Neuroplastic processes associated with the adoption of virtual reality: a systematic review highlighting a new approach to mental disorders treatment

Processi neuroplastici associati all’adozione della realtà virtuale: una revisione sistematica verso un nuovo approccio del trattamento dei disturbi mentali

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\textbf{ABSTRACT}

The application of virtual reality (VR) is attracting the interest of clinicians and researchers in various fields such as neuropsychology, rehabilitation and education. The shared utility is to promote a process of improvement of services for the well-being of the person towards the realization of proximity support. The research question of the present work focuses on the investigation of the neural correlate that mediates the relationship of psycho-cognitive and motor changes with the use of virtual reality. To this end, a systematic review is conducted following the PRISMA guidelines, investigating the time frame 2016–2022. The qualitative analysis of the articles supports the hypothesis that virtual reality is associated with neuroplastic processes characterized by the repair, albeit partial, of the damage suffered or the restructuring of neural activation networks.

\textbf{SINTESI}

L’applicazione della realtà virtuale (VR) sta attirando l’interesse di clinici e ricercatori in vari campi come quello neuropsicologico, riabilitativo ed educativo. L’utilità condivisa è di promuovere un processo di miglioramento dei servizi per il benessere della persona verso la realizzazione del sostegno di prossimità. La domanda di ricerca del presente lavoro si focalizza sull’indagine del correlato neurale che media la relazione dei cambiamenti psico-cognitivi e motori con l’uso della realtà virtuale. A tal fine, è stata condotta una revisione sistematica seguendo le linee guida PRISMA, indagando nell’arco temporale 2016–2022. L’analisi qualitativa degli articoli supporta l’ipotesi che la realtà virtuale sia associata a processi neuroplastici caratterizzati dalla riparazione, anche se parziale, del danno subito o dalla ristrutturazione delle reti di attivazione neurale.

\textbf{KEYWORDS}: virtual reality, neuroplasticity, brain plasticity

\textbf{PAROLE CHIAVE}: realtà virtuale, neuroplasticità, plasticità cerebrale
**Introduction**

Virtual reality was first used in the treatment of mental disorders (pathological impairment, affecting cognitive, and psychological functions, of a neurological or psychiatric nature). Its application has aroused the interest of clinicians and researchers, and it has become a potential tool for use in psychological evaluation and neurorehabilitation.

Virtual reality (VR) is a technology with a set of informatics that provides interactive environments to patients. VR systems provide a multidimensional experience within an immersive, semi-immersive, or non-immersive perspective, enabling users to interact with virtual simulated environments in stroke rehabilitation settings. Virtual environments (VEs) in VR can be used to present richly complex multimodal sensory information to the user and can elicit a substantial feeling of realness and agency, despite its artificial nature (Adamovich et al., 2010).

VR could easily simulate any specific physical environment, such as a mountain, a forest, a beach, or a savannah, which could evoke positive emotions and hence improve cognitive abilities. Because VR creates a storytelling experience, it is also capable of profoundly influencing how we see ourselves and the world around us.

In stroke patients, movement visualization, through the use of VR, contributed to the observation of limb movement, which activated the mirror neuron system in the frontoparietal cortex area (Huo et al., 2021).

VR can enhance neuroplasticity and recovery after a stroke by providing more intensive, repetitive, and engaging training due to several advantages, including tasks with various difficulty levels for rehabilitation, augmented real-time feedback, more immersive and engaging experiences, more standardized rehabilitation, and safe simulation of real-world activities of daily living. The immersive and amusing nature of VR systems can motivate individuals to devote more time to training.

VR can motivate patients’ participation by increasing enjoyment and gamification – the process of adding game-design elements and game principles to something (e.g., task) so as to encourage participation – thereby increasing task repetition (intensity).

Neuroplasticity is the ability of the human brain to adapt to certain experiences, environments, and extreme changes, including brain damage.

Biologically, it is mediated by strengthening or attenuation of synaptic transmission, remodeling of synaptic connections, reshaping of dendritic spines, reorganization of neuronal morphology and neurogenetic processes (Markham & Greenough, 2004). Direct evidence of these molecular changes is not easily accessible, but neuroimaging can certainly help provide partial evidence of these changes. The aim of this paper is to identify the effects of virtual reality on brain plasticity. The review of the “state-of-the-art” revealed studies that attempted to answer questions related to our objective.
Scientific research is pushing the manipulation of neuroplasticity to improve rehabilitation in cases of brain injury or degeneration, or neurodiversity associated with below-average cognitive performance – such as autism spectrum disorder and specific learning disorders (Dimyan & Cohen, 2011).

VR, in combination with motor imagery, could also elicit excitability in the motor cortex and reduced intracortical inhibition to regenerate nerves in patients after stroke. Neural plasticity represents the substrate through which the damaged central nervous system (CNS) re-learns lost behaviors in response to rehabilitation. In persons with multiple sclerosis (MS), rehabilitation can therefore exploit the potential of neural plasticity to restore CNS functions beyond the spontaneous mechanisms of recovery from MS-related damage (Prosperini & Di Filippo, 2019). More relevant mechanisms to neurodevelopmental disorders and rehabilitation likely involve strengthening of previously silent, hardly-used connections (e.g., ipsilateral corticospinal tract spinal projections), through long-term synaptic potentiation, production of new synapses, fiber sprouting, and myelin changes (Dan, 2019). These neural changes have the effect of improving the patient’s cognitive performance and psychological well-being.

The work of Crosson and colleagues (2019) is cited in support of this claim: functional and structural neuroimaging studies indicate that aphasia treatments can recruit both residual and new neural mechanisms to improve language function, and that neuroimaging modalities may hold promise in predicting treatment outcome. In relatively small clinical trials, both non-invasive brain stimulation and behavioral manipulations targeting activation or suppression of specific cortices can improve aphasia treatment outcomes.

The development of neuroplasticity therefore induces an improvement in mental disorders as it increases in neurotrophins, improvements in synaptic structure and function, the enhancement of interhemispheric connections, the promotion of neural regeneration, the acceleration of neural function reorganization, and the facilitation of compensation beyond the infarcted tissue. Brain functioning therefore improves, and the patient is allowed to live a dignified life by increasing well-being.

The interaction between the human mind and virtual realities has been demonstrated to improve also cognitive functions and to reduce neuropsychological symptoms (Liao et al., 2020). It also influences physical sensations in interventions, such as pain management or stress and anxiety reduction (Van Ooteghem & Geets, 2019); induces necessary emotions, such as empathy (Schutte & Stilinovic, 2017); or aims at achieving higher goals, such as self-development (Howard, 2019). The company Idego has demonstrated the adaptability and operational effectiveness of VR system as an E-therapy tool in several clinical psychology areas (Barbato & Di Natale, 2019). VR is therefore a tool that lends itself well to the process of change, whether it be psychodynamic insight or the reorganization of cognitive schemas. One of the main benefits connected to the use of VR in therapy derives from the possibility of manipulating many variables of the scenario in which the patient will be immersed.
Practices reproduced in virtual reality present a unique advantage over in vivo practices, as the intervention protocols can be controlled (think of the intensity or quantity of a stimulus), repeated, set to the patient’s needs, and the stimuli can be presented gradually (Di Natale & Barbato, 2018).

The pathophysiological consequences of such cortical plasticity may underlie the development of phantom sensations and pain by targeting somatosensory neural reorganization after injury. Therefore, addressing neuropathic pain remains a major challenge (Soler et al., 2010). One of the most recent non-pharmacological and non-invasive intervention tools for neuropathic pain is the use of virtual reality.

One review (Georgiev et al., 2021), which predates our work, focused on a question similar to ours: does virtual reality-mediated treatment have neuroplasticity-mediated neurorehabilitation effects?

Some of the articles they selected are common to those included in our review. Georgiev and colleagues concluded that VR allows recovery of acquired motor deficits, improvement of mood and cognitive functions, and has a positive impact in general on quality of life.

The authors conclude that «VR promises a plethora of experiences to people who engage in it, and induces states of mind ranging from simplified to overwhelming. Contemporary use of VR goes far beyond entertainment. It can be beneficial for training, for research purposes, and for neurorehabilitation. BCIs may assist the replacement of lost functions, such as moving or speaking, thereby restoring severely paralyzed or locked-in patients’ ability to communicate with the surrounding world. VR may additionally support the perception of an embodiment for precise control over bionic devices that extend the capabilities of the human body» (Georgiev et al., 2019, p. 221). So, they explore important medical applications of VR technologies that significantly improve the quality of life in patients with neurological deficits. They also conclude with the promises that the use of virtual reality offers to healthy individuals for self-improvement and personal development.

Our work intends to broaden the criteria from neurological deficits to mental disorders and to investigate the link between neural correlates and behavioral change: Georgiev and colleagues highlighted the effects of VR in rehabilitation, whereas we aim to show that VR is effective in that it is associated with the development of neuroplasticity, which leads to the improvement of cognitive and psychological symptoms of mental disorders.

1. Materials and methods

About a decade after the last version, a major update of the PRISMA statement, the most rigorous guidance in reporting systematic reviews with or without meta-analysis, has been produced. PRISMA stands for Preferred Reporting Items for Systematic reviews and Meta-Analyses. The systematic review serves the function of summarizing the state of knowledge in a field in order to identify new avenues.
of research or problems or to generate divergent ideas (Page et al., 2020). The source of information used was the PubMed database: the research has used combined terms “virtual reality brain plasticity” and “virtual reality neuroplasticity”. It was decided to use both the terms neuroplasticity and brain plasticity, as they were used for the same purpose and the intention was not to lose studies relevant to the objective. It took into account only studies published between 2016 and January 2022. The PubMed search engine was chosen as it collects scientific literature in the biomedical field, in line with this review, and is free of charge. All types of results were included such as review, clinical trial, randomized controlled trial (RCT), comparative study, and qualitative and quantitative method. Eligibility criteria are defined in the next paragraph and the analysis of each paper was carried out by a single reviewer who produced a comparison between them.

1.1. Inclusion and exclusion criteria

Systematic review has been conducted on studies published in English. The purpose was to identify the papers studying the neuroplastic effects of the application of virtual reality. All types of scientific articles are accepted. The search generated 135 papers (obtained from the above research methods), of which 48 were not free full text. Therefore, 87 papers were considered, and analyzed, as they were free full text, of which 18 were duplicates. 69 papers were obtained from this further procedure. The selection criterion required that the work should focus on the neuroplastic effects of virtual reality so, for example, articles that focused on integrated therapies or which were centered on psycho-cognitive and non-neural effects were excluded. In conclusion, 20 articles were selected for comparison, the steps taken are illustrated in the figures below.

**Figure 1** – The figure summarizes the procedures for selecting papers following a search for the keyword “virtual reality brain plasticity”
Figure 2 – The figure summarizes the procedures for selecting papers following a search for the keyword “virtual reality neuroplasticity”
1.2. Research strategy

The work combined two search procedures, each with the following terms: “virtual reality brain plasticity” and “virtual reality neuroplasticity”. It took into account only studies published between 2016 and 2022, searching the electronic PubMed databases.
Boolean logic has enabled the appropriate combination of operators (and, or, not, adj, near, then, etc.) for the purposes of database query syntax (Catania, 2004). The Figure 3 shows the processes implemented following PRISMA flow diagram.

Each reference has been evaluated for potential relevance, and then the research has applied the inclusion criteria. 20 papers were selected (through the procedures explained above) and their contents are subsequently summarized.

The AMSTAR 2 guidelines were followed for the critical appraisal of the methods adopted in the review (Beverley et al., 2017).

The 16 items of the instrument were adhered to by engaging two practitioners, who were responsible for item collection and selection and operated independently.

The 20 selected papers were studied and analyzed by identifying for each study authors, type of article, key points, and results.

2. Results

20 selected papers were analyzed and summarized in order to structure a qualitative comparison. Table 1 below shows the main information of the papers.

<table>
<thead>
<tr>
<th>Number</th>
<th>Authors</th>
<th>Type</th>
<th>Type of mental disorder</th>
<th>Summary and key points</th>
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<tbody>
<tr>
<td>1</td>
<td>Won-Seok et al., 2020</td>
<td>Narrative review</td>
<td>Stroke</td>
<td>Virtual reality-based rehabilitation is associated with neuroplastic processes. The authors have shown that neuroplasticity is particularly favored by the integration of VR with new therapeutic modalities such as BCI and noninvasive brain stimulation for upper limb motor rehabilitation in stroke.</td>
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<td>2</td>
<td>Patel et al., 2019</td>
<td>Clinical trial</td>
<td>Stroke</td>
<td>The study focuses on specialized, intensive virtual reality/robotic based upper limb training after stroke. Experimental results demonstrated neuroplastic changes superior to those found in conventional rehabilitation sessions.</td>
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<td>Virtual reality protocol – VR group: this group began training as inpatients within the first month post-stroke. This was initiated as soon as possible after pre-testing was completed. The greater changes in the VR group were not paralleled with augmented changes in ipsilesional FDI (flexor digitorum superficialis) muscle cortical organization, as similar patterns of change were demonstrated in the UC group as well. However, the gains in upper limb impairment and behavior in our VR group would be greater than our UC (standard treatment) group.</td>
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<tr>
<td>No.</td>
<td>Authors, Year</td>
<td>Study Type</td>
<td>Condition</td>
<td>Abstract</td>
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<tr>
<td>3</td>
<td>Gauthier et al., 2017</td>
<td>Clinical</td>
<td>Stroke</td>
<td>Constraint-induced movement therapy (CI therapy), mediated by virtual reality, is shown to reduce disability, increase use of the more affected arm/hand, and promote brain plasticity for individuals with upper extremity hemiparesis post-stroke. The therapy was centered on the use of a virtual reality game characterized by the restraint of the healthy arm. One range of motion metric particularly relevant to stakeholders is kinematic reaching volume, defined as the percentage of space that an individual accesses (convex hull of observed movements) relative to the volume that could be accessed if full range of motion were present.</td>
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<td>4</td>
<td>Keller et al., 2020</td>
<td>Clinical</td>
<td>Stroke</td>
<td>Virtual anatomical interactivity (VAI) presents a digital game-like format in which ABI (individuals with acquired brain injuries) survivors with upper limb paresis use an unaffected limb to control a standard input device and a commonplace computer mouse to control virtual limb movements and tasks in a virtual world. Significant increases in grey matter volume in the motor and premotor regions of affected hemisphere and correlations of motor skills and volume in non-affected brain regions were present, suggesting marked changes in structural brain plasticity. The motor improvement was higher for the group treated only with VAI than for the groups treated either only with standard therapy (physical/occupational therapy) or with the dual method.</td>
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<td>5</td>
<td>Marin-Pardo et al., 2020</td>
<td>Pilot study</td>
<td>Stroke</td>
<td>In this pilot study, they evaluate the feasibility and efficacy of an EMG (electromyography) based variant of our REINVENT virtual reality neurofeedback rehabilitation system to increase volitional muscle activity while reducing unintended co-contractions. They found that training improved scores on standardized clinical assessments, equivalent to those previously reported for brain-computer interfaces. Additionally, training may have induced changes in corticospinal communication. These results are interpreted as resulting from neural reorganization.</td>
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<td>6</td>
<td>Wang et al., 2017</td>
<td>Clinical</td>
<td>Stroke</td>
<td>The present study explored the effects of a Leap Motion-based virtual reality system on subacute stroke. After four weeks of treatment, the motor functions of the affected upper limbs were significantly improved in all the patients, with the improvement in the experimental group being significantly better than in the control group. The activation intensity and the laterality index of the contralateral primary sensorimotor cortex increased in both the experimental and control groups. Before training, when using the affected hand, the bilateral or ipsilateral SMC, the bilateral or unilateral SMA</td>
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(supplementary motor area), and *cerebellum* were mainly activated in both groups. After training, a shift in the SMC (sensorimotor cortex) activation from the ipsilateral or bilateral to contralateral regions was found after intensive use of the paretic limb in both groups.

<table>
<thead>
<tr>
<th>7</th>
<th>Montana et al., 2019</th>
<th>Systematic review</th>
<th>Mnestic deficit</th>
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<td></td>
<td>The results of this systematic review demonstrate that all studies suggest that patients improved their spatial memory following treatment. This result highlights the potential of navigational tasks performed in virtual environments (VEs) for enhancing navigation and orientation abilities in patients with spatial memory disorders. VR training can facilitate neurorehabilitation, promoting brain plasticity processes through complex mechanisms related to the reactivation of brain neurotransmitter capacities, maximizing the results compared to those obtained by conventional treatment.</td>
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<th>8</th>
<th>Xiao et al., 2017</th>
<th>Clinical trial</th>
<th>Stroke</th>
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<td></td>
<td>This study aimed to evaluate cortical reorganization after virtual reality-enhanced treadmill (VRET) training in subacute stroke survivors. Increased activation in the primary sensorimotor cortex (SMC) of the lesioned hemisphere and supplementary motor areas (SMA) of both sides of the paretic foot (p&lt;0.01) was observed post-intervention. Statistically significant improvements were observed in gait velocity (p&lt;0.05). The phase of reorganization showed hyperactivation in ipsilesional SMC. Improved SMC activation in the affected hemisphere is one of the common mechanisms underlying functional recovery of the paretic limbs. Expansion of SMC activation after stroke probably reflect the “unmasking” of preexisting but normally inactive representations or “recruitment” of neurons/connections not normally devoted to this function. Repetitive practice of the affected limb may increase efficacy of existing synapses and facilitate synaptic proliferation and axonal sprouting from surviving neurons, thus increase neuroplasticity and associated motor improvement.</td>
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<td></td>
<td>Study Authors, Year</td>
<td>Study Type</td>
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<td>9</td>
<td>Irmen et al., 2020</td>
<td>Clinical trial</td>
<td>Healthy subjects</td>
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<tr>
<td>10</td>
<td>Vourvopoulos et al., 2019</td>
<td>Case study</td>
<td>Stroke</td>
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<tr>
<td>11</td>
<td>Leemhuis et al., 2021</td>
<td>Review</td>
<td>Spinal cord injuries</td>
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</table>
imagining oneself walking has short-term positive and long-term analgesic effects on NP.

| 12 | Baumann et al., 2020 | Clinical trial | ADHD | In the experiment, they aimed to exploit behavioral tagging to enhance long-term memory consolidation (24h) in children and adolescents with ADHD. Specifically, we intended to improve intentional learning of a word list through the active exploration of a novel virtual environment. This strengthens the idea of a behavioral tagging and capture process, where, during a sensitive period of consolidation, salient stimuli are able to influence the synaptic plasticity processes underlying memory formation. According to behavioral tagging, the exposure to a novel environment provides additional PRPs that can be captured by weakly stimulated synapses. Neurobiologically, this could be due to a hypofunction of the dopaminergic system in ADHD, which is specifically expressed in low tonic dopamine (DA) levels. Importantly, functional models of novelty processing predict that experiencing novelty, for example the exploration of a novel environment, leads to an increase in the number of tonically firing neurons in the SN and VTA. The additional release of DA caused by the novel environment might not have led to memory enhancement. |
| 13 | Coco-Martin et al., 2020 | Review | Amblyopia | They used VR mediated by head mounted displays (HMDs) for the visual rehabilitation in amblyopia of childhood. HMDs provide stereoscopic images for fully immersing experiences, and motion capture systems allow the creation of visual-motor correlations between the user’s movements and those of an avatar (virtual representation of the user). This system used specially configured software to preferentially stimulate the amblyopic eye without compromising the vision of the unaffected (dichoptic stimulation), and its potential to improve visual acuity in amblyopia has been proved. Therapy induces an improvement in visual impairment even after the critical period of visual development. This improvement is related to neuroplastic processes. |
| 14 | Goncalves et al., 2018 | Clinical trial | Stroke | Virtual reality appears to have a positive impact on brain plasticity, leading to the reduction of motor deficits. Repetition and movement intensity act directly are promoters of neural plasticity. Improvement was observed in all upper limb functional scales after stroke. Virtual reality is considered a computer technology that simulates |
motor learning. Adult brain neurons often increase the rate of firing in the sensorimotor cortex regions when participants observe or perform mirrored movements. The activation of this system, called mirror neurons, includes areas of the frontal, parietal, and temporal lobes, and may induce cortical reorganization after injury to the central nervous system.

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<tr>
<th>15</th>
<th>Leemhuis et al., 2021</th>
<th>Article</th>
<th>Spinal cord injuries</th>
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<td></td>
<td>They analyze the impact of the VR on spinal cord injuries (SCIs). Neurologically. A typical setup creates an interactive virtual moving system, where patients can see their own body aligned with the avatar’s body, reproducing the same movements in real time and creating the illusion that they are controlling the avatar’s movement (Toyra System). The system associates VR with tactile sensations to make movements more real. The bidirectional flow of perceptual and motor information by combining action observation and execution of lower limb movements has proven useful for rebuilding motor memories and improving neuronal synergies on sensorimotor cortical activity. The attempted, imagined, and observed foot movements activate cortical motor networks in SCI patients that still project through uninjured parts of the spinal cord onto muscle effectors.</td>
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<th>16</th>
<th>Yang et al., 2018</th>
<th>Clinical trial</th>
<th>ASD</th>
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<td></td>
<td>The researchers adopted a virtual reality social cognition training on individuals with autism spectrum disorder (ASD). Two significant brain behavior changes were identified. First, the right posterior superior temporal sulcus, a hub for socio-cognitive processing, showed increased brain activation to social versus unsocial stimuli in individuals with greater gains on a theory-of-mind measure. Second, the left inferior frontal gyrus, a region for socio-emotional processing, tracked individual gains in emotion recognition with decreased activation to social versus unsocial stimuli.</td>
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<tr>
<th>17</th>
<th>Hinze et al., 2021</th>
<th>Review</th>
<th>Phobia</th>
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<td></td>
<td>They explore the Phobia treatment with VR. Although in vivo exposure provides an excellent treatment option, patients are often reluctant to leverage the treatment options. Research using fMRI to examine brain activation while participants explore VR environments shows that identical anxiety-related brain regions are activated as with real life photographs. The treatment enables improved activation of the prefrontal neural network.</td>
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<tr>
<td>Study</td>
<td>Authors</td>
<td>Study Type</td>
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<tr>
<td>18</td>
<td>Kubica et al., 2019</td>
<td>Clinical trial</td>
<td>Healthy elderly</td>
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<tr>
<td>19</td>
<td>Ballester et al., 2017</td>
<td>Clinical trial</td>
<td>Stroke</td>
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<tr>
<td>20</td>
<td>Fluet et al., 2017</td>
<td>Case report</td>
<td>Stroke</td>
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**Table 1 – Overview of reviewed studies**
3. Discussion

The selected articles highlighted the potential of VR to stimulate brain plasticity in order to promote rehabilitation/habilitation processes. However, the effects have been observed to be more evident in combination with the integration of VR treatments with other therapeutic modalities such as standard therapies, BCI, and non-invasive brain stimulation (1). Training programs are deficit-specific and therefore aim at the recovery of lost or to-be-acquired abilities.

Most of the studies (11 papers out of 20) focus on patients affected by ischemic attack, resulting in neuromotor deficits, therefore neuroplastic evidence is higher in correspondence with VR treatments for motor rehabilitation. Rehabilitation of stroke patients by VR induces different effects.

(2) They observed a reduction in the impairment of motility in the affected hand, compared to the limb of subjects in the control group, which is related to a cortical reorganization of the ipsilesional FDI muscle. (3) They observe an association between increased range of motion of the hand and arm and the development of brain plasticity evident in follow-ups by neuroimaging. VAI, in particular, determines significant increases in the volume of grey matter in the motor and premotor regions of the damaged hemisphere that are associated with clear improvements in motor type (4), the subjects studied are individuals with acquired brain injuries. (6) On the other hand, they found a shift in SMC activation from ipsilateral or bilateral regions to contralateral regions in subjects with brain damage associated with impairment of upper limb motor skills. (8) They measured increased activation in the primary sensorimotor cortex (SMC) of the injured hemisphere and in the SMA bilaterally, areas involved in foot movement. (10) They demonstrated the onset of plastic changes such as the recruitment of areas, previously with a deficit function, in the primary and supplementary motor cortex of the lesioned hemisphere. (14) They found a cortical reorganization with increased activation of the sensorimotor cortex. This process is mediated by a functional activation of the mirror neuron system in the frontal, parietal, and temporal areas in response to the interaction between patient and avatar. (19) They observed an increase in corticospinal excitability for the adductor pollicis brevis muscles and a shift in cortical activation towards the damaged hemisphere. Also, (20) they demonstrated the link between VR and upregulation of the damaged primary motor cortex. (5) In cases of severe impairment of limb movement, they observed changes in cortico-spinal communication in response to neural reorganizations that as a consequence generated an increase in volitional motor activity and a reduction in involuntary contractions.

The remaining 9 articles focus on the rehabilitation of patients with different pathologies. The evidence is not only related to the neuroplastic process of motor areas, VR also induces cognitive improvements.

(7) They have shown that virtual environments facilitate the neurorehabilitation of spatial mnemonic capacities: they promote brain plasticity processes through complex mechanisms linked to the reactivation of brain neurotransmitter capacities.
VR is also associated with neuroplastic processes that mediate new learning in healthy subjects: (9) they observed significant changes in a left hemispheric subcortical cluster underlying the ventral premotor cortex region. This change was associated with the acquisition of ability to handle new tools such as the endoscope. (11) VR restores the lost coherence between body motor output and sensory feedback in SCI cases to treat NP. (12) Synaptic plasticity effects underlying memory formation in ADHD subjects through virtual exploration of a new environment emerge. (13) Visual rehabilitation through VR, in cases of amblyopia, has demonstrated an improvement in the visual deficit determined by neuroplastic processes. (15) In subjects with SCI the system associates VR with tactile sensations to make movements more real. The bidirectional flow of perceptual and motor information by combining action observation and execution of lower limb movements has proven useful for rebuilding motor memories and improving neuronal synergies on sensorimotor cortical activity. (16) In subjects with ASD neuroplastic changes emerged at the right posterior superior temporal sulcus and the left inferior frontal gyrus. An improvement in emotional and social skills was observed at the behavioral level. (17) VR treatment with phobia patients shows a change in the activation of the prefrontal neural network that is associated with an improvement in mental disorder. (18) The VBT motor treatment program in elderly subjects resulted in a significant decrease in SMA activity, which testifies to the acquisition of automatisms and motor learning.

It is important to consider that post-stroke motor recovery mostly follows a non-linear trajectory reaching asymptotic levels a few months after injury. This pattern suggests the existence of a period of high plasticity, in which the patient seems to be more responsive to treatment, the so-called “critical window” for recovery. In order to characterize the temporal structure of recovery, animal models and clinical research have identified a combination of mechanisms underlying neurological repair that appears to be unique to the injured brain, including neurogenesis, gliogenesis, axonal sprouting, and the rebalancing of excitation and inhibition in cortical networks (Ward, 2017). This state of enhanced plasticity is transient, and interacts closely with training to facilitate recovery.

However, the studies selected in this paper show that it is also possible to induce neuroplasticity even after this critical window, it is however clarified that the performance enhancing effects have a lower significance and lower probability of occurring. Positive correlations between the neural plasticity changes and functional recovery elucidates the mechanisms of VR-based therapeutic effects in stroke rehabilitation.

This review certainly requires a deeper systematic understanding of the neurophysiological mechanisms of VR-based rehabilitation but summarizes the emerging evidence for the ongoing innovation of VR systems and application in rehabilitation. In this review, the comparison of the results of the selected studies revealed in detail the neuroplastic process by which virtual reality is associated with the improvement of cognitive and psychological symptoms in mental disorders.
Conclusions

The access to computer-generated worlds changes the way we feel, how we think, and how we solve problems.

With the introduction of intelligent technology in clinical settings, objective functional evaluation and effective treatments can be provided in real-time.

Future upgrades of virtual reality-based technologies promise to help humans transcend the limitations of their biological bodies and neuropsychological disease.

The combination of traditional rehabilitation therapies and intelligent therapies has the potential to improve the rehabilitation of motor dysfunctions and enhance clinical efficiency. Continuous improvements in intelligent technology may open the door to routine clinical use. VR-based therapies can induce cortical reorganization and promote the activation of different neuronal connections over a wide range of ages, leading to contrasted improvements in motor and functional skills.

VR technology can be used to deliver meaningful and relevant stimulation to the brain and thereby trigger neuroplasticity mechanisms to promote the rehabilitation.

However, virtual reality also has the potential to improve the general well-being of healthy individuals.

This review shows that numerous studies demonstrate that VR has the potential to determine neuroplastic effects in patients suffering from different pathologies. However, generalization is complex as it is difficult to find subjects with the same neurological characteristics, even if they suffer from the same disease. Moreover, the individual’s personality and psycho-social dimensions influence the effectiveness of the treatment.

This study concludes with a new research question: can VR be adopted as a primary treatment for overcoming the symptoms of mental disorders?

This review was subject to certain limitations. An extensive literature search was conducted to provide these results, however, only one database was queried. A second limitation consisted of only two alternatives for the searched keywords. The inclusion criteria narrowed the focus to only studies according to the objectives of the review and the availability of free full text. A third limitation might be that the discussion of VR therapy cannot draw definitive conclusions due to the heterogeneity of interventions. Furthermore, the difficulty to find a homogeneous group of patients is the reason why most of the experimental studies, reported in the literature, are based on the treatment of a single patient or a small group of patients. The fourth limitation cuts across all systematic reviews, namely that the research findings are limited by the search terms and refinements used (e.g., journals included and publication period). Although the systematic review may not accurately reflect all existing literature relevant to this study, it does provide insight into current research findings and the impact of VR on neuroplasticity. Another limitation of this review is the wide spectrum of the considered items: we have
decided not to limit the type of studies as the subject is still in the research and development phase so we would have lost a lot of important information.

The final limitation is that despite PRISMA’s quality criteria and the authors’ adherence to AMSTAR 2 guidelines to ensure a certain methodological rigor, the authors cannot fully control publication bias and therefore cannot guarantee full access to the data within this systematic review.

As our results are positive, we hope that the literature will soon be enriched with clinical studies investigating the effectiveness of VR in more specific and larger clinical populations.

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