Virtual Reality meets Noninvasive Brain Stimulation: a new tool for cognitive rehabilitation of Mild Cognitive Impairment

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Abstract

Mild Cognitive Impairment (MCI) usually refers a perceived decline in cognitive functions which deeply impacts on elders' quality of life. It represents a critical risk factors for the developing of dementia, thus early detection of MCI and its cognitive rehabilitation are crucial. For this purpose current neuropsychological interventions have been integrated with two solutions: on one hand Virtual Reality (VR), in which the user is immersive in a controlled, ecological, and secure testing environments, that revealed positive clinical outcomes in either cognitive and motor rehabilitation. On the other hand noninvasive brain stimulations (NIBS), transcranial magnetic or electric stimulation of different brain regions, that emerged as promising cognitive treatment on MCI and Alzheimer disease. So far, these two methods have been employed separately except for few studies suggesting their integration in motor rehabilitation. Thus, we suggest to extend this integration to cognitive rehabilitation as well. On one hand NIBS provide magnetic or electrical stimulations in a specific frail brain area. On the other hand VR is a simulative technology that provide multisensorial stimulation, higher sense of presence, engagement and motivation. We suggest that the integration of these two technologies could provide a multimodal stimulation that could enhance cognitive training, resulting in a more efficient rehabilitation. Details and advantages will be discussed in the perspective.

1. Introduction

Diagnosis and rehabilitation of mild cognitive impairment (MCI) are crucial to prevent its evolution into dementia. In fact, MCI refers to a subtle clinical condition between cognitive changes that occur within aging and what might constitute dementia (1). Depending on the type (memory or other cognitive domains) and quantity of cognitive domains impaired, MCI is usually divided in single or multiple domain, amnesic (aMCI) or non-amnesic (naMCI) subtypes (1). MCI can in some cases revert to normal condition, be stable or critically evolve to dementia (2).

Frequently both elderlies and their caregivers report concern about the perceived worsening, crucially impacting on their wellbeing. In fact, the objective decline in one or more cognitive domains prevents them from being autonomous in their daily activities (e.g. grocery shopping, doctor visits, housework), significantly influencing their quality of life, autonomy and safety (3). Concerning usually refers to a subtle decline in memory domain; however, impairments also affect executive functions, lexical-semantic processing and spatial navigation. More, MCI individuals have lower Instrumental activities of daily living (IADL) than their healthy counterparts (4), that contributes to increase the development of dementia (5). More, this subclinical form of dementia is usually associated with neuropsychiatric symptoms such as depression, apathy and personality changes. MCI is most likely referred to a degenerative etiology (i.e. A.D., Frontotemporal Dementia, Dementia with Lewy Bodies). Vascular (i.e. vascular cognitive impairment), psychiatric (e.g. depression), genetic (APOE and TOMM40 genes) and other medical condition (e.g. uncompensated heart failure, poorly controlled diabetes mellitus, or chronic obstructive pulmonary disease) could contribute to determine cognitive impairment as well (6,7).

Neurobiological studies revealed that cognitive impairment is associated with altered neural activity: entorhinal cortex and the hippocampus are firstly affected by histopathological changes, followed by parahippocampal gyrus, temporal pole, inferior and middle temporal gyri (6,8–11). While primary cortices seem to be less vulnerable to deterioration, associative areas are the most compromised: among them, prefrontal cortex (PFC) shows a higher decline (12). Recognizing neural changes occurring in typical aging or in a pathological diseases is essential to accurate diagnosis and an efficacious treatment (13). In fact, a too late or a non-efficacious intervention could unavoidably lead to a degenerative condition. Thus, this long “intermediate” phase would provide a critical opportunity for therapeutic intervention (14). Current cognitive rehabilitations are heterogeneous in terms of methods and contents. Considering that MCI is characterized by both cognitive-behavioural and neural impairments, a successful rehabilitation process should address both of them.

Increasing scientific and clinical efficacy evidence supports the importance of stroke rehabilitation in remodeling the brain thanks to neuroplasticity (15). Effectiveness of cognitive rehabilitation is far more crucial considering that MCI patients can turn into dementia if they don’t receive appropriate interventions (14). Virtual reality (VR) can be one of the favorite candidates for a successful intervention thanks to its psychological (e.g., degree of interaction and augmented feedback) and technological (e.g., degree of immersion) characteristics.

Overall, we firstly aim at briefly reviewing current evidence on the benefits of newest technologies, VR and noninvasive brain stimulation (NIBS), on cognitive rehabilitation of MCI. Secondly, we aim at proposing an integrated intervention approach that encompasses both cognitive stimulation in VR and a specific kind of NIBS, such as transcranial magnetic stimulation (TMS). Joining these two kinds of interventions may allow to a more sensitive rehabilitation of cognitive

symptoms, strengthened by modulation of the impaired neural circuits. It is plausible to think that the implementation of neural modulation with a tool that provided an ecological environment would allow elderly to benefit even more than stand-alone intervention. Besides, available intervention for MCI are frequently conducted in isolated and artificial situations, thus allowing evaluation biases. A resounding change might be fostered by integrating existing technologies in a novel approach that guarantees an ecological setting and takes action on different aspects of this clinical entity.

In this regard, this perspective aims at integrating rather than replacing existing and efficient rehabilitation methods in order to obtain a comprehensive intervention that targets and fosters cognitive rehabilitation, by acting either on neural-cognitive and behavioral- cognitive aspects of MCI. We aim to propose a new integrated, multimethod approach for MCI cognitive rehabilitation on the basis of their well-known cognitive symptoms and newer, efficient technologies, TMS and VR.

2.0 A new integrated approach

This section will summary two existing intervention for MCI, VR and TMS, the recent literature about their integration in motor rehabilitation of MCI and in other clinical application, and a discussion of a novel approach that will integrate them for cognitive rehabilitation.

2.1 Virtual reality

As introduced before, available methods for MCI consist in cognitive stimulation, usually in the form of paper and pencil style, conducted in isolated and artificial situations. Recently, a new technology has been developed and increasingly implemented in clinical setting, thanks to its capability to provide realistic, multisensory immersive simulation of daily situations. VR is a 3-dimensional computer-generated technology capable of generating life-like contexts. Its ability to resemble daily situations with high degree of sense of presence and ‘being there’ experience in an ecological, safe, controlled setting, have determined its increasing use in clinical rehabilitation (16). Depending on its degree of immersiveness, VR can fall into three categories: non immersive (i.e. user interacts with the environment with the keyboard and mouse); semi-immersive (i.e. user usually stand in front of a large screen and gesture and location could be tracked); fully immersive (i.e. users wears head-mounted display (HMD) that involves the entire vision or is immersed in the cave automatic virtual environment (CAVE) that guarantee a stronger sense of presence). VR also allows to interact with objects and to receive augmented feedback (e.g. visual, auditory, kinesthetic), complimentary to those received from the sensory system (17,18), that participate in making the virtual experience realistic. The possibility to create safe, ecological and standardized settings has supported its employment in neurorehabilitation because it allows cognitive trainings that are relevant for real contexts. In fact, VR allows personalized therapies in a controlled way, according to the needs of the patients. Several studies have investigated its role in foster cognitive rehabilitation (19–21), supported by its potential to promote neuroplasticity (22–24).

With respect to MCI cognitive rehabilitation, several studies have showed VR greater potential to the enhancement of cognitive functions (for reviews see 22,23). Optale and colleagues (27) showed that 36 sessions of VR memory training in a fully immersive environment - provided by a HMD-enriched by visual and auditory stimuli, improved Mini Mental State Examination (MMSE), compared

to the control group - who received musical therapy intervention - whose MMSE scores decreased. Improvements were observed also in memory domain, as assessed by digit span forward and verbal story recall. Similar promising results were observed in a MCI sample after non-immersive VR sessions consisting in performing tasks and navigating in a virtual home and supermarket (28). Significant improvements in Montreal Cognitive Assessment (MoCA) and IADL were exhibited after 3 weeks VR-based cognitive and physical training: interestingly, after the VR intervention, functional near-infrared spectroscopy (NIRS) revealed decreased brain activation of the prefrontal areas as result of increased neural efficiency during the training (29). In fact, according to the compensatory model, demented brain shows broader activation as a compensatory strategy to preserve intact cognitive functions (30,31). In this regard, this study expanded previous literature about VR efficacy to improve neural efficiency in prefrontal areas (29). Besides cognitive enhancement, VR treatments give raise to positive feelings: participants reported to feel more enthusiastic, relaxed, energetic and, most importantly, less worried, stressed and anxious (32)

2.2 Transcranial magnetic stimulation

TMS is a noninvasive brain technique that induces an electrical field through a coil placed on the surface of the scalp over a targeted stimulation site (33). Depending on selected parameters (i.e. frequency, intensity, number of pulses delivered, type of coil and location of the stimulation), TMS pulses can either excite or inhibit cortical activity and induce long or short-term neural and behavioral changes (34). Depending on the number of pulses delivered, TMS can be single-pulse when only one stimulus at time is employed, paired-pulse when pairs of stimuli separated by an interval are delivered and repetitive (rTMS) in case of trains of stimuli (35).

TMS is increasingly being applied in several research and clinical fields (36). Chou and colleagues (37) examined TMS potential in modulating cognitive functions both in MCI and AD: the majority of the studies employed high-frequency (>5 Hz) multiple sessions rTMS over the left, the right or the bilateral DLPFC. Overall, TMS appeared feasible in significantly improving memory and executive functions. For example, Drumond Marra and colleagues (38) reported long-term memory improvements after 10 high-frequency rTMS sessions over the left DLPFC. More, they showed an improvement in executive functioning during the follow-up. Padala and colleagues (39) considered rTMS effectiveness in reducing apathy, a symptom frequently reported in MCI patients. The intervention aimed at comparing high frequency rTMS sessions over the left DLPFC to sham condition. A significant improvement in apathy scores resulted following 10 sessions of active TMS. Interestingly, authors observed positive outcomes in executive functions, as assessed by Trial Making Test (40).

Long-term cognitive benefits resulting from TMS interventions can be explained by the reorganization of the brain networks following the induced changes in cortical excitability. In other words, high frequency rTMS sessions may determine an improvement in terms of synaptic plasticity, with implication in cognitive domains reorganization (41,42).

2.3 Virtual reality and noninvasive brain stimulation

The jointly application of NIBS and VR have been already investigated in different clinical setting to improve the clinical outcomes of conventional therapies.

Bassolino and colleagues (43) combined TMS over corticospinal tract and VR to induce embodiment for an artificial hand. Through VR authors provided matching visual feedback to mimic involuntary movements evoked by active TMS. When TMS and VR feedback were synchronous, patients reported a deep embodiment. Notzon and colleagues (44) assessed one session of VR+ intermittent theta burst stimulation (iTBS) efficacy for spider phobia treatment. While VR was effective in inducing subjective anxiety and increased heart rate and skin conductance whereas iTBS did not proved to be effective in reducing anxiety symptoms and heart rate instead.

Different studies have investigated the potential of joining VR and tDCS/TMS for the rehabilitation of the upper limb, one of the most common deficits that follows a stroke (45–49) . For example, Joo Kang and colleagues (2012) (50) investigated changes in corticospinal excitability after TMS stimulation in the context of motor rehabilitation with a virtual mirror. Results showed greater corticospinal facilitation in the virtual condition compared to the control group that used a real mirror. Kim and colleagues (2014) (51) found similar promising results from the combination of tDCS and VR for motor rehabilitation: they showed that VR wrist exercise after tDCS had greater immediate and sustained corticospinal facilitation effects than exercise without tDCS or than tDCS without exercise. Furthermore, this corticospinal facilitation lasted for 20 min after the exercise in the VR+tDCS conditions compared to the control groups. More, a metanalysis (49) proved the effectiveness and suitability of NIVS-VR integration for the motor rehabilitation of the upper limb. Massetti reviewed (48) 11 studies in which tDCS and VR were jointly applied. Positive results were found in terms of improvements in pain management, body sway, stroke recovery, gait and vegetative reactions. While different studies have proved the efficacy of the jointly application of NIBS and VR for motor rehabilitation, to our knowledge no studies have investigated the same approach for cognitive rehabilitation.

2.4 Virtual reality and transcranial magnetic stimulation for cognitive rehabilitation

This section will discuss an integrated intervention approach that encompasses both TMS and a training VR for cognitive rehabilitation of MCI. Overall, results coming from the application of TMS for cognitive rehabilitation are heterogeneous and ambivalent; although some studies revealed benefits, as mentioned before, other reported no efficacy in enhancing cognitive functions (52). On the contrary, VR interventions proved positive outcomes in cognitive and motor functioning of patients with MCI or dementia, as reported by a recent metanalysis (21). Therefore, high-frequency rTMS over the left DLPFC could not only recruit more neural resources from the prefrontal cortex by inducing an electrophysiologically excitatory effect, but also enhance efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing. In other words, rTMS could strengthen VR effects by inducing a greater activation and efficacy of prefrontal cortex, region known to be involved in executive functions (53).

Based on previous promising scientific evidence, this section will discuss a novel approach that will integrate two existing efficient rehabilitation methods. In fact, an eclectic approach to cognitive rehabilitation achieves greater improvements based on the assumption that cognitive deficits are also determined and influenced by physiological, emotional, social, motivational, perceptual features (54).

The intervention will include 10 training sessions, composed by rTMS (active or sham) and the virtual-based training. Before the 1st session and at the end of the 10th, patients will receive a neuropsychological assessment.

Firstly, high-frequency rTMS will be delivered over the left DLPCF, region known to be involved in executive functions and in long-term memory due to its interaction with medial-temporal network, including hippocampus (55–57). After each session of rTMS, patients will be immersed inside a CAVE¹ at I.R.C.C.S. Istituto Auxologico Italiano (Milan, Italy), a virtual room-sized cube, in which they will be exposed to two different environment (58). Firstly, patients will be immersed in a virtual supermarket (Figure 1) in which they are able to move around thanks to an Xbox controller. Tasks consist in selecting different products on shelves according to precise rules, with increasing difficulty. Every task, according to rules and goals, requires both executive (e.g. planning, problem solving and divided attention) and memory functioning (e.g. remembering rules). Secondly, they will be immersed in a virtual city (Figure 2) in which they are required to perform two tasks. At the beginning they are placed in the center of a square and asked to move around in the virtual city, looking for some objects. Then, they are placed in a random location in the city and asked to retrieve the position of the previous object. This city-task aims at enhancing spatial memory, navigation and planning strategies. Before starting, the clinician explains to the patient the tasks and the rules in order to plan the different steps needed to solve them.

The neuropsychological assessment will target the general cognitive functioning through Addenbrooke's Cognitive Examination (ACE-R) (59) and Montreal Cognitive Assessment (MoCA) (60). More, executive functioning (planning, initiating and monitoring) will be assessed with Trial Making Test (TMT version A and B) (40) and with Stroop test (61). Memory abilities will be evaluated by Digit Span (62) and Babcock (Spinnler and Tognoni, 1987). Visuo-spatial abilities will be evaluated by Tower of London (ToL) (63). Lastly, patients will be required to self-report their daily activities through activities of daily living (ADL) (64) and IADL (65).

3. Discussion and conclusion

Given that MCI is a transitional clinical entity between normal and pathological aging, early interventions are essential to preserve cognitive functioning and to prevent its development into dementia. MCI may benefit from an efficacious intervention considering that the brain might still be able to compensate its deficiencies and to support the acquisition and retention of the impaired

¹ The CAVE is a virtual room-sized cube in which the 3D visualization of the Virtual Environments occurs thanks to the combination of four stereoscopic projectors and four screens. Two Graphics Workstations, mounting Nvidia Quadro K6000 GPU with dedicated Quadro Sync cards, are responsible for the projection surfaces, user tracking and functional logic. A Vicon motion tracking system, with four infrared cameras, allows the tracking of specific reflective markers positioned on target objects and a correct reading of the simulated spaces and distances with a 1:1 scale ratio, thus enhancing the feeling of being immersed in the virtual scene.

cognitive functions. On the contrary, with progression of the pathological disease, and with spreading of lesions, the brain might not be able to compensate its abilities anymore (66,67). Thus, a prompt rehabilitation is far more crucial.

Given that both VR-based training and neuromodulation capitalize on neuroplasticity, their findings can complementary enhance the therapeutic mechanisms. On one hand, rTMS aims at increasing excitability within the lesioned hemisphere and at suppressing stimulation to the contralesional hemisphere, namely reducing inter-hemispheric inhibition from the contralesional side (68–71). Specifically in MCI patients, DLPFC is characterized by abnormal functional connectivity, determining several cognitive and emotional impairments (72). Stimulation over this region is expected to enhance activation and efficiency of the prefrontal cortex, responsible both of executive functions (e.g. working memory and flexibility) and of long-term memory due to its connection with medial temporal network (e.g., hippocampus) (55–57).

On the other hand, VR-based intervention will provide patients with life-like functional tasks (like doing groceries and walking around the city) that involve cognitive domains, physical activity and emotional-behavioral aspects. Given VR potential to guarantee an ecological and immersive setting, along with immediate feedback, the repetitive practice of these functional tasks would facilitate a complex cognitive processing, strengthened by enjoyment and attractiveness which might facilitate motivation and engagement. Patients will be required to tap into their attentional, mnemonic, planning, flexibility and navigation abilities to accomplish the virtual tasks. It is plausible to expect that this multi-sessions, multi-modal intervention would facilitate the transfer of these abilities also into real-life daily activities.

According to previous promising results, we expect that this integrated approach will determine improvements in general cognitive, memory, visuospatial, and particularly in executive functioning. On one hand, high frequency rTMS over the left DLPFC would both recruit more neural resources from the prefrontal cortex by inducing an electrophysiologically excitatory effect and enhance efficiency of resources to deploy for conflict resolution during multiple stages of cognitive control processing. In other hand, VR effect could be strengthened by rTMS potential in increasing prefrontal cortex activation and efficiency. Interestingly, neuroimaging studies focusing on structure-function relationship occurring in MCI revealed that TMT-B is associated with left DLPFC activity (73). Most of all, we expect an improvement in autonomy of daily activities, detectable by IADL and ADL scores.

A study based on this approach might have some limitations: among them, the different etiologies of MCI sample and the different stage of functional level could provide heterogeneous results. More, patients could experience dizziness and cybersickness when immersed in virtual environments, although studies revealed that VR is well tolerated by elderly (74).

This novel approach aims at integrating rather than replacing existing and efficient rehabilitation methods in order to obtain an eclectic rehabilitation training. More, previous studies showed promising results in the integration of neuromodulation and VR technologies for motor rehabilitation in stroke patients (45,51). On one hand, TMS enabled shifts in cortical activity from contralesional to ipsilesional motor areas, on the other hand VR provided repetitive, intensive, and motivating movements tasks with real time multimodal feedback, applying motor learning principles for stroke neurorehabilitation (24).

Consistently with both empirical evidence and scientific background, we thus expect that the

272 combination of two approaches (TMS+ VR) tapping into the same mechanism will yield deeper and
273 longer clinical outcomes in MCI patients.

274 **Figure legend**

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278 Figure 1: Virtual supermarket task. The patient could both stand or be sat in the center of the CAVE if
279 he/she experiences dizziness or cybersickness. Thanks to a controller the patient navigates into the
280 supermarket accomplishing different tasks, following specific rules.

Figure 2: Virtual city task. The patient could both stand or be sat in the center of the CAVE if he/she experiences dizziness or cybersickness. By moving buttons on the controller, the patient could navigate into the city.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

V.M. and C.S.B. conceived, defined and wrote the first draft of the perspective. All the authors revised the final version of the manuscript. G.R. supervised the study.

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References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med.* 2004;256(3):183–94.
2. Koepsell TD, Monsell SE. Reversion from mild cognitive impairment to normal or near-Normal cognition; Risk factors and prognosis. *Neurology.* 2012;79(15):1591–8.
3. Gold DA. An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *J Clin Exp Neuropsychol.* 2012;34(1):11–34.
4. Nygård L. Instrumental activities of daily living: A stepping-stone towards alzheimer's disease diagnosis in subjects with mild cognitive impairment? *Acta Neurol Scand Suppl.* 2003;107(1):42–6.
5. Jekel K, Damian M, Wattmo C, Hausner L, Bullock R, Connelly PJ, et al. Mild cognitive impairment and deficits in instrumental activities of daily living: A systematic review. *Alzheimer's Res Ther.* 2015;7(1):17.
6. Petersen RC. Mild cognitive impairment. *Contin Lifelong Learn Neurol.* 2016;22(2).
7. Roses AD, Lutz MW, Amrine-Madsen H, Saunders AM, Crenshaw DG, Sundseth SS, et al. A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease. *Pharmacogenomics J.* 2010;10(5):375–84.
8. Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hänninen T, Laakso MP, et al. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol Aging.* 2004;25(3):303–10.
9. Schmidt-Wilcke T, Poljansky S, Hierlmeier S, Hausner J, Ibach B. Memory performance correlates with gray matter density in the ento-/perirhinal cortex and posterior hippocampus in patients with mild cognitive impairment and healthy controls - A voxel based morphometry study. *Neuroimage.* 2009;47(4):1914–20.
10. Fennema-Notestine C, Hagler Jr DJ, McEvoy LK, Fleisher AS, Wu EH, Karow DS, et al. Structural MRI Biomarkers for Preclinical and Mild Alzheimer's Disease. *Hum Brain Mapp.* 2009;30(10):3238–53.
11. McDonald CR, McEvoy LK, Gharapetian L, Fennema-Notestine C, Hagler DJ, Holland D, et al. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. *Neurology.* 2009;73(6):457–65.
12. Raz N, Rodrigue KM. Differential aging of the brain: Patterns, cognitive correlates and modifiers.

- 335 Neurosci Biobehav Rev. 2006;30(6):730–48.
- 336 13. Leal SL, Yassa MA. Perturbations of neural circuitry in aging, mild cognitive impairment, and
337 Alzheimer’s disease. Ageing Res Rev [Internet]. 2013;12(3):823–31. Available from:
338 <http://dx.doi.org/10.1016/j.arr.2013.01.006>
- 339 14. Sperling RA, Aisen PS, Beckett LA, Bennet DA, Craft S. Toward defining the preclinical stages of
340 alzheimer’s disease: Recommendations from the national institute on aging. Alzheimer’s Dement.
341 2011;7(3):280–92.
- 342 15. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: Implications for
343 rehabilitation after brain damage. J Speech, Lang Hear Res. 2008;
- 344 16. Slater M, Wilbur S. A framework for immersive virtual environments (FIVE): Speculations on the role
345 of presence in virtual environments. Presence Teleoperators Virtual Environ. 1997;6(6):603–16.
- 346 17. Riva G, Baños RM, Botella C, Mantovani F, Gaggioli A. Transforming experience: The potential of
347 augmented reality and virtual reality for enhancing personal and clinical change. Front Psychiatry.
348 2016;7:164.
- 349 18. Cipresso P, Giglioli IAC, Raya MA, Riva G. The past, present, and future of virtual and augmented
350 reality research: A network and cluster analysis of the literature. Front Psychol. 2018;9:2086.
- 351 19. Massetti T, da Silva TD, Crocetta TB, Guarnieri R, de Freitas BL, Bianchi Lopes P, et al. The Clinical
352 Utility of Virtual Reality in Neurorehabilitation: A Systematic Review. J Cent Nerv Syst Dis. 2018;10.
- 353 20. Riva G, Wiederhold BK, Mantovani F. Neuroscience of Virtual Reality: From Virtual Exposure to
354 Embodied Medicine. Cyberpsychology, Behav Soc Netw. 2019;22(1):82–96.
- 355 21. Kim O, Pang Y, Kim JH. The effectiveness of virtual reality for people with mild cognitive impairment
356 or dementia: A meta-analysis. BMC Psychiatry. 2019;19(1):1–10.
- 357 22. Henderson A, Korner-Bitensky N, Levin M. Virtual reality in stroke rehabilitation: A systematic
358 review of its effectiveness for upper limb motor recovery. Top Stroke Rehabil. 2007;14(2):52–61.
- 359 23. Saposnik G, Teasell R, Mamdani M, Hall J, McIlroy W, Cheung D, et al. Effectiveness of virtual
360 reality using wii gaming technology in stroke rehabilitation: A pilot randomized clinical trial and proof
361 of principle. Stroke. 2010;41(7):1477–84.
- 362 24. Saposnik G, Levin M. Virtual reality in stroke rehabilitation: A meta-analysis and implications for
363 clinicians. Stroke. 2011;42(5):1380–6.
- 364 25. Ge S, Zhu Z, Wu B, McConnell ES. Technology-based cognitive training and rehabilitation
365 interventions for individuals with mild cognitive impairment: A systematic review. BMC Geriatr.
366 2018;18(1):213.
- 367 26. D’Cunha NM, Nguyen D, Naumovski N, McKune AJ, Kellett J, Georgousopoulou EN, et al. A mini-
368 review of virtual reality-based interventions to promote well-being for people living with dementia and
369 mild cognitive impairment. Gerontology. 2019;65(4):430–40.
- 370 27. Optale G, Busato V, Marin S, Piron L, Priftis K, Gamberini L, et al. Controlling memory impairment in
371 elderly adults using virtual reality memory training: A randomized controlled pilot study. Neurorehabil
372 Neural Repair. 2010;24(4):348–57.

28. Man DWK, Chung JCC, Lee GYY. Evaluation of a virtual reality-based memory training programme for Hong Kong Chinese older adults with questionable dementia: A pilot study. *Int J Geriatr Psychiatry*. 2012;27(5):513–20.
29. Liao YY, Tseng HY, Lin YJ, Wang CJ, Hsu WC. Using virtual reality-based training to improve cognitive function, instrumental activities of daily living and neural efficiency in older adults with mild cognitive impairment. *Eur J Phys Rehabil Med*. 2020;56(1):47–57.
30. Lustig C, Shah P, Seidler R, Reuter-Lorenz PA. Aging, training, and the brain: A review and future directions. *Neuropsychol Rev*. 2009;19(4):504–522.
31. Belleville S, Clément F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain*. 2011;134(6):1623–34.
32. Appel L, Appel E, Bogler O, Wiseman M, Cohen L, Ein N, et al. Older Adults With Cognitive and/or Physical Impairments Can Benefit From Immersive Virtual Reality Experiences: A Feasibility Study. *Front Med*. 2020;6(1):329.
33. Sandrini M, Umiltà C, Rusconi E. The use of transcranial magnetic stimulation in cognitive neuroscience: A new synthesis of methodological issues. *Neurosci Biobehav Rev*. 2011;35(3):516–36.
34. Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. *Nat Rev Neurosci*. 2017;18(11):685.
35. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120(12):2008–39.
36. Brunoni AR, Sampaio-Junior B, Moffa AH, Aparício LV, Gordon P, Klein I, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. *Brazilian J Psychiatry*. 2019;41(1):70–81.
37. Chou YH, Ton That V, Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* [Internet]. 2020;86:1–10. Available from: <https://doi.org/10.1016/j.neurobiolaging.2019.08.020>
38. Drumond Marra HL, Myczkowski ML, Maia Memória C, Arnaut D, Leite Ribeiro P, Sardinha Mansur CG, et al. Transcranial Magnetic Stimulation to Address Mild Cognitive Impairment in the Elderly: A Randomized Controlled Study. *Behav Neurol*. 2015;2015.
39. Padala PR, Padala KP, Lensing SY, Jackson AN, Hunter CR, Parkes CM, et al. Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: A double-blind, randomized, sham-controlled, cross-over pilot study. *Psychiatry Res*. 2018;261:312–8.
40. Reitan RM. The relation of the Trail Making Test to organic brain damage. *J Consult Psychol*. 1955;19(5):393.
41. Hoogendam JM, Ramakers GMJ, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul*. 2010;3(2):95–118.
42. Siebner HR, Hartwigsen G, Kassuba T, Rothwell JC. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex*. 2009;45(9):1035–42.
43. Bassolino M, Franza M, Bello Ruiz J, Pinardi M, Schmidlin T, Stephan MA, et al. Non-invasive brain

- stimulation of motor cortex induces embodiment when integrated with virtual reality feedback. *Eur J Neurosci.* 2018;47(7):790–9.
44. Notzon S, Deppermann S, Fallgatter A, Diemer J, Krocze A, Domschke K, et al. Psychophysiological effects of an iTBS modulated virtual reality challenge including participants with spider phobia. *Biol Psychol.* 2015;112:66–76.
45. Lee SJ, Chun MH. Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Arch Phys Med Rehabil* [Internet]. 2014;95(3):431–8. Available from: <http://dx.doi.org/10.1016/j.apmr.2013.10.027>
46. Viana RT, Laurentino GEC, Souza RJP, Fonseca JB, Silva Filho EM, Dias SN, et al. Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: A pilot randomized controlled trial. *NeuroRehabilitation.* 2014;34(3):437–46.
47. Johnson NN, Carey J, Edelman BJ, Doud A, Grande A, Lakshminarayan K, et al. Combined rTMS and virtual reality brain-computer interface training for motor recovery after stroke. *J Neural Eng.* 2018;15(1).
48. Massetti T, Crocetta TB, Silva TD da, Trevizan IL, Arab C, Caromano FA, et al. Application and outcomes of therapy combining transcranial direct current stimulation and virtual reality: a systematic review. *Disabil Rehabil Assist Technol.* 2017;12(6):551–9.
49. Subramanian SK, Prasanna SS. Virtual Reality and Noninvasive Brain Stimulation in Stroke: How Effective Is Their Combination for Upper Limb Motor Improvement?—A Meta-Analysis. *PM R* [Internet]. 2018;10(11):1261–70. Available from: <https://doi.org/10.1016/j.pmrj.2018.10.001>
50. Kang YJ, Park HK, Kim HJ, Lim T, Ku J, Cho S, et al. Upper extremity rehabilitation of stroke : Facilitation of corticospinal excitability using virtual mirror paradigm. 2012;1–8.
51. Kim YJ, Ku J, Cho S, Kim HJ, Cho YK, Lim T, et al. Facilitation of corticospinal excitability by virtual reality exercise following anodal transcranial direct current stimulation in healthy volunteers and subacute stroke subjects. *J Neuroeng Rehabil.* 2014;11(1):1–12.
52. Neville IS, Zaninotto AL, Hayashi CY, Rodrigues PA, Galhardoni R, De Andrade DC, et al. Repetitive TMS does not improve cognition in patients with TBI: A randomized double-blind trial. *Neurology.* 2019;93(2):E190–9.
53. Funahashi S, Andreau JM. Prefrontal cortex and neural mechanisms of executive function. *J Physiol Paris* [Internet]. 2013;107(6):471–82. Available from: <http://dx.doi.org/10.1016/j.jphysparis.2013.05.001>
54. Herrmann D, Parenté R. The multimodal approach to cognitive rehabilitation. *NeuroRehabilitation.* 1994;4(3):133–42.
55. Blumenfeld RS, Ranganath C. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *J Neurosci.* 2006;26(3):916–25.
56. Ranganath C, Cohen MX, Brozinsky CJ. Working memory maintenance contributes to long-term memory formation: Neural and behavioral evidence. *J Cogn Neurosci.* 2005;17(7):994–1010.
57. Yuan B, Chen J, Gong L, Shu H, Liao W, Wang Z, et al. Mediation of episodic memory performance by the executive function network in patients with amnesic mild cognitive impairment: A resting-state functional MRI study. *Oncotarget.* 2016;7:64711.

- 452 58. Pedroli E, Serino S, Cipresso P, Leo G De, Goulene K, Morelli S, et al. An Immersive Cognitive
453 Rehabilitation Program : A Case Study. In: International Conference on NeuroRehabilitation [Internet].
454 Springer International Publishing; 2018. p. 711–5. Available from: http://dx.doi.org/10.1007/978-3-030-01845-0_142
455
- 456 59. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke’s Cognitive Examination
457 revised (ACE-R): A brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry*.
458 2006;21(11):1078–85.
- 459 60. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal
460 Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*.
461 2005;53(4):695–9.
- 462 61. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A. Una versione abbreviata del test di Stroop: Dati
463 normativi nella popolazione Italiana. *Nuova Riv di Neurol*. 2002;12(4):111–5.
- 464 62. Blackburn HL, Benton AL. Revised administration and scoring of the Digit Span Test. *J Consult*
465 *Psychol*. 1957;21(2):139.
- 466 63. Allamanno N, Della Sala S, Laiacona M, Pasetti C, Spinnler H. Problem solving ability in aging and
467 dementia: Normative data on a non-verbal test. *Ital J Neurol Sci*. 1987;
- 468 64. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged: The Index of
469 ADL: A Standardized Measure of Biological and Psychosocial Function. *JAMA J Am Med Assoc*.
470 1963;185(12):914–9.
- 471 65. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of
472 daily living. *Gerontologist*. 1969;9(3):179–86.
- 473 66. Friston KJ, Price CJ. Degeneracy and redundancy in cognitive anatomy. *Trends in Cognitive Sciences*.
474 2003.
- 475 67. Prvulovic D, Van De Ven V, Sack AT, Maurer K, Linden DEJ. Functional activation imaging in aging
476 and dementia. *Psychiatry Res - Neuroimaging*. 2005;140(2):97–113.
- 477 68. Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-
478 controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology*.
479 2005;64(10):1802–4.
- 480 69. Carey JR, Deng H, Gillick BT, Cassidy JM, Anderson DC, Zhang L, et al. Serial treatments of primed
481 low-frequency rTMS in stroke: Characteristics of responders vs. nonresponders. *Restor Neurol*
482 *Neurosci*. 2014;32(2):323–35.
- 483 70. Carey JR, Evans CD, Anderson DC, Bhatt E, Nagpal A, Kimberley TJ, et al. Safety of 6-Hz primed
484 low-frequency rTMS in stroke. *Neurorehabil Neural Repair*. 2008;22(2):185–92.
- 485 71. Takeuchi N, Izumi SI. Maladaptive plasticity for motor recovery after stroke: Mechanisms and
486 approaches. *Neural Plast*. 2012;
- 487 72. Liang P, Wang Z, Yang Y, Jia X, Li K. Functional disconnection and compensation in mild cognitive
488 impairment: Evidence from DLPFC connectivity using resting-state fMRI. *PLoS One*. 2011;6(7).
- 489 73. McDonald CR, Delis DC, Norman MA, Tecoma ES, Iragui-Madoz VJ. Is impairment in set-shifting
490 specific to frontal-lobe dysfunction? Evidence from patients with frontal-lobe or temporal-lobe

- 491 epilepsy. J Int Neuropsychol Soc. 2005;11(4):477–81.
- 492 74. Benoit M, Guerchouche R, Petit PD, Chapoulie E, Manera V, Chaurasia G, et al. Is it possible to use
493 highly realistic virtual reality in the elderly? A feasibility study with image-based rendering.
494 Neuropsychiatr Dis Treat. 2015;11:557–63.
- 495
- 496
- 497