Serious video games and virtual reality for prevention and neurorehabilitation of cognitive decline because of aging and neurodegeneration

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Purpose of review
Cognitive decline because of aging and neurodegeneration has become increasingly prevalent. This calls for the implementation of efficacious, motivating, standardized and widely available cognitive interventions for the elderly. In this context, serious video games and virtual reality may represent promising approaches. Here, we review recent research on their potential for cognitive prevention and neurorehabilitation of age-related cognitive decline and mild cognitive impairment (MCI).

Recent findings
The majority of currently available data in this evolving domain lacks the methodological quality to draw reliable conclusions on the potential of novel technology for cognitive training in older people. However, single well designed randomized controlled trials have reported promising effects of cognitive interventions involving serious video games and virtual reality. The cognitive benefits of exergames promoting physical exercise with and without combined cognitive training remain unclear.

Summary
The immersion into stimulating and motivating environments along with training content based on neuroscientific and neuropsychological models may represent a significant advance as compared with conventional computerized cognitive training. Additional research with sound methodology including sufficient sample sizes, active control groups and meaningful outcome measures of everyday function is needed to elucidate the potential of serious video games and virtual reality in multifactorial neurorehabilitation of cognitive decline in aging and neurodegeneration.

Keywords
aging, cognitive neurorehabilitation, computerized cognitive training, exergames, neurotechnology, serious video games, virtual reality

INTRODUCTION

As the proportion of older individuals increases in the general population and neurological practice, we will face cognitive decline more frequently. Among other challenges, this calls for efficacious interventions for prevention and neurorehabilitation of cognitive decline in the elderly. According to some large-scale studies, conventional neuropsychological interventions may not only improve the targeted domains but also benefit everyday life function in healthy older adults (HOA) and people with mild cognitive impairment (MCI). For instance, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) randomized controlled trial (RCT) in 2832 HOA reported domain-specific effects of 10 sessions of inductive reasoning versus processing speed versus verbal

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KEY POINTS

- Serious video games and virtual reality are promising approaches for cognitive training and neurorehabilitation in older people.
- This novel technology can increase motivation and training effects through immersion in stimulating environments.
- Closed-loop adaptivity of difficulty in real-time may represent a major advance in cognitive training.
- The currently available data do not allow drawing reliable conclusions on the efficacy and assumed advantages of serious video games and virtual reality.
- Large-scale RCTs with state-of-the-art methodology are required to elucidate the potential of this neurotechnology for cognitive training and neurorehabilitation of cognitive decline related to aging or neurodegeneration.

episodic memory training [1,2]. Although no self-reported instrumental activities of daily living (IADL) benefits were observed in either group at 2 years after training [1], inductive reasoning training was associated to IADL improvements at 5-year follow-up [3]. Somewhat surprisingly, such distal transfer from specific cognitive training to everyday life function appeared in all three interventional groups at the ten-year follow-up [4]. A recent RCT in 145 individuals with MCI comparing 16 h of training on strategies for memory and attentional control (MEMO+) to a psychosocial training and a no-contact control group reported specific improvements in memory performance on cognitive testing and in everyday mnemonic strategies as assessed by the Multifactorial Memory Questionnaire in the MEMO+ group [5■■]. The effects persisted at follow-up assessments after 3 and 6 months.

Distal transfer and long-term persistence of benefits constitute the ultimate objectives of cognitive interventions, but have been rarely observed [6]. Proximal and transient transfer, from the trained cognitive function to a related cognitive domain, has been reported more frequently. Furthermore, the majority of current clinical and experimental procedures aiming at prevention or deceleration of cognitive decline because of aging and neurodegeneration have only yielded limited benefits [7,8]. In the era of information and communication technology, a part of the scientific community has started developing digital solutions to extend standard neuropsychological approaches for cognitive training and overcome the main limitations of currently available cognitive interventions for HOA and people with MCI. Interventions encompassing novel technology have become widely accepted in cognitive neurorehabilitation [9]. Here, we review recent research in this area, with a particular focus on the past 2 years and the use of neurotechnology, such as serious video games and virtual reality.

COMPUTERIZED COGNITIVE TRAINING

Computerized cognitive training (CCT) usually represents translation and digitalization of standard neuropsychological interventions in a computerized framework. Digitalization offers several advantages, such as a high level of standardization and reproducibility, time efficiency and the possibility for remote training. Of note, already the ACTIVE trial discussed above employed CCT for processing speed training [2]. Furthermore, an RCT involving 30 HOA and 30 younger adults indicated that 8 h of computerized divided attention training improved specifically attentional control capacities and dual-task performance in HOA as opposed to sequential training on the same tasks that required focused attention [10■■]. Transfer was reported with respect to dual-tasking in an ecological virtual reality scenario, but no effects were found on the self-reported Cognitive Failures Questionnaire. Overall, systematic literature reviews on CCT in HOA and patients with dementia have suggested significant albeit modest positive effects [11,12]. However, the available evidence indicates only limited transfer in HOA and is insufficient with respect to benefits of CCT in MCI [13]. Apart from the processes underlying cognitive decline and potentially limiting the effects of training irrespective of the modality, these modest benefits could be because of a relative lack of motivation and personalization in conventional neuropsychological interventions, irrespective of whether digital tools are used.

FROM COMMERCIAL TO SERIOUS VIDEO GAMES

The fun and joy of video games could enhance the inherent motivation for training in people with cognitive decline [14]. An RCT in 36 HOA found that, when compared with a no-contact control group, playing the action video game Super Mario Bros three times a week over 2 months yielded more wide-spread cognitive improvement (with a particular emphasis on the visuospatial and working memory domains) than the same training dose of the reasoning-oriented, off-label Dr Kawashima's Brain Training [15■]. Although these data indicate that the rich environment and broad challenges of commercial action video games

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without cognitive specificity may afford a more global improvement in cognitive function, the only significant interaction across all three conditions favored Dr Kawashima's Brain Training with respect to specific improvement in the Stroop test. In a similar vein, an RCT in 54 HOA showed that 60 h of an off-label, gamified visual attention and processing speed CCT (PositScience InSight) outperformed the commercial action video game Crazy Taxi and a no-contact control group [16▪] in the Useful Field of View (UFOV) assessment of processing speed, selective and divided attention [17]. No significant differences between the groups were found on IADL.

These outcomes may reflect the controversy in defining useful and meaningful outcome measures in research on cognitive interventions. Yet, it may also suggest that a lack of cognitive specificity and neuroscience-informed design limits the utility of commercial video games for cognitive neurorehabilitation. Furthermore, commercial action video games have been typically designed for younger individuals, and may not be well accepted and tolerated by older people [18]. In contrast, commercially available, computerized puzzle games are enjoyed by HOA [19].

Combining the specific elements of CCT and the motivational aspects of commercial video games has led to the development of serious video games [20,21]. Through integration of neuroscientific models, neuropsychological content with immersive graphics and soundtrack, serious video games may bear a significant potential for cognitive neurorehabilitation across several neurological and psychiatric conditions [20,22,23]. Furthermore, serious video games can be designed to involve monitoring of multiple measures, such as reaction time, response accuracy, precise duration of practice, as well as physiological indicators like heart rate, skin conductance, eye movements or brain activity. These measures can be used for real-time feedback, detailed recording of training performance and progression, as well as closed-loop adaptation [24]. Closed-loop adaptive video games (CLAVs) incorporate real-time, performance-driven adaptation of game challenges [20]. A landmark study in 46 HOA showed that a custom-designed dual-task CLAV improved significantly divided attention as opposed to single-task and no-contact control conditions [25]. The data also indicated transfer to sustained attention and working memory that were not targeted directly. Furthermore, training benefits persisted at 6 months follow-up. Good acceptance of serious video games has been reported among individuals with neurodegenerative disease [26].

EXERGAMES

Physical exercise alone has been shown to yield cognitive effects in older people [27,28]. However, the adherence to physical exercise is difficult to maintain. Exergames are defined as video games aiming primarily at physical training [29]. Although exergames do not appear to outperform conventional physical training in terms of cognitive effects [30], they may be a motivating vector to promote adherence to physical exercise. Recent meta-analyses and systematic reviews indicated that playing exergames can benefit executive function, attention and visuospatial processing in HOA and MCI [30,31], although the results of the former have been challenged [32]. In an RCT in 78 individuals with MCI, playing sports video games on the Nintendo Wii for 30 min three times a week over 10 weeks yielded more significant effects in the digit span (working memory) and also health-related quality of life than the same dose of the CoTras CCT program [33▪]. Conversely, no differential effects were found in verbal learning, short-term verbal memory or long-term visual memory.

As the combination of physical and cognitive training appears to outperform physical or cognitive exercise alone in terms of cognitive benefits [34,35], coupling exergames with cognitive training may be a promising avenue. In this respect, a recent promising RCT in 44 individuals with MCI evaluated the cognitive and electrophysiological effects of the off-label Dr Kawashima's Body and Brain Exercises on the Microsoft Xbox 360 Kinect that allows tracking movement in response to cognitive tasks displayed on a large screen [36▪▪]. The control group performed nondigital motion range exercises without cognitive content and the training dose in each group was 25–30 min, 5 days a week during 6 weeks (12.5–15 h). As compared with the control, the cognitive exergame afforded significant benefits on the Mini-Mental State Examination and Montreal Cognitive Assessment scores, as well as the Trail Making Test B assessing cognitive flexibility. Some electrophysiological effects were also described. However, these encouraging results may have been somewhat confounded by probable differences in the expectancy of cognitive benefits between the two training groups [37]. Between-group differences other than the training content, such as training location or the presence of a therapist can further increase the divergence in expectancy, and thus training outcomes.

The Aerobic and Cognitive Exercise Study (ACES) enrolled 111 older participants (including 83 individuals with suspected MCI) to evaluate the effects of stationary cycling exercise coupled with a serious video game versus cycling in a virtual landscape (with 45 and 46 participants, respectively).

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Both the landscape and video game were displayed on a screen mounted on the stationary bike. A game-only condition without physical exercise was also conducted, with five randomized and ten attributed participants. However, no participant completed the 6-month training in this control group. In the other two conditions, only seven participants per principal condition completed 6 months of training, representing an attrition of 87%. The study comprised pretraining and post-training structural MRI, saliva exosome analyses, as well as plasma protein assays for brain-derived neurotrophic factor, C-reactive protein, insulin-like growth factor 1, interleukin 6 and vascular endothelial growth factor. No differences between the more passive and the cognitively demanding exergame were found on the primary cognitive outcome measures [38]. However, the exer-tour cycling without elevated cognitive demands afforded significantly greater benefits on the secondary outcomes verbal memory, physical fitness and everyday life cognition. The greater effects for passive cycling as opposed to exergaming contradicted the results of a preceding ACES study [39]. The same research group also evaluated the off-label, home-based interactive Physical and Cognitive exercise system (iPACes) that involved pedaling on an elliptical and completing a list of errands along a virtual bike path displayed on a tablet-laptop. In the absence of a control group, 10 out of 31 enrolled older individuals completed a twice-weekly training over 3 months and exhibited significant improvement in the Stroop test and Alzheimer's Disease Assessment scale delayed word recall that measure inhibition control and verbal memory, respectively [40]. Eight participants with MCI or mild dementia completed another pilot study comparing stationary cycling coupled with cognitive challenges (such as avoiding cars or shopping in a supermarket) to a no-contact control group. The trial did not find significant differences in cognitive outcomes [41]. The question of whether the inclusion of cognitive training in an exergame context may be useful for maintaining or rehabilitating cognitive function, thus remains largely open.

VIRTUAL REALITY FOR TRAINING AND ASSESSMENT

Virtual reality may represent another important neurotechnology for optimization of cognitive training. This technology allows immersion and interaction in virtual environments. The use and manipulation of such environments may open novel perspectives for cognitive neurorehabilitation [42–44]. Although cognitive training on a desktop screen has also been described as virtual reality, because of recent technological and conceptual progress, only immersion in a virtual environment via a room-sized cube (CAVE system) or head-mounted displays should be referred to as virtual reality.

Of particular significance for older adults, virtual reality allows personalized and ecological assessment and training of IADL. In a study across 25 HOA and individuals with MCI without a control condition, nonimmersive computerized IADL training was reported to improve visual memory, attention and cognitive flexibility, but without affecting everyday life cognition [45]. Recent research in 42 older individuals with MCI concluded that IADL training and physical exercise in and outside virtual reality yield largely similar outcomes, with the immersive virtual reality group showing more benefits on the Trail Making Test B (cognitive flexibility) and gait cadence during cognitive–motor dual tasking [46▪].

Exposure to and immersive interaction with virtual environments may also be useful for assessing and training spatial, episodic and prospective memory [47–49]. Furthermore, patients with MCI and dementia have been reported to prefer immersive virtual reality to paper-and-pencil interventions [50]. This was particularly the case for participants suffering from apathy, further underlining the motivational value of novel technology. Additional, carefully designed RCTs are needed to assess the true potential of immersive virtual reality for cognitive neurorehabilitation in HOA and people with MCI.

TOWARDS MULTIMODAL NEUROTECHNOLOGICAL AND MULTIFACTORIAL INTERVENTIONS

The potential of more holistic, multifactorial interventions addressing several functional domains to improve physical and cognitive health has become increasingly recognized [51]. The 2-year longitudinal Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study indicated that a multifactorial intervention involving diet, exercise, cognitive training and vascular risk monitoring could improve or maintain cognitive function in 1260 older people at-risk of cognitive decline [52]. The currently ongoing ENGAGE RCT represents an interesting attempt at integrating cognitive training with novel technology and leisure activities [53]. One hundred and forty-four older adults with subjective memory deficits will be assigned to either the ENGAGE-MUSIC/SPANISH interventional or the ENGAGE-DISCOVERY active control condition for a total of 48 h over 4 months. ENGAGE-MUSIC/SPANISH consists of learning

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Table 1. A summary of the design and outcomes of recent studies on neurotechnology for cognitive training in healthy older adults and people with mild cognitive impairment, including cognitive strategy training, computerized cognitive training, video games and virtual reality

First author	Year	Cognitive domain	Population N randomized (N analyzed)	Age	Design and time points for cognitive evaluation number	Conditions	Training dose	Outcome measures	Main results
Cognitive strategy training									
Belleville	2018	Memory	145 aMCI (127)	55+	RCT - T0 - T1 - T2 (FU at 3mo) - T3 (FU at 6mo)	Cognitive strategy training ($N=49$) Psychosocial intervention (active control; $N=49$) No contact ($N=47$)	16h (2h × 1d × 8w)	Proximal transfer - Memory composite scores - Psychosocial health measures Distal transfer - Everyday life questionnaires (Metamemory Questionnaire, Complex ADL, Self-reported memory)	Cognitive strategy training significantly improved delayed memory and strategy use in daily life
Computerized cognitive training									
Bier	2018	Attention	30 HOA & 30 YA (27 HOA)	~60-80	RCT - T0 - T1	Variable priority training (flexible divided attention; $N=15$) Single-task training (focused attention; $N=15$)	8h (4d × 1h × 2w)	Direct training effect - In the trained tasks (visual detection task; alphanumeric equation task); Transfer in a VR dual task - In similar tasks involving the same cognitive skills (virtual car ride; alpha span task)	Attention modulation improved only in those HOA undergoing variable priority training. The variable priority training group improved dual-task cost on both transfer tasks, whereas single-task training only improved Alpha span task performance
Buitenweg	2019	Cognitive flexibility (working memory, reasoning, attention)	158 HOA (142)	60-80	RCT - T0 - T0.5 (6w training) - T1 - T2 (FU at 1mo)	Frequent task switching ($N=56$) Infrequent task switching ($N=33$) Mock training (active control; $N=50$)	29h (3d × 0.5h × 1w + 5d × 0.5h × 11w)	Distal transfer: - SF-36 - CFQ - DEX - IADL - HAD - CIS-F - Subjective memory problems questionnaire	No significant effects of training or group differences between T0 and T1 (posttraining) Significant improvement on CFQ and DEX at T2 (follow-up) as compared with all other timepoints in all groups
Flak	2019	Working memory	85 MCI (68)	43-88	RCT - T0 - T1 - T2 (FU at 4mo)	Adaptative working memory training ($N=42$) Nonadaptative working memory training ($N=43$)	12.5–16.75h (5d × 0.5–0.67h × 5w)	Proximal transfer Primary outcome: - Working memory (Digit and spatial span backward, letter-number sequencing) Secondary outcome: - NPS assessments of attention, processing speed, verbal and visuospatial memory, EF	No significant group differences
Video games									
Perrot	2019	EF, processing speed and visuospatial abilities	36 HOA (35)	60-71	RCT - T0 - T1	Kawashima Brain Training (KBT; $N=12$) Super Mario Bros (SMB; $N=12$) No contact ($N=12$)	24h (3d × 1h × 8w); 24h (3d × 1h × 8w); 0h	Proximal transfer - Cognitive flexibility (TMT-B) - Inhibition (Stroop) - Reasoning (Matrix, WAIS) - Speed and visuomotor coordination (DSST) - Spatial memory (Corsi) - Speed and spatial relations (number comparison, DAT5)	Inhibition: KBT > SMB and KBT >> Ctrl; Reasoning: KBT & SMB > Ctrl; Speed and visuomotor: SMB > Ctrl; Spatial memory: SMB ≥ Ctrl; Speed and spatial relations: SMB > Ctrl

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Table 1 (*Continued*)

First author	Year	Cognitive domain	Population N randomized (N analyzed)	Age	Design and time points for cognitive evaluation number	Conditions	Training dose	Outcome measures	Main results
Belchior	2019	Mixed	71 HOA (54)	65-86	RCT - T0 - T1 - T2 (FU at 3mo)	Crazy Taxi (*N*=26) PositScience InSight (CCT; *N*=20) No contact control (*N*=25)	60h (5d × 1h × 12w); 60h (5d × 1h × 12w); 0h	Improvement in game skills: - Crazy Taxi - InSight Proximal transfer Primary outcome: - attention: UFOV Secondary outcomes: - Visual attention (Multiple object tracking, attentional blinks) - Visuospatial (block design, judgment of line orientation, mental rotation, object rotation) Distal transfer - Road sign test - IADL - Pos. and neg. affect scale - Geriatric Depression Scale - Verbal memory (HVLT)	Direct - Improved performance on trained task in both training groups Proximal transfer - UFOV: InSight >> Crazy Taxi at T1 and T2 - Multiple object tracking: similar benefits in both training groups at T1 - Attentional blinks: Crazy Taxi >> InSight (T1), Crazy Taxi = InSight (T2) Distal transfer - Both training groups became faster in IADL at T2 - Geriatric Depression Scale: Crazy Taxi > InSight at T2
Exergames									
Park and Park	2018	Mixed	78 aMCI (78)	60+	RCT - T0 - T1	Nintendo Wii sports games (*N*=39) CoTras – Specific CCT (attention, memory, and visual spatial abilities; *N*=39)	15h (3d × 0.5h × 10w)	Proximal transfer: - working memory (WAIS digit span) - visuo-spatial abilities (WAIS-Revised Block Design Test) and memory (ROCFT) - verbal learning (RAVLT) - cognitive flexibility (TMT-B) - inhibition (Stroop) Distal transfer: - SF-36	Nintendo Wii training only yielded significantly greater benefits in working memory and several aspects of health-related quality of life
Amjad	2019	Global cognition, speed processing, EF	44 MCI (38)	N/A	RCT - T0 - T1	Xbox 360 Kinect cognitive exergames (*N*=22) Range of motion exercises (stretching, gentle movements; *N*=22)	~15h (5d × ~0.5h × 6w)	Global cognition: - MMSE - MoCA Processing speed and EF: - TMT (A and B)	Significant improvements on MMSE, MoCA, TMT-A and TMT-B in the Exergame group only. but no time × group interaction analysis
Anderson-Hanley	2018a	EF	83 MCI and 28 HOA (42)	~58-98	RCT[a] - T0 - T1 - T2 (FU at 3mo)	Exer-score (cycling and playing; high cognitive load; *N*=46) Exer-tour (cycling in a virtual landscape; low cognitive load; *N*=45) Cognitive game without exercise (*N*=20[a]) Pedal-only (*N*=; 33[a])	0–3mo: From 7.9h (2d × 0.33h × 12w) to ~45h (5d × 0.75h × 12w); From 3mo to 6mo: ~45h (5d × 0.75h × 12w)	Proximal transfer: - Inhibition (Stroop) - Cognitive flexibility (Color Trails) - Working memory (Digit span) Distal transfer: - MoCA - Subjective cognitive function (Ecological Validity Questionnaire) - Verbal memory (ADAS Word List) - Physical ability (get-up-and-go test)	The interactions time × condition did not reach significance. Overall, the high cognitive load training yielded less benefits after 3 months of training than the low cognitive load training, and similar benefits after 6 months training completion. Of note, only 14 participants adhered to the full 6 months of training.

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Table 1 (*Continued*)

First author	Year	Cognitive domain	Population N randomized (N analyzed)	Age	Design and time points for cognitive evaluation number	Conditions	Training dose	Outcome measures	Main results
Anderson-Hanley	2018b	EF	24 MCI (15)	50+	Pilot - T0 - T0.5: 6 w - T1	Home-based exergame at least 2×/w ($N=10$) Home-based exergame ≤ 1×/w ($N=5$)	12–30h (2–5d × 0.5h × 12w); 0–6h (1d × 0.5h × 12w)	Proximal transfer: - Inhibition (Stroop) - Cognitive flexibility (Color Trails) - Working memory (Digit span) Distal transfer: - Verbal memory (ADAS Word List)	Significantly higher benefits in inhibition and verbal memory for high versus low-dose training
Jirayucharoensak	2019	Mixed (mainly attention)	65 aMCI and 54 HOA (119[a])	~60-80	RCT[a] - T0 - T1	Neurofeedback training ($N=25$) Exergame training ($N=58$) Care as usual (no contact; $N=36$[a])	10h (in total 20 sessions of 0.5h × 2–3d × 12w)	Proximal transfer - NPS battery: CANTAB - spatial working memory (SWM) - short & long term memory (DMS and PRM); - speed processing (RVP) - verbal working memory and attention (SSP)	The neurofeedback group showed specific benefits in working memory and sustained visual attention
Mrakic-Sposa	2018	Mixed	6 MCI and 4 dementia (8)	65+	RCT - T0 - T1	Cycling exergame with ADL tasks ($N=5$) No-contact control group ($N=5$)	13.25h (3d × 0.67h × 1w + 3d × 0.75h × 5w)	Proximal transfer: - MMSE - Episodic verbal memory (RAVLT_I and RAVLT_D) - Visuo-spatial functions (ROCFT, - Attentional Matrices Test, TMTA) - EF (FAB, TMT-B) - Verbal fluency test - FAQ	No significant differences between the groups
Virtual reality									
Gamito	2019	Mixed	25 MCI and HOA (22)	65-85	Single-arm - T0 - T1	ADL and navigation in a nonimmersive environment ($N=25$)	6h (2d × 0.5h × 6w)	Proximal transfer Global cognition: - MMSE - MoCA - NPS battery (EF, visuoconstructive abilities, visual memory, attention/concentration) Distal transfer - Mood - Functional behavior	Significant improvement in perseveration (perseverative errors in the WCST, visual memory (Rey complex figure memory trial total score) and visual attention (d2 errors)
Liao	2019	Mixed	42 MCI (34)	65+	RCT - T0 - T1	Immersive physical exercise and ADL and sports game scenarios ($N=21$) Physical exercise combined with motor-cognitive dual-tasks and ADL training outside of VR ($N=21$)	36h (3d × 1h × 12w)	- TMT-A and TMT-B - Stroop	Comparable outcomes, apart from significantly greater improvement in the VR group on the TMT-B

ADAS, Alzheimer's Disease Assessment Scale; (I)ADL, (Instrumental) Activities of Daily Living; CCT, computerized cognitive training; CFQ, Cognitive Failure Questionnaire; CSI-F, Checklist Individual Strength-Fatigue; CT, computerized training; Ctrl, control; d2, d2 Test of Attention; DAT5, Differential Aptitude Test; DEX, Dysexecutive Functioning Questionnaire; DMS, Delayed Matching to Sample; DSST, Digit-Symbol Substitution Test; EF, Executive Functions; FAB, Frontal Assessment Battery; FAQ, Functional Activity Questionnaire; HAD, Hospital Anxiety Depression Scale; HOA, Healthy older adults; HVLT, Hopkins Verbal Learning Test; MCI, mild cognitive impairment (aMCI = amnestic MCI); MMSE, Mini-Mental State Evaluation; mo, months; MoCA, Montreal Cognitive Assessment; NPS, Neuropsychological tests; PRM, Pattern Recognition Memory; RAVLT-I/D, Rey Auditory Verbal Learning Test – Immediate/Delayed recall; ROCFT, Rey–Osterrieth Complex Figure Test; ROM, Range of Motion; RVP, Rapid Visual Information Processing; SF-36, Short Form Health Survey 36 items; SSP, Spatial Span Length; TMT-A/B, Trail Making Test version A/B; UFOV, Useful Field of View; VR, Virtual Reality; w, Weeks; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.
[a](Partially) nonrandomized assignment; time points: T0 = baseline; T0.5 = mid-training; T1 = posttraining (see dose for training duration); T2 and T3 = follow-up (FU).

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attentional control and memory strategies, applying this knowledge to a leisure activity (learning music or Spanish as a second language), and playing commercially available video games targeting attention. ENGAGE-DISCOVERY involves psychoeducation (on cognition and the brain), cultural and social interactions (documentary viewing with discussions) and playing commercial video games with a low cognitive load. The primary outcome is an episodic memory composite score. Secondary outcome measures focus on attentional control. Furthermore, the study will assess effects on psychological health and daily life as well as structural and functional brain plasticity. In addition, evaluation of potential covariates such as cognitive reserve (education and lifestyle), sex and genotype (apolipoprotein E4, brain-derived neurotrophic factor and catechol-O-methyltransferase) will be used towards differentiated data interpretation. Multifactorial interventions targeting not only specific cognitive functions and emotional processing but also meta-cognitive abilities, as well as physical and social activities appear more promising than single-domain training.

Other neurotechnological approaches should also be considered as alternatives or additional elements in multifactorial interventions. For instance, positive cognitive effects of a neurofeedback brain–computer interface approach were shown in a recent study [54▪]. One hundred and nineteen HOA and people with MCI were assigned to three conditions: 10 h of neurofeedback + standard care, 10 h of exergame + standard care and standard care alone. In the neurofeedback condition, participants were trained to control a set of desktop video games by optimizing their sustained attention-related power ratio of beta to alpha frequency bands recorded by electroencephalography. The exergame condition consisted of five serious video games combining physical and cognitive challenges. The games were displayed on a giant screen and controlled by optical whole-body movement tracking. Both HOA and MCI participants in the neurofeedback condition exhibited significant improvements in sustained attention and spatial working memory strategy as compared with the exergame and standard care conditions. Conversely, individuals in the cognitive exergame condition showed greater improvements in visuospatial working memory (spatial span length).

CONCLUSION AND OUTLOOK

Taken together, the domain of serious video games and virtual reality for cognitive training and neurorehabilitation has just started to evolve. Single well designed and sufficiently powered RCTs over the past 2 years shed light on the potential of CCT, serious video games with and without coupled physical exercise and virtual reality for improving cognition in older people (Table 1). However, so far, the majority of research published in this realm lacks the methodological quality to afford reliable conclusions on the efficacy of this technology.

Future research using state-of-the-art methodology will help evaluate whether serious video games and virtual reality can be efficacious in preventing cognitive decline related to normal and pathological aging. Such RCTs should employ approaches that are easily accessible and accepted by older people [22,26], as adherence may represent a significant issue [38,40]. The intervention design should take into account the specific needs of the elderly population [18]. This would not only ensure sufficient sample sizes for data interpretation but also indicate feasibility of the interventions in real life.

Irrespective of the vector, the training content is a key factor. Mere computerization of cognitive training appears insufficient for harnessing the considerable opportunities afforded by information and communication technology [6]. In addition to the highly engaging contexts, serious video games and particularly immersive virtual reality may transport the training participants outside of the clinical or interventional environment, and thus, further promote motivation, adherence and performance. Virtual reality may become a cost-efficient and mobile tool for highly ecological yet standardized cognitive training [22,44,46▪,55] and evaluation [55–57]. Most important, virtual reality allows environmental manipulations that would be impossible otherwise or require substantial efforts and resources [44].

Adaptivity is considered a key advantage of serious video games, although CCT can also be endowed with adaptivity. Closed-loop real-time adaptivity is believed to maintain the participant in an optimal range of effort, and thus, promote training effects [20]. The nature and time scale of adaptivity may play an important role. Level-wise adaptivity to constantly maximal effort did not enhance cognitive training effects when compared with similar nonadaptive CCT or video games [58,59]. Instant adaptation of training with both increases and reductions in difficulty based on performance [25] or correlates of brain activity [24] may, therefore, be more useful.

Furthermore, the choice of an appropriate active control condition appears indispensable. The absence of control groups or a no-contact control group do not allow for sufficiently meaningful conclusions. The active control should match the expectancy of the intervention without targeting the same cognitive mechanisms [37,60]. Defining useful primary and secondary outcome measures

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that assess not only specific training effects but also transfer to related cognitive domains (proximal transfer) and everyday life function (distal transfer) represents another significant challenge [61]. Ultimately, an important follow-up goal related to real-life and clinical use of interventions yielding promising initial effects will be to determine the optimal training intensity and dose.

Most important, among others, the studies reviewed here highlighted the compensatory potential of both HOA and individuals with MCI. One may argue that the underlying processes diminish the utility and, in particular, long-term benefits of cognitive interventions in the elderly. However, similar to younger patients with neurological conditions [62,63], lower cognitive ability appears to predispose to greater cognitive benefits after training in older people [45,64]. This may also illustrate the need for personalized interventions tailored to the individual's specific needs and deficits. This personalization or stratification may also involve information beyond the cognitive profile, such as brain volumetry [65] or multimodal analyses of brain connectivity and its relationship to behavior [66]. If pharmacological options halting or decelerating neurodegeneration become available, cognitive interventions in MCI may eventually evolve into neurorehabilitation aiming at recovery.

In a nutshell, serious video games and virtual reality may complement existing neuropsychological interventions by affording a more engaging, standardized yet personalized context for cognitive training and neurorehabilitation. However, additional research with well designed content and control conditions taking into account the specific needs and expectations of the elderly and using state-of-the-art methodology is required to elucidate the true potential of this neurotechnology. Given previous evidence, it appears unlikely that serious video games or virtual reality approaches will become standalone, highly efficacious approaches for age-related cognitive decline or MCI. They will rather complement multifactorial interventions involving physical exercise, diet, lifestyle adaptation, cognitive training and learning meta-cognitive strategies for coping and compensation. Neurotechnological approaches could represent a decisive component in multifactorial interventions for prevention and neurorehabilitation of cognitive decline related to normal aging and neurodegeneration.

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Conflicts of interest

M.B.A. has been an employee of MindMaze SA, Lausanne, Switzerland.

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