Cognitive Training in Mild Cognitive Impairment

Benjamin Boller, Laura Prieto del Val, and Sylvie Belleville

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Abstract Alzheimer's disease is characterised by a slow progression and by an extensive prodromal phase during which symptoms are dormant or very mild. The term mild cognitive impairment (MCI) has been used to refer to older adults who do not meet the criteria for dementia but who present cognitive complaints and whose cognitive abilities do not fall within the expected range given their age and education. Longitudinal studies have found that many persons with MCI will later meet these criteria and are thus in the pre-dementia phase of Alzheimer's disease. The potential impact of cognitive training could be remarkable, and these individuals make for ideal candidates for training as they retain the ability to acquire new skills. This chapter describes some of the studies that have measured the efficacy of cognitive training in MCI. One of the goals is to provide guidelines regarding the approach that may be most appropriate for persons with MCI based on cognitive outcomes, subjective out-

B. Boller (✉)
Research Center, Institut universitaire de gériatrie de Montréal and Psychology Department, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada
e-mail: benjamin.boller@uqtr.ca

L. P. del Val
Department of Physiology, Anatomy and Cellular Biology, Pablo de Olavide University, Sevilla, Spain

S. Belleville
Research Center, Institut universitaire de gériatrie de Montréal and Psychology Department, Université de Montréal, Montreal, QC, Canada

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comes, well-being, and outcomes of everyday life. It also describes some of the results obtained through brain imaging and discusses neuroscience-based models of training. Neuroimaging studies have demonstrated the presence of training-induced neural changes in individuals with MCI. These changes indicate that the integrity of the compensatory and restorative neural mechanisms may be relatively preserved in this population. According to the INTERACTIVE model, the neural response to training is not only modulated by the severity of the disease but also by the training modalities and personal factors such as expertise and level of cognitive reserve.

Introduction

Dementia is diagnosed when acquired cognitive impairment significantly affects the autonomy of the individual. Although dementia can have many causes, Alzheimer's disease (AD) is recognised as the most common aetiology in older adults. The cognitive changes that characterise AD are progressive and the disease evolves over up to 20 years before patients meet criteria for dementia. During this extensive prodromal phase, symptoms are dormant or very mild. The term mild cognitive impairment (MCI) has been used to refer to individuals who may be in a pre-dementia phase of AD and who have an elevated likelihood of progressing to the disease. The presence of a subjective complaint, which indicates that the individual is aware of their cognitive changes, is a main characteristic of MCI. For this reason, and because the ability to learn new skills and strategies is preserved in this population, persons with MCI are particularly well suited to benefit from cognitive stimulation, which could significantly improve their quality of life. This chapter is a qualitative review of the studies measuring the impact of cognitive training in persons with MCI. Section "Mild Cognitive Impairment as a Target for Cognitive Training" will introduce the concept of MCI and the reasons why this phase is believed to be appropriate for cognitive training. Section "Memory Training" will present studies on memory training, section "Training of Attentional Control" studies on attentional or executive training, and section "Training Imbedded in Real Life: Virtual Reality and Leisure Approaches to Cognitive Training" will present strategies to promote generalisation of the acquired skills in everyday life. Finally, studies relying on neuroimaging will be presented, followed by models of the training-induced brain changes.

Mild Cognitive Impairment as a Target for Cognitive Training

MCI represents a cognitive decline that is greater than what is considered normal based on the individual's age and educational level, but that is not significant enough to limit independence in daily life activities and meet criteria for dementia. Though the original MCI concept required the presence of memory difficulties, its current definition includes impairment in non-memory domains and the possibility that MCI may progress to neurodegenerative diseases other than AD (Albert et al. 2011). A person with MCI can be categorised based on whether one or more cognitive domains are affected (i.e. single vs. multiple domain MCI) and whether they are amnestic (a-MCI) or non-amnestic MCI. The a-MCI subtype has received considerable attention since it is the subtype that most likely represents prodromal AD.

Appropriate models of cognitive training for MCI should rely on an understanding of which functions are impaired and which are preserved. Cognitive functions have been greatly researched in MCI and a pattern characteristic of MCI symptomatology is emerging (Belleville et al. 2008). Episodic memory, which is the ability to encode and retrieve new information that is embedded in a spatio-temporal context, appears to be the cognitive component that is the most impaired. Working memory (see Könen et al., this volume), the ability to manipulate maintained information, is also impaired in a-MCI, whereas short-term memory and implicit memory seem to be preserved. Executive functions (see Karbach and Kray, this volume), on the other hand, including response inhibition, switching, cognitive flexibility, and abstract thinking, seem to diminish in MCI.

Many factors make MCI a suitable target population for cognitive training: (i) given that pharmacological treatment such as cholinesterase inhibitors (ChEIs) has not been successful in MCI (Petersen et al. 2005), non-pharmacological treatment may be an appropriate and risk-free alternative to improve cognitive functions; (ii) individuals with MCI maintain a certain degree of cognitive plasticity that allows them to learn and apply new strategies; (iii) symptomatic treatment would produce the maximum benefit when applied at the earliest time point of the AD process; (iv) observational studies indicate that cognitive stimulation can have an impact on cognitive decline and dementia; (v) a cognitively stimulating lifestyle has found to be among the most important protective factors against dementia (Barnes and Yaffe 2011).

One major support for cognitive stimulation is that it protects against age-related cognitive decline and dementia. Education, learning new things, or enjoying a challenging job are mentally invigorating and represent life course models of mental stimulation. There is growing evidence that differences in cognitive lifestyles affect age-related cognitive decline and resistance to neurodegenerative diseases. Most of the evidence comes from observational studies examining the association between different lifestyle factors and cognitive decline or dementia. Barnes and Yaffe (2011) indicated that cognitive inactivity, most often measured with level of formal education, was associated with a 59% increased risk of developing AD and was estimated to account for about 19% of AD cases worldwide. The authors estimated that reducing the prevalence of low education attainment by 10% would reduce the incidence of AD by about 534,000 cases. Thus, observational studies indicate that cognitive stimulation across the lifespan determines differences in the risk for age-related neurodegenerative diseases and that reducing cognitive inactivity has the potential to substantively affect the prevalence of cognitive impairment.

Memory Training

Episodic memory is the most severely affected cognitive function and the main complaint in MCI. Thus, cognitive training as a way of promoting the maintenance and improvement of episodic memory in older adults with MCI has attracted major attention. Memory training programs typically focus on teaching strategies to encourage richer encoding or to facilitate retrieval (see also Wenger et al., this volume) and they rely on aspects of memory that are relatively well preserved in MCI such as semantic knowledge, visual imagery, or implicit retrieval. A large number of mnemonic strategies and procedures have been used including errorless learning, spaced retrieval, mind mapping, cueing, semantic organisation and elaboration, mental imagery, and the method of loci. Some are quite effortful and demand strong metacognitive abilities such as the method of loci, which requires the individual to produce an interactive image between items he/she is to learn and a series of loci in a familiar environment. Other procedures rely on more automatic memory systems such as space retrieval, where information is recalled multiple times at increasingly longer intervals. Most studies employ a combination of mnemonic strategies so as to provide patients with a broad set of tools. Most programs comprise a face-to-face intervention in which a therapist teaches these strategies and provides guidance and practice on either an individual or small-group basis.

Several studies have found that these strategies improve proximal memory measures, whether they are tested with immediate or delayed free recall of words (Belleville et al. 2006; Olchik et al. 2013), recognition (Herrera et al. 2012), event-related prospective memory (Tappen and Hain 2014), or face-name associations (Belleville et al. 2006). Some of them show that an active control comparison group (Herrera et al. 2012; Olchik et al. 2013; Tappen and Hain 2014) benefited less than the group receiving memory training, suggesting that performance gains are not entirely attributable to non-specific stimulation. Subjective memory seems to also benefit from memory training when the program introduces the notion that older adults can cope with memory problems or when cognitive restructuring of memory-related beliefs is provided (Belleville et al. 2006; Rapp et al. 2002). Targeting these components in MCI is relevant, as it can contribute to increasing self-efficacy – the perception that individuals have control over their memory – and can reduce MCI-related anxiety and depression. Overall, these studies indicate that memory interventions are promising and can increase memory performance in persons with MCI. They also suggest that the benefits can generalise to non-cognitive domains.

Some of these studies have imbedded memory training within broader multimodal interventions to maximise the cognitive training effect (Belleville et al. 2006; Kinsella et al. 2009; Schmitter-Edgecombe and Dyck 2014). Belleville and collaborators (2006) developed a multifactorial approach to be used with healthy older adults and persons with MCI (*Méthode d'entraînement pour une mémoire optimale*, MEMO). The program teaches different mnemotechniques (e.g. method of loci, face-name association, interactive imagery, text hierarchisation, semantic elaboration) and includes training on attention and visual imagery abilities. It also provides general psychoeducational information on cognitive aging and lifestyle factors and includes a number of features to promote self-efficacy and generalisation. Belleville et al. (2006, 2018) found improvement on objective episodic memory. Results from a randomised, controlled, single-blind trial using the MEMO program in persons with MCI showed improvement on episodic memory and on strategy use in everyday life and these gains were maintained 6 months following the intervention (Belleville et al. 2018). Kinsella et al. (2009) reported a multifactorial intervention that involved memory strategies, lifestyle, education, and psychotherapeutic techniques and that included family partners. They showed improvement on everyday memory, suggesting a generalisation of the effect to broader domains and contexts. Schmitter-Edgecombe and Dyck (2014) reported similar results with a program that involved care partners and comprised an educational workshop, multifamily memory strategy training, and problem-solving sessions. The involvement of family partners may facilitate the transfer of learned strategies to everyday functioning by providing support and feedback to their relatives with MCI.

Multimodal computerised training programs have also shown interesting results when applied to individuals with MCI. These programs are designed to target a general population of brain-damaged patients and typically include exercises for a wide range of cognitive functions (e.g. attention, perception, language, gnosias, calculation) in addition to memory. Rozzini (2007) reported that treatment with ChEIs alone did not reduce memory impairment in MCI subjects, but that combining computerised cognitive training with ChEIs resulted in significant memory improvements. Whether computerised training is as effective as face-to-face training has not yet been directly tested. Notably, however, Gaitán et al. (2013) tested the efficacy of multimodal computerised training with MCI persons who already received conventional face-to-face cognitive training and found that it did not produce further memory improvement. There is no strong evidence thus far that multimodal computerised training leads to a significant transfer to complex or daily activities.

Despite the positive effects of memory training described above, some randomised-controlled studies have reported negative findings (Unverzagt et al. 2007; Vidovich et al. 2015). For instance, Unverzagt et al. (2007) found no benefit from memory training in a memory-impaired subgroup from the ACTIVE cohort. Vidovich and collaborators (2015) reported improvement on attentional control and quality of life following memory training in MCI but no improvement on primary cognitive outcomes. The lack of systematic improvement makes it difficult to determine whether cognitive training interventions are able to affect a broad set of memory-related activities. A range of factors could explain the negative findings; for instance, it may be due to the fact that the selected outcome is insufficiently sensitive to change or is not sensitive to the processes improved by the intervention. Furthermore, the training format may also be an issue. Thus, there is a need for more studies aiming to disentangle the characteristics of an effective memory training program in MCI and its impact on complex memory-related activities. There are interesting avenues researchers could take: one may be to provide interventions that include additional cognitive or non-cognitive components; another would be to involve family partners in the intervention program.

Training of Attentional Control

Attentional control and executive functions are highly involved in everyday life and executive impairment is predictive of disability in older adults. Surprisingly, very few studies have focused on exercising these comprehensive abilities. Yet, there is evidence that training can improve attentional control in older adults (Karbach and Kray, this volume). For instance, Strobach et al. (2015) found that hybrid dual-task training, i.e. training with blocks that contain both dual-task and single-task trials, improved coordination skills. The authors also found that the effect was still present when tested with slightly different tasks, suggesting a near transfer of improved coordination skills. Divided attention capacities can be trained using variable priority training as opposed to fixed priority training. In both cases, participants practice divided attention tasks but in the variable priority training, individuals are also asked to prioritise one task over the other and to vary their attentional priority across different blocks of practice. Many authors reported that variable priority training is more effective in improving dual tasking than fixed priority (Bier et al. 2014; Gagnon and Belleville 2011; Kramer et al. 1995; Lee et al. 2012; Voss et al. 2012; Zendel et al. 2016) perhaps because it allows individuals to practice top-down regulatory control and hence increases self-control capacities over attention (Bier et al. 2014). Gagnon and Belleville (2012) compared the efficacy of variable and fixed priority training in persons with MCI who experience difficulties with executive control and found that variable priority increased dual-tasking capacities when compared to fixed priority training. These results suggest that training attention with programs that promote self-monitoring and metacognition can increase dual-tasking abilities in persons with MCI. Some evidence of training efficacy on attentional control were also found from a 5-week multi-domain training that combined cognitive training with elements from cognitive rehabilitation and stimulation. Trained MCI individuals exhibited a reduced decline of attention on a 2-year follow-up compared to MCI individuals who received a control-non-specific educational program (Vidovich et al. 2015). However, more studies are needed as only a few studies have focused on training attentional control in MCI.

Training Imbedded in Real Life: Virtual Reality and Leisure Approaches to Cognitive Training

Ultimately, the goal of cognitive training is to ensure that it results in significant changes in patients' lives (Taatgen, this volume). Traditional training programs are extremely variable in their ability to show far- or even near-transfer effects. Complex cognitively stimulating activities such as volunteer work, learning new languages, or engaging in interesting hobbies have the potential to meet these requirements. These activities involve learning a range of cognitive challenges that are of increasing complexities. They promote continuous learning, are pleasurable, and hopefully promote engagement, motivation, and transfer to everyday life, particularly in those who may not feel comfortable with academic activities. They are also multimodal by nature, as they involve social interactions and require that older adults explore new environments and be physically active. Interestingly, observational studies have identified these types of activities as being protective against cognitive decline and dementia. Programs based on similar activities have been shown to promote cognition in older adults. For instance, the SYNAPSE project (Park et al. 2014), which involves photography and/or learning how to quilt, was found to improve memory when compared to a placebo condition. In the Baltimore Experience Corps study (Carlson et al. 2008), in which older adults tutored elementary school pupils, improvement was found in cognition, health, and well-being. Within the Canadian Consortium on Neurodegeneration in Aging program, the ENGAGE program (Belleville et al. 2019) combined formal memory and attentional training strategies with leisure activities (Spanish learning or music lessons) and assessed whether it improves cognitive, psychosocial, and brain variables in persons with subjective cognitive decline (SCD), i.e. individuals who worry about their cognition but who are not cognitively impaired according to conventional neuropsychological tests. Because they are rooted in the community and are enjoyable, it is expected that cognitive programs that are embedded in real life such as ENGAGE, SYNAPSE, or Experience Corps will have more enduring effects, that their efficacy will transfer more readily to everyday life, and that it will be easier to offer them largely.

Developments in technology can also contribute to introducing interventions into real-life settings and promote transfer. Virtual reality (VR), for instance, allows the creation of three-dimensional, computer-generated, interactive environments. VR reproduces daily life situations into near-realistic environments that simulate the impression of being there, and a few studies have used VR to potentiate cognitive training effects in persons at risk of AD. For instance, Man and collaborators (2012) used a virtual environment that simulated a home setting and a convenience store to train the memory of individuals with MCI. VR training involved memorising virtual objects and retrieving them within the virtual environment with a range of presentation modalities, distractors, and levels of complexity, and its efficacy was compared with a face-to-face memory training condition. The results showed greater memory performance after having trained in the VR condition but better subjective memory following the face-to-face condition. This suggests that while the memory of individuals with MCI may benefit from the enhancing effects of being trained in a virtual environment, traditional approaches may be more appropriate for addressing self-efficacy and metacognition. VR can also be used to measure transfer of cognitive training effects to activities of daily living (Shuchat et al. 2012). For instance, Bier, Ouellet, and Belleville (2018) found evidence of transfer effects in healthy older participants in close to real-life environments using a "virtual car ride." Other studies focusing on the development of an immersive VR task called the "virtual shop" are very promising to assess gains from training in situations close to everyday life (Corriveau-Lecavalier et al. 2018; Ouellet et al. 2018). Results from these studies showed that the "virtual shop" was found to be a feasible and valid measure of everyday memory in older adults. Thus, recent advances in the field of virtual reality provide new opportunities to enhance the ecological validity of cognitive training and to assess real-life cognition in MCI individuals.

The Effect of Training on Brain Structure and Function

Brain imaging can establish the neural mechanisms by which training enhances cognitive functioning and indicate the training-induced neural changes (Guye et al., Wenger and Kühn, this volume). It can show whether the intervention modified specialised regions, i.e. regions that are normally involved in the task, or activated alternative brain regions, i.e. regions that are not normally active during the task and that are newly engaged. Brain imaging can also indicate whether the intervention focused on improving the function or brain region impaired (restorative effect) or relied on the intact functions and network (compensatory effect).

The few studies that have explored neural activity changes following cognitive training in MCI suggest that it can have both compensatory and restorative effects. Belleville et al. (2011) reported that strategic memory training increased brain activation in regions involved in memory encoding before training and induced new activations in regions that were not active prior to training in individuals with MCI. Interestingly, the differences between memory encoding-related brain patterns in MCI compared to healthy older controls were attenuated after training, suggesting that some restoration took place. Furthermore, the performance improvement was correlated with a newly activated region, the right parietal area, which was normalised in MCI. These results suggest that strategic cognitive training facilitates the recruitment of an intact alternative network to compensate the impaired primary network but can also contribute to meaningful restoration. Hampstead (2012) found increased activation almost exclusively in specialised regions after associative memory training in MCI individuals. They reported increased activation during both encoding and retrieval in hippocampal regions that were less activated compared to healthy older controls before training. These results show that associative memory training has a restorative effect on the primary network. Similarly, Förster (2011) showed that a multimodal intervention reduced decline in brain glucose metabolism in MCI and early AD, suggesting that it had an effect on neuronal injury.

Cognitive training was also found to have an effect on the structure of the brain in prodromal AD. Engvig et al. (2014) reported increased grey matter volume in regions encompassing the episodic memory network following strategic associative memory training in individuals with SCD. Interestingly, the strongest volume differences were found in the right prefrontal cortex, which is activated during contextual monitoring and episodic retrieval. Thus compensatory mechanisms may mediate training-related structural adaptation. Despite no significant hippocampal volume changes, there was a significant correlation between volume change and post-training memory improvement suggesting that individual differences may modulate the extent of the structural hippocampal restoration in SCD individuals. No study has looked at the effect of cognitive training on beta amyloid (βA) deposits, which is one of the main neuropathologies associated with AD. Showing that cognitive training reduces βA deposition would be of tremendous consequences and may not be that far-fetched, as observational studies have reported that a cognitively stimulating lifestyle is associated with lower levels of βA deposits in older adults (Landau et al. 2012).

The Contribution of Brain Imaging to Models of Training

Models of brain changes associated with aging are interesting to interpret the effect of cognitive training on the brain. For instance, according to the CRUNCH model (Reuter-Lorenz and Cappell 2008), compensation in older adults is supported by both increased activation of specialised brain regions and strategic recruitment of alternative regions. Interestingly, results from neuroimaging studies suggest that individual differences such as educational attainment or cognitive level of job can modulate the effect of age on brain structure and function. For instance, higher education has been associated with less reduced brain volume in older adults (Boller et al. 2017; Solé-Padullés et al. 2009). These results are consistent with the STAC-r model which proposes that individual differences in life course events can modify neural resources and compensatory capacities (Reuter-Lorenz and Park 2014). Studies reporting training-induced brain changes show that the regions modified by training generally reflect the purported active ingredient of the intervention. Cognitive training that is strategic and that targets preserved cognitive capacities in MCI increases activation in preserved brain regions, which is indicative of compensation. In contrast, cognitive training approaches that rely on adaptive learning or repeated practice are more likely to reduce activation in specialised regions. Additionally, a range of individual factors, the genetic potential for brain plasticity, and educational background may facilitate reliance on alternative networks or structural remodelling. The location and severity of structural impairment in brain-damaged individuals may also influence the success of a compensatory vs. a restorative approach, as restoration may be impossible when structural damage is too severe, for example. Thus, the INTERACTIVE model (Belleville et al. 2014b) proposes that characteristics of subjects (i.e. cognitive reserve, severity of the disease) and training modalities (i.e. format, target) modulate the type of neural changes induced by cognitive training.

Conclusion and Future Directions

Whether cognitive training and stimulation provided later in life can be used as protective tools against cognitive decline is a major research question. Observational studies have shown an effect of early life (education) and whole-life (profession, hobbies) cognitive stimulation on age-related cognitive decline, AD, and dementia. Compensatory neuroplasticity processes are particularly active during the silent phase of AD (Clément and Belleville 2010) and could be increased to postpone the cognitive decline that leads to the more severe symptoms that define dementia. Although many studies have revealed encouraging findings when using cognitive and brain markers, researchers and clinicians still need to address numerous important questions. First, we need to gain a better understanding of the critical period during which training or stimulation should be provided. The pathological cascade leading to AD, which probably starts many years prior to the diagnosis of dementia, suggests that these programs are likely to have their highest effect when provided early during the MCI phase or perhaps prior to that stage. However, demonstrating that early training has a long-lasting effect will certainly be very challenging if the outcome is clinical, and there will therefore be a need to adapt the method to those challenges. Furthermore, the efficacy of cognitive training might benefit from better characterising those with MCI that will convert to dementia. Several studies have shown that cognitive tests can distinguish those who will later progress to dementia from those who will remain stable (e.g. Belleville et al. 2014a, 2017). Additionally, it will be critical to document the effect of individual differences on cognitive training efficacy (see also Karbach and Kray, Katz et al., this volume). For instance, younger age and higher level of education were associated with larger training gain when individuals with MCI were trained with a strategic memory training program (Belleville et al. 2006). One other critical question is whether the brain processes promoted in late-life cognitive training are the same as those that underlie differences in cognitive reserve or cognitive resilience. The findings that training increases brain activation in alternative compensatory brain networks are consistent with the notion that cognitive reserve reflects more flexible brain networks. Finally, one other major issue that needs to be addressed is the notion of transfer, as cognitive training is intended to have an effect beyond the laboratory or task that is being trained (Könen and Auerswald, Schmiedek, Taatgen, this volume). It appears that older adults may be less prone to generalise learned strategies than younger adults, and whether MCI poses limits to the generalisation of learning is an important question that will need to be resolved.

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