were observed are subserved largely by frontal-subcortical systems, and decline in these areas is indeed associated with advancing PD pathology.

However, Leung and colleagues concluded that better data on the durability of CT treatment effects and its utility for secondary prevention of cognitive decline in PD required further investigation with larger scale RCTs. Gavelin and colleagues' recent comprehensive systematic review and meta-analysis [22••] yielded similar conclusions of small to medium effects on cognitive test scores in individuals with PD, mostly evident in those with MCI due to PD rather than PD dementia, following CT. However, they cautioned that well-powered, larger scale studies were needed to clarify questions about treatment effectiveness and durability. Following another large systematic review, Orgeta and colleagues [29•] reported no evidence that individuals with either MCI or dementia due to PD exhibit substantial cognitive improvement following participation in CT protocols lasting 4 to 8 weeks. However, their conclusions were based on analysis of the small number of scientifically rigorous studies available, and many of the included studies involved relatively small samples comprised of individuals with differing degrees of cognitive impairment. Therefore, Orgeta and colleagues highlighted the need for more rigorous and adequately powered studies to better delineate the effectiveness of CT in PD.

Such technology-based interventions are generally more accessible and less costly than interactive treatment provided by a clinician. In addition, they are adaptable based on user performance [6], an important characteristic given that CT interventions are typically most effective when tasks increase in difficulty once lower-difficulty tasks have been mastered [7]. However, the cognitive benefits of these interventions as operationalized by neuropsychological test performance appear to be short-lived, disappearing in as few as 12 months in individuals with prodromal or early clinical-stage AD. Further, cognitive benefits appear to be small and of unclear duration in individuals with PD.

Regardless of the durability of cognitive test score improvements observed in these studies, many have questioned the clinical significance of those improvements and, relatedly, whether rote practice or didactic instruction of cognitive skills improve the execution of cognitively demanding daily activities [30]. Some studies have shown modest benefits for performance of such activities, such as improved memory in medication management activities following a CT memory intervention in a large-scale study [17], but many others [31] have failed to find an association between CT and either improvements in broader cognitive skills or cognitive ability in daily activities. These conflicting findings could be explained by variability in the scientific rigor of relevant studies as well as the extreme heterogeneity in the clinical populations and interventions the studies employed. Nevertheless, the limited generalizability of CT-based training to real-world activities is commonly seen in clinical practice and has been well-established in the general population [32] as well as in TBI survivors [7] and individuals with MCI [33].

Although consistently not associated with improvements in specific cognitive domains or neuropsychological test performance, virtual reality (VR) interventions have been developed to improve the ecological validity and generalizability of CT [34, 35] by using simulated environments to train cognitive skills vital to daily functioning or train performance of specific real-world tasks. VR provides a completely controllable, constant, and safe environment in which techniques, such as errorless learning and vanishing cues, can help individuals with dementia re-learn skills needed for some instrumental activities of daily living (IADLs).

VR-based CT interventions have generally been studied in both single subject and group designs using variably immersive environments, such as a simulated building without landmarks to reteach spatial navigation skills [36], a simulated kitchen to reteach meal preparation skills [37], and a simulated market in which executive functioning skills needed for efficient shopping could be trained [38]. In such studies, participants with MCI or dementia due to AD generally demonstrate skill improvement characterized by medium effect sizes after repeated practice in the simulator, and caregivers have reported good transfer of training to real-world activities that require the skills that were retrained [39••, 40, 41••]. However, longitudinal data on the durability of these training effects are limited. Nevertheless, Cheng and colleagues [42] reported improvements in neuropsychological test scores in the domains of memory, executive functioning, and simple visuospatial processing up to 3 months following completion of a 10-session protocol involving CT delivered via VR immediately following transcranial magnetic stimulation (TMS) of the left dorsolateral prefrontal cortex. Importantly, test score improvements were greater than those observed in individuals who received TMS alone.

Cognitive Rehabilitation

Despite the face validity of many CT interventions and the promising but preliminary data from studies employing them, more interventions that adequately address the limited generalizability of CT paradigms are needed. Real-world activities require multiple cognitive skills, and compensatory methods often must be adapted to fit the characteristics of the individual, their daily activities, and the environment in which they function [7, 8]. Cognitive rehabilitation (CR) is a more comprehensive, holistic approach that aims to address this limitation and maximize generalizability by using an individually tailored approach [8, 12]. CR can include repetitive cognitive exercises and/or didactic training in cognitive compensatory methods. However, in CR these interventions are embedded within a broader therapeutic framework that includes coaching-style interventions to facilitate the individual's development of cognitive skills and competence in compensatory methods as well as facilitate application of those skills to the individual's specific daily activities in a manner consistent with the individual's baseline functioning, treatment goals, and personal values. CR can also include psychotherapeutic interventions to improve emotional adjustment to cognitive disability and the need for cognitive supports, thereby improving skill learning and treatment compliance. The CR process allows the clinician to select, trial, and refine as needed those interventions deemed of greatest potential benefit to the individual. CR also often involves partners and family members, providing them with ongoing education about neuropsychological manifestations of the affected individual's disease and ways in which they can support the individual's use of skills learned in treatment. Involvement of family members in CR can also help improve functioning within marital and larger family relationships and has been shown to decrease caregiver burden [9–11].

We are not aware of any empirical studies that have yet to fully capture the dynamic and holistic nature of CR within an experimental or RCT framework. Relatedly, the question of whether the limited effectiveness of CS and CT interventions in neurodegenerative disease is improved when embedded in the more comprehensive CR treatment has yet to be thoroughly studied, but the progressive nature of cognitive deficits in those diseases is likely to pose a substantial barrier to significant, enduring treatment effects despite even the most comprehensive, individualized treatment. However, the compensatory method training component of CR has been associated with demonstrable albeit overall modest cognitive benefits in those with MCI or mild to moderate cognitive decline due to AD as well as reduced caregiver burden 1 year after treatment [10, 11].

Further, the findings of several studies suggest that cognitive treatment embedded within a more comprehensive, multicomponent treatment program can yield beneficial effects. For example, computerized CT delivered within a program also consisting of exercise, wellness education, and both patient and partner support groups has been associated with attenuated declines in attention and processing speed after 12 months [43].

Straubmeier and colleagues [44] conducted arguably one of the most scientifically rigorous and generalizable studies examining CR for cognitive impairment due to neurodegenerative disease, a multicenter RCT of the MAKS (motor, activities of daily living, cognitive, social) intervention in over 300 individuals with MCI or mild to moderate dementia across 32 skilled nursing facilities (SNFs). MAKS is a standardized, manualized program comprised of activities designed to "activate" sensorimotor (e.g., gross and fine motor skills and sensory perception), cognitive (e.g., memory, language comprehension, and reasoning skills), and daily living (e.g., common housework or craftwork) skills. The program was provided for 2 h per day, 5 days per week, for 6 months. MAKS was associated with a stabilization in scores on the MMSE and the Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment (ETAM), a valid and reliable measure of capability in performance of ADLs, whereas the SNF standard of care comparison group evidenced a mean one-point decline in MMSE score over the study period. There was also evidence of delayed onset of neuropsychiatric symptoms in participants who received the MAKS intervention. Importantly, a prior study found that this stability in MMSE score was present 1 year after treatment in facility-dwelling individuals who received the MAKS intervention [45].

In a representative study using an RCT design, Fonte and colleagues [16•] investigated the effectiveness of a 6-month CR program comprised of training in metacognitive memory techniques and compensatory methods for memory loss provided by neuropsychologists as compared to a standard of care control group. They reported that individuals with MCI due to AD exhibited a mean 5-point score difference on the MMSE and improvements on measures of attention and set shifting both immediately and 3 months after completion of the program. The MMSE score difference observed in Fonte and colleagues' study is arguably clinically significant given that the mean score for those who received CR was above the cutoff for impairment while the mean score for those in the control group was below the cutoff. Individuals with AD dementia showed similar score improvements, but these improvements disappeared rapidly after completion of CR, suggesting that individuals with dementia require more constant treatment to maintain cognitive benefits. The study also made a novel comparison between CR and a physical training program involving moderate intensity and endurance training provided by kinesiologists. Findings suggested similarly durable treatment effects for individuals with MCI due to AD who received the physical training alone.

Consistent with the holistic nature of CR that incorporates multifaceted and often complimentary, non-cognitive interventions, enhanced treatment effects have frequently been demonstrated when cognitive interventions are used synergistically with other, non-cognitive treatments, such as acupuncture or aerobic exercise [46–48]. Numerous systematic reviews and meta-analyses of studies examining the association between aerobic exercise programs and cognitive outcomes have demonstrated positive effects on measures of general cognition and aspects of memory and executive functioning in individuals with MCI [49, 50]. Such data are unsurprising given the well-established association between cardiovascular health and cognitive aging.

Regardless of treatment type or modality, Shao and colleagues' systematic review and meta-analysis of studies of non-cognitive interventions [51] concluded that more frequent intervention and interventions of longer duration are associated with more appreciable and durable treatment effects, with 60 to 120 min of treatment per week for 12 weeks or more yielding the most benefit across most types of single and multicomponent interventions. This dose–response relation between treatment, degree of cognitive improvement, and extent to which cognitive decline can be delayed is consistent with the clinically significant and progressive nature of cognitive symptoms in MCI and dementia.

Conclusions

Review of the literature on cognitive interventions in neurodegenerative disease suggests the following: CS interventions confer at least temporary, nonspecific benefits by providing structured, cognitively, and/or socially engaging activity and might slightly reduce dementia risk for neurologically healthy individuals. The more specific and targeted interventions comprising CT can improve discrete cognitive functions and perhaps lead to more generalized cognitive improvements, but the durability and real-world utility of those improvements are generally limited in the setting of advancing neuropathology due to degenerative disease. VR-based CT is a more ecologically valid intervention on its face, but a sufficient understanding of the generalizability and durability of its effects are still evolving, and accessibility of the technology is relatively limited at present. The holistic, multi-faceted, and flexible CR treatments provided by rehabilitation specialists are difficult to simulate and study under the highly standardized conditions of an experimental study or RCT, and determining appropriate outcome measures in such studies poses an equally significant challenge. However, multicomponent interventions—perhaps the best approximation of the CR provided by specialists in clinical settings—show promise for palliatively addressing cognitive and mood symptoms.

Many fundamental questions about the use of CR in neurodegenerative disease remain. As a result of these uncertainties as well as the obvious allure of developing a potential treatment for as of now incurable conditions, studies investigating cognitive interventions in neurodegenerative disease have proliferated significantly in recent years. The select portions of the growing body of literature described here in fact represent a mere fraction of the hundreds of studies of variable scientific rigor published over the last decade.

Created and historically advanced in response to the needs of large groups of individuals with acute neurological trauma, CR did not emerge until the World War I era in Europe and then gained wider global attention after World War II but did not begin to germinate in US medical centers until the late 1970s and early 1980s [52]. Currently, CR is offered at many medical centers and by community-based providers, generally by clinical psychologists or occupational therapists, some of whom have earned credentials attesting to their specialized training and experience, such as board certification in rehabilitation psychology by the American Board of Professional Psychology (ABPP). CR is commonly offered within physical medicine and rehabilitation departments as a treatment for brain injury survivors, while services and programs designed for individuals with neurodegenerative disease are less common and therefore more challenging to access. The services are covered by Medicare if deemed medically necessary by a referring provider, but availability varies by geographic location and services are most reliably found in metropolitan areas.

Despite its growing sophistication and acceptance in clinical settings, cognitive rehabilitation is still a young practice. By comparison, although psychotherapy has existed in its major contemporary forms for up to 100 years, its roots can be traced to the Middle Ages and the work of early medical pioneers, such as Paracelsus [53]. Similarly, modern physical therapy has developed over the last 100 to 200 years, but its practices are built on concepts first documented in Ancient Greece by the classical period physician Hippocrates [54].

Despite their long traditions, these two more common and well-developed therapies still vary in their effectiveness due to the wide range of characteristics of the provider, patient, collaterals, and the intangible dynamic that develops among them as the treatment progresses. Further, these therapies are not a single intervention delivered in a standardized manner to all individuals at the same intensity or duration. Rather, the clinician must remain competent in a variety of techniques and select a combination of those approaches to be delivered in a manner best tolerated by and useful for the individual patient. Although specific interventions might provide limited and/or temporary benefits, particularly for the least cognitively impaired individuals, it follows that the best tack for cognitive rehabilitation specialists treating individuals with neurodegenerative disease is to regularly review and critically evaluate the rapidly growing literature on potential interventions so they can continually add clinical tools to their proverbial toolbox.

Clearly, the treatment must be well-tolerated by the patient and caregivers and be relevant to the patient's specific cognitive limitations as well as to their daily activities, goals, and values. In addition, the progressive nature of neurodegenerative disease necessitates that treatment be consistent, open-ended in duration, and dynamic enough to meet the changing needs of the patient as their disease progresses and their family or other collateral supports endure greater caregiver burden. Cognitive rehabilitation in neurodegenerative disease must indeed take various forms and comprise numerous interventions, for example, intensive cognitive skills training with a strong coaching component to aid in generalization for the high-functioning individual with MCI; instruction in cognitive compensatory skills and psychotherapy to address adjustment to cognitive disability for the individual with early-stage dementia; and reminiscence therapy and supportive psychotherapy for the individual with moderate-stage dementia with an equal emphasis on education and support for their caregivers. Cognitive rehabilitation specialists must, therefore, make a profound commitment to the patients and families they treat, a commitment to provide truly holistic, person-centered care, the clinical effect of which can range from palliative to transformative.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent. This article does not contain any studies with human or animal subjects performed by any of the authors.

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