

Review

Virtual Reality for Neurorehabilitation and Cognitive Enhancement

Danko D. Georgiev ^{1,*}, Iva Georgieva ¹, Zhengya Gong ², Vijayakumar Nanjappan ²
and Georgi V. Georgiev ²¹ Institute for Advanced Study, 9010 Varna, Bulgaria; ivavgeorgieva@gmail.com² Center for Ubiquitous Computing, University of Oulu, FI-90014 Oulu, Finland; zhengya.gong@oulu.fi (Z.G.); vijayakumar.nanjappan@oulu.fi (V.N.); georgi.georgiev@oulu.fi (G.V.G.)

* Correspondence: danko@q-bits.org

Abstract: Our access to computer-generated worlds changes the way we feel, how we think, and how we solve problems. In this review, we explore the utility of different types of virtual reality, immersive or non-immersive, for providing controllable, safe environments that enable individual training, neurorehabilitation, or even replacement of lost functions. The neurobiological effects of virtual reality on neuronal plasticity have been shown to result in increased cortical gray matter volumes, higher concentration of electroencephalographic beta-waves, and enhanced cognitive performance. Clinical application of virtual reality is aided by innovative brain–computer interfaces, which allow direct tapping into the electric activity generated by different brain cortical areas for precise voluntary control of connected robotic devices. Virtual reality is also valuable to healthy individuals as a narrative medium for redesigning their individual stories in an integrative process of self-improvement and personal development. Future upgrades of virtual reality-based technologies promise to help humans transcend the limitations of their biological bodies and augment their capacity to mold physical reality to better meet the needs of a globalized world.

Keywords: brain cortex; cognition; motor control; neurorehabilitation; perception; robotic devices; self-enhancement; virtual reality



Citation: Georgiev, D.D.; Georgieva, I.; Gong, Z.; Nanjappan, V.; Georgiev, G.V. Virtual Reality for Neurorehabilitation and Cognitive Enhancement. *Brain Sci.* **2021**, *11*, 221. <https://doi.org/10.3390/brainsci11020221>

Academic Editor: Rocco Salvatore Calabrò

Received: 28 December 2020

Accepted: 6 February 2021

Published: 11 February 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The rapid development of digital technologies has transformed societies across the world [1,2]. Access to electronic devices and the internet exposes our minds to virtual computer-generated worlds, which greatly impact our daily lives [3–5]. If exposure to virtual realities is subordinate to achieving long-term personal goals, digital technologies are able to improve the overall well-being of healthy individuals [6–8]. Furthermore, technologies employing virtual realities may be helpful to older adults suffering from cognitive decline and social isolation [9], may assist neurorehabilitation of patients with stroke [10] or traumatic brain injury [11], and may even be an essential ingredient for the replacement of lost functions through an appropriate brain–computer interface (BCI) that controls robotic devices [12–16].

The interaction between the human mind and virtual realities has been demonstrated to improve cognitive functions [17–22]. Biologically, this effect cannot be achieved without the activation of some forms of neural plasticity, such as strengthening or attenuation of synaptic transmission [23], remodeling of synaptic connections [24], reshaping of dendritic spines [25–28], reorganization of neuronal morphology [29–31], or modulation of electric excitability [32–34]. Direct evidence for the underlying molecular changes at the level of individual neurons, however, is beyond the reach of current methods for functional brain imaging. Nevertheless, electroencephalography (EEG) [35,36], magnetoencephalography (MEG) [37,38], near-infrared spectroscopy (NIRS) [39,40], positron emission tomography (PET) [41–43], and magnetic resonance imaging (MRI) [44–46] can resolve functional brain

states with macroscopic resolution (e.g., EEG has a temporal resolution of milliseconds and MRI has a spatial resolution of millimeters) that can detect cumulative changes in brain volume or excitability acquired over several weeks of training or rehabilitation.

In this present review, we will first portray different types of virtual reality (VR) employed in biomedical practice and will concisely describe their measurable impact upon brain structure and cognitive performance. Then, we will explore important medical applications of VR technologies that significantly improve the quality of life in patients with neurological deficits. Lastly, we will conclude with the promises VR use offers healthy individuals for self-improvement and personal development.

2. Types of Virtual Reality

Computer-generated worlds provide digital experiences, which are referred to as virtual realities. Depending on the intensity and quality of feelings elicited by the computer-generated world, several main types of virtual realities can be differentiated.

2.1. Non-Immersive Virtual Reality

In this type of reality, the person is not fully immersed in the virtual world [47]. It is the most common type of VR encountered by us while working with personal computers, tablets, smartphones, television sets, or other electronic devices. Because the virtual world is displayed on computer monitors or large television screens, and the interaction happens through input devices like keyboards, mice, or controllers, the person does not have the feeling of being present inside the virtual world. Instead, the person may experience simultaneously both the real world, e.g., the physical surroundings in the room, and the contents of the virtual world, e.g., the position of an avatar inside a computer game.

2.2. Fully Immersive Virtual Reality

In this type of reality, the person is fully immersed and has the feeling of presence in the virtual world [48,49]. The person enters into the virtual world with the help of specialized hardware, such as a head-mounted display (HMD), a bodysuit, data gloves, and an immersive room. The purpose of this extra equipment is to eliminate the sensory flow of information from the real world [50] and substitute it with the computer-generated one. This sustains the illusion experienced by the person that the virtual world is the actual real world. Sensors attached to the bodysuit can be used to monitor the person's movements, and an EEG cap can be used to track brain activity. Thus, the act of immersion is accompanied by the generation and recording of large amounts of experimental data, which can be collected and analyzed in a retrospective fashion.

2.3. Augmented Reality

A characteristic feature of augmented reality is that some components of the virtual world are superimposed on the surrounding world [51,52]. The person experiences computer-generated perceptual information that is overlaid on physical objects residing in the real-world environment. Electronic devices equipped with cameras, such as smartphones and tablets, currently allow for capturing snapshots of the real world that can be enhanced with animations or other digital information selected from VR applications. A practical way for augmenting reality is through the visual system using hands-free wearables, such as smart glasses. In augmented reality, the user can see the components of the virtual world but is not able to interact with them.

2.4. Mixed Reality

This type of hybrid reality is a form of augmented reality in which the real elements and the virtual elements are able to interact with one another, thereby granting the user the ability to interact with both real and virtual objects [53–55]. Further development of digital technologies may even allow for the projection of three-dimensional holograms in real space and user interaction with projected digital controllers as needed.

2.5. Extended Reality

Extended reality (XR) is a general term that encompasses all immersive technologies, including present-day technologies, such as the aforementioned augmented reality (AR), VR, or mixed reality (MR), plus future technologies that are still to be created. The application of such advanced technologies in the context of health emergencies deserves further consideration as this will create opportunities for effective non-human interaction.

3. Cortical Localization of Cognitive Functions

The seat of human consciousness is located in the brain cortex, which forms the outer layer of the cerebrum [56–58]. In large mammals and primates, the brain cortex is folded into grooves (sulci) and ridges (gyri), which are tightly packed within the limited space available inside the skull [59,60]. Although different higher cognitive functions seem to be flawlessly integrated into a single stream of conscious experience [61,62], different parts of the brain cortex have been shown to play different specialized roles, as evidenced by localized cerebral lesions [63,64]. This localization of cognitive functions in the brain cortex has been further corroborated by modern techniques for functional brain imaging [65,66] and can be exploited by VR technologies that rely on BCIs [67,68].

Knowledge of the cortical anatomy is essential for the accurate description of the localization of cognitive functions and proper understanding of the localized nature of observed changes in gray matter volumes or EEG power spectra after VR exposure. With an interdisciplinary audience of biomedical engineers, computer scientists, health professionals, and neuroscientists in mind, we briefly outline the characteristic anatomical features of the human brain cortex and summarize their relevance to cognition.

Structurally, the cerebrum consists of two cerebral hemispheres, designated as left and right respectively. Each hemisphere has an outer layer of gray matter, referred to as the cortex, and an inner layer of white matter. The cortex is further divided by large grooves into four lobes: frontal lobe, temporal lobe, parietal lobe, and occipital lobe. Each lobe contains ridges, referred to as gyri, specialized in the execution of specific cognitive functions.

3.1. Frontal Lobe

The frontal lobe is located at the front of the head [56] (Figure 1). In VR applications, it is actively involved in working memory and motor control [69,70]. The precentral gyrus contains the primary motor cortex, which exercises control over voluntary movement through stimulating contraction of skeletal muscles. The superior frontal gyrus is implicated in self-awareness [71] and the generation of laughter [72]. The middle frontal gyrus (Figure 2) exerts control over automatic behavior [73], contributes to maintaining information in consciousness, and is recruited primarily when information must be manipulated in working memory [74–76]. The inferior frontal gyrus of the dominant hemisphere contains Broca's area, which controls the production of speech and expressive language [77]. The cingulate gyrus (Figure 3) is involved in sensory perception of pain induced by noxious stimuli [78], the encoding of negative memories [79], and avoidance learning for physical events that are associated with negative outcomes [80].

3.2. Temporal Lobe

The temporal lobe is located on the side of the head above the ear [56] (Figure 2). In VR applications, it is actively involved in the semantic processing of information and episodic memory [81,82]. The superior temporal gyrus of the dominant hemisphere contains Wernicke's area, which is essential for the understanding of written and spoken language [83]. The middle temporal gyrus is involved in sound recognition, semantic retrieval, semantic memory, and language processing [84]. The inferior temporal gyrus contributes to the execution of word-retrieval tasks [85]. The fusiform gyrus contributes to the processing of color information and face recognition [86]. The parahippocampal gyrus (Figure 3) is responsible for the encoding and retrieving of memories [87].

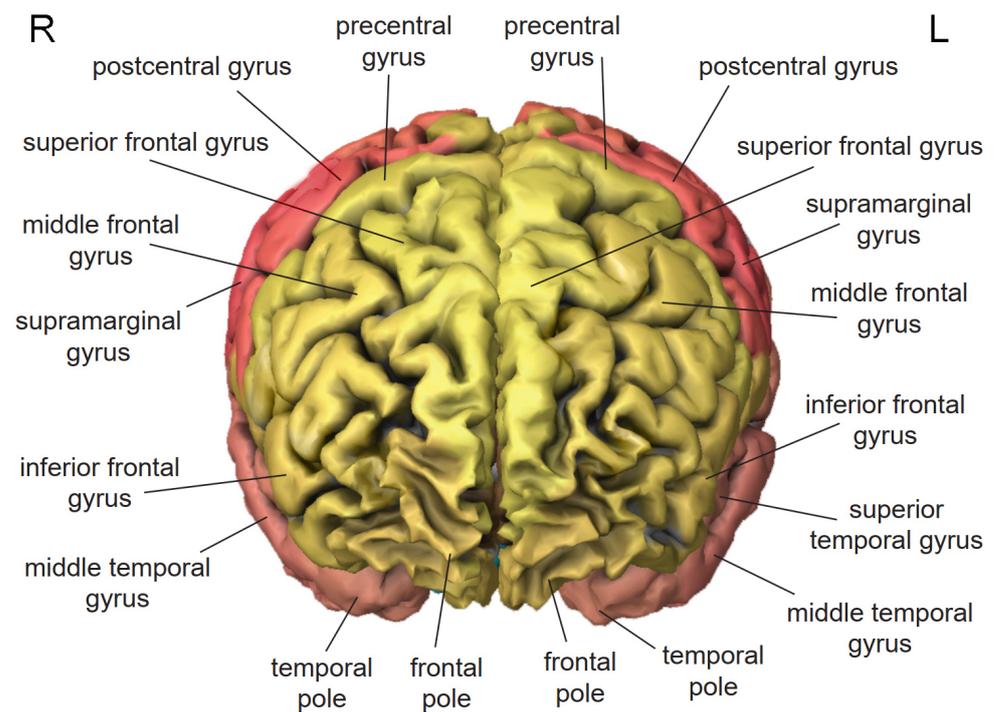


Figure 1. Frontal view of the human brain based on H0351.2002 dataset in Allen Brain Atlas. Frontal lobe (yellow), parietal lobe (red), temporal lobe (pink). L, left; R, right.

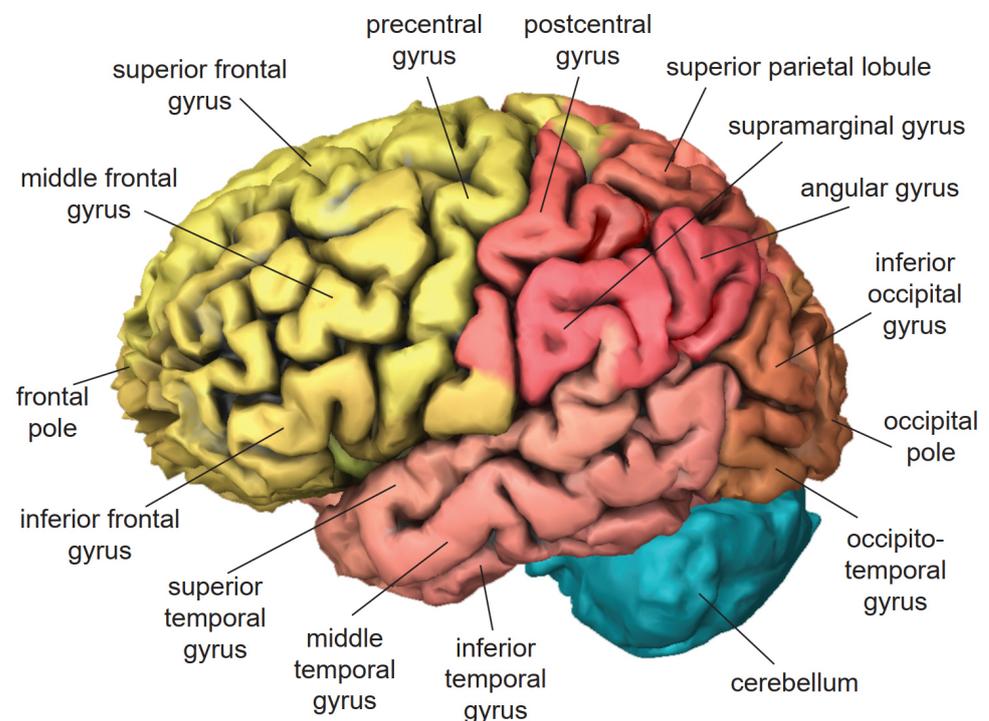


Figure 2. Lateral view of the left hemisphere of the human brain based on H0351.2002 dataset in Allen Brain Atlas. Frontal lobe (yellow), parietal lobe (red), temporal lobe (pink), occipital lobe (salmon), cerebellum (turquoise).

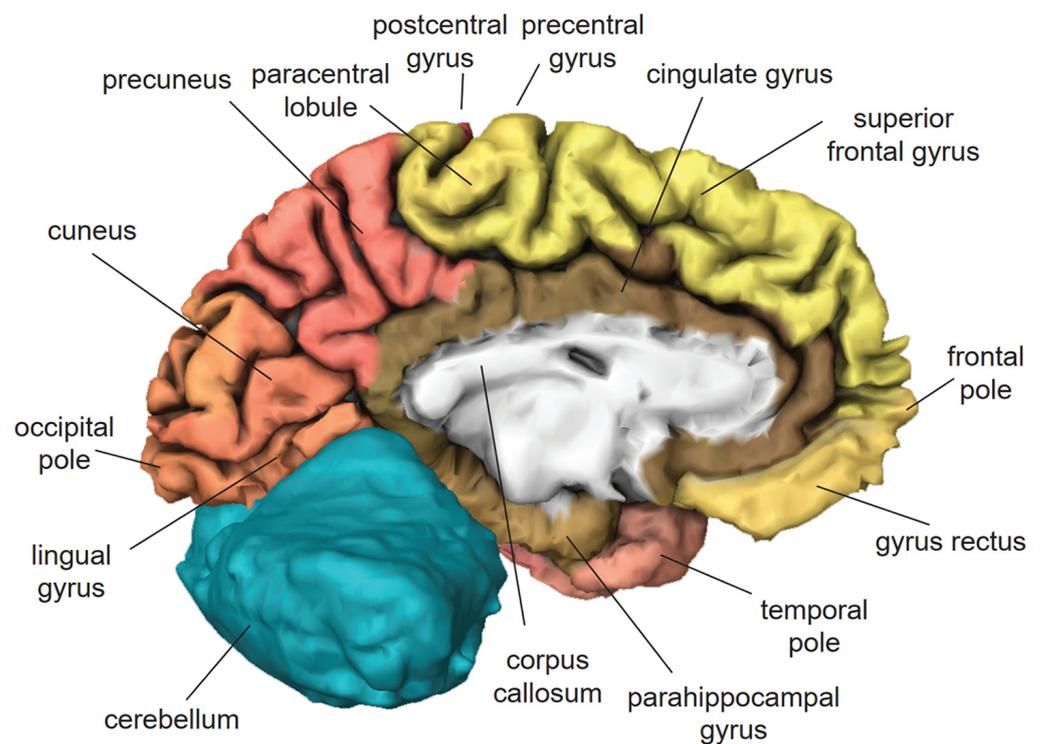


Figure 3. Midsagittal view of the left hemisphere of the human brain based on H0351.2002 dataset in Allen Brain Atlas. Frontal lobe (yellow), parietal lobe (red), temporal lobe (pink), occipital lobe (salmon), limbic system (brown), corpus callosum (white), cerebellum (turquoise).

3.3. Parietal Lobe

The parietal lobe is located in the middle-upper part of the head above the temporal lobe [56] (Figure 2). In VR applications, it is actively involved in creating the feeling of presence [88–91]. The postcentral gyrus contains the primary somatosensory cortex, which generates somatic sensations and the feeling of embodiment [92]. The superior parietal lobule (Figure 4) is involved in visual imagery [93], mental transformations of the body-in-space [94], and regulation of emotions [95]. The supramarginal gyrus contributes to proprioception [96], emotional responses [95], and the phonological processing of spoken and written language [97,98]. The angular gyrus plays a role in mental calculation [99], the encoding and retrieval of schema-associated memories [100], and imagination [101]. The precuneus (Figure 3) contributes to visuospatial imagery, retrieval of episodic memories, and self-processing operations, such as taking a first-person perspective or experiencing agency [102].

3.4. Occipital Lobe

The occipital lobe is located at the back of the head [56] (Figure 4). In VR applications, it is actively involved in creating visual images [103,104]. The primary visual cortex, which is responsible for vision, is mostly buried in the calcarine fissure located on the medial surface of the occipital lobe [105–107], but it also extends in the cuneus and the lingual gyrus, which flank the calcarine fissure on the top and bottom, respectively. The cuneus is involved in the basic processing of visual information received from the retina [108,109]. The lingual gyrus plays an important role in the process of reading, namely, the identification and recognition of words [110]. The superior, middle, and inferior occipital gyri contain visual association cortices, which interpret and give additional meaning to visual signals [111].

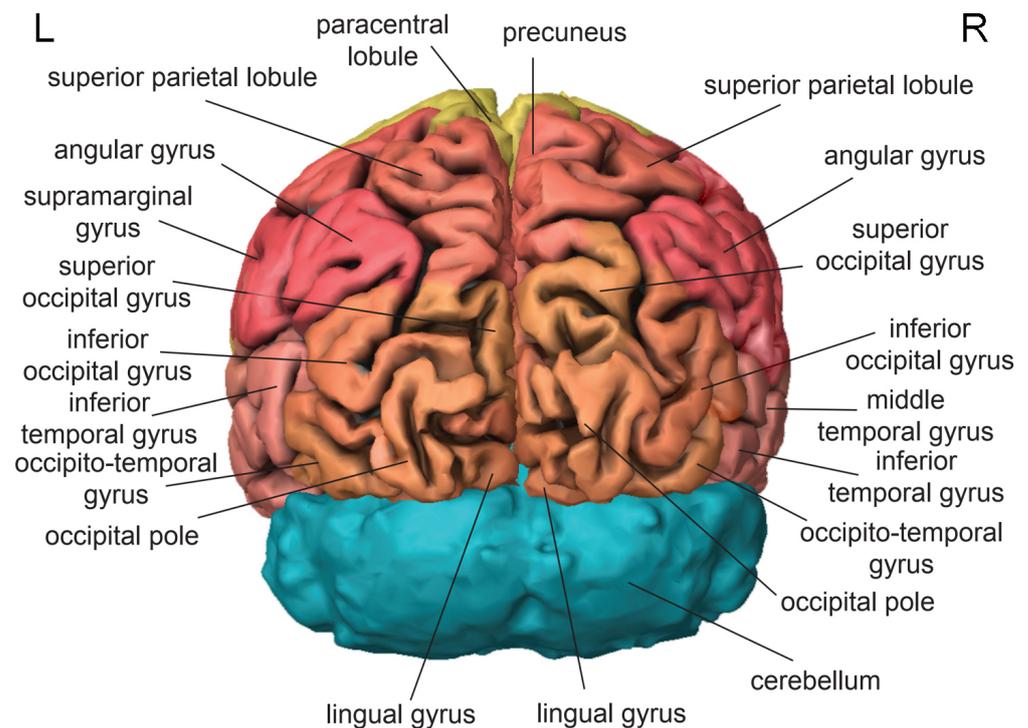


Figure 4. Posterior view of the human brain based on H0351.2002 dataset in Allen Brain Atlas. Frontal lobe (yellow), parietal lobe (red), temporal lobe (pink), occipital lobe (salmon), cerebellum (turquoise). L, left; R, right.

4. Virtual Reality for Neurorehabilitation

Brain injury is a serious medical condition that disrupts the normal functioning of the brain and severely impacts a person's life. Two major causes of brain damage are mechanical trauma, which is the most common type of brain injury seen in younger adults (<45 yo) [112], and vascular incidents (stroke), more commonly seen in older adults (>45 yo) [113]. Traumatic brain injury (TBI) and stroke lead to cognitive, neurological, and psychological disabilities that can be partially recovered by neurorehabilitation [114]. The most common types of disability resulting from brain injury are: paralysis or impaired motor control; sensory disturbances, including pain; cognitive disturbances, including compromised understanding or language use (aphasia), and impaired thinking and memory; and emotional disturbances, including feelings of fear, anxiety, frustration, or sadness. Inclusion of VR in the rehabilitation process has shown a promise for better functional outcomes, including the recovery of the damaged neural tissue and compensation of any functional alterations resulting from the injury [115].

4.1. Motor Rehabilitation

VR provides a safe, controlled environment for performing customizable, engaging rehabilitation activities that promote learning of motor skills [116]. Furthermore, because VR is fun and enjoyable, it motivates children to participate in the rehabilitation interventions [117]. The therapeutic effect of VR can be easily combined with computer-assisted cinematic analysis of motor deficits after brain lesions [118]. This allows for a reliable documentation of the degree of motor impairment in brain-injured patients undergoing rehabilitation therapy. Because the virtual environments are highly interactive, they strongly activate visual, vestibular, and proprioceptive systems during the execution of a virtual task, such as playing a video game. Immersion into the game can be achieved using head-mounted displays [119], which are accessible for all segments of the population at a relatively low cost and can be used for rehabilitation even in a typical home environment [120].

The main therapeutic effect of VR on upper limb motor activity is to increase the active range of motion (AROM) of the shoulder, elbow, and wrist [121,122]. Significant gray matter increases were detected by MRI with voxel-based morphometry in five brain areas: the tail of the hippocampus, the left caudate nucleus, the rostral cingulate zone, the depth of the central sulcus, and the visual cortex [122]. Furthermore, the gray matter volumes of motor, premotor, and supplementary motor cortices correlated positively with the power and AROM measured in motor tests [122]. Interestingly, EEG recordings showed significantly increased EEG concentration (indicated by strong beta waves) in the frontopolar 2 (FP2) and frontal 4 (F4) areas, and enhanced brain activity (indicated by higher average wave frequency) in the frontopolar 1 (FP1) and frontal 3 (F3) areas in an upper-extremity training group using VR [123]. The most important feature of VR interventions, however, is that the improved upper limb motor function recovers activities of daily living (ADL) of brain-injured patients and enhances their quality of life [124].

Brain injuries that affect motor cortex areas innervating the lower limb may result in impairments in the gait, maintenance and adaptation of balance, or postural control for a range of activities of daily living [125]. Because the working load on the lower limbs during walking also includes support of the person's body weight, gait rehabilitation is greatly assisted by robotic devices, which allow a smaller workforce and a longer exercise session with greater intensity compared to traditional treatment [126]. Lokomat is one such robotic device equipped with electronic control that allows connection to a non-immersive VR screen on which an avatar delivers visual feedback of the patient's movements. Inclusion of the VR feedback was found to significantly improve the patient's mood, perception of physical well-being, global cognitive functions, executive functions (such as perseveration, planning, and classification), cognitive flexibility, and selective attention—all of which impacted positively on the patient's quality of life [126]. Gait and balance interventions may also include a moving platform with an integrated treadmill that participants use to interact with a virtual environment. Projection of synchronized VR environments on a 180 degree cylindrical screen allows subjects to walk around and move in an attractive and engaging environment, which is particularly beneficial for the rehabilitation of children [127]. Similar to upper limb rehabilitation, the act of learning to control a walking avatar in the absence or presence of visuomotor perturbations lead to observable cortical adaptations in EEG activities [128], which indicates underlying neural plasticity and neural reorganization.

4.2. Cognitive Rehabilitation

The use of VR allows for a reproducible, objective assessment of cognitive processes underlying attention, memory, information processing, logical sequencing, and problem-solving [47,129]. VR also provides a safe environment in which to assess skills that might be too dangerous or risky to perform in the real world (e.g., cooking or driving), and the tested subjects are able to make mistakes without suffering the real consequences [129–131]. The stimulating effect of VR on the human mind is highly beneficial for cognitive rehabilitation. Brain injuries often display impairments of attention, memory, affectivity, behavior, planning, or executive functions [132]. Prospective memory failure, which is manifested as an inability to recall delayed intentions, is a serious problem that hinders everyday activities and heavily burdens the patients that experience it [133]. Non-immersive VR-based cognitive rehabilitation programs that run on a desktop computer allows for cost-effective training of patients [134] by enabling them to practice prospective memory tasks, such as preparing coffee in a virtual kitchen [131,135], operating an automated teller machine (ATM) to access their bank accounts [136], or purchasing items from a shopping list in a virtual convenience store [133,137]. Such VR-based training is well accepted by the patients and has demonstrated encouraging improvement in cognitive attributes that depend on frontal lobe functions, including immediate recall of prospective memory tasks and accurate execution of event-based, time-based, and ongoing tasks [138]. Significant improvements in learning following a VR exercise program are thought to be associated

with changes in neuronal plasticity that enhance the working memory [139]. VR also significantly increases cognitive flexibility, shifting skills, and selective attention, leading to better behavioral outcomes in brain-injured patients [140]. Improvement in selective memory processes and problem-solving skills facilitate social reintegration and leads to better vocational outcomes [141].

4.3. Emotional Rehabilitation

Brain injury often leads to anxiety, depression, emotional lability, and mood swings. Medication with antidepressants [142] or mood stabilizers [143] could be potentiated by emotional rehabilitation [144,145] that helps the patient overcome the pain of loss and return to a more stable, healthier place. Training in VR utilizes the positive effects of environmental enrichment [146] to trigger the neural mechanisms of recovery, including hippocampal neuroplasticity and neurogenesis [147,148], which have been implicated in the stress response and control of emotions [149], and are essential for the behavioral effects of antidepressants [150–152]. VR could also be used as a novel engagement tool that helps patients to understand their condition better, thereby increasing the reported level of understanding, comfort, and satisfaction [153]. The use of immersive VR further allows the combining of experiential enrichment and physical exercise, which greatly improves social, psychological, and emotional health [154]. The beneficial effects of exercise originate from structural and neurochemical adaptations in the central nervous system [155], including changes in several neurotransmitter systems, such as increased levels of catecholamines [156–159], which in turn increase attention, sharpen focus on performed tasks, enhance memory storage, and induce feelings of happiness [160].

4.4. Sensory Rehabilitation

Sensory deficits, including pain, may persist as long-term symptoms of traumatic injuries. In such cases, immersive VR could be used as a form of distraction analgesia alone or in combination with a pharmacological intervention (such as opioid administration) [161]. Maladaptive plasticity of the primary sensorimotor cortex, following deprivation of sensory input due to limb amputation, may lead to phantom pain, the management of which can be challenging [162]. One therapeutic method with proven efficacy for patients with post-amputation pain is the extended viewing in a mirror box of the movements performed by their intact limb [163,164]. Recent developments in immersive VR technologies allow the implementation of a VR mirror box, which was found to activate the primary sensorimotor cortex much more potently than the classical mirror box condition [165]. Thus, VR can build upon and improve the efficacy of conventional methods for pain management.

5. Virtual Reality for Replacement of Function

Severe brain injuries, which cause irreversible damage to neural tissue, may result in permanent loss of motor or sensory function. However, because the seat of human consciousness is located in the brain cortex, it is possible to replace lost functions with the use of BCIs, provided that the damage involves only the peripheral nervous system or the peripheral effector organs. In other words, the brain cortex can be directly connected to bionic devices, which are engineered to perform the lost functions of the damaged peripheral organs.

5.1. Replacement of Motor Function

Severe paralysis may be caused by different pathogenetic mechanisms, such as spinal cord trauma [166], neurodegenerative diseases affecting the motor neurons [167], autoimmune diseases causing muscle weakness [168], or genetic muscular dystrophies [169]. For severely paralyzed people, the use of a BCI permits successful re-establishment of communication with the surrounding world [170,171]. Because the muscles of paralyzed patients undergo disuse atrophy [172], the replacement of motor function is usually achieved through control of robotic devices. Surgically implanted BCIs detect electric signals from the cortical

surface using electrocorticography (ECoG), which ensures high spatial resolution [173]. For reliable control of external robotic devices, however, the electric activity should be recorded from regions of the brain cortex where voluntary mental operations could elicit certain discernible wavefronts, such as sensorimotor rhythms (SMRs) or the so-called P300 evoked response. SMR signals recorded over the sensorimotor cortex can be elicited voluntarily through motor imagination [67,68,174]. For example, during the act of imagined opening/closing of the hand, an event-related synchronization/desynchronization can be recorded on the ipsilateral/contralateral cortex in the EEG frequency band of 8–13 Hz [175]. The P300 response recorded from the parietal lobe [176,177] is an event-related potential component, which is elicited in the process of decision-making [178]. Because it is quite difficult to control one's own EEG signals, training protocols need to provide visual feedback that allows the subjects to monitor their progress [179]. VR can provide such feedback for tracking the progress of a BCI-controlling task [180] and can even sustain the illusion of embodiment through suitable sensory stimulation to reward specific brain-activity patterns [181–186]. Indeed, transcranial magnetic stimulation (TMS) has been successfully applied to achieve a sense of ownership and a sense of agency over an avatar in immersive VR [187]. The substitution of one's own body with a virtual body results in corresponding changes in perception, attitude, and behavior [188]. While the experimental swapping of bodies [189–192] and the body ownership illusion [188,193] may be considered as recreational applications in healthy individuals, the sense of embodiment provides disabled individuals with much more precise and reliable control over BCI-connected robotic devices. Thus, with the advent of VR technologies, it is possible to embody paralyzed individuals and endow them with BCI control over robotic devices, such as robotic arms, spellers, wheelchairs, or drones, all embedded with sensors and running specialized software for the purpose of connecting and exchanging data with other devices or systems over the internet [175]. Replacement of lost functions through BCIs in paralyzed or locked-in patients [15,194,195] gives them the chance of having a meaningful, dignified life.

5.2. Replacement of Sensory Function

Direct electric stimulation of the brain cortex is able to elicit conscious experiences in awake subjects (e.g., during neurosurgery) [196]. This fact could be exploited for the restoration of vision in blind patients through BCIs implanted in the visual cortex [197,198]. Traumatic injury of the eyes and their retinas leads to blindness due to malfunction of the peripheral sensory transduction of incoming light images into a series of electric spikes. For a functional replacement of the retina, bionic devices consisting of a charge-coupled device (CCD) digital camera connected to a portable computer, which processes the image in order to detect edges and perform black/white reversal, could be used. The processed image can then be delivered through electric stimulation of the visual cortex to produce phosphenes, which are colorless flashes of light on a black background [198–201]. Through the experience of phosphenes, a patient with bionic vision was capable of accomplishing a complex task, such as walking across a room, pulling a ski hat off a wall, and correctly putting the hat on the head of a mannequin [198,202]. The same patient also demonstrated that the bionic vision is useful for navigation in unfamiliar environments as he was able to ride the subway of a large city [198]. Thus, the bionic restoration of senses greatly improves the quality of life and facilitates social integration.

6. Virtual Reality for Self-Enhancement

VR shapes modern life, including entertainment and digital health. As with every tool, the quality of its use depends on the intentions of the user. Augmented reality provides easy access to vast amounts of computer-stored data, which is an ideal way to enhance users' creative problem-solving and decision-making [203–206]. VR could easily simulate any specific physical environment, such as a mountain [207], a forest [208], a beach [209], or a savannah [210], which could evoke positive emotions and hence improve cognitive

abilities. Because VR creates a storytelling experience, it is also able to profoundly affect the way we view ourselves and the surrounding world. This provides us with an opportunity to arrange individual life events into a story, which unfolds in settings that are designed to aid the self (for coping with frustration or resolving psychological conflicts). The presence of challenging experiences may profoundly change the way in which individuals perceive their life narratives and store their memories. Immersion in VR enables exploration of alternative scenarios that supply a vision of one's overall life trajectory in a more sensible and healthier way [211,212]. Taking into consideration the importance of the narrative self for discovering an individual's purpose in life, VR immersion could be utilized as a medium for the construction of a new storyline with a different attitude toward the past [7,8]. This approach will also revisit the attitudes toward the present moment and the future, and thus will better shape the narrative of the self for achieving healthier life experiences [213,214]. Thus, VR technology is ideally suited to aid self-improvement, which is about ending negative behaviors, and promote personal-development, which is about learning, growing, expanding awareness, and developing one's full potential. Maintaining a healthy state of mind and body facilitated by VR experiences allows one to live an exciting life in which one can take one's dreams and aspirations to the next level.

7. Conclusions

VR presents a breakthrough in the capability of technology to recreate reality and so it embodies the philosophical concept of the virtual [215] into a practical mode of experience. The concept of the virtual originates from the ontological concept of the illusion of reality [216]. Present-day VR, however, is a brilliant new medium that exceeds illusion and brings about tangible results in reality with unlimited potential for large-scale application in art, entertainment, relaxation, learning, exercise, training, and treatment or therapy. VR visualizes not only events but also psychological conditions and personalized perceptions [217–220], induces a sense of ownership [221,222] and of presence [223–227], offers immersion [228], and renders the self in different reality modes, such as being represented by avatar or having a different gender [229,230]. It also influences physical sensations in interventions, such as pain management [231,232] or stress and anxiety reduction [233]; induces necessary emotions, such as empathy [234]; or aims at achieving higher goals, such as self-development [235].

VR promises a plethora of experiences to people who engage in it and induces states of mind ranging from simplified to overwhelming. The scale of these states goes from pure excitement or fear [236,237] to more sophisticated ones that are combined with body states induced by exercise or meditation, such as training and learning new skills [238], deep relaxation, and general support of well-being [239,240]. VR may also help healthy individuals to redesign themselves in view of achieving a much more meaningful, purposeful, and exciting life.

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.

Author Contributions: Conceptualization, D.D.G., I.G. and G.V.G.; methodology, D.D.G., I.G. and G.V.G.; software, D.D.G. and G.V.G.; validation, D.D.G. and G.V.G.; formal analysis, D.D.G. and G.V.G.; investigation, D.D.G., I.G., Z.G., V.N. and G.V.G.; resources, D.D.G. and G.V.G.; data curation, D.D.G.; writing—original draft preparation, D.D.G.; writing—review and editing, D.D.G., I.G., Z.G., V.N. and G.V.G.; visualization, D.D.G. and Z.G.; supervision, D.D.G. and G.V.G.; project administration, D.D.G.; funding acquisition, G.V.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research has been partially financially supported by the European Union’s research and innovation programme Horizon 2020 under grant agreement No 856998, Academy of Finland 6Genesis Flagship (grant 318927), and by EDUFI Fellowship (grant TM-20-11342).

Data Availability Statement: H0351.2002 dataset used for rendering images of the human brain is publicly available from Allen Brain Atlas (<https://www.brain-map.org>). All brain reconstructions were rendered with Brain Explorer 2.3.5 (<https://human.brain-map.org/static/brainexplorer>), which can be freely downloaded and installed on Windows or Mac Operating Systems.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

ADL	activities of daily living
AR	augmented reality
AROM	active range of motion
ATM	automated teller machine
BCI	brain–computer interface
CCD	charge-coupled device
ECoG	electrocorticography
EEG	electroencephalography
HMD	head-mounted display
MEG	magnetoencephalography
MR	mixed reality
MRI	magnetic resonance imaging
NIRS	near-infrared spectroscopy
PET	positron emission tomography
SMR	sensorimotor rhythm
TBI	traumatic brain injury
TMS	transcranial magnetic stimulation
VR	virtual reality
XR	extended reality

References

1. Fenwick, T.; Edwards, R. Exploring the impact of digital technologies on professional responsibilities and education. *Eur. Educ. Res. J.* **2015**, *15*, 117–131. [[CrossRef](#)]
2. Hilbert, M. Digital technology and social change: The digital transformation of society from a historical perspective. *Dialogues Clin. Neurosci.* **2020**, *22*, 189–194. [[CrossRef](#)]
3. Chassiakos, Y.R.; Radesky, J.; Christakis, D.; Moreno, M.A.; Cross, C. Children and adolescents and digital media. *Pediatrics* **2016**, *138*, e20162593. [[CrossRef](#)]
4. Small, G.W.; Lee, J.; Kaufman, A.; Jalil, J.; Siddarth, P.; Gaddipati, H.; Moody, T.D.; Bookheimer, S.Y. Brain health consequences of digital technology use. *Dialogues Clin. Neurosci.* **2020**, *22*, 179–187. [[CrossRef](#)]
5. Ghahramani, F.; Wang, J. Impact of smartphones on quality of life: A health information behavior perspective. *Inf. Syst. Front.* **2020**, *22*, 1275–1290. [[CrossRef](#)]
6. Cohen, J.; Bancelhon, J.M.; Grace, T. Digitally connected living and quality of life: An analysis of the Gauteng City-Region, South Africa. *Electron. J. Inf. Syst. Dev. Ctries.* **2018**, *84*, e12010. [[CrossRef](#)]
7. Georgieva, I.; Georgiev, G.V. Redesign me: Virtual reality experience of the line of life and its connection to a healthier self. *Behav. Sci.* **2019**, *9*, 111. [[CrossRef](#)] [[PubMed](#)]
8. Georgieva, I.; Georgiev, G.V. Reconstructing personal stories in virtual reality as a mechanism to recover the self. *Int. J. Environ. Res. Public Health* **2020**, *17*, 26. [[CrossRef](#)]
9. Lee, L.N.; Kim, M.J.; Hwang, W.J. Potential of augmented reality and virtual reality technologies to promote wellbeing in older adults. *Appl. Sci.* **2019**, *9*, 3556. [[CrossRef](#)]
10. Cortés-Pérez, I.; Nieto-Escamez, F.A.; Obrero-Gaitán, E. Immersive virtual reality in stroke patients as a new approach for reducing postural disabilities and falls risk: A case series. *Brain Sci.* **2020**, *10*, 296. [[CrossRef](#)]
11. Aulísio, M.C.; Han, D.Y.; Glueck, A.C. Virtual reality gaming as a neurorehabilitation tool for brain injuries in adults: A systematic review. *Brain Inj.* **2020**, *34*, 1322–1330. [[CrossRef](#)] [[PubMed](#)]

12. Hochberg, L.R.; Serruya, M.D.; Friehs, G.M.; Mukand, J.A.; Saleh, M.; Caplan, A.H.; Branner, A.; Chen, D.; Penn, R.D.; Donoghue, J.P. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* **2006**, *442*, 164–171. [[CrossRef](#)]
13. Onose, G.; Grozea, C.; Anghelescu, A.; Daia, C.; Sinescu, C.J.; Ciurea, A.V.; Spircu, T.; Mirea, A.; Andone, I.; Spânu, A.; et al. On the feasibility of using motor imagery EEG-based brain–computer interface in chronic tetraplegics for assistive robotic arm control: A clinical test and long-term post-trial follow-up. *Spinal Cord* **2012**, *50*, 599–608. [[CrossRef](#)]
14. Vansteensel, M.J.; Pels, E.G.M.; Bleichner, M.G.; Branco, M.P.; Denison, T.; Freudenburg, Z.V.; Gosselaar, P.; Leinders, S.; Ottens, T.H.; Van Den Boom, M.A.; et al. Fully implanted brain-computer interface in a locked-in patient with ALS. *N. Engl. J. Med.* **2016**, *375*, 2060–2066. [[CrossRef](#)]
15. Pandarinath, C.; Nuyujukian, P.; Blabe, C.H.; Sorice, B.L.; Saab, J.; Willett, F.R.; Hochberg, L.R.; Shenoy, K.V.; Henderson, J.M. High performance communication by people with paralysis using an intracortical brain-computer interface. *eLife* **2017**, *6*, e18554. [[CrossRef](#)]
16. Leeb, R.; Perez-Marcos, D. Brain-computer interfaces and virtual reality for neurorehabilitation. In *Handbook of Clinical Neurology*; Elsevier: Amsterdam, The Netherlands, 2020; Volume 168, pp. 183–197. [[CrossRef](#)]
17. Hwang, J.; Lee, S. The effect of virtual reality program on the cognitive function and balance of the people with mild cognitive impairment. *J. Phys. Ther. Sci.* **2017**, *29*, 1283–1286. [[CrossRef](#)]
18. Bauer, A.C.M.; Andringa, G. The potential of immersive virtual reality for cognitive training in elderly. *Gerontology* **2020**, *66*, 614–623. [[CrossRef](#)] [[PubMed](#)]
19. Gamito, P.; Oliveira, J.; Alves, C.; Santos, N.; Coelho, C.; Brito, R. Virtual reality-based cognitive stimulation to improve cognitive functioning in community elderly: A controlled study. *Cyberpsychol. Behav. Soc. Netw.* **2020**, *23*, 150–156. [[CrossRef](#)] [[PubMed](#)]
20. Liao, Y.Y.; Tseng, H.Y.; Lin, Y.J.; Wang, C.J.; Hsu, W.C. 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*, 47–57. [[CrossRef](#)] [[PubMed](#)]
21. Mancuso, V.; Stramba-Badiale, C.; Cavedoni, S.; Pedroli, E.; Cipresso, P.; Riva, G. Virtual reality meets non-invasive brain stimulation: Integrating two methods for cognitive rehabilitation of mild cognitive impairment. *Front. Neurol.* **2020**, *11*, 1117. [[CrossRef](#)]
22. Thapa, N.; Park, H.J.; Yang, J.G.; Son, H.; Jang, M.; Lee, J.; Kang, S.W.; Park, K.W.; Park, H. The effect of a virtual reality-based intervention program on cognition in older adults with mild cognitive impairment: A randomized control trial. *J. Clin. Med.* **2020**, *9*, 1283. [[CrossRef](#)]
23. Citri, A.; Malenka, R.C. Synaptic plasticity: Multiple forms, functions, and mechanisms. *Neuropsychopharmacology* **2007**, *33*, 18–41. [[CrossRef](#)]
24. Hortsch, M.; Umemori, H. *The Sticky Synapse: Cell Adhesion Molecules and Their Role in Synapse Formation and Maintenance*; Springer: Dordrecht, The Netherlands, 2009. [[CrossRef](#)]
25. Hering, H.; Sheng, M. Dendritic spines: Structure, dynamics and regulation. *Nat. Rev. Neurosci.* **2001**, *2*, 880–888. [[CrossRef](#)] [[PubMed](#)]
26. Bock, J.; Gruss, M.; Becker, S.; Braun, K. Experience-induced changes of dendritic spine densities in the prefrontal and sensory cortex: Correlation with developmental time windows. *Cereb. Cortex* **2005**, *15*, 802–808. [[CrossRef](#)] [[PubMed](#)]
27. Holtmaat, A.J.G.D.; Trachtenberg, J.T.; Wilbrecht, L.; Shepherd, G.M.; Zhang, X.; Knott, G.W.; Svoboda, K. Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* **2005**, *45*, 279–291. [[CrossRef](#)]
28. Zhou, Y.; Lai, C.S.W.; Bai, Y.; Li, W.; Zhao, R.; Yang, G.; Frank, M.G.; Gan, W.B. REM sleep promotes experience-dependent dendritic spine elimination in the mouse cortex. *Nat. Commun.* **2020**, *11*, 4819. [[CrossRef](#)] [[PubMed](#)]
29. Chklovskii, D.B. Synaptic connectivity and neuronal morphology: Two sides of the same coin. *Neuron* **2004**, *43*, 609–617. [[CrossRef](#)]
30. Markham, J.A.; Greenough, W.T. Experience-driven brain plasticity: Beyond the synapse. *Neuron Glia Biol.* **2004**, *1*, 351–363. [[CrossRef](#)]
31. Hamilton, D.A.; Silasi, G.; Magcalas, C.M.; Pellis, S.M.; Kolb, B. Social and olfactory experiences modify neuronal morphology of orbital frontal cortex. *Behav. Neurosci.* **2020**, *134*, 59–68. [[CrossRef](#)]
32. Zhang, W.; Linden, D.J. The other side of the engram: Experience-driven changes in neuronal intrinsic excitability. *Nat. Rev. Neurosci.* **2003**, *4*, 885–900. [[CrossRef](#)]
33. Schulz, D.J. Plasticity and stability in neuronal output via changes in intrinsic excitability: It’s what’s inside that counts. *J. Exp. Biol.* **2006**, *209*, 4821–4827. [[CrossRef](#)]
34. McKay, B.M.; Matthews, E.A.; Oliveira, F.A.; Disterhoft, J.F. Intrinsic neuronal excitability is reversibly altered by a single experience in fear conditioning. *J. Neurophysiol.* **2009**, *102*, 2763–2770. [[CrossRef](#)] [[PubMed](#)]
35. Parvizi, J.; Kastner, S. Promises and limitations of human intracranial electroencephalography. *Nat. Neurosci.* **2018**, *21*, 474–483. [[CrossRef](#)] [[PubMed](#)]
36. Racz, F.S.; Stylianou, O.; Mukli, P.; Eke, A. Multifractal and entropy analysis of resting-state electroencephalography reveals spatial organization in local dynamic functional connectivity. *Sci. Rep.* **2019**, *9*, 13474. [[CrossRef](#)]
37. Hill, R.M.; Boto, E.; Holmes, N.; Hartley, C.; Seedat, Z.A.; Leggett, J.; Roberts, G.; Shah, V.; Tierney, T.M.; Woolrich, M.W.; et al. A tool for functional brain imaging with lifespan compliance. *Nat. Commun.* **2019**, *10*, 4785. [[CrossRef](#)]

38. Tierney, T.M.; Mellor, S.; O'Neill, G.C.; Holmes, N.; Boto, E.; Roberts, G.; Hill, R.M.; Leggett, J.; Bowtell, R.; Brookes, M.J.; et al. Pragmatic spatial sampling for wearable MEG arrays. *Sci. Rep.* **2020**, *10*, 21609. [[CrossRef](#)] [[PubMed](#)]
39. Quaresima, V.; Ferrari, M. Functional near-infrared spectroscopy (fNIRS) for assessing cerebral cortex function during human behavior in natural/social situations: a concise review. *Organ. Res. Methods* **2016**, *22*, 46–68. [[CrossRef](#)]
40. Causse, M.; Chua, Z.; Peysakhovich, V.; Del Campo, N.; Matton, N. Mental workload and neural efficiency quantified in the prefrontal cortex using fNIRS. *Sci. Rep.* **2017**, *7*, 5222. [[CrossRef](#)] [[PubMed](#)]
41. Varvatsoulias, G. The physiological processes underpinning PET and fMRI techniques with an emphasis on the temporal and spatial resolution of these methods. *Psychol. Thought* **2013**, *6*, 173–195. [[CrossRef](#)]
42. Wehrli, H.F.; Hossain, M.; Lankes, K.; Liu, C.C.; Bezrukov, I.; Martirosian, P.; Schick, F.; Reischl, G.; Pichler, B.J. Simultaneous PET-MRI reveals brain function in activated and resting state on metabolic, hemodynamic and multiple temporal scales. *Nat. Med.* **2013**, *19*, 1184–1189. [[CrossRef](#)]
43. Jamadar, S.D.; Ward, P.G.D.; Close, T.G.; Fornito, A.; Premaratne, M.; O'Brien, K.; Stäb, D.; Chen, Z.; Shah, N.J.; Egan, G.F. Simultaneous BOLD-fMRI and constant infusion FDG-PET data of the resting human brain. *Sci. Data* **2020**, *7*, 363. [[CrossRef](#)]
44. Raichle, M.E. A brief history of human brain mapping. *Trends Neurosci.* **2009**, *32*, 118–126. [[CrossRef](#)]
45. Bijsterbosch, J.; Harrison, S.J.; Jbabdi, S.; Woolrich, M.; Beckmann, C.; Smith, S.; Duff, E.P. Challenges and future directions for representations of functional brain organization. *Nat. Neurosci.* **2020**, *23*, 1484–1495. [[CrossRef](#)]
46. Tian, Y.; Margulies, D.S.; Breakpear, M.; Zalesky, A. Topographic organization of the human subcortex unveiled with functional connectivity gradients. *Nat. Neurosci.* **2020**, *23*, 1421–1432. [[CrossRef](#)]
47. Ventura, S.; Brivio, E.; Riva, G.; Baños, R.M. Immersive versus non-immersive experience: Exploring the feasibility of memory assessment through 360° technology. *Front. Psychol.* **2019**, *10*, 2509. [[CrossRef](#)]
48. Sanchez-Vives, M.V.; Slater, M. From presence to consciousness through virtual reality. *Nat. Rev. Neurosci.* **2005**, *6*, 332–339. [[CrossRef](#)] [[PubMed](#)]
49. Bohil, C.J.; Alicea, B.; Biocca, F.A. Virtual reality in neuroscience research and therapy. *Nat. Rev. Neurosci.* **2011**, *12*, 752–762. [[CrossRef](#)]
50. Matthews, D. Virtual-reality applications give science a new dimension. *Nature* **2018**, *557*, 127–128. [[CrossRef](#)]
51. Porter, M.E.; Heppelmann, J.E. Why every organization needs an augmented reality strategy. *Harv. Bus. Rev.* **2017**, *95*, 46–57.
52. Invitto, S.; Spada, I.; De Paolis, L.T. Augmented reality, embodied cognition and learning. In *Augmented and Virtual Reality*; Lecture Notes in Computer Science; De Paolis, L.T., Mongelli, A., Eds.; Springer: Cham, Switzerland, 2015; pp. 125–134. [[CrossRef](#)]
53. Hu, X.; Georgiev, G.V.; Casakin, H. Mitigating design fixation with evolving extended reality technology: An emerging opportunity. *Proc. Des. Soc. Des. Conf.* **2020**, *1*, 1305–1314. [[CrossRef](#)]
54. Hu, X.; Georgiev, G.V. Opportunities with uncertainties: The outlook of virtual reality in the early stages of design. In *Proceedings of the Sixth International Conference on Design Creativity (ICDC 2020)*; Boujut, J.F., Cascini, G., Ahmed-Kristensen, S., Georgiev, G.V., Iivari, N., Eds.; The Design Society: Oulu, Finland, 2020; pp. 215–222. [[CrossRef](#)]
55. Park, E.; Yun, B.J.; Min, Y.S.; Lee, Y.S.; Moon, S.J.; Huh, J.W.; Cha, H.; Chang, Y.; Jung, T.D. Effects of a mixed reality-based cognitive training system compared to a conventional computer-assisted cognitive training system on mild cognitive impairment: A pilot study. *Cogn. Behav. Neurol.* **2019**, *32*, 172–178. [[CrossRef](#)]
56. Georgiev, D.D. *Quantum Information and Consciousness: A Gentle Introduction*; CRC Press: Boca Raton, FL, USA, 2017. [[CrossRef](#)]
57. Georgiev, D.D. Inner privacy of conscious experiences and quantum information. *Biosystems* **2020**, *187*, 104051. [[CrossRef](#)]
58. Georgiev, D.D. Quantum information theoretic approach to the mind–brain problem. *Prog. Biophys. Mol. Biol.* **2020**, *158*, 16–32. [[CrossRef](#)]
59. Van Essen, D.C.; Donahue, C.J.; Glasser, M.F. Development and evolution of cerebral and cerebellar cortex. *Brain Behav. Evol.* **2018**, *91*, 158–169. [[CrossRef](#)]
60. Georgiev, D.D.; Kolev, S.K.; Cohen, E.; Glazebrook, J.F. Computational capacity of pyramidal neurons in the cerebral cortex. *Brain Res.* **2020**, *1748*, 147069. [[CrossRef](#)]
61. Popper, K.R.; Eccles, J.C. *The Self and Its Brain: An Argument for Interactionism*; Routledge & Kegan Paul: London, UK, 1983. [[CrossRef](#)]
62. Eccles, J.C. *Facing Reality: Philosophical Adventures by a Brain Scientist*; Heidelberg Science Library; Springer: Berlin, Germany, 1970; Volume 13. [[CrossRef](#)]
63. Phillips, C.G.; Zeki, S.; Barlow, H.B. Localization of function in the cerebral cortex: Past, present and future. *Brain* **1984**, *107*, 328–361. [[CrossRef](#)]
64. Gross, C.G. *A Hole in the Head: More Tales in the History of Neuroscience*; MIT Press: Cambridge, MA, USA, 2009. [[CrossRef](#)]
65. Posner, M.I.; Petersen, S.E.; Fox, P.T.; Raichle, M.E. Localization of cognitive operations in the human brain. *Science* **1988**, *240*, 1627–1631. [[CrossRef](#)]
66. Ross, E.D. Cerebral localization of functions and the neurology of language: fact versus fiction or is it something else? *Neuroscientist* **2010**, *16*, 222–243. [[CrossRef](#)] [[PubMed](#)]
67. Vourvopoulos, A.; Bermudez, I.B.S. Motor priming in virtual reality can augment motor-imagery training efficacy in restorative brain-computer interaction: A within-subject analysis. *J. Neuroeng. Rehabil.* **2016**, *13*, 69. [[CrossRef](#)]
68. Vourvopoulos, A.; Pardo, O.M.; Lefebvre, S.; Neureither, M.; Saldana, D.; Jahng, E.; Liew, S.L. Effects of a brain-computer interface with virtual reality (VR) neurofeedback: A pilot study in chronic stroke patients. *Front. Hum. Neurosci.* **2019**, *13*, 210. [[CrossRef](#)]

69. Wiederhold, B.K.; Wiederhold, M.D. Virtual reality with fMRI: A breakthrough cognitive treatment tool. *Virtual Real.* **2008**, *12*, 259–267. [[CrossRef](#)]
70. Calabrò, R.S.; Naro, A.; Russo, M.; Leo, A.; De Luca, R.; Balletta, T.; Buda, A.; La Rosa, G.; Bramanti, A.; Bramanti, P. The role of virtual reality in improving motor performance as revealed by EEG: A randomized clinical trial. *J. Neuroeng. Rehabil.* **2017**, *14*, 53. [[CrossRef](#)]
71. Goldberg, I.I.; Harel, M.; Malach, R. When the brain loses its self: Prefrontal inactivation during sensorimotor processing. *Neuron* **2006**, *50*, 329–339. [[CrossRef](#)]
72. Fried, I.; Wilson, C.L.; MacDonald, K.A.; Behnke, E.J. Electric current stimulates laughter. *Nature* **1998**, *391*, 650. [[CrossRef](#)] [[PubMed](#)]
73. Kübler, A.; Dixon, V.; Garavan, H. Automaticity and reestablishment of executive control—An fMRI study. *J. Cogn. Neurosci.* **2006**, *18*, 1331–1342. [[CrossRef](#)]
74. Raye, C.L.; Johnson, M.K.; Mitchell, K.J.; Reeder, J.A.; Greene, E.J. Neuroimaging a single thought: Dorsolateral PFC activity associated with refreshing just-activated information. *NeuroImage* **2002**, *15*, 447–453. [[CrossRef](#)] [[PubMed](#)]
75. Zhang, J.X.; Leung, H.C.; Johnson, M.K. Frontal activations associated with accessing and evaluating information in working memory: An fMRI study. *NeuroImage* **2003**, *20*, 1531–1539. [[CrossRef](#)]
76. Babiloni, C.; Ferretti, A.; Del Gratta, C.; Carducci, F.; Vecchio, F.; Romani, G.L.; Rossini, P.M. Human cortical responses during one-bit delayed-response tasks: An fMRI study. *Brain Res. Bull.* **2005**, *65*, 383–390. [[CrossRef](#)] [[PubMed](#)]
77. Dronkers, N.F.; Plaisant, O.; Iba-Zizen, M.T.; Cabanis, E.A. Paul Broca’s historic cases: High resolution MR imaging of the brains of Leborgne and Lelong. *Brain* **2007**, *130*, 1432–1441. [[CrossRef](#)]
78. Kwan, C.L.; Crawley, A.P.; Mikulis, D.J.; Davis, K.D. An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. *Pain* **2000**, *85*, 359–374. [[CrossRef](#)]
79. Foland-Ross, L.C.; Hamilton, P.; Sacchet, M.D.; Furman, D.J.; Sherdell, L.; Gotlib, I.H. Activation of the medial prefrontal and posterior cingulate cortex during encoding of negative material predicts symptom worsening in major depression. *Neuroreport* **2014**, *25*, 324–329. [[CrossRef](#)] [[PubMed](#)]
80. Shackman, A.J.; Salomons, T.V.; Slagter, H.A.; Fox, A.S.; Winter, J.J.; Davidson, R.J. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat. Rev. Neurosci.* **2011**, *12*, 154–167. [[CrossRef](#)] [[PubMed](#)]
81. Binney, R.J.; Ralph, M.A.L. Using a combination of fMRI and anterior temporal lobe rTMS to measure intrinsic and induced activation changes across the semantic cognition network. *Neuropsychologia* **2015**, *76*, 170–181. [[CrossRef](#)]
82. Bréchet, L.; Mange, R.; Herbelin, B.; Theillaud, Q.; Gauthier, B.; Serino, A.; Blanke, O. First-person view of one’s body in immersive virtual reality: Influence on episodic memory. *PLoS ONE* **2019**, *14*, e0197763. [[CrossRef](#)] [[PubMed](#)]
83. Price, C.J.; Price, C.J.; Wise, R.J.S.; Warburton, E.A.; Moore, C.J.; Howard, D.; Patterson, K.; Frackowiak, R.S.J.; Friston, K.J. Hearing and saying: The functional neuro-anatomy of auditory word processing. *Brain* **1996**, *119*, 919–931. [[CrossRef](#)] [[PubMed](#)]
84. Xu, J.; Wang, J.; Fan, L.; Li, H.; Zhang, W.; Hu, Q.; Jiang, T. Tractography-based parcellation of the human middle temporal gyrus. *Sci. Rep.* **2015**, *5*, 18883. [[CrossRef](#)]
85. Buckner, R.L.; Koutstaal, W.; Schacter, D.L.; Rosen, B.R. Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming. *Brain* **2000**, *123*, 620–640. [[CrossRef](#)] [[PubMed](#)]
86. Nasr, S.; Tootell, R.B.H. Role of fusiform and anterior temporal cortical areas in facial recognition. *NeuroImage* **2012**, *63*, 1743–1753. [[CrossRef](#)]
87. Takahashi, E.; Ohki, K.; Miyashita, Y. The role of the parahippocampal gyrus in source memory for external and internal events. *NeuroReport* **2002**, *13*, 1951–1956. [[CrossRef](#)]
88. Ehrsson, H.H.; Holmes, N.P.; Passingham, R.E. Touching a rubber hand: Feeling of body ownership is associated with activity in multisensory brain areas. *J. Neurosci.* **2005**, *25*, 10564–10573. [[CrossRef](#)]
89. Slater, M.; Pérez Marcos, D.; Ehrsson, H.; Sanchez-Vives, M. Inducing illusory ownership of a virtual body. *Front. Neurosci.* **2009**, *3*, 29. [[CrossRef](#)] [[PubMed](#)]
90. Kilteni, K.; Groten, R.; Slater, M. The sense of embodiment in virtual reality. *Presence* **2012**, *21*, 373–387. [[CrossRef](#)]
91. Clemente, M.; Rey, B.; Rodríguez-Pujadas, A.; Barros-Loscertales, A.; Baños, R.M.; Botella, C.; Alcañiz, M.; Ávila, C. An fMRI study to analyze neural correlates of presence during virtual reality experiences. *Interact. Comput.* **2014**, *26*, 269–284. [[CrossRef](#)]
92. Brecht, M. The body model theory of somatosensory cortex. *Neuron* **2017**, *94*, 985–992. [[CrossRef](#)]
93. Andersson, P.; Ragni, F.; Lingnau, A. Visual imagery during real-time fMRI neurofeedback from occipital and superior parietal cortex. *NeuroImage* **2019**, *200*, 332–343. [[CrossRef](#)] [[PubMed](#)]
94. Bonda, E.; Petrides, M.; Frey, S.; Evans, A. Neural correlates of mental transformations of the body-in-space. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 11180–11184. [[CrossRef](#)] [[PubMed](#)]
95. Wadden, K.P.; Snow, N.J.; Sande, P.; Slawson, S.; Waller, T.; Boyd, L.A. Yoga practitioners uniquely activate the superior parietal lobule and supramarginal gyrus during emotion regulation. *Front. Integr. Neurosci.* **2018**, *12*, 60. [[CrossRef](#)]
96. Ben-Shabat, E.; Matyas, T.A.; Pell, G.S.; Brodtmann, A.; Carey, L.M. The right supramarginal gyrus is important for proprioception in healthy and stroke-affected participants: A functional MRI study. *Front. Neurol.* **2015**, *6*, 248. [[CrossRef](#)] [[PubMed](#)]
97. Celsis, P.; Boulanouar, K.; Doyon, B.; Ranjeva, J.P.; Berry, I.; Nespoulous, J.L.; Chollet, F. Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. *NeuroImage* **1999**, *9*, 135–144. [[CrossRef](#)]

98. Oberhuber, M.; Hope, T.M.H.; Seghier, M.L.; Parker Jones, O.; Prejawa, S.; Green, D.W.; Price, C.J. Four functionally distinct regions in the left supramarginal gyrus support word processing. *Cereb. Cortex* **2016**, *26*, 4212–4226. [[CrossRef](#)]
99. Stanescu-Cosson, R.; Pinel, P.; van de Moortele, P.F.; Le Bihan, D.; Cohen, L.; Dehaene, S. Understanding dissociations in dyscalculia: A brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. *Brain* **2000**, *123*, 2240–2255. [[CrossRef](#)]
100. van der Linden, M.; Berkers, R.M.W.J.; Morris, R.G.M.; Fernández, G. Angular gyrus involvement at encoding and retrieval is associated with durable but less specific memories. *J. Neurosci.* **2017**, *37*, 9474–9485. [[CrossRef](#)] [[PubMed](#)]
101. Tanaka, S.; Kirino, E. Increased functional connectivity of the angular gyrus during imagined music performance. *Front. Hum. Neurosci.* **2019**, *13*, 92. [[CrossRef](#)]
102. Cavanna, A.E.; Trimble, M.R. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* **2006**, *129*, 564–583. [[CrossRef](#)] [[PubMed](#)]
103. Glickstein, M. The discovery of the visual cortex. *Sci. Am.* **1988**, *259*, 118–127. [[CrossRef](#)] [[PubMed](#)]
104. Bekrater-Bodmann, R.; Foell, J.; Diers, M.; Kamping, S.; Rance, M.; Kirsch, P.; Trojan, J.; Fuchs, X.; Bach, F.; Çakmak, H.K.; et al. The importance of synchrony and temporal order of visual and tactile input for illusory limb ownership experiences—An fMRI study applying virtual reality. *PLoS ONE* **2014**, *9*, e87013. [[CrossRef](#)]
105. Tootell, R.B.H.; Hadjikhani, N.K.; Vanduffel, W.; Liu, A.K.; Mendola, J.D.; Sereno, M.I.; Dale, A.M. Functional analysis of primary visual cortex (V1) in humans. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 811–817. [[CrossRef](#)]
106. Bridge, H. Mapping the visual brain: How and why. *Eye* **2011**, *25*, 291–296. [[CrossRef](#)]
107. Kawachi, J. Brodmann areas 17, 18, and 19 in the human brain: An overview. *Brain Nerve* **2017**, *69*, 397–410. [[CrossRef](#)]
108. Vanni, S.; Tanskanen, T.; Seppä, M.; Uutela, K.; Hari, R. Coinciding early activation of the human primary visual cortex and anteromedial cuneus. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 2776–2780. [[CrossRef](#)]
109. Yang, Y.L.; Deng, H.X.; Xing, G.Y.; Xia, X.L.; Li, H.F. Brain functional network connectivity based on a visual task: Visual information processing-related brain regions are significantly activated in the task state. *Neural Regen. Res.* **2015**, *10*, 298–307. [[CrossRef](#)]
110. Mechelli, A.; Humphreys, G.W.; Mayall, K.; Olson, A.; Price, C.J. Differential effects of word length and visual contrast in the fusiform and lingual gyri during reading. *Proc. R. Soc. Lond. Ser. B* **2000**, *267*, 1909–1913. [[CrossRef](#)]
111. Dong, Y.; Fukuyama, H.; Honda, M.; Okada, T.; Hanakawa, T.; Nakamura, K.; Nagahama, Y.; Nagamine, T.; Konishi, J.; Shibasaki, H. Essential role of the right superior parietal cortex in Japanese kana mirror reading: An fMRI study. *Brain* **2000**, *123*, 790–799. [[CrossRef](#)]
112. Faul, M.; Coronado, V. Epidemiology of traumatic brain injury. In *Handbook of Clinical Neurology*; Grafman, J., Salazar, A.M., Eds.; Elsevier: Amsterdam, The Netherlands, 2015; Volume 127, Chapter 1, pp. 3–13. [[CrossRef](#)]
113. Guzik, A.; Bushnell, C. Stroke epidemiology and risk factor management. *Contin. Lifelong Learn. Neurol.* **2017**, *23*, 15–39. [[CrossRef](#)]
114. Castor, N.; El Massioui, F. Traumatic brain injury and stroke: Does recovery differ? *Brain Inj.* **2018**, *32*, 1803–1810. [[CrossRef](#)]
115. Weiss, P.L.T.; Keshner, E.A.; Levin, M.F. *Virtual Reality for Physical and Motor Rehabilitation*; Virtual Reality Technologies for Health and Clinical Applications; Springer: New York, NY, USA, 2014. [[CrossRef](#)]
116. Aida, J.; Chau, B.; Dunn, J. Immersive virtual reality in traumatic brain injury rehabilitation: A literature review. *NeuroRehabilitation* **2018**, *42*, 441–448. [[CrossRef](#)] [[PubMed](#)]
117. Levac, D.; Miller, P.; Missiuna, C. Usual and virtual reality video game-based physiotherapy for children and youth with acquired brain injuries. *Phys. Occup. Ther. Pediatr.* **2012**, *32*, 180–195. [[CrossRef](#)] [[PubMed](#)]
118. Piron, L.; Cenni, F.; Tonin, P.; Dam, M. Virtual Reality as an assessment tool for arm motor deficits after brain lesions. *Stud. Health Technol. Inform.* **2001**, *81*, 386–392. [[CrossRef](#)] [[PubMed](#)]
119. Gatica-Rojas, V.; Mendez-Rebolledo, G. Virtual reality interface devices in the reorganization of neural networks in the brain of patients with neurological diseases. *Neural Regen. Res.* **2014**, *9*, 888–896. [[CrossRef](#)]
120. Saposnik, G.; Teasell, R.; Mamdani, M.; Hall, J.; McIlroy, W.; Cheung, D.; Thorpe Kevin, E.; Cohen Leonardo, G.; Bayley, M. Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation. *Stroke* **2010**, *41*, 1477–1484. [[CrossRef](#)]
121. Fernandes, A.B.; Passos, J.O.; Brito, D.P.; Campos, T.F. Comparison of the immediate effect of the training with a virtual reality game in stroke patients according side brain injury. *NeuroRehabilitation* **2014**, *35*, 39–45. [[CrossRef](#)]
122. Keller, J.; Stetkarova, I.; Macri, V.; Kuhn, S.; Petioky, J.; Gualeni, S.; Simmons, C.D.; Arthanat, S.; Zilber, P. Virtual reality-based treatment for regaining upper extremity function induces cortex grey matter changes in persons with acquired brain injury. *J. Neuroeng. Rehabil.* **2020**, *17*, 127. [[CrossRef](#)]
123. Lee, S.H.; Kim, Y.M.; Lee, B.H. Effects of virtual reality-based bilateral upper-extremity training on brain activity in post-stroke patients. *J. Phys. Ther. Sci.* **2015**, *27*, 2285–2287. [[CrossRef](#)]
124. Jung, S.M.; Choi, W.H. Effects of virtual reality intervention on upper limb motor function and activity of daily living in patients with lesions in different regions of the brain. *J. Phys. Ther. Sci.* **2017**, *29*, 2103–2106. [[CrossRef](#)]
125. Bonuzzi, G.M.G.; de Freitas, T.B.; Palma, G.; Soares, M.A.A.; Lange, B.; Pompeu, J.E.; Torriani-Pasin, C. Effects of the brain-damaged side after stroke on the learning of a balance task in a non-immersive virtual reality environment. *Physiother. Theory Pract.* **2020**. [[CrossRef](#)]

126. Maggio, M.G.; Torrisi, M.; Buda, A.; De Luca, R.; Piazzitta, D.; Cannavo, A.; Leo, A.; Milardi, D.; Manuli, A.; Calabrò, R.S. Effects of robotic neurorehabilitation through Lokomat plus virtual reality on cognitive function in patients with traumatic brain injury: A retrospective case-control study. *Int. J. Neurosci.* **2020**, *130*, 117–123. [[CrossRef](#)] [[PubMed](#)]
127. Biffi, E.; Beretta, E.; Cesareo, A.; Maghini, C.; Turconi, A.C.; Reni, G.; Strazzer, S. An immersive virtual reality platform to enhance walking ability of children with acquired brain injuries. *Methods Inf. Med.* **2017**, *56*, 119–126. [[CrossRef](#)]
128. Luu, T.P.; He, Y.; Brown, S.; Nakagame, S.; Contreras-Vidal, J.L. Gait adaptation to visual kinematic perturbations using a real-time closed-loop brain-computer interface to a virtual reality avatar. *J. Neural Eng.* **2016**, *13*, 036006. [[CrossRef](#)] [[PubMed](#)]
129. Zhang, L.; Abreu, B.C.; Masel, B.; Scheibel, R.S.; Christiansen, C.H.; Huddleston, N.; Ottenbacher, K.J. Virtual reality in the assessment of selected cognitive function after brain injury. *Am. J. Phys. Med. Rehabil.* **2001**, *80*, 597–604. [[CrossRef](#)] [[PubMed](#)]
130. Zhang, L.; Abreu, B.C.; Seale, G.S.; Masel, B.; Christiansen, C.H.; Ottenbacher, K.J. A virtual reality environment for evaluation of a daily living skill in brain injury rehabilitation: Reliability and validity. *Arch. Phys. Med. Rehabil.* **2003**, *84*, 1118–1124. [[CrossRef](#)]
131. Besnard, J.; Richard, P.; Banville, F.; Nolin, P.; Aubin, G.; Le Gall, D.; Richard, I.; Allain, P. Virtual reality and neuropsychological assessment: The reliability of a virtual kitchen to assess daily-life activities in victims of traumatic brain injury. *Appl. Neuropsychol. Adult* **2016**, *23*, 223–235. [[CrossRef](#)] [[PubMed](#)]
132. Maggio, M.G.; De Luca, R.; Molonia, F.; Porcari, B.; Destro, M.; Casella, C.; Salvati, R.; Bramanti, P.; Calabrò, R.S. Cognitive rehabilitation in patients with traumatic brain injury: A narrative review on the emerging use of virtual reality. *J. Clin. Neurosci.* **2019**, *61*, 1–4. [[CrossRef](#)] [[PubMed](#)]
133. Canty, A.L.; Fleming, J.; Patterson, F.; Green, H.J.; Man, D.; Shum, D.H. Evaluation of a virtual reality prospective memory task for use with individuals with severe traumatic brain injury. *Neuropsychol. Rehabil.* **2014**, *24*, 238–265. [[CrossRef](#)] [[PubMed](#)]
134. Johnson, D.A.; Rose, F.D.; Rushton, S.; Pentland, B.; Attree, E.A. Virtual reality: A new prosthesis for brain injury rehabilitation. *Scott. Med. J.* **1998**, *43*, 81–83. [[CrossRef](#)] [[PubMed](#)]
135. Allain, P.; Foloppe, D.A.; Besnard, J.; Yamaguchi, T.; Etcharry-Bouyx, F.; Le Gall, D.; Nolin, P.; Richard, P. Detecting everyday action deficits in Alzheimer’s disease using a nonimmersive virtual reality kitchen. *J. Int. Neuropsychol. Soc.* **2014**, *20*, 468–477. [[CrossRef](#)]
136. Fong, K.N.; Chow, K.Y.; Chan, B.C.; Lam, K.C.; Lee, J.C.; Li, T.H.; Yan, E.W.; Wong, A.T. Usability of a virtual reality environment simulating an automated teller machine for assessing and training persons with acquired brain injury. *J. Neuroeng. Rehabil.* **2010**, *7*, 19. [[CrossRef](#)]
137. Levy, C.E.; Miller, D.M.; Akande, C.A.; Lok, B.; Marsiske, M.; Halan, S. V-Mart, a virtual reality grocery store: A focus group study of a promising intervention for mild traumatic brain injury and posttraumatic stress disorder. *Am. J. Phys. Med. Rehabil.* **2019**, *98*, 191–198. [[CrossRef](#)]
138. Yip, B.C.; Man, D.W. Virtual reality-based prospective memory training program for people with acquired brain injury. *NeuroRehabilitation* **2013**, *32*, 103–115. [[CrossRef](#)] [[PubMed](#)]
139. Grealy, M.A.; Johnson, D.A.; Rushton, S.K. Improving cognitive function after brain injury: The use of exercise and virtual reality. *Arch. Phys. Med. Rehabil.* **1999**, *80*, 661–667. [[CrossRef](#)]
140. De Luca, R.; Maggio, M.G.; Maresca, G.; Latella, D.; Cannavo, A.; Sciarrone, F.; Lo Voi, E.; Accorinti, M.; Bramanti, P.; Calabrò, R.S. Improving cognitive function after traumatic brain injury: A clinical trial on the potential use of the semi-immersive virtual reality. *Behav. Neurol.* **2019**, *2019*, 9268179. [[CrossRef](#)]
141. Man, D.W.; Poon, W.S.; Lam, C. The effectiveness of artificial intelligent 3-D virtual reality vocational problem-solving training in enhancing employment opportunities for people with traumatic brain injury. *Brain Inj.* **2013**, *27*, 1016–1025. [[CrossRef](#)]
142. Mysiw, W.J.; Jackson, R.D. Tricyclic antidepressant therapy after traumatic brain injury. *J. Head Trauma Rehabil.* **1987**, *2*, 34–42. [[CrossRef](#)]
143. Kalra, I.D.; Watanabe, T.K. Mood stabilizers for traumatic brain injury-related agitation. *J. Head Trauma Rehabil.* **2017**, *32*, E61–E64. [[CrossRef](#)] [[PubMed](#)]
144. Neumann, D. Treatments for emotional issues after traumatic brain injury. *J. Head Trauma Rehabil.* **2017**, *32*, 283–285. [[CrossRef](#)]
145. Neumann, D.; Malec, J.F.; Hammond, F.M. Reductions in alexithymia and emotion dysregulation after training emotional self-awareness following traumatic brain injury: A phase I trial. *J. Head Trauma Rehabil.* **2017**, *32*, 286–295. [[CrossRef](#)]
146. Clemenson, G.D.; Stark, C.E.L. Virtual environmental enrichment through video games improves hippocampal-associated memory. *J. Neurosci.* **2015**, *35*, 16116–16125. [[CrossRef](#)] [[PubMed](#)]
147. Toda, T.; Parylak, S.L.; Linker, S.B.; Gage, F.H. The role of adult hippocampal neurogenesis in brain health and disease. *Mol. Psychiatry* **2019**, *24*, 67–87. [[CrossRef](#)]
148. Berdugo-Vega, G.; Arias-Gil, G.; López-Fernández, A.; Artegiani, B.; Wasielewska, J.M.; Lee, C.C.; Lippert, M.T.; Kempermann, G.; Takagaki, K.; Calegari, F. Increasing neurogenesis refines hippocampal activity rejuvenating navigational learning strategies and contextual memory throughout life. *Nat. Commun.* **2020**, *11*, 135. [[CrossRef](#)]
149. Cameron, H.A.; Glover, L.R. Adult neurogenesis: Beyond learning and memory. *Annu. Rev. Psychol.* **2015**, *66*, 53–81. [[CrossRef](#)]
150. Malberg, J.E.; Eisch, A.J.; Nestler, E.J.; Duman, R.S. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* **2000**, *20*, 9104–9110. [[CrossRef](#)]
151. Santarelli, L.; Saxe, M.; Gross, C.; Surget, A.; Battaglia, F.; Dulawa, S.; Weisstaub, N.; Lee, J.; Duman, R.; Arancio, O.; et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **2003**, *301*, 805–809. [[CrossRef](#)] [[PubMed](#)]

152. Eisch, A.J.; Petrik, D. Depression and hippocampal neurogenesis: A road to remission? *Science* **2012**, *338*, 72–75. [[CrossRef](#)] [[PubMed](#)]
153. Collins, M.K.; Ding, V.Y.; Ball, R.L.; Dolce, D.L.; Henderson, J.M.; Halpern, C.H. Novel application of virtual reality in patient engagement for deep brain stimulation: A pilot study. *Brain Stimul.* **2018**, *11*, 935–937. [[CrossRef](#)]
154. Grealy, M.A.; Heffernan, D. The rehabilitation of brain injured children: The case for including physical exercise and virtual reality. *Pediatr. Rehabil.* **2000**, *4*, 41–49. [[CrossRef](#)]
155. Fordyce, D.E.; Farrar, R.P. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. *Behav. Brain Res.* **1991**, *46*, 123–133. [[CrossRef](#)]
156. Etnier, J.L.; Landers, D.M. Brain function and exercise. Current perspectives. *Sport. Med.* **1995**, *19*, 81–85. [[CrossRef](#)]
157. Etnier, J.L.; Salazar, W.; Landers, D.M.; Petruzzello, S.J.; Han, M.; Nowell, P. The influence of physical fitness and exercise upon cognitive functioning: A meta-analysis. *J. Sport Exerc. Psychol.* **1997**, *19*, 249–277. [[CrossRef](#)]
158. Lin, T.W.; Kuo, Y.M. Exercise benefits brain function: The monoamine connection. *Brain Sci.* **2013**, *3*, 39–53. [[CrossRef](#)]
159. Basso, J.C.; Suzuki, W.A. The effects of acute exercise on mood, cognition, neurophysiology, and neurochemical pathways: A review. *Brain Plast.* **2017**, *2*, 127–152. [[CrossRef](#)]
160. Loonen, A.J.M.; Ivanova, S.A. Circuits regulating pleasure and happiness—Mechanisms of depression. *Front. Hum. Neurosci.* **2016**, *10*, 571. [[CrossRef](#)]
161. Hoffman, H.G.; Richards, T.L.; Van Oostrom, T.; Coda, B.A.; Jensen, M.P.; Blough, D.K.; Sharar, S.R. The analgesic effects of opioids and immersive virtual reality distraction: Evidence from subjective and functional brain imaging assessments. *Anesth. Analg.* **2007**, *105*, 1776–1783. [[CrossRef](#)]
162. Makin, T.R.; Scholz, J.; Filippini, N.; Henderson Slater, D.; Tracey, I.; Johansen-Berg, H. Phantom pain is associated with preserved structure and function in the former hand area. *Nat. Commun.* **2013**, *4*, 1570. [[CrossRef](#)]
163. Ramachandran, V.S.; Rogers-Ramachandran, D. Synaesthesia in phantom limbs induced with mirrors. *Proc. R. Soc. Lond. Ser. B Biol. Sci.* **1996**, *263*, 377–386. [[CrossRef](#)]
164. Guenther, K. ‘It’s all done with mirrors’: V. S. Ramachandran and the material culture of phantom limb research. *Med Hist.* **2016**, *60*, 342–358. [[CrossRef](#)] [[PubMed](#)]
165. Diers, M.; Kamping, S.; Kirsch, P.; Rance, M.; Bekrater-Bodmann, R.; Foell, J.; Trojan, J.; Fuchs, X.; Bach, F.; Maass, H.; et al. Illusion-related brain activations: A new virtual reality mirror box system for use during functional magnetic resonance imaging. *Brain Res.* **2015**, *1594*, 173–182. [[CrossRef](#)] [[PubMed](#)]
166. Ahuja, C.S.; Wilson, J.R.; Nori, S.; Kotter, M.R.N.; Druschel, C.; Curt, A.; Fehlings, M.G. Traumatic spinal cord injury. *Nat. Rev. Dis. Prim.* **2017**, *3*, 17018. [[CrossRef](#)]
167. Brown, R.H.; Al-Chalabi, A. Amyotrophic lateral sclerosis. *N. Engl. J. Med.* **2017**, *377*, 162–172. [[CrossRef](#)]
168. Gilhus, N.E. Myasthenia gravis. *N. Engl. J. Med.* **2016**, *375*, 2570–2581. [[CrossRef](#)] [[PubMed](#)]
169. Mendell, J.R.; Campbell, K.; Rodino-Klapac, L.; Sahenk, Z.; Shilling, C.; Lewis, S.; Bowles, D.; Gray, S.; Li, C.; Galloway, G.; et al. Dystrophin immunity in Duchenne’s muscular dystrophy. *N. Engl. J. Med.* **2010**, *363*, 1429–1437. [[CrossRef](#)]
170. Wolpaw, J.R.; Birbaumer, N.; McFarland, D.J.; Pfurtscheller, G.; Vaughan, T.M. Brain-computer interfaces for communication and control. *Clin. Neurophysiol.* **2002**, *113*, 767–791. [[CrossRef](#)]
171. Hashimoto, Y.; Ushiba, J.; Kimura, A.; Liu, M.; Tomita, Y. Change in brain activity through virtual reality-based brain-machine communication in a chronic tetraplegic subject with muscular dystrophy. *BMC Neurosci.* **2010**, *11*, 117. [[CrossRef](#)] [[PubMed](#)]
172. Rudrappa, S.S.; Wilkinson, D.J.; Greenhaff, P.L.; Smith, K.; Idris, I.; Atherton, P.J. Human skeletal muscle disuse atrophy: Effects on muscle protein synthesis, breakdown, and insulin resistance—A qualitative review. *Front. Physiol.* **2016**, *7*, 361. [[CrossRef](#)] [[PubMed](#)]
173. Leinders, S.; Vansteensel, M.J.; Branco, M.P.; Freudenburg, Z.V.; Pels, E.G.M.; Van der Vijgh, B.; Van Zandvoort, M.J.E.; Ramsey, N.F.; Aarnoutse, E.J. Dorsolateral prefrontal cortex-based control with an implanted brain–computer interface. *Sci. Rep.* **2020**, *10*, 15448. [[CrossRef](#)] [[PubMed](#)]
174. Skola, F.; Tinkova, S.; Liarokapis, F. Progressive training for motor imagery brain-computer interfaces using gamification and virtual reality embodiment. *Front. Hum. Neurosci.* **2019**, *13*, 329. [[CrossRef](#)] [[PubMed](#)]
175. Coogan, C.G.; He, B. Brain-computer interface control in a virtual reality environment and applications for the internet of things. *IEEE Access* **2018**, *6*, 10840–10849. [[CrossRef](#)]
176. Chapman, R.M.; Bragdon, H.R. Evoked responses to numerical and non-numerical visual stimuli while problem solving. *Nature* **1964**, *203*, 1155–1157. [[CrossRef](#)]
177. Rohani, D.A.; Sorensen, H.B.; Puthusserypady, S. Brain-computer interface using P300 and virtual reality: A gaming approach for treating ADHD. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2014**, *2014*, 3606–3609. [[CrossRef](#)]
178. Regaçone, S.F.; Lima, D.D.B.; Banzato, M.S.; Gução, A.C.B.; Valenti, V.E.; Frizzo, A.C.F. Association between central auditory processing mechanism and cardiac autonomic regulation. *Int. Arch. Med.* **2014**, *7*, 21. [[CrossRef](#)]
179. Ron-Angevin, R.; Diaz-Estrella, A. Brain-computer interface: Changes in performance using virtual reality techniques. *Neurosci. Lett.* **2009**, *449*, 123–127. [[CrossRef](#)] [[PubMed](#)]
180. Salisbury, D.B.; Dahdah, M.; Driver, S.; Parsons, T.D.; Richter, K.M. Virtual reality and brain computer interface in neurorehabilitation. *Bayl. Univ. Med Cent. Proc.* **2016**, *29*, 124–127. [[CrossRef](#)]

181. Juliano, J.M.; Spicer, R.P.; Vourvopoulos, A.; Lefebvre, S.; Jann, K.; Ard, T.; Santarnecchi, E.; Krum, D.M.; Liew, S.L. Embodiment is related to better performance on a brain-computer interface in immersive virtual reality: A pilot study. *Sensors* **2020**, *20*, 1204. [[CrossRef](#)] [[PubMed](#)]
182. Yee, N.; Bailenson, J. The Proteus effect: The effect of transformed self-representation on behavior. *Hum. Commun. Res.* **2007**, *33*, 271–290. [[CrossRef](#)]
183. Azocar, A.F.; Mooney, L.M.; Duval, J.F.; Simon, A.M.; Hargrove, L.J.; Rouse, E.J. Design and clinical implementation of an open-source bionic leg. *Nat. Biomed. Eng.* **2020**, *4*, 941–953. [[CrossRef](#)]
184. Graczyk, E.L.; Resnik, L.; Schiefer, M.A.; Schmitt, M.S.; Tyler, D.J. Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. *Sci. Rep.* **2018**, *8*, 9866. [[CrossRef](#)] [[PubMed](#)]
185. Ortiz-Catalan, M.; Mastinu, E.; Sassu, P.; Aszmann, O.; Brånemark, R. Self-contained neuromusculoskeletal arm prostheses. *N. Engl. J. Med.* **2020**, *382*, 1732–1738. [[CrossRef](#)] [[PubMed](#)]
186. Lim, H.; Kim, W.S.; Ku, J. Transcranial direct current stimulation effect on virtual hand illusion. *Cyberpsychol. Behav. Soc. Netw.* **2020**, *23*, 541–549. [[CrossRef](#)] [[PubMed](#)]
187. Bassolino, M.; Franza, M.; Bello Ruiz, J.; Pinardi, M.; Schmidlin, T.; Stephan, M.A.; Solca, M.; Serino, A.; Blanke, O. Non-invasive brain stimulation of motor cortex induces embodiment when integrated with virtual reality feedback. *Eur. J. Neurosci.* **2018**, *47*, 790–799. [[CrossRef](#)] [[PubMed](#)]
188. Banakou, D.; Kishore, S.; Slater, M. Virtually being Einstein results in an improvement in cognitive task performance and a decrease in age bias. *Front. Psychol.* **2018**, *9*, 917. [[CrossRef](#)] [[PubMed](#)]
189. Cebolla, A.; Herrero, R.; Ventura, S.; Miragall, M.; Bellosta-Batalla, M.; Llorens, R.; Baños, R.M. Putting oneself in the body of others: A pilot study on the efficacy of an embodied virtual reality system to generate self-compassion. *Front. Psychol.* **2019**, *10*, 1521. [[CrossRef](#)]
190. Serino, S.; Pedroli, E.; Keizer, A.; Triberti, S.; Dakanalis, A.; Pallavicini, F.; Chirico, A.; Riva, G. Virtual reality body swapping: A tool for modifying the allocentric memory of the body. *Cyberpsychol. Behav. Soc. Netw.* **2015**, *19*, 127–133. [[CrossRef](#)]
191. Serino, S.; Polli, N.; Riva, G. From avatars to body swapping: The use of virtual reality for assessing and treating body-size distortion in individuals with anorexia. *J. Clin. Psychol.* **2019**, *75*, 313–322. [[CrossRef](#)]
192. Tacikowski, P.; Weijs, M.L.; Ehrsson, H.H. Perception of our own body influences self-concept and self-incoherence impairs episodic memory. *iScience* **2020**, *23*, 101429. [[CrossRef](#)]
193. Slater, M.; Pérez Marcos, D.; Ehrsson, H.; Sanchez-Vives, M. Towards a digital body: The virtual arm illusion. *Front. Hum. Neurosci.* **2008**, *2*, 6. [[CrossRef](#)]
194. Birbaumer, N.; Murguialday, A.R.; Cohen, L. Brain-computer interface in paralysis. *Curr. Opin. Neurol.* **2008**, *21*, 634–638. [[CrossRef](#)] [[PubMed](#)]
195. Okahara, Y.; Takano, K.; Nagao, M.; Kondo, K.; Iwadate, Y.; Birbaumer, N.; Kansaku, K. Long-term use of a neural prosthesis in progressive paralysis. *Sci. Rep.* **2018**, *8*, 16787. [[CrossRef](#)]
196. Penfield, W. *The Mystery of the Mind: A Critical Study of Consciousness and the Human Brain*; Princeton University Press: Princeton, NJ, USA, 1978.
197. Lewis, P.M.; Ackland, H.M.; Lowery, A.J.; Rosenfeld, J.V. Restoration of vision in blind individuals using bionic devices: A review with a focus on cortical visual prostheses. *Brain Res.* **2015**, *1595*, 51–73. [[CrossRef](#)] [[PubMed](#)]
198. Dobbela, W.H. Artificial vision for the blind by connecting a television camera to the visual cortex. *ASAIO J.* **2000**, *46*, 3–9. [[CrossRef](#)] [[PubMed](#)]
199. Yoshor, D.; Bosking, W.H.; Ghose, G.M.; Maunsell, J.H.R. Receptive fields in human visual cortex mapped with surface electrodes. *Cereb. Cortex* **2007**, *17*, 2293–2302. [[CrossRef](#)]
200. Bosking, W.H.; Sun, P.; Ozker, M.; Pei, X.; Foster, B.L.; Beauchamp, M.S.; Yoshor, D. Saturation in phosphene size with increasing current levels delivered to human visual cortex. *J. Neurosci.* **2017**, *37*, 7188–7197. [[CrossRef](#)]
201. Bosking, W.H.; Beauchamp, M.S.; Yoshor, D. Electrical stimulation of visual cortex: Relevance for the development of visual cortical prosthetics. *Annu. Rev. Vis. Sci.* **2017**, *3*, 141–166. [[CrossRef](#)]
202. Georgiev, D.D. Electric and magnetic fields inside neurons and their impact upon the cytoskeletal microtubules. In *Rhythmic Oscillations in Proteins to Human Cognition*; Bandyopadhyay, A., Ray, K., Eds.; Studies in Rhythm Engineering, Springer: Singapore, 2021; Chapter 3, pp. 51–102. [[CrossRef](#)]
203. Georgiev, G.V.; Georgiev, D.D. Enhancing user creativity: Semantic measures for idea generation. *Knowl. Based Syst.* **2018**, *151*, 1–15. [[CrossRef](#)]
204. Georgiev, G.V.; Georgiev, D.D. Semantic analysis approach to studying design problem solving. *Proc. Des. Soc. Int. Conf. Eng. Des.* **2019**, *1*, 1823–1832. [[CrossRef](#)]
205. Georgiev, G.V.; Georgiev, D.D. Semantic analysis of engineering design conversations. *Proc. Des. Soc. Des. Conf.* **2020**, *1*, 1265–1274. [[CrossRef](#)]
206. Gong, Z.; Georgiev, G.V. Literature review: Existing methods using VR to enhance creativity. In *Proceedings of the Sixth International Conference on Design Creativity (ICDC 2020)*; Boujut, J.F., Cascini, G., Ahmed-Kristensen, S., Georgiev, G.V., Iivari, N., Eds.; The Design Society: Oulu, Finland, 2020; pp. 117–124. [[CrossRef](#)]

207. Howett, D.; Castegnaro, A.; Krzywicka, K.; Hagman, J.; Marchment, D.; Henson, R.; Rio, M.; King, J.A.; Burgess, N.; Chan, D. Differentiation of mild cognitive impairment using an entorhinal cortex-based test of virtual reality navigation. *Brain* **2019**, *142*, 1751–1766. [[CrossRef](#)]
208. Browning, M.H.E.M.; Mimnaugh, K.J.; van Riper, C.J.; Laurent, H.K.; LaValle, S.M. Can simulated nature support mental health? Comparing short, single-doses of 360-degree nature videos in virtual reality with the outdoors. *Front. Psychol.* **2020**, *10*, 2667. [[CrossRef](#)] [[PubMed](#)]
209. Nijman, S.A.; Veling, W.; Greaves-Lord, K.; Vermeer, R.R.; Vos, M.; Zandee, C.E.R.; Zandstra, D.C.; Geraets, C.N.W.; Pijnenborg, G.H.M. Dynamic Interactive Social Cognition Training in Virtual Reality (DiSCoVR) for social cognition and social functioning in people with a psychotic disorder: Study protocol for a multicenter randomized controlled trial. *BMC Psychiatry* **2019**, *19*, 272. [[CrossRef](#)]
210. Dakoure, C.; Ben Abdesslem, H.; Boukadida, M.; Cuesta, M.; Bruneau, M.A.; Belleville, S.; Frasson, C. Virtual savannah: An effective therapeutic and relaxing treatment for people with subjective cognitive decline. In *Brain Function Assessment in Learning; Lecture Notes in Computer Science*; Frasson, C., Bamidis, P., Vlamos, P., Eds.; Springer: Cham, Switzerland, 2020; Volume 12462, pp. 107–112. [[CrossRef](#)]
211. Georgieva, I. The similarity between the virtual and the real self—how the virtual self can help the real self. *Stud. Health Technol. Inform.* **2011**, *167*, 20–25. [[CrossRef](#)]
212. Georgieva, I. Trauma and self-narrative in virtual reality: Toward recreating a healthier mind. *Front. ICT* **2017**, *4*, 27. [[CrossRef](#)]
213. Freeman, D.; Reeve, S.; Robinson, A.; Ehlers, A.; Clark, D.; Spanlang, B.; Slater, M. Virtual reality in the assessment, understanding, and treatment of mental health disorders. *Psychol. Med.* **2017**, *47*, 2393–2400. [[CrossRef](#)]
214. Slater, M.; Sanchez-Vives, M.V. Enhancing our lives with immersive virtual reality. *Front. Robot. AI* **2016**, *3*, 74. [[CrossRef](#)]
215. Heim, M. *The Metaphysics of Virtual Reality*; Oxford University Press: Oxford, UK, 1994.
216. Goddard, M.N. Genealogies of immersive media and virtual reality (VR) as practical aesthetic machines. In *Practical Aesthetics*; Herzogenrath, B., Ed.; Bloomsbury Academic: London, UK, 2020; pp. 171–181. [[CrossRef](#)]
217. Banakou, D. The Impact of Virtual Embodiment on Perception, Attitudes, and Behaviour. Ph.D. Thesis, Department of Clinical Psychology and Psychobiology, University of Barcelona, Barcelona, Spain, 2017.
218. Lee, M.; Lee, S.A.; Jeong, M.; Oh, H. Quality of virtual reality and its impacts on behavioral intention. *Int. J. Hosp. Manag.* **2020**, *90*, 102595. [[CrossRef](#)]
219. Martens, M.A.; Antley, A.; Freeman, D.; Slater, M.; Harrison, P.J.; Tunbridge, E.M. It feels real: Physiological responses to a stressful virtual reality environment and its impact on working memory. *J. Psychopharmacol.* **2019**, *33*, 1264–1273. [[CrossRef](#)]
220. Schutte, N.S. The impact of virtual reality on curiosity and other positive characteristics. *Int. J. Hum. Comput. Interact.* **2019**, *36*, 661–668. [[CrossRef](#)]
221. Jo, D.; Kim, K.; Welch, G.F.; Jeon, W.; Kim, Y.; Kim, K.H.; Kim, G.J. The impact of avatar-owner visual similarity on body ownership in immersive virtual reality. In *Proceedings of the 23rd ACM Symposium on Virtual Reality Software and Technology*; Association for Computing Machinery: Gothenburg, Sweden, 2017; p. 77. [[CrossRef](#)]
222. Waltemate, T.; Gall, D.; Roth, D.; Botsch, M.; Latoschik, M.E. The impact of avatar personalization and immersion on virtual body ownership, presence, and emotional response. *IEEE Trans. Vis. Comput. Graph.* **2018**, *24*, 1643–1652. [[CrossRef](#)] [[PubMed](#)]
223. Riva, G.; Mantovani, F.; Capideville, C.S.; Preziosa, A.; Morganti, F.; Villani, D.; Gaggioli, A.; Botella, C.; Alcañiz, M. Affective interactions using virtual reality: The link between presence and emotions. *Cyberpsychol. Behav.* **2007**, *10*, 45–56. [[CrossRef](#)] [[PubMed](#)]
224. Diemer, J.; Alpers, G.W.; Peperkorn, H.M.; Shiban, Y.; Mühlberger, A. The impact of perception and presence on emotional reactions: A review of research in virtual reality. *Front. Psychol.* **2015**, *6*, 26. [[CrossRef](#)] [[PubMed](#)]
225. Gonçalves, G.; Melo, M.; Vasconcelos-Raposo, J.; Bessa, M. Impact of different sensory stimuli on presence in credible virtual environments. *IEEE Trans. Vis. Comput. Graph.* **2020**, *26*, 3231–3240. [[CrossRef](#)]
226. Ochs, M.; Mestre, D.; de Montcheuil, G.; Pergandi, J.M.; Saubesty, J.; Lombardo, E.; Francon, D.; Blache, P. Training doctors' social skills to break bad news: Evaluation of the impact of virtual environment displays on the sense of presence. *J. Multimodal User Interfaces* **2019**, *13*, 41–51. [[CrossRef](#)]
227. Uhm, J.P.; Lee, H.W.; Han, J.W. Creating sense of presence in a virtual reality experience: Impact on neurophysiological arousal and attitude towards a winter sport. *Sport Manag. Rev.* **2020**, *23*, 588–600. [[CrossRef](#)]
228. Olmos-Raya, E.; Ferreira-Cavalcanti, J.; Contero, M.; Castellanos, M.C.; Giglioli, I.A.C.; Alcañiz, M. Mobile virtual reality as an educational platform: A pilot study on the impact of immersion and positive emotion induction in the learning process. *Eurasia J. Math. Sci. Technol. Educ.* **2018**, *14*, 2045–2057. [[CrossRef](#)]
229. Steed, A.; Pan, Y.; Zisch, F.; Steptoe, W. The impact of a self-avatar on cognitive load in immersive virtual reality. In *Proceedings of the 2016 IEEE Virtual Reality (VR)*; Institute of Electrical and Electronics Engineers: Greenville, South Carolina, 2016; pp. 67–76. [[CrossRef](#)]
230. Wiederhold, B.K. How will virtual reality impact our understanding of sexuality? *Cyberpsychol. Behav. Soc. Netw.* **2018**, *21*, 147–148. [[CrossRef](#)] [[PubMed](#)]
231. Jones, T.; Skadberg, R.; Moore, T. A pilot study of the impact of repeated sessions of virtual reality on chronic neuropathic pain. *Int. J. Virtual Real.* **2018**, *18*, 19–34. [[CrossRef](#)]

232. Ahmadpour, N.; Randall, H.; Choksi, H.; Gao, A.; Vaughan, C.; Poronnik, P. Virtual reality interventions for acute and chronic pain management. *Int. J. Biochem. Cell Biol.* **2019**, *114*, 105568. [[CrossRef](#)]
233. Van Ooteghem, G.; Geets, X. Virtual reality animations, a new strategy to reduce patients' anxiety induced by radiotherapy. *Radiother. Oncol.* **2019**, *133*, S280. [[CrossRef](#)]
234. Schutte, N.S.; Stilinović, E.J. Facilitating empathy through virtual reality. *Motiv. Emot.* **2017**, *41*, 708–712. [[CrossRef](#)]
235. Howard, M.C. Virtual reality interventions for personal development: A meta-analysis of hardware and software. *Hum. Comput. Interact.* **2019**, *34*, 205–239. [[CrossRef](#)]
236. Lambrakopoulos, G.; Begetis, N.; Katifori, A.; Karvounis, M.; Ioannidis, Y. Experimental evaluation of the impact of virtual reality on the sentiment of fear. In *Proceedings of the 23rd International Conference on Virtual System & Multimedia (VSMM)*; Goodman, L., Addison, A., Eds.; Institute of Electrical and Electronics Engineers: Dublin, Ireland, 2017; pp. 20–26. [[CrossRef](#)]
237. Pan, D.; Xu, Q.; Ma, S.; Zhang, K. The impact of fear of the sea on working memory performance: A research based on virtual reality. In *Proceedings of the 24th ACM Symposium on Virtual Reality Software and Technology*; Association for Computing Machinery: Tokyo, Japan, 2018; p. 38. [[CrossRef](#)]
238. Vázquez, C.; Xia, L.; Aikawa, T.; Maes, P. Words in motion: Kinesthetic language learning in virtual reality. In *Proceedings of the 18th International Conference on Advanced Learning Technologies (ICALT)*; Institute of Electrical and Electronics Engineers: Mumbai, India, 2018; pp. 272–276. [[CrossRef](#)]
239. Schutte, N.S.; Bhullar, N.; Stilinović, E.J.; Richardson, K. The impact of virtual environments on restorativeness and affect. *Ecopsychology* **2017**, *9*, 1–7. [[CrossRef](#)]
240. Singh, D.K.A.; Rahman, N.N.A.; Seffiyah, R.; Chang, S.Y.; Zainura, A.K.; Aida, S.R.; Rajwinder, K.H.S. Impact of virtual reality games on psychological well-being and upper limb performance in adults with physical disabilities: A pilot study. *Med J. Malays.* **2017**, *72*, 119–121.