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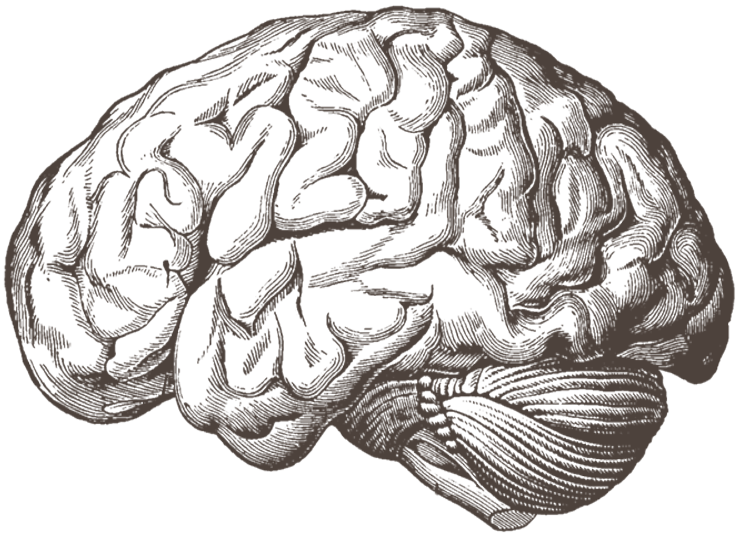

Integrating Robotics and Virtual Reality to Enhance Neuroplasticity and Stroke Rehabilitation

A Brief Review

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Introduction

Stroke rehabilitation has traditionally relied on equipment like stationary bicycles, treadmills, handrails, steps, resistant training, and so on. In recent decades, however, advances in various technologies have led to their gradual inclusion in rehabilitation practices. Among these technologies are virtual reality (VR) and robotics. Since the mid-1990s, there has been a growing literature documenting the development of, and supporting evidence for, the use of virtual reality for clinical applications (Greenleaf and Tovar 1994, Rizzo and Koenig 2017). Until recently, the cost and size of the technology made the widespread use of VR in clinical settings impractical. This began to change in the first decade of the 21st century as low-cost and efficient systems evolved. The advances in robotic technologies have followed a similar trajectory (Aisen et al 1997, Straudi and Basaglia 2017). Unfortunately, unlike VR, robotic technologies are not yet cost-effective enough for widespread use. In this paper, I will briefly review the use of virtual reality and robotics in the rehabilitation of stroke or other neurological injuries. This white paper will not provide a comprehensive synthesis of the available literature, but it will serve as a basic introduction. It will also explore the proposed neuroscientific foundations for the use of a platform that integrates these technologies to create Immersive Simulation. I suggest that this type of platform may more effectively enhance neuroplastic processes and thereby improve outcomes in stroke recovery.

Any reasonable understanding of how virtual reality and robotics impact neuroplasticity requires that one have a basic conceptual framework related to the organization and architecture of the brain, as well as the basic principles of neuroplasticity. Therefore, I will provide a high-level summary of these principles before providing a brief review of the available literature on the subjects.

Basics of Multimodal Brain Organization

Our brains constantly monitor the bombardment of sensory information from the environment and respond to it in ways that are meaningful and adaptive. With each passing millisecond, we integrate millions of bits of data to construct a unified sensory experience. Most of this data is relayed from peripheral neurons to the thalamus, the deep brain structure that acts as a sensory gateway through which the environmental information flows on its way to primary sensory cortices where basic perceptual information is registered. This is true for somatic, visual, and auditory modalities.

The primary cortex for each modality subsequently relays this information to unimodal association cortices where basic featural information about the world, its nature, its location, and so forth is compared to – and integrated with – previously stored information from the same sensory modality. Consequently, information is relayed to regions that integrate information from multiple modalities, known as multimodal association cortex. Thus visual, auditory, and somatosensory percepts may be integrated and subsequently compared to and combined with representations of previously acquired knowledge and past experiences in multimodal cortical regions.

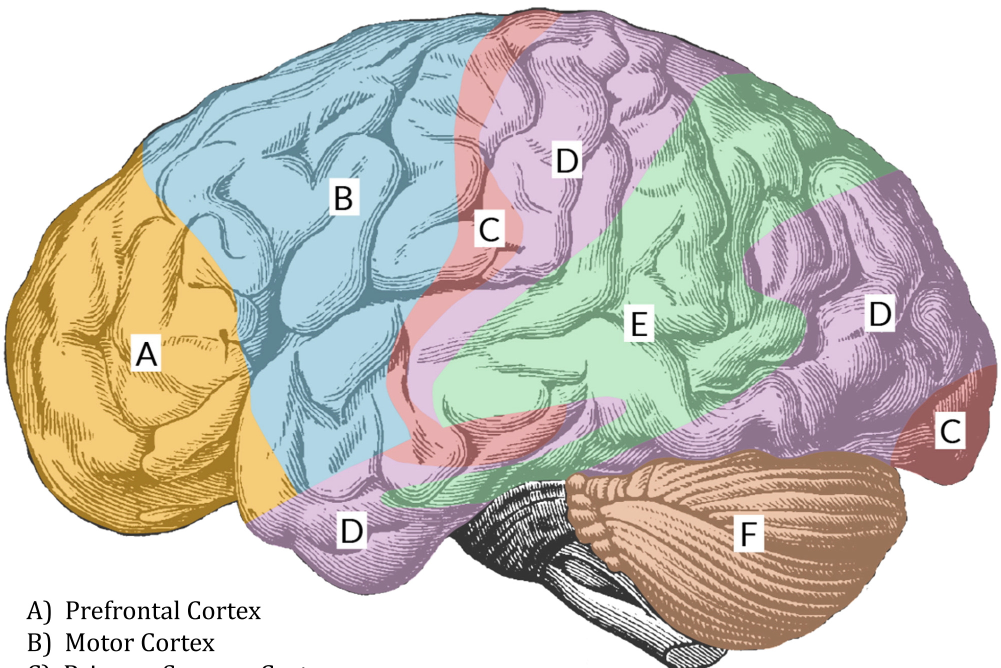
In addition to their high-level cortical connections, multimodal cortical regions are also robustly interconnected with more primitive and deeper brain regions. These deeper regions are responsible for constantly appraising sensory experience and tagging it with a valence of pleasure, reward, fear, excitement, safety, danger, security, risk, and so on… (e.g. amygdala, limbic system, dorsal striatum, ventral striatum, and brainstem). Information flows via interconnected loops, constantly responding to the environment, and activity is smoothly coordinated via structures like the cerebellum.

Multimodal cortical and subcortical information is relayed to frontal cortical regions that:

- Evaluate and organize complex perceptual information, sequence actions and responses, solve problems and plan solutions, hold concepts mentally online in the form of working memory, shift thoughts or actions from one set to another (set-shifting), and other executive functions (prefrontal and dorsolateral prefrontal cortex),
- Assign the value of actions, of ourselves, and motivate us to act (medial frontal cortex and anterior cingulate cortex)
- Inhibit inappropriate actions (orbital frontal cortex), and
- Plan and initiate actions (supplementary and primary motor cortex).

Basics of Multimodal Brain Organization, cont'd.

Based on this ongoing sophisticated appraisal of cortical and subcortical information, motor actions may be initiated. Relevant regions in the primary motor cortex activate and relay neural signals through deep brain regions and down the spinal cord. We live our lives, in part, based on our instantaneous responses to everything we see, feel, hear, and smell – always present in, and responding to, the environment in which we are immersed. The mechanisms for responding to the environment and continually adapting to it are collectively called "neuroplasticity."



A) Prefrontal Cortex
B) Motor Cortex
C) Primary Sensory Cortex
D) Unimodal Association Cortex
E) Multimodal Association Cortex
F) Cerebellum

Neuroplasticity

Neuroplasticity is the catch-all term for the processes by which global brain functioning, neuronal connectivity, and dendritic changes adapt in response to both internal and external stimuli. It is the foundation of brain organization and the integration of modality-specific sensory experiences (e.g. bodily sensations, sight, hearing) with motor responses. Modality-specific regions specialize in unique functions. Nevertheless, the various modal regions are robustly interconnected with one another via multi-modal processing and integration. Thus we can conceptualize brain functioning as both localized for specific functions, as well as distributed in integration and holistic operations.

Neuroplasticity involves changes in both large-scale cortical reorganization and small-scale intracellular processes. For example, neuroplastic changes involve neocortical cells (neurons and glial cells), short and long cortical networks (changes in neuronal activation and cortical maps), inter-cellular mechanisms (changes in synaptic strength, including sprouting) as well as intracellular (e.g. mitochondrial functions) (Straudi 2017). The neural changes made via these processes are, to a large extent, responsive to sensory and motor experience; thus neuroplasticity is "experience-dependent".

Injury and Neuroplastic Responses

When one has a stroke, specific localized regions are damaged, resulting in impairment in capabilities such as motor functions, vision, or language. Because of the rich interconnection of all brain regions, the effect of the injury does not stop there; it impacts numerous other functions that are distributed throughout the brain.

After brain tissue is damaged, neuroplastic activity immediately starts to heal what has been injured. Initially, there are changes in intracellular processes, followed by neuronal sprouting, synaptic reorganization, and even regional brain activity (Kleim 1996, Kleim 2004, Nudo 2007).

As healing proceeds, neighboring neurons are recruited to help carry out the functions of the damaged cells. Eventually, neurons that are farther away – even neurons from other modalities or the other hemisphere – may be recruited to participate in the healing process. The potential result of this massive recruit-and-repair job is cortical and motor map reorganization.

Neuroplasticity is responsive to sensory and motor experience. With each environmental stimulus and each corresponding motor response, new motor patterns and memories are formed. If the healing process is aligned with normal brain functioning and with multimodal brain organization, the process is called "organized neuroplasticity." The goal is to form new motor memories in the same way that they were learned during development. We learn to walk, move our arms, and every other type of behavior, while immersed in a multidimensional world. We form our initial motor functions at the same time we are hearing, feeling, and seeing all that surrounds us. At the same time, we have to sort through all of those sensations, make sense of them, and organize our actions. This means that they

Injury and Neuroplastic Responses, cont'd.

were learned during development. We learn to walk, move our arms, and every other type of behavior, while immersed in a multidimensional world. We form our initial motor functions at the same time we are hearing, feeling, and seeing all that surrounds us. At the same time, we have to sort through all of those sensations, make sense of them, and organize our actions. This means that we do not learn how to move our muscles in isolation; we learn to move our muscles while immersed in the real world. Therefore, in order to achieve the most organized healing possible, there should be an integration of the interconnected circuits that are responsible for all of these functions. By contrast, if healing is not aligned with normal brain functioning and organization, the process may be conceptualized as "disorganized neuroplasticity." Such non-functional reorganization is associated with less successful recovery (Cheatwood 2008, Carey 2006).

Leveraging neuroplasticity is the basis for all forms of neurorehabilitation. Most relevant to our current discussion is the data suggesting that robotic therapies and virtual reality-based therapies enhance neuroplasticity and foster a more organized restoration of functioning. This will be discussed below.

Neurorehabilitation and Task-Oriented Therapy

Experience-dependent, Task-Oriented Training (TOT) has emerged as one of the dominant approaches to restoring functional ability after stroke. This type of training generally focuses on fine motor activities and isolated motor functions. However, it may also encompass the tasks of movement, navigation within the environment, and large-scale activities. Several principles of TOT are required for successful rehabilitation (Kleim and Jones 2008, Wade and Winstein 2011). These principles should be incorporated into clinical rehabilitation, with the aim of improving functional recovery, activities, and quality of life (Straudi 2017). Some essential principles of effective TOT include providing:

- Activation of Specific Brain Regions
- Adequate Repetition
- Adequate Intensity
- Salient and Challenging Experiences that are interesting and meaningful

Both Virtual Reality and Robotic Rehabilitation have been shown to enhance all these principles.

Virtual Reality

Virtual reality has been defined as a computer-based generation of realistic, three-dimensional visual, auditory, and tactile environments in which a user can explore and interact with virtual objects (Greenleaf and Tovar 1994). Virtual reality (VR) based rehabilitation is characterized by the integration of cognitive and physical tasks within a multimodal sensory environment (Rizzo and Koenig 2017, Wade and Winstein 2011). The integration of VR into the rehabilitation process offers several advantages. It allows us to recreate the complexity of the physical world in a simulated environment and to evaluate natural movements in the controlled environment of the clinic or the lab. Likewise, in a virtual environment, one can have precise control over a large number of physical variables that influence behavior while continually recording physiological and kinematic responses (Carrozzo M, Lacquaniti 1998, Keshner 2004). As technology has become more accessible and affordable, research on VR in rehabilitation has become more prevalent. The use of virtual reality is now often used in rehabilitation settings but is not yet standard practice (Laver et al 2017). Gaming consoles are now ubiquitous, and low-cost commercial gaming systems are being used as an alternative way of delivering virtual reality (Levac et al 2015). While these systems were originally designed for recreation, they are now being adapted for therapeutic purposes in affordable and innovative ways. In addition, interactive video games are being specifically designed for rehabilitation (Lange et al 2010; Lange et al 2012).

Among the characteristics that therapeutic VR provides are:

- Control the stimulus a patient is exposed to and to ensure that it is consistent
- Real-time feedback regarding how they are performing the activity
- Practice skills independently, without the need for someone to be constantly assisting them
- Stimulus and response experiences that can be fine-tuned to meet the user's physical or cognitive abilities
- Conduct certain therapeutic tasks without the physical risk of injury that can be present in the non-virtual world
- Exposure to stimulation or activities can be carefully adjusted
- Divert the patient's attention from distractions that could impact their therapy
- Degree of motivation to keep performing the therapeutic tasks (Keshner 2004).

Fundamental to VR systems are presence and immersion. Presence is considered the subjective feeling of being present in a simulated environment, whereas immersion is a measure of the VR platform's ability to induce a sensation of being in a real-world (Weiss 2006). The combination of presence and immersion facilitates the multi-modal integration of cognitive and physical systems, a key to producing organized neuroplasticity. Evidence suggests that a transfer of training from the virtual to the physical environment is increased if immersion and presence are maximized (Rizzo et al 2004). A substantial benefit of VR is its ability to increase reward-based learning.

Reward-based learning relies on the activation of networks in both cortical and subcortical structures (with emphasis on the ventral striatum and the nucleus accumbens). The primary neurotransmitter

Virtual Reality, cont'd.

involved with the reward system is dopamine. The dopamine-mediated reward processing system is one role of the mesolimbic network. This network has been shown via functional magnetic resonance imaging to be activated by virtual reality-based rewards (Marsh 2010, O'Doherty 2004). VR provides patients with a more realistic, varied, and enhanced sensory perception experience and also facilitates motor learning based on various feedback mechanisms (Ustinova 2011, Cort'ez 2014).

Virtual Reality training may also improve cortical reorganization and neuroplasticity by simply encouraging more movement than traditional, less engaging systems (Cikajlo 2010, Yan 2008, You 2005). Rehabilitation research consistently shows that repetitive practice of the same exercises during conventional rehabilitation leads to reduced engagement by patients (Emery 2007). Repeating the same motor movements over and over becomes boring and people often fail to perform as much of the actions that could maximize their healing. Creating a degree of fun increase a patient's attention span and enjoyment. The result is that they spend more time doing their rehabilitation activities. The elements of fun, excitement, and facing challenges can increase the production of norepinephrine, a neurotransmitter that modulates and induces neuroplasticity (Marzo et al 2009).

Kafri (2014) examined the effect of virtual reality on energy expenditure in patients after stroke. Participants displayed an improvement in activity and reported that they described the game as enjoyable (Kafri 2014). Virtual reality also provides immediate visual feedback and can empower patients with a sense of control over their recovery (Betker 2006, Lam 2006). It has been argued that the act of observing one's own actions contributes to motor recovery by mirror motor neuron activation (Johansson 2011); something in VR that uses self-representational avatars. It is conceivable then that patients who train with virtual reality may potentiate their functional improvement via interacting with the virtual world.

Virtual Reality has been used to address deficits associated with upper extremity (UE) and lower extremity (LE) motor control, hands and fingers, gait training, balance, wheelchair use, cognition, mental practice, community living, and spatial neglect (Wade and Winstein 2011, Lucca 2009, Crosbie 2007, Holden 2005, Deutsch 2007). VR has also been used as an adjunct to rehabilitation in the stroke population (Yavuzer 2008, Saposnik 2010). Combining VR with treadmill use, or other mechanical assistance can increase stroke patients' walking speed and distance (Lamontaigne 2007, Afzal 2015). One randomized controlled trial demonstrated that participation in virtual reality balance-related games was more effective than performing conventional exercises to maintain postural stability during walking (Rajaratnam 2013). These results are thought to stem from adaptations of the neuromuscular system that are specific to virtual reality games (Singh 2012).

While many studies have demonstrated the potential benefit of VR for neurorehabilitation, the data is limited by its low quality and heterogeneity. A Cochrane review from 2017 provides a systematic evaluation of the current body of literature. This review included 72 trials that involved 2,470 participants from 2004 to 2016. Study sample sizes were generally small, and interventions varied in terms of both the goals of treatment and the virtual reality devices used. The risk of bias present in many studies was unclear due to poor reporting. Thus, while there are a large number of randomized

Virtual Reality, cont'd.

controlled trials, the evidence remains mostly low quality when rated using the GRADE system. These factors make it difficult to arrive at any sort of definitive statement about how VR alone might enhance stroke rehabilitation.

Twenty-four studies reviewed in the Cochrane paper used commercially available gaming consoles such as the Playstation Eye Toy, Nintendo Wii, and the Microsoft Kinect. Eight studies used the GestureTek IREX (a system for upper limb rehabilitation that uses flat-screen images), one used the Armeo (robotic system for upper limb), one used the Lokomat, and one used the more immersive CAREN system. The remainder of the studies used customized virtual reality solutions. When pooling the data, the clinical results for using VR alone as compared to conventional therapy were not significant. However, the combination of VR plus usual care did demonstrate a positive benefit when compared to usual care alone without VR with regards to upper extremity improvement.

Robotics

Robotic devices allow for repeated intensive practice of skilled motor tasks. At different phases of rehabilitation (acute, sub-acute, and chronic), robotic systems may assist human movements by providing various types of guidance (passive, active, supported). Moreover, during robotic sessions, kinematic and spatio-temporal parameters (i.e. velocity, smoothness) can be recorded with the aim of monitoring online performances and acquiring clinical information on subjects' characteristics. Finally, as in the case of VR, a patient's motivation and engagement are more likely to be sustained during robotic training (Straudi 2017). Robotic therapy is an efficient medium for the delivery of intensive motor therapy and has been shown to induce primary motor cortex neuroplasticity in patients with stroke (Tran 2016).

The rationale of robotics in neurorehabilitation is based on several principles, and since 1994 robotic devices have been introduced in clinical settings. Robot-assisted devices can deliver the repetitive motor practice required for neuroplastic motor learning and post-lesion recovery (Lang 2009). Brain imaging studies of stroke patients have shown evidence for reorganization of affected regions demonstrating functional plasticity, even into the chronic phase of recovery when many rehabilitation programs assume that no further recovery is possible. Robotics may increase the duration of rehabilitation, as well as the possibility for improved long-term outcomes (Lazaridou 2013). Robotic training has been shown to enhance motor outcomes in patients with stroke that is maintained for over three years (Volpe 2005). Many other clinical studies have shown the benefits of using robot-assisted therapy in patients during neurological recovery (Aisen 1997, Volpe 1999, Volpe 2000, Volpe 2001, Volpe 2002, Volpe 2005, Ferraro 2003, Fasoli 2004, Daly 2005, Macclellan 2005, Finley 2005, Prange 2006). One potential added benefit is that the implementation of robotic rehabilitation technologies might reduce rehabilitation costs overall or increase cost-effectiveness by reducing physical therapists' workload (Straudi 2017).

Asymmetrical Training and Balanced Resistance

Stroke survivors might lose their walking and balancing abilities, but many studies have pointed out that cycling is an effective treatment for lower limb rehabilitation. While it may seem counterintuitive, the motor movements of cycling also facilitate improvement in walking movements, or gait. Unfortunately, during cycle training, the unaffected limb tends to compensate for the affected one, which results in asymmetrical muscle activation and suboptimal rehabilitation. Many studies have suggested that using cycling as a rehabilitation tool could improve lower body extremity function of stroke patients (Yin et al 2016). Cycling requires participants to move both of their lower limbs alternately with equal force, but, for hemiparetic patients, the unaffected limb often compensates for the lack of activation in the affected limb. The unaffected limb may mask the insufficiency of the affected limb and result in uncoordinated training, which may reduce potential benefits and intensify gait dissymmetry of the hemiparesis patient (Yin 2016, Kautz et al 2006, Janssen 2008); resulting in poorly integrated neural reorganization. To most effectively engage robotics for stroke patients, biomechanical technology or software that compensates for this asymmetrical functioning should be a core feature.

Integrated Technologies and Immersive Simulation

Both virtual reality and robotics have been shown to improve post-stroke recovery. A consistent finding is that when the two are combined, the results are even better (Howard et al 2017, Manuli et al 2020, Wade and Winstein 2011). In 2011 Wade and Winstein suggested that when VR and robotics-based technologies have sufficiently evolved, the next step will be to develop ways of using VR and robotics-based technologies as embedded components of evidence-based Task-Oriented Therapy rehabilitation programs. Virtual reality reward-based training and robotic therapy are complementary technologies that, taken together, increase the intensity of reward-based learning. This type of learning is mediated by the dorsolateral prefrontal cortex, orbital frontal cortex, and nucleus accumbens in the ventral striatum. These structures weigh the magnitude of rewards, process abstract rewards, and manage motivation plus reinforcement respectively (Tran 2016). The primary neurotransmitter involved with reward-based learning is dopamine. Increased dopaminergic activity is associated with increased neuroplasticity. Thus, the integration of these two technologies may be expected to increase neuroplasticity by increasing dopaminergic activity as well as increasing noradrenergic activity as previously discussed.

Studies have proposed several advantages concerning the combination of VR and existing rehabilitation methods (Burdea 2003, Gregg 2007). As discussed earlier, robotic therapy can induce neuroplasticity by delivering intense, reproducible, and functionally meaningful interventions. Robotic therapy also provides an apt platform for virtual reality, which boosts learning by engaging reward circuits. The future of stroke rehabilitation should target distinct molecular, synaptic, and cortical sites through personalized multimodal treatments to maximize motor recovery. Because both robotics and VR improve neuroplasticity at distinct levels, their combination has the potential to augment one another and improve motor outcomes beyond current conventional treatment (Tran

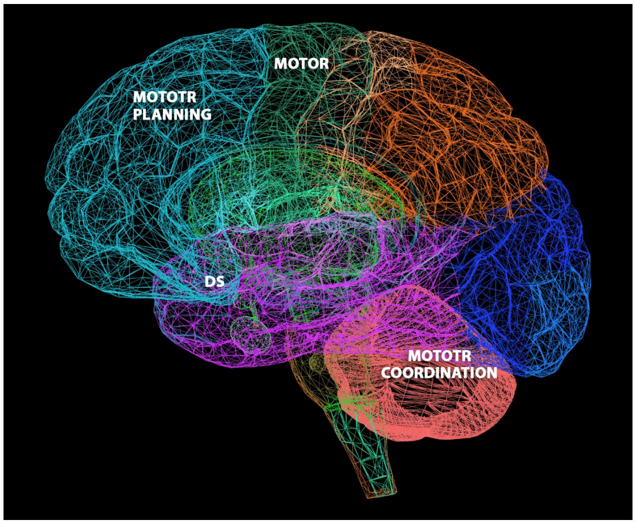
2016). Furthermore, VR programs that are typically coupled with robotics can simulate training that is functionally meaningful. This is important since functionally meaningful tasks are correlated with better motor memory (Bayona 2005, Nudo 2003). The integration of advanced robotic technologies with sophisticated virtual reality can produce a simulated experience in which the patient (or rider) experiences every sensation and every movement encountered in the virtual environment. Thus, both presence and immersion are significantly more intense than in either system alone. Such an integrated system is known as Immersive Simulation.

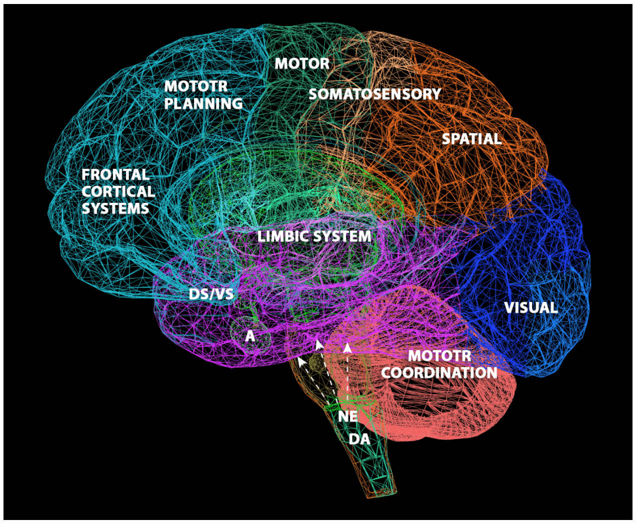
A person using a virtual reality system can experience that they illusion that they have a different body. That is, they have a sense of what is called "embodied presence" (Riva et al 2004, Riva et al 2019). Thus embodied, when one looks down towards the location of their physical body, what they see is a virtual body, or avatar, that is spatially coincident with their real body (Slater and Sanchez-Vives 2014). This experience is intensified in an Immersive Simulation system. An example of an Immersive Simulation system designed for neurorehabilitation is the one being developed by Torque3. In the Torque3 process, a patient is placed in a secured quad cycle in which they can safely explore the virtual environment. In this environment, it is the avatar that navigates through the virtual world, not the real-world, physical person. Immersive environments can be fine tuned so that a user can have a very calm and gentle experience, or one that feels more challenging.

The activities can be intense enough to require physical effort and cognitive activity, but not so intense that they exceed what is optimal for a given patient. They can be novel, unexpected, and when intensified, can create a sense of surprise, urgency, or even the illusion of risk. For one who is cognitively or physically impaired, facing a risk can be a real challenge. It can feel daunting, anxiety provoking, and perhaps even a bit scary. However, when adjusted to the patient's level of abilities, these challenges may be conceptualized as "desirable difficulties". The illusion of risks, and facing and overcoming them, becomes an integral part of the entire experience and intensifies the illusion of embodied presence. The temporarily stressful experiences and excitement markedly increase norepinephrine. Overcoming these challenges is rewarding and increases dopaminergic activity. Both of these increases will enhance neuroplasticity (Borodovitsyna et al 2018).

What we see then is that a sophisticated Immersive Simulation system would allow for the fine-tuning of a user's experiences and ideally achieve a harmonious balance between the difficulty of the tasks on the one hand, and the patient's physical and cognitive abilities on the other. It would engage all aspects of sensory and motor modalities, i.e. be multimodal. Furthermore, because the system requires a patient to navigate through a complex spatial environment, it should more effectively engage the visual and physical spaces in both hemispheres. The engagement of the hemisphere that is contralateral to the injury would theoretically induce greater cross-hemispherical neuron recruitment and integration. An Immersive Simulation platform would engage all brain regions that play a role in visuospatial perception, attention control, motor planning and action, threat detection, enjoyment, fun, emotional experience, and reward/satisfaction (see figure on next page).

Integrated Technologies and Immersive Simulation, cont'd.





Traditional stroke rehabilitation of impaired motor function generally focuses on repetitive exercises of isolated muscle groups. Thus, it primarily involves motor strength and coordination and activates specific and limited brain regions.

Immersive Simulation, on the other hand, engages those same regions but also involves all brain regions that play a role in visuospatial perception, attention control, threat detection, enjoyment, fun, emotional experience, reward, and satisfaction in the neuroplastic healing process.

1. Primary, Unimodal, and Multimodal sensory cortical regions – responsible for the analysis and elaboration of sensory information
2. Motor and Supplementary Motor Areas responsible for planning and initiation motor activity
3. Frontal Cortical systems – responsible for executive functions, motivation, preparing and initiating motor actions
4. Amygdala (A) – constantly scans the environment for potential challenges, threats, and risks
5. Dorsal Striatum (DS) – a key component of coordinating motor activity
6. Ventral Striatum (VS) including the nucleus accumbens and extending into the septal region – key components of reward, pleasure, and emotional experience
7. Limbic system – elaborates upon primary emotional experiences and places them in the context of personal space and time
8. Cerebellum – helps coordinate motor function
9. Norepinephrine (NE) and Dopamine (DA) neurotransmitter systems that have multiple functions related to motor learning, pleasure, excitement, attention, and many others. These are both increased during virtual and robotic therapies and enhance neuroplasticity

Measuring Outcomes

Measuring the outcomes of any intervention is an essential requirement for guiding evidence-based practice. VR technology can objectively measure motor behavior in ecologically sound environments while maintaining control over the stimulus delivered (Rizzo 2002). Likewise, data collected using robotics are more precise than observational data from conventional therapy. Such data can be used to monitor the progress of an individual during therapy. It can also be aggregated into larger data sets to monitor population or group outcomes and to inform evidence-based treatments. When contrasted with the current methodology of collecting data and creating standardized programs, the more reliable data provided by Immersive Simulation systems can make it easier to standardize both research and treatment protocols within and between treatment centers (Loureiro 2011).

Conclusion

The practice of neurorehabilitation has been increasingly incorporating virtual reality and robotic technologies. These technologies both enhance neuroplasticity through a number of mechanisms as detailed in the sections above. By integrating these technologies one can deepen the user experience via Immersive Simulation, which, I suggest, should multiply the impact of either modality individually, and lead to improved outcomes for stroke survivors.

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