



# How brain imaging provides predictive biomarkers for therapeutic success in the context of virtual reality cognitive training

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## ABSTRACT

As Virtual reality (VR) is increasingly used in neurological disorders such as stroke, traumatic brain injury, or attention deficit disorder, the question of how it impacts the brain's neuronal activity and function becomes essential. VR can be combined with neuroimaging to offer invaluable insight into how the targeted brain areas respond to stimulation during neurorehabilitation training. That, in turn, could eventually serve as a predictive marker for therapeutic success. Functional magnetic resonance imaging (fMRI) identified neuronal activity related to blood flow to reveal with a high spatial resolution how activation patterns change, and restructuring occurs after VR training. Portable and quiet, electroencephalography (EEG) conveniently allows the clinician to track spontaneous electrical brain activity in high temporal resolution. Then, functional near-infrared spectroscopy (fNIRS) combines the spatial precision level of fMRIs with the portability and high temporal resolution of EEG to constitute an ideal measuring tool in virtual environments (VEs). This narrative review explores the role of VR and concurrent neuroimaging in cognitive rehabilitation.

## 1. Introduction

Treatment options in neuropsychological rehabilitation have evolved in recent years to exploit technological developments such as virtual reality (VR). Virtual environments (VEs) are not only providing potentially better assessment tools, they are also allowing clinicians to devise more precise rehabilitation programs.

Few virtual reality programs have been designed to retrain performance of activities of daily living for people undergoing neurological rehabilitation. Simulating activities of daily living, this VR programs include task specific practise to improve cognitive functions. For example, the virtual "classroom" aimed at the assessment of Attention Deficit Hyperactivity Disorder (Rizzo et al., 2000), the virtual "grocery shopping" (Laver et al., 2012) which uses a novel approach to interaction between the user or the virtual reality working-memory-training program (VR-WORK-M, Ansado et al., 2018) recreating a restaurant environment where participants must complete a working memory task which consists in repeating a series of items.

In the past decade, the use of VR has been coupled with both

traditional and new neuroimaging technologies, essentially yielding two possibilities: 1) a before-after scheme that maps neural networks preceding and following a VR training program, and 2) a real-time rendering of brain activity during a VR task. The neuroimaging techniques that are typically used are functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS).

The combination of VR with neuroimaging is increasingly being explored in the clinical field due to the potential advantages for neuropsychologists offering treatment. An introduction to these novel possibilities is presented in a recent review by Teo et al. (2016). Focusing on EEG and fNIRS, it surveys different contexts in which participants have benefited from a monitoring of their cerebral activity while immersed in VR. While Teo et al. focus mainly on retraining motor functions and balance in neuropathologies such as cerebral palsy and Parkinson's, or exposure therapy in anxiety and PTSD, the present literature review delves more into how fMRI, fNIRS, or EEG combine with VR to support the rehabilitation of various cognitive functions by allowing clinicians to identify biomarkers that predict success in

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therapy. Specifically, stroke, traumatic brain injury (TBI) and attention deficit disorder, with or without hyperactivity (ADHD), are of particular interest here because they are among the best illustrations of the recent progress that has been made with VR applications and of the promising step forward that simultaneous neuromonitoring can be.

It is the examination of this advancement that constitutes the main objective of this narrative review. Specifically, our claim is that when multimodal neuroimaging and VR are combined, a neurorehabilitation program can be individually optimized to reflect the naturally unique pattern in which the respective individual person's brain's activity pattern is affected by the trauma. Starting with a brief overview of pathologies that can benefit greatly from this technology, this narrative literature review will explore how simultaneous multimodal neuroimaging can constitute an added value for the rather young field of neurorehabilitation with VR.

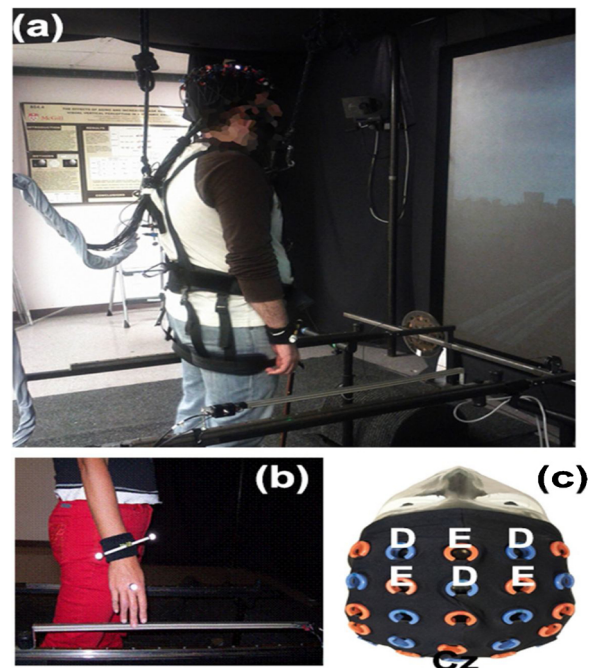
## 2. Using neuroimaging to assess impact of virtual reality training on neurorehabilitation: a promising avenue

Neuroimaging is typically used in this context to determine which specific brain regions respond to stimulation or training and compare intensity of activation. State-of-the-Art clinical neuroimaging allows to better understanding how cognitive training impacts neuroplasticity measuring, regional brain volume, functional activity, and functional or structural connectivity. Functional MRI scanning, requiring large equipment, relies on a measurement of neuronal activity related to blood flow (i.e., neuro-vascular effects) in high spatial resolution to various regions of the brain to determine which ones are most intensively solicited. The EEG procedure involves placing electrodes over the scalp in order to record in high temporal resolution brain waves associated with cerebral electrical activity. Resulting patterns on the graph can then be studied to identify anomalies or other noteworthy elements. Lastly, fNIRS uses a near-infrared light spectrum range within which human skin and tissue are most transparent and hemoglobin is most visible. The contrast makes a real-time rendition of brain activity possible by following the path of hemoglobin and deoxygenated hemoglobin.

In studies using fMRI, the participant usually needs to keep their head and trunk as still as possible while they are lying in the scanner, so the task will usually involve moving a finger or hand in a VR environment that is displayed to them by means of an HMD or through a device built into the MRI scanner. The alternative would be to scan participants at various time points, such as before, during and after treatment. On the other hand, EEG equipment can be portable and thereby offers participants the option to sit upright or even walk within a restrained area, depending on the necessities of the experimental design. Then, as Sangani et al. (2015) point out, fNIRS allows for a best of both worlds compromise since it offers the convenience of portability and a temporal resolution similar to that of an fMRI scan. The authors offer an example of an experimental setup allowing the patient to undergo fNIRS imaging while remaining mobile (see Fig. 1). These three imaging techniques provide different elements of information and the choice of which technology is best to use depends on the goal of the VR training considered.

The temporal information provided by an EEG is typically adequate for protocols involving neurofeedback or a simple monitoring of brain activity during performance. On the other hand, more sophisticated neuroimaging techniques like fMRI or fNIRS not only permit a precise spatial mapping of activated brain regions, but also allow for a detailed analysis of how activation levels change over time (i.e. the course of a VR training program).

When it comes to stroke, for example, Teo et al. (2016) discuss some of the challenges faced by therapists in using VR in rehabilitation, most of them stemming from the fact that early VR applications and games targeted a general audience and, hence, were ill-equipped for rehabilitative purposes. Developers have progressively been improving



**Fig. 1.** Experimental setup of a mixed-reality system incorporating both VR and haptic touch. Reproduced with permission from Elsevier.

(a) Participant on walking on a treadmill while wearing a NIRS cap to probe sensorimotor control of gait and posture. Treadmill walking while swinging the arms resulted in a global activation of the frontal and sensorimotor cortices in the stroke patient. (b) Haptic bar on the side of the treadmill provides somatosensory input upon fingertip contact. Steady walking in the light haptic touch condition resulted in increased ipsilesional activation of the affected hemisphere, visible by a more symmetrical activation of the sensorimotor cortices for the stroke patient (c) NIRS cap showing the locations of emitter and detector optodes.

this by adding clinically relevant features, such as intensity grading that adapts to individual progress, therapist-controlled task difficulty and characteristics, and recording of movements to provide a realistic picture of progression and motor recovery. These features also turn out to be some of the key advantages of VR as applied to rehabilitation when coupled with neuroimaging and as Teo et al. gathered from their meta-analysis, outcomes using this technology are typically positive or, at the very least, non-detrimental. This is also what was observed in the following studies, looking at both traditional pre- and post-treatment monitoring as well as the more innovative intra-VE neuromonitoring using neuroimaging in vivo.

A detailed summary of findings from each of the studies reviewed, with an emphasis on neuroimaging results and the identification of possible predictive biomarkers, is presented in Table 1 (in vivo neuroimaging investigation) and Table 2 (pre/post neuroimaging measurements).

### 2.1. In vivo neuroimaging investigation of neurofunctional changes induced by VR training

It is crucial to be able to simultaneously monitor functional recovery and plastic changes in the brain during the virtual treatment's progress. To face this challenge, some studies were conducted using respectively EEG, fNIRS and fMRI (see Table 1).

#### 2.1.1. Simultaneous EEG monitoring helps patients progress through virtual reality training

The first in vivo studies were conducted using the EEG. i Badia et al. (2013) designed an experiment incorporating a hybrid brain-computer interface (BCI) and VR system, coupled with an EEG for simultaneous monitoring of brain activity. Participants sat at a table facing a desktop

**Table 1**

Summary of neurofunctional changes identified by neuroimaging investigation in vivo in participants at completion of a VR task or a training program.

Authors	Participants	Neuroimaging technique/VR task	Associated neurofunctional changes
Cho et al., 2004	N = 28. Healthy adolescents (aged 14–18). A.) Control gp. (n = 9) : no training over 2 weeks; B.) VR gp. (n = 10) : 8 sessions of VR training over 2 weeks; C.) Non-VR gp. (n = 9)	EEG/VR -Virtual Classroom - Neurofeedback training	<b>Higher mean <math>\beta</math> wave ratio:</b> (1) correlation between $\beta$ wave ratio and number of correct hits; and (2) correlation between $\beta$ wave ratio and commission errors
i Badia et al. 2012	N = 9. Adults healthy (M = 28.3 years old, SD = 5.3)	EEG/VR - Personalized motor training - Neurofeedback	More engagement of motor areas: (1) $\alpha/\mu$ band : $\uparrow$ neural synchronization; (2) $\beta$ band : synchro-nization/desynchronization depending on condition; (3) $\gamma$ band : a) lowest synchronized activity level for motor activity condition ; b) bimodal activity map for both imagery conditions present : synchronous activity enhanced in the central areas. - $\uparrow$ activation of motor networks
Steinisch et al., 2013	N = 2. Healthy participants	EEG/ Robotics/VR - VR ppplication for training of movements	Feasibility study (for post-stroke rehabilitation): Increasing of recruitment within key networks (processing of vision and visuo-motor coordination)
Snider et al., 2013	N = 44–22 patients with diagnosed (PD) - 22 age-matched healthy controls	EEG/VR - Visual, auditory, and haptic interactions in VRE	Feasibility study: simultaneous collection of both neural and behavioral data from participants with a small 40 ms total latency
Merians et al., 2009	N = 4–3 healthy participants - 1 patient who had a right subcortical stroke	fMRI/VR - Hand & Arm Training System	Activation of brain areas during training (if appropriated visual feedback) : - $\uparrow$ activation (by at least 10 voxels) of contralesional PMC when left virtual hand was moved using patient's unaffected hand
Beck et al. (2010)	N = 12 healthy right-handed male (M = 25.8 years)	fMRI/VR - Spatial processing paradigm	Brain areas involved during spatial processing in VR differ from those involved in spatial processing in the real world : (1) VR far-space objects: brain activations along the dorsal stream; (2) VR near-space objects : brain activations along the ventral stream
Holper et al. (2010; 2013)	N = 23 - N = 15, 'unilateral' group (right-handed) - N = 8, 'bilateral' group (others) (M = 26 y, 22–33 y)	fNIRS/VR - Grasping task performed by a virtual limb	$\uparrow$ of related cortical oxygenation $\Delta$ [O2Hb] in the action-observation system as measured by fNIRS in F3 : - Unilateral group, $\Delta$ [O2Hb] changes for motor imagery and imitation; - Bilateral group $\Delta$ [O2Hb] change for observation in the ipsilateral hemisphere
Prochnow et al. (2013)	N = 18 All right-handed - 10 healthy males - 8 healthy females (M = 24 +/- 3 years)	fMRI/VR Rehabilitation Gaming System (RGS): training of visuomotor processing	Engagement of mirror mechanisms. Activations related to imagery of catching the balls relative to baseline: (1) left SMA; (2) IFG, superior frontal gyrus and IPL in the left cerebral hemisphere

Abbreviation. N: number of participants. gp: group. M: age mean. SD: standard deviation. PD: Parkinson disease. SMA: supplementary motor area. IFG: inferior frontal gyrus. IPL: inferior parietal lobule.

computer used to display the VE (avatar<sup>1</sup> hands seemingly extending from the participant's own limbs), while their EEG recordings were transferred to another computer, forming the BCI. The goal was to exploit the observation and execution mechanism of the brain. The study in fact consisted in two experiments; the first one to map brain activity in the sensory-motor areas under the various training paradigms, and the second one to gauge the feasibility of having participants control the avatar using only their imagery.

There were four different conditions: 1) in *passive observation*, participants only observed the virtual limb in action; 2) in *motor activity*, participants observed the virtual limb in action while imagining it was their own; 3) *motor activity and motor imagery* required participants to imitate the avatar's movements while picturing them in their mind; and 4) *motor imagery* had participants imagine themselves perform the movements while watching the avatar execute them. The *passive observation* condition was considered the control measure as it would most likely produce the lowest frequency waves, which were used as a baseline with which to compare activity maps from the other three conditions.

This study came with the added functionality of neurofeedback, a growing sector in neurorehabilitation. While the feedback can come under more than one form, here, it consists of a loop comprising the BCI, the EEG, the VR system with its avatar, and the participant. The BCI obtains feedback directly from the EEG and learns to classify different EEG waves into one of three commands (no movement; move

right arm; move left arm) for the participant to control the avatar using only motor imagery. Data collected for the *passive observation* (control) condition showed that most activity was situated in lower frequency bands, with a consistent synchronized activity in the  $\alpha/\mu$  and  $\beta$  bands typical of an absence of motor activity. When compared with the activity generated by the other three conditions, it was possible to determine the patterns solicited by the different motor activity paradigms.

The results of the study indicated that for the *motor activity and motor imagery* condition, there was enhanced neural synchronization in the  $\alpha/\mu$  and  $\beta$  bands; this condition recruited the most task-related networks when compared with the other three experimental conditions. In contrast, the *motor activity* and the *motor imagery* conditions displayed similar patterns of desynchronization in the  $\beta$  band. Also, the *motor activity* condition triggered the lowest synchronized activity level in the  $\gamma$  band (even falling below control levels). It was gathered from the activation patterns that the *motor activity* condition required less concentration than the *motor activity and motor imagery* one, however the latter condition was considered to be recruiting not only attentional processes, but other systems also. Results from the second part of the experiment showed that participants could control the avatar through imagery using the neurofeedback loop, however they demonstrated better functional than precision control. In conclusion, this was deemed a suitable activity for patients that have suffered severe motor impairment. It is also worth noting that this is a practical tool to keep patients interested in a rehabilitation task and can prove to become a very efficient tool in autonomous therapy within a home setting.

In a same perspective of a real time neuroimaging investigation of electrophysiological changes inducted by VR, Steinisch et al. (2013) performed a feasibility study in which they assessed the design and

<sup>1</sup> Note. An avatar is a graphical representation of the user or another actual person, as opposed to a virtual character, which refers to a more generic term describing the synthetic representation of a virtual human.

**Table 2**  
 Post-VR training neurofunctional changes and associated biomarkers. Summary of various neurofunctional changes and cognitive improvements identified by pre and a post neuroimaging investigation in participants at completion of a VR training program.

Authors	Participants	Pre and post neuroimaging technique /VR training	Cognitive improvements	Neurofunctional changes
Jang et al., 2005	N = 10 -Exp. gp.: N = 5. Right-handed patients (3 f) ; Age: 59.8 ± 3.4 years; Suffering from hemiparesis following stroke; VR training : 5 times a week x 4 weeks - Control gp.: N = 5 stroke patients, no VR intervention. Single case-study. 24-year-old male with TBI who was presenting memory deficits	fMRI/VR VR training program: Motor tasks soliciting the use of the paretic limb  fMRI/VR -Virtual town (London). 90 min, 3 times a week for 5 weeks	Significantly improved motor function in stroke participants  Improved visuo-spatial learning in TBI participant, maintained at follow-up assessments	- ↑ Activation of ipsilesional SMI and ↓ aberrant SMI activations when using paretic limb. - Laterality index ↓ from .08 to .90, shift to ipsilesional activation  ↑ activation in left hippocampus, right hippocampal cortex during a verbal task, and ↑ activation in VTA, medial prefrontal cortex (mesolimbic network)
Caglio et al., 2012	Single case-study. - 75-year-old male stroke patient	EEG (T1 & T2) Robotics/VR training: 5 VR applications for training of movements. 3 times per week for 4 weeks	Improved motor function and kinematic parameters in stroke patient	Clear ERD in α and β bands Shift towards ERD pattern at trial onset in contralateral hemisphere. (1) ↓ activation in sensorimotor network for ipsilesional hemisphere and; (2) ↓ bilateral cerebellum activation
Comani et al., 2015	N = 2. Stroke patients. - P1: 63-year-old right-handed male - P2: 47-year-old right-handed male	fMRI/VR T1: baseline period. T2: two weeks after intervention. T3: a three-month follow-up VR training tasks: Toy Catching, Catch the Carrot, Tomato Juggling 4 weeks of treatment (5 weekly sessions)	Improved upper limb function in stroke patients, gains maintained at follow-up	P1: ↓ ipsilesional activation of bilateral SMI, SMA, dPMC P2: shift from bilateral activation of SMI, SMA, dPMC to predominantly right SMI activation; ↑ activation of right SMA

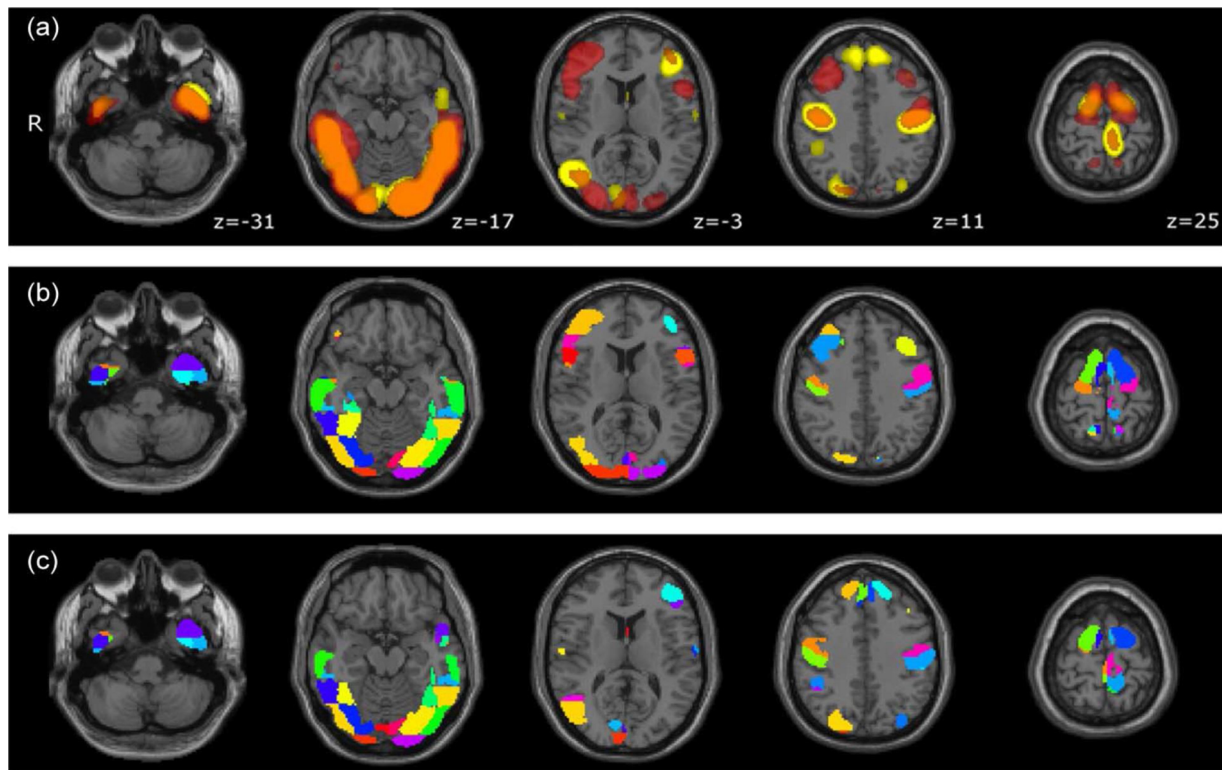
Abbreviation. Exp. gp: experimental group. SMI: primary sensorimotor cortex. TBI: traumatic brain injury. VTA: ventral tegmental area. ERD: event-related desynchronization. dPMC : dorsal premotor cortex.

functionality of their neuro-motor rehabilitation system for the recovery of upper limb mobility in stroke patients. The system included a passive robotic device called Track-Hold™, a set of VR applications and high-resolution EEG recording. The role of Track-Hold was to record kinematic activity and provide gravitational counterbalancing while the patient progressively regained control of the upper limbs. EEG activity was synchronously recorded to identify temporal movement events and brain regions with highest activity. The participants in this study were two healthy right-handed volunteers (a 50-year-old male and a 24-year-old female), but authors specified that the protocol used is suggested for the rehabilitation of stroke patients. Participants sat at a desk, with their right hand installed in the passive robotic device, in front of a computer screen presenting the VR tasks. The device did not provide any active assistance to participants, only serving to counterbalance the weight, and was adjustable. An advantage of this setup is the integration of these three components into a simple interface that allows a clinician to control task difficulty and other characteristics, data collection by Track-Hold, and the EEG cap from one single screen.

Here, five VR training applications simulating ADLs were tested: *Sponge*, *Bug Hunt*, *Grab 2D*, *Grab 3D*, and *Twirl*. *Sponge* required participants to “wipe” the screen with a tiny square in a circular motion to reveal a picture underneath. *Bug Hunt* displayed an avatar hand holding a fly swatter which participants had to manipulate in order to squash bugs that appeared at random locations on a brick wall. *Grab 2D* asked participants to reach for and grab various common objects (e.g. a coffee cup or fruit) located at different positions on the table and to hand them over to a virtual character sitting across the table. In *Grab 3D*, the participant needed to reach for butterflies dispersed in a garden using a virtual hand; a virtual fence and shadows were used to assist in gauging distance and depth. Lastly, *Twirl* consisted in unwrapping a black and white image by moving a colored square along a circular path displayed on the screen as a blue circle. Each application is run for five minutes and participants repeat as many trials as they can (with inter-trial breaks of seven seconds) in that time frame. Activations of subject 1 and subject 2 for the *Grab 3D* application are shown in Fig. 2.

EEG source activations showed that structures from key networks were recruited, confirming that the VR tasks were targeting the right functions. For example, activations in the bilateral middle and inferior temporal gyrus, the left temporal pole and the right fusiform cortex were identified as part of the ventral visual pathway, involved in the visual recognition of objects. Activations in the left postcentral gyrus and superior parietal lobule and bilateral precuneus were instead associated with the dorsal visual pathway, considered the main stream responsible for determining object location and movement properties, which would be necessary in order to grab something. Results demonstrated that this system is viable for stroke patients and easy and pleasant to use for participants. For clinicians, the combination of EEG with kinematic data allows for a precise tracking of patient progress, verifiable by the information collected on the patient’s movements, brain activation patterns, and clinical test batteries. Furthermore, because the VR tasks involve skills needed to perform ADLs, they feel relevant and interesting for the patients. Nonetheless, some of the drawbacks of this system are that, for one, Track-Hold only measures hand movements, which can be restrictive for clinicians needing more information, on shoulder mobility, for example. Second, given that it is a passive robotic device, patients would still need to have some minimal form of mobility when using the system to benefit from it. Overall, it is a promising setup for clinical use in neurorehabilitation after stroke.

Always in the perspective of a real time neuroimaging investigation of neurofunctional changes induced by VR, Cho et al. (2004) presented a slightly different experiment with a population whose disorder has been less explored in terms of coupling VR training and neuroimaging. For youngsters with ADHD, the use used a head-mounted display (HMD) inside a virtual classroom environment is the typical neurorehabilitation approach used. However, the application of VEs and neuroimaging in the rehabilitation of problematic attributes such as



**Fig. 2.** Source reconstruction images and anatomical labeling maps of two participants during a 3D VR application. Reproduced with permission (request in progress) from *IEEE Transactions on Neural Systems and Rehabilitation Engineering*.

(a) Images of subject 1 and 2 activations relative to the *Grab 3D* training application, which consisted in moving a cursor from a set position to a target location in a linear fashion, mapped onto a standard SPM8 T1 template. Participant 1 activations appear in red, subject 2 activations in yellow, and regions common to both in orange. (b) Anatomical labeling maps of active volumes for subject 1 while performing the *Grab 3D* task include the precentral gyrus (primary motor cortex), the postcentral gyrus (primary somatosensory cortex), the superior parietal lobule and supplementary and pre-supplementary motor areas, implying adequate solicitation of the sensorimotor network. (c) Anatomical labeling maps for subject 2 while performing the *Grab 3D* task. (Images shown following radiological convention)

attention deficit or impulsiveness is still relatively unexplored. In this study, the authors looked at 28 adolescent males, aged 14–18, who had committed crimes and been placed in isolation. While these youths had not been formerly diagnosed with ADHD, for all of them, inattention, impulsiveness, hyperactivity, and difficulty learning were active symptoms. Similar to their 2002 study, the 28 male participants were randomly assigned to one of three groups: control ( $n = 9$ ), VR ( $n = 10$ ), and non-VR ( $n = 9$ ). Both the VR and non-VR groups were able to “experience” the virtual classroom, but non-VR participants only saw it displayed on a monitor, while VR participants wore an HMD and head tracker, were immersed in the virtual classroom, could look around in the room and feel present as if they were really there.

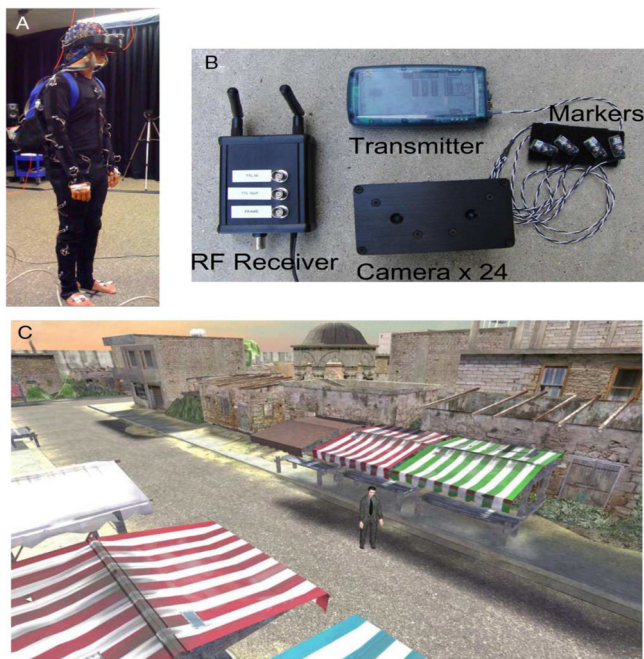
Once again, the VR and non-VR groups underwent eight 20-minute sessions over a two-week period, while the control group was waitlisted during the same period. This experiment used EEG monitoring in order to deploy neurofeedback. For this study, it was determined that the  $\beta$  wave ratio was to blame when it came to attention and impulsiveness, so when participants displayed a  $\beta$  wave ratio that was above a pre-determined baseline threshold, they were rewarded with points in the VE. As they accumulated points, they saw a dinosaur egg progressively rise from the desk and eventually split open to release puzzle pieces of a dinosaur image. When the image was completely put together, participants heard the dinosaur roar.

Attentional capacity was measured with a Continuous Performance Test (CPT) in a pre-post treatment fashion. Post-treatment results showed that both the VR and non-VR groups saw an increase in the number of correct hits, with the VR group showing a significantly higher improvement rate. The same relationship (inversed) was true of the decrease in commission errors. This was correlated with a higher mean  $\beta$  wave ratio at each of the eight sessions, except the first and the

fourth. Furthermore, the VR group displayed a faster reaction time post-treatment, evidence of higher attentiveness and a quicker decision-making process. This study provided generally favorable evidence for the usefulness of neurorehabilitation with neurofeedback in the presence of symptoms such as attention deficit and impulsiveness, which are common to nearly all ADHD patients.

Snider et al. (2013) realized a simple study in which they only confirmed the suitability of a full-scale immersive VR environment with the added benefit of functioning with synchronous EEG recording while the participant is fully mobile in the VE (for an example of the setup, see Fig. 3). Here, the goal was to evaluate how comfortable potential users would feel in this fully immersive 3D world and whether their use of the VE and their sensations inside it would be compatible with a clinical application. Hence, the immersive environment had two Phantom robots to collect haptic data, an optoelectronic PhaseSpace system to track motion and head movement, and the participant was fed a complete 3D-rendering of the 20 ft.  $\times$  20 ft. space through an HMD. All the data collected was streamed to one single computer, facilitating readability and analysis. In order to prove feasibility in populations suffering from a neurological disorder, exactly half of the 44 participants were Parkinson’s disease patients while the other half were age-matched healthy controls.

While the authors do not explain the tasks in more detail, it is clear that participants were submitted to reach-and-grasp tasks, with some requiring a minimal presence of 30 min inside the VE in order to be completed correctly. This was done on purpose to determine how long participants could comfortably stay in the VE and whether any sickness or discomfort developed. For most participants, questionnaires revealed that they felt a high sense of presence in the VE, with several of them attributing the maximum rating on the scale. Authors also reported that



**Fig. 3.** Example of a VR setup in an immersive environment with simultaneous EEG monitoring. Reproduced with permission (request in progress) from *IEEE Transactions on Biomedical Circuits and Systems*.

(A) Participant wearing PhaseSpace bodysuit, head-mounted display (Sensics Inc., x-Sight 6123), and mobile EEG system (Biosemi Inc.). (B) PhaseSpace system components used to relay real-time position data of the participant. The system was used to test reaching and grasping of a virtual object in 44 participants, 22 of which had Parkinson's disease. After approximately 20 trials, all participants had sufficiently familiarized with the equipment and adapted to the immersive environment to achieve a grasp success rate of 95 % (C) Example of an immersive virtual environment rendered in real time.

the combination of a movement tracking device, an HMD for immersive VR experience, and an EEG recording device allowed for simultaneous collection of both neural and behavioral data from participants with a small 40 ms total latency, which authors pointed out, is well below neural processing delays. On average, 20 trials were required for participants to master the task, at which point the success rate rose to 95 %, even for Parkinsonian patients. The proposed system was deemed a viable new mode of investigating and treating dysfunctional brain-behavior relations, such as in the case of motor disorders.

To recapitulate, EEG monitoring *in vivo*, whether integrated into a BCI or not, provides a good avenue to explore in terms of high-scale clinical VR applications and can be of great service in the rehabilitation of more generalized motor dysfunctions such as hemiparesis, that are difficult to work on when the participant is only sitting at a desk in front of a monitor. Given the low cost and portability of EEG, it is a relatively undemanding technique to use, especially when activating certain regions is the main goal of the treatment, with or without neurofeedback. When the clinician is aiming for more complex data, opting for one of the next imaging technologies is the logical choice.

### 2.1.2. *In vivo* imaging with fMRI/fNIRS targets key regions and optimizes training outcomes

Despite the technical constraints of using VR materials in MRI scanner, several studies have been carried out *in vivo*. fMRI compatible VR can be used to assess and track neural activation during neurorehabilitation. The goal of the first study reported, as of several others in this review, was to identify the brain correlates of rehabilitation using VR. Similar to i Badia's design described above, Merians et al. (2009) devised a three-component system incorporating a haptic device capable of tracking upper limb movements, displaying virtual hands, and

collecting fMRI images simultaneously. In this particular case, functional improvement of the hand and arm was the main objective of the training system. Participants were presented with a set of simulation paradigms, consisting of tasks to perform in the VE that would trigger use of the upper limbs (i.e. playing piano, reaching for items or catching falling objects). In a first experimental setup, a set of 18 stroke participants divided into three different training modes (hand, hand and arm, or bilateral training) and completed sessions of upper limb rehabilitation in the VE. While the authors did not collect any imaging data from these participants, clinical tests revealed clear improvement in motor function of the affected limb.

For its part, the main experiment instead comprised two conditions in the VE: 1) participants watch the virtual hands performing some activity with the intent of performing the same activity with their own hands after; and 2) participants perform an activity with their own hands and watch the real-time visual feedback of the virtual hands (actualized by participants moving their physical hands). Authors hypothesized that manipulating a virtual hand corresponding to the affected hemisphere using the unaffected hand would stimulate motor areas of the lesioned hemisphere. This was tested on a handful of healthy participants and one hemiparetic stroke patient; the results confirmed that this technique was effective in stimulating activity in the sensorimotor cortex of the affected hemisphere. For the stroke participant, there was significantly greater activation (i.e. over the threshold level of  $P < 0.001$  and extending by at least 10 voxels) of the contralesional (right) primary motor cortex when the left virtual hand was activated through movement of the patient's unaffected hand. Similar results were obtained with the healthy participants.

In a similar way of combining VR and fMRI, Prochnow et al. (2013) proposed a study using their VR-based Rehabilitation Gaming System (RGS) designed for neurological patients. A similar setup was realized by Bermudez i Badia, who also contributed to this experiment. The main difference here is that an fMRI scan was part of the experimental design. Instead of participants sitting at a desk and the researcher working with EEG recordings, participants were lying supine in an MRI scanner while stimuli were displayed on a mirror attached to their head coil and reflecting the images shown on a projector inside the scanner room. The conditions tested remained quite similar, though, with participants seeing balls flying randomly at them as their avatar stood (in first person or third person position) in front of an open field. In the *action* condition, participants need to actively catch the balls using the avatar hands. They signaled 'catching the ball' by pressing a button with their right or left index finger. In the *observation* condition, participants were instructed to observe the virtual character catching the balls, while in the *imagination* condition, the balls disappeared in their flight and participants needed to imagine catching them at the right time (once again, indicating this using their index finger). In this study, participants were ten healthy males and eight healthy females with a mean age of 24.3 years, all right-handed.

This experiment focused on the rehabilitative properties of mirror neurons, known to be mainly located in the inferior frontal gyrus and the anterior inferior parietal lobule (Prochnow et al., 2013). Consistent with the hypothesis of the authors, scan results showed that key sensorimotor areas and mirror neuron networks were activated during the *imagination* condition, notably in the left SMA, the left inferior frontal gyrus, left posterior insula, left postcentral gyrus, and left inferior parietal lobe. In the *action* condition, BOLD activity significantly increased in the medial frontal gyrus, right parahippocampal fusiform gyri, and left hippocampus, while simply observing the virtual character catching balls activated the occipital and temporal lobes bilaterally, along with the cerebellum, left posterior cingulate, right anterior cingulate cortex, left medial frontal gyrus, and right superior frontal gyrus. Furthermore, the authors highlighted that, even though participants used both hands, there was a dominant left activation pattern of the brain. Some other noteworthy points were the fact that reaction time in the first-person perspective was significantly better than in the

third-person perspective and there was an average delay of 55 s in response time for the *imagination* condition versus the *action* one, with a success rate of only approximately 75 % in the former condition.

While many studies show how VEs can be manipulated to selectively activate targeted brain regions, the next one looks at another basic question: is VR perceived the same way as the objective physical reality? In this Beck et al. (2010) study, images collected by fMRI were used to compare activation patterns resulting from participant interaction with 3-dimensional (3D) objects inside a VE with those documented from studies using various line bisection paradigms to assess visual processing in the physical world. Twelve healthy male participants, with a mean age of 25.8 years, were shown objects placed horizontally or vertically. Each object was presented at a length of approximately 60 cm (near condition) and at 150 cm (far condition). Participants were asked to identify whether the object was centered or shifted to one side or the other. The authors reasoned that if the human brain processes visual stimuli in VR in a similar manner as those in the physical world, then the brain activation patterns corresponding to visual processing of objects in both environments should be similar.

Beck et al. specified that further research is necessary to confirm their findings, but their results seem to indicate that the brain processes objects in VR differently than in the physical reality. Regardless of their orientation, objects in the far-space condition heavily recruited dorsal stream structures, such as the inferior and superior parietal lobe and the postcentral gyrus, while objects in the near-space condition strongly activated the lingual gyrus and the middle temporal lobe (ventral stream). Authors pointed out that this went against imaging results from studies of real-world visual processing, in which close objects increasingly activated dorsal stream structures while objects further away activated ventral stream ones. This suggested that objects in VR seem to be perceived without any spatial reference, treated by the brain like objects in the 2D plane, and that distance viewed in VR was apparently inequivalent to distance in real-life. However, this interpretation must also take into account factors that may contribute to the plausibility and realism of the experience in VR, such as pictorial realism, shaders and lighting, or any incongruence with the physical reality that may alter multisensory integration and believability of the experience. Beck et al. (2010) suggestion would have implications for therapies exploiting VR as it suggests that the brain may not treat visual stimuli from a VE like it does those from the physical reality. This should not, however, constitute an impediment to the use of VR in cognitive rehabilitation; it should rather be a starting point for further research in the field to establish the best way to reap all the benefits from VR.

Using fNIRS, Holper et al. (2010; 2013) presented a variant of experimental design in which the emphasis was placed on upper limb rehabilitation through the use of the mirror neuron system and the assistance of VR to, once again, trigger the activation of damaged brain areas. They designed a setup where participants saw two upper limbs lying on a table facing them, as if their own limbs were prolonging themselves into the computer screen. The movements made in the physical reality by the arms and hands of the participants were synchronized and mirrored by the virtual limbs using arm position sensors and data gloves. The goal here was to provoke the activation of motor regions in the brain through simple observation of movement. Participants were randomly assigned to one of two groups: unilateral monitoring or bilateral monitoring. This determined whether brain images were collected only from the left hemisphere (all participants were right-handed) or from both hemispheres. In this study, fNIRS wireless technology was used for monitoring with a focus on secondary motor areas, by means of a wireless, wearable device positioned over F3.

Participants in the unilateral group were tested under four conditions: 1) passively observing the virtual limb in action; 2) observing the virtual limb in action while imagining it is their own; 3) imagining themselves performing the action with no visual input; and 4) imitating the action performed by the virtual limb while watching it on the

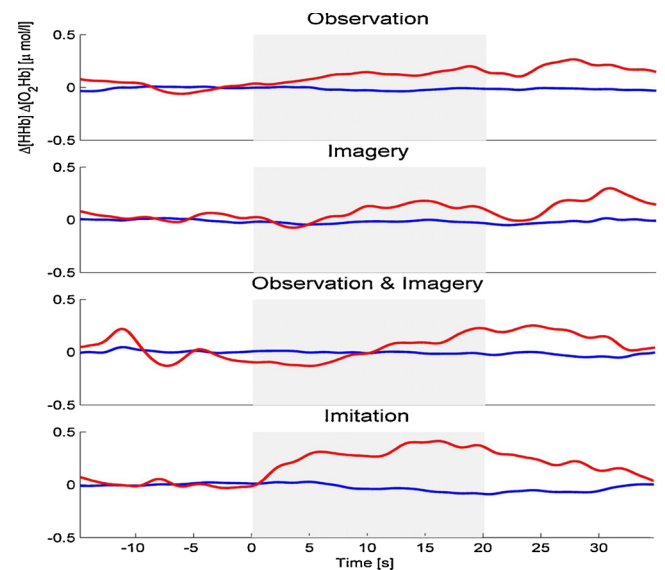


Fig. 4. Example of oxygenation changes from rest to stimulation under different conditions. Reproduced with the permission from BioMed Central.

Oxygenation changes ( $\Delta[\text{O}_2\text{Hb}]$  and  $\Delta[\text{HHb}]$  ( $\mu\text{mol/l}$ ) from rest (30 s) to stimulation (20 s) in a participant from the unilateral group for each of the four conditions. Results showed that, for the unilateral group, mean changes in  $\text{O}_2\text{Hb}$  were significant for the *imagery* and *imitation* conditions in a grasping task performed by a virtual hand. Therefore, participants imagining themselves perform the action and imitating the action shown by the virtual limb activated the action-observation system in the contralateral primary motor cortex, premotor cortex, and supplementary motor area, suggesting this is a viable method to stimulate contralateral hemisphere activity for a paretic limb, for example.

screen. One function of bilateral scanning was to confirm that images were indeed being retrieved from the correct side. For this reason, in the bilateral group, conditions 2 and 3 were dropped as they were expected to yield patterns similar to those already collected.

Results showed that, in the unilateral group, the mean increase in oxyhemoglobin was largest in the IM condition, in which participants observed and imitated the virtual hand. In the bilateral group, for both hemispheres, the highest mean increase in oxyhemoglobin occurred in the IM\_L condition, where participants observed and imitated a left virtual hand. Therefore, there was increased activation in secondary motor areas when use of the non-dominant hand was solicited. An example of blood oxygenation changes for one participant is shown in Fig. 4. As per the research hypothesis, the action-observation system of the brain was activated by the VR task and the portable fNIRS device proved to be an efficient and comfortable imaging option that could be used both for testing and neurorehabilitation situations.

VR training combined with fMRI/fNIRS is a powerful tool to dissipate some if not all symptomatology resulting from cerebral lesions. Tasks in VR can effectively stimulate activity in the sensorimotor cortex of a paretic hemisphere and secondary motor areas can be monitored using fNIRS wireless technology in a wearable device. Most importantly, participants who underwent VR training reported being able to spontaneously perform useful actions with their affected hand after the intervention that were impossible before.

## 2.2. Identification of VR neurofunctional changes and associated biomarkers with cognitive training using pre/post neuroimaging measurements (EEG & fMRI)

One of the main reasons for neuroimaging during a VR training program is to reveal the brain regions activated by different tasks and the neural networks that were modified over the course of the activity or the whole training (see Table 2). The logic behind that is simple. For VR to elicit therapeutic effects, it must first impact and change the

brain's neuronal activity which, in turn, causes behavioral change. Therefore, tracking the brain's neural activity in different regions can provide monitoring and prediction of therapeutic progress.

Following up on neurorehabilitation after stroke, [Comani et al. \(2015\)](#) presented a single case-study design with the same setup as in [Steinisch et al.'s](#) feasibility study. The participant was a 75-year-old male stroke survivor with a lesion to the right parietal cortex who was suffering from left arm motor impairment that made performing ADLs difficult or impossible without assistance. The VR-based rehabilitation began 21 days post-stroke. As in the previous study, the system consisted of the Track-Hold passive robotic device, a monitor with the same five VR training applications, and high-resolution EEG recording. The rehabilitation system, in this case, was introduced in addition to conventional therapy given three times per week for four weeks. At the first and last rehabilitation sessions, a high-resolution EEG recording was performed, and clinical tests were administered to evaluate the severity of the patient's upper limb impairment.

Imaging results demonstrated a clear pattern of event-related desynchronization (ERD) in the  $\alpha$  and  $\beta$  bands after training applications, evidence of cortical activation involved in movement planning. At trial onset, a shift toward an ERD pattern was also noticeable in the contralateral hemisphere for all applications. Likewise, important decreases in activation levels within the sensorimotor network were recorded in the ipsilesional hemisphere. There was also a reduced bilateral activation of the cerebellum, correlating with the recovery of motor function. Imaging data was corroborated by the patient's improved performance on clinical tests of motor function and kinematic parameters, who displayed nearly complete recovery of arm function in the impaired limb (*Motricity Index* score) along with a recovered ability to perform ADLs (*Barthel Index* score). The proposed rehabilitation system was tested on one stroke patient, but the authors specified that an even better study was on its way, one in which the experimental setup would include a comparison with a control group subjected only to conventional therapy.

The other majority of the studies to examine VR neurofunctional changes and cognitive training using pre/post neuroimaging measurements were conducted in MRI.

[Jang et al. \(2005\)](#) also devised an experiment where VR rehabilitation sessions were designed to provoke cortical reorganization and they used pre-intervention and post-intervention fMRI scanning to measure changes. [Jang et al.](#) recruited five right-handed participants (3 females, 2 males, mean age  $59.8 \pm 3.4$  years) suffering from hemiparesis following stroke and submitted them to a VR training program consisting of various motor tasks soliciting the use of the paretic limb. The training was composed of three different VR protocols, or games, each designed to exercise motor skills such as grasping, reaching, or lifting. Participants had to perform each exercise five times for a total of 60 min per day; the sessions took place five times a week for four weeks. The control group, also composed of five participants who had suffered a stroke, did not receive any intervention.

Before intervention, all patients displayed increased activation of the contralesional premotor cortex (PMC), contralesional or ipsilesional supplementary motor area (SMA), and the bilateral primary sensorimotor cortex (SM1) while moving the affected limb. Post-intervention imaging revealed that all five participants from the experimental group displayed significantly increased ipsilesional SM1 activation, while it was organized contralesionally before VR training (see [Fig. 5](#)). More specifically, four participants also showed a decrease or disappearance of aberrant SM1 activations when using their affected limb. Moreover, the laterality index during movement of the affected limb increased from 0.08 to 0.90 ( $P < 0.05$ ). Hence, VR training achieved cortical reorganization in most patients, moving from a contralesional activation to an ipsilesional one according to the laterality index. Participants who underwent VR training also reported that, after the intervention, they were able to spontaneously perform motor functions, like picking

up a glass or buttoning a shirt, that they could not have executed before VR training.

[Schuster-Amft et al. \(2015\)](#) delivered a feasibility study also based on the mirror neuron system. Recruiting two stroke survivors in the chronic phase as participants and comparing VR-based therapy with traditional therapy for upper limb rehabilitation, this study provided a clearer view of the benefits of VR-based rehabilitation therapy and the contrast between it and conventional methods. The study used an A-B-A design with a two-week baseline period, four weeks of treatment (with five weekly sessions), and a three-month follow up session. Patient 1 (P1) was a 63-year-old right-handed male, four years after an ischemic stroke, and Patient 2 (P2) was a 47-year-old right-handed male, three years after a brain hemorrhage.

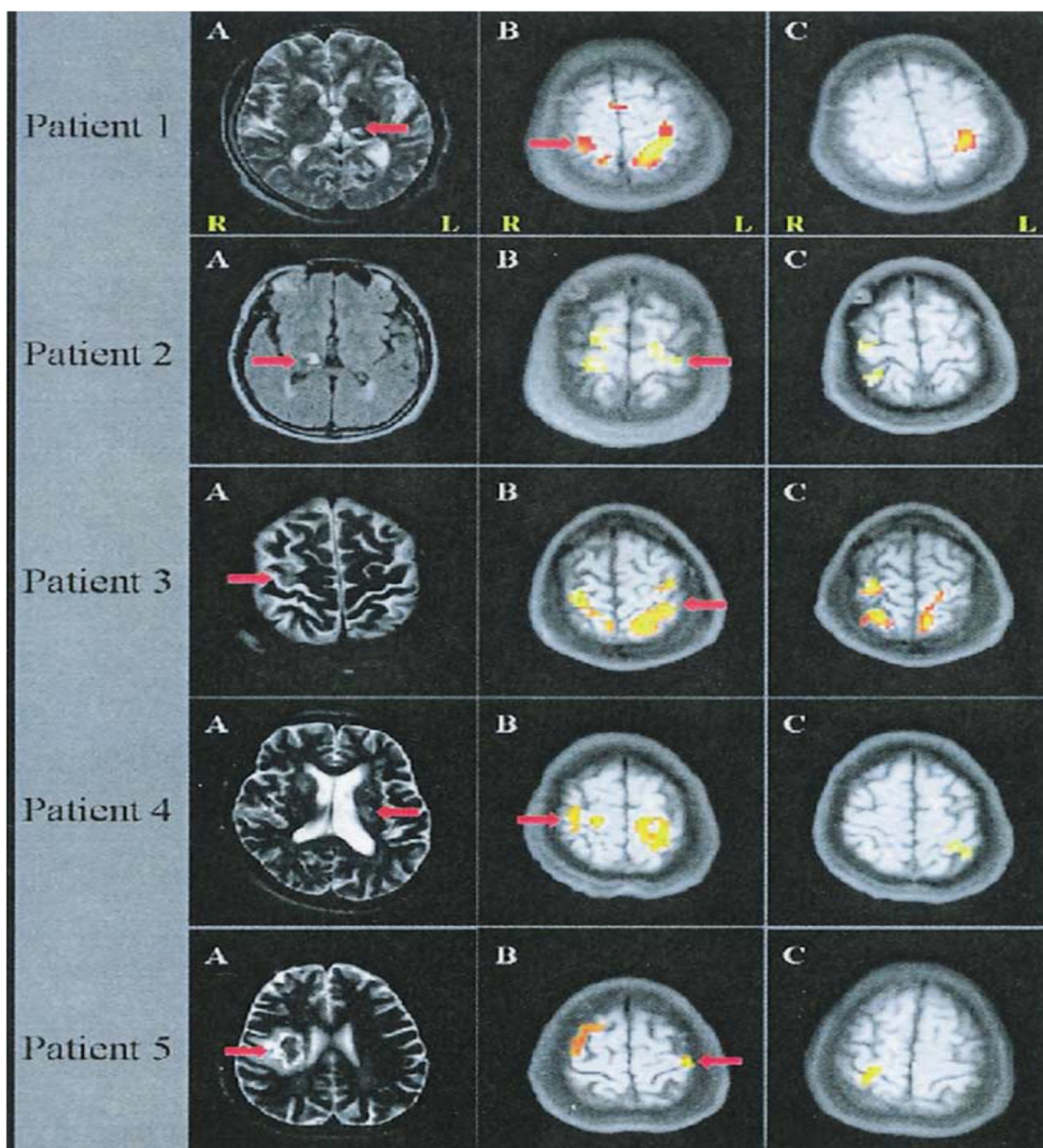
During the baseline and follow-up periods, P1 went to the clinic's gym once or twice per week and attended weekly physiotherapy sessions focusing on balance, gait, and walking. For P2, no form of therapy was provided during baseline or follow-up. The treatment phase consisted of four weeks of supervised VR training with five 45-minute sessions per week. For training, patients were seated at a table in front of a screen displaying avatar hands in the first-person perspective, lying on a table surface. They were equipped with data gloves that controlled the avatar hands in one of three manners: 1) the physical hands controlled the corresponding virtual left/right hands; 2) one of the physical hands controlled both of the virtual hands (with mirror effect on the paretic limb such that even when it is resting, the corresponding virtual hand is moving); and 3) same as condition 2 without the mirror effect.

Patients had to perform three different VR training tasks with their hands. The *Toy Catching* task consisted in reaching for and grasping various objects in movement using both virtual hands. The *Catch the Carrot* task required patients to grasp carrots growing out of the ground and place them in one of the baskets at either side of the screen; there was also a rabbit that came to steal the carrots and patients would have to fend it off with their other hand. The last task, *Tomato Juggling*, asked participants to use two circular pads with their arms placed in supine position and juggle one falling object at a time, placing in the right basket (tomatoes to the right and eggs to the left).

An fMRI scans were performed during the baseline period, two weeks after intervention conclusion and at a three-month follow-up. For P1, using repetitive force pulses of the paretic limb, results showed that, at baseline, there was initial cortical activation of the bilateral SM1, the SMA, and the dorsal premotor cortex. As treatment progressed, the next two fMRI measurements revealed that the ipsilesional activation of these three areas dramatically decreased, while a weak but constant neural response of the contralesional M1 appeared in all 3 scans. For P2, there was a shift from bilateral activation of SM1, SMA, and dorsal premotor cortex to a predominantly right-sided activation of SM1 and increased neural response of the right SMA. Authors concluded that this suggested a reorganization of the ipsilesional hemisphere's sensorimotor network. Pre-treatment, in-treatment, and post-treatment fMRI imaging is shown for both patients in [Fig. 6](#). It is also important to note that both patients exhibited significant improvement on traditional measures of upper limb mobility, such as the Chedoke Arm and Hand Activity Inventory (CAHAI) and this was maintained at follow-up. Overall, authors considered this VR training system as safe, feasible, and enjoyable for stroke survivors.

Lastly, [Caglio et al. \(2012\)](#) conducted a study using neuroimaging in rehabilitation by VR of a 24-year-old male with TBI who was presenting memory deficits. The patient had shown no improvement in neuropsychological tests after two standard rehabilitation protocols, indicating that general practice effects were unlikely to affect post-training improvements. Researchers began the VR protocol one year after the event so spontaneous recovery was unlikely. Rehabilitation training took place in a virtual town (London) and the patient was asked to explore and cut down trees and poles along the way (explicit task). The implicit task was spatial memory since, while exploring the





**Fig. 5.** Pre-VR and post-VR activations of the bilateral primary sensorimotor cortex (SM1) in chronic stroke patients. Reproduced with permission from Elsevier. (A) T2-weighted brain MR images showing lesion location indicated by the arrow. (B) Pre-VR training bilateral activations in primary sensorimotor cortices (SM1). (C) Post-VR SM1 bilateral/contralateral activity has disappeared for patients 1, 2, 4, and 5 and decreased for patient 3 while moving the affected limb (the arrow shows the activation site).

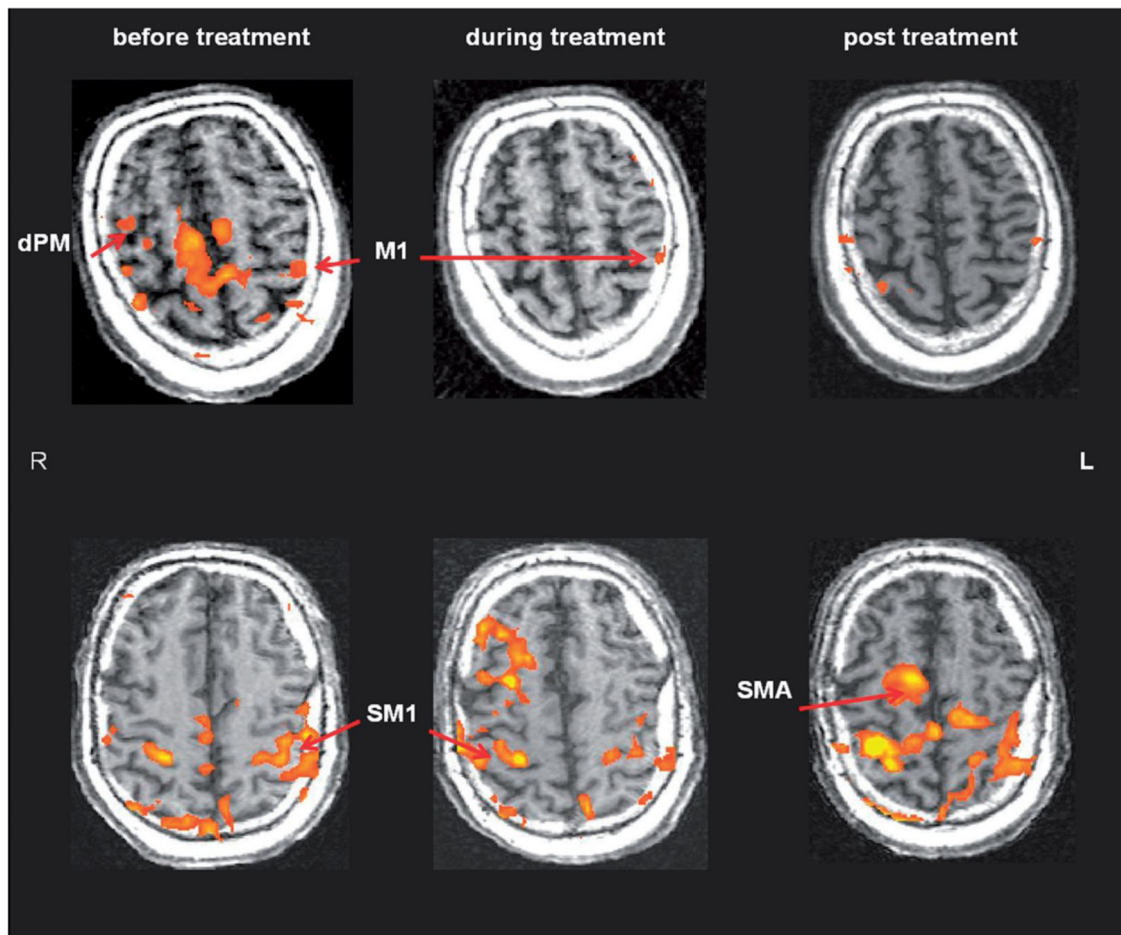
town, the patient had to avoid re-using the same roads. Training sessions lasted 90 min, three times a week for five weeks, with seven-minute breaks every 20 min.

Researchers evaluated the efficacy of treatment by measuring neurophysiological changes and used fMRI to measure modification of cerebral activations. It was also used to assess hippocampal and parahippocampal activation during a memory task using Paired Associate Learning as mnemonic content. During the scan, the patient was presented with seven pairs of words and was then asked to recall them outside of the scan. The patient underwent three fMRI sessions, one pre-training, one post-training and another two months after discontinuation of training. A series of neuropsychological assessments were also administered before and after each training session, two months later and one year later.

Post-training neuroimaging results showed increased bilateral activation in the superior and middle temporal gyrus, cerebellum, and

hippocampus, as well as in the left anterior cingulate. There was specifically increased metabolism in the left hippocampus and the right para-hippocampal cortex (involved in memory-processing). Additionally, there was more extensive activation in the left ventral tegmental area (VTA), linked to the reward system part of the mesolimbic network, the left hippocampus, left medial frontal gyrus, bilateral medial frontal gyrus, right hippocampal gyrus, and the right cuneus and precuneus. The authors hypothesized that the virtual training had also activated a VTA-hippocampal loop responsible for the entry of information into long-term memory. Meanwhile, neuropsychological testing revealed that the participant had clearly improved in terms of spatial memory learning. The follow-up neuroimaging data showed that, overall, gains were maintained.

Taken altogether, these studies lead to the conclusion that monitoring VR therapy with pre and post neuroimaging is a promising step. The concept underlying VR therapy as a treatment for cognitive



**Fig. 6.** Brain activity of two stroke patients as measured by fMRI before, during, and after VR training of upper limb movements. Reproduced with permission from Taylor & Francis Group.

Three applications trained bimanual reaching, grasping, hand opening in a virtual environment for two stroke patients (P1 and P2) with upper limb impairments. Functional MRI scans performed before, immediately after training and at a 3-month follow-up showed that for: P1) there was initially a strong ipsilesional activation of the primary sensorimotor cortex (SM1), the supplementary motor area (SMA) and the dorsal premotor cortex (dPM) that decreased over the three measurements; P2) there was a bilateral activation of the same three areas at the initial measurement that shifted to a predominantly right primary sensorimotor cortex activation along with increased response of the supplementary motor area. This suggested a reorganization of the sensorimotor network was taking place in the ipsilesional hemisphere.

dysfunction is to improve neuroplasticity of the brain by engaging users in multisensory training. A practical approach to study experience-dependent plasticity in humans is to investigate longitudinal changes in brain structure or function following exposure to training using pre and post neuroimaging measurements.

### 3. Conclusion and perspectives

The use of VR in neuropsychology has grown over the past decade to become a valuable tool for clinicians both in assessment and rehabilitation of patients (Rizzo and Bouchard, 2019). To take advantage of it, designing a VE that delivers a credible enough representation of reality that the patient will feel comfortable exploring their weaknesses and training their strengths is an essential component of creating a successful cyber-therapy. VEs also have the definite advantage of suiting both physically impaired patients, who may be unable to ambulate for example, as well as those suffering from exclusively cognitive deficiencies.

The next technological step was to introduce simultaneous neuroimaging, a potential added value for the rather young field of neurorehabilitation in VR. This allows the clinician to identify and target the respective individual's spatial and temporal brain activation patterns, thereby tailoring the training modules to the individual patient. This is

the key aspect to consider because it is important to note that when neuroimaging is performed on a patient immersed in a VE, it may appear less rigorous from an experimental setup standpoint than other classic designs generally used. However, our review shows that, even when several cognitive functions are solicited in a multisensory setting, it is still possible for clinicians to properly identify the biomarkers of therapeutic progress. Even more promising, is the fact that they are also able to spot the links between different brain regions, or separate functions, working together to allow the participant to perform certain actions. This would not be detectable in a patient performing a single task under fMRI observation, for example. Hence, the ecological validity of neuropsychological assessments and the concrete real-life gains of rehabilitation programs can potentially be boosted by the use of VR, while success rates can be increased as the combination of cyber-therapy and neuroimaging is further explored.

The practical gains of VR use in neurorehabilitation have been mostly well established, however it is also clear that there is still much left to learn from the presence of this novel tool in the clinical setting. One central issue is the individualization of the therapeutic application of VR: the more the spatial and temporal settings of VR therapy are tailored to the capacities or incapacities of the individual participant's behavior and underlying brain's neuronal activity, the more likely it is that VR will exert therapeutic effects. Combining VR therapy with brain

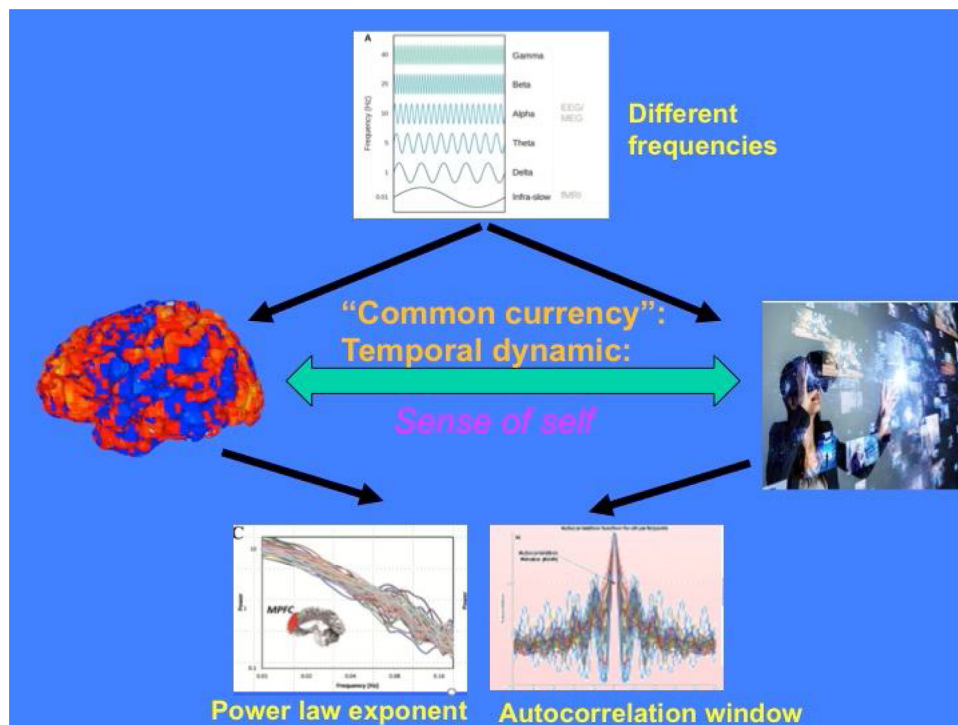


Fig. 7. Temporal dynamic as “common currency” of VR, brain, and self.

imaging (EEG, fMRI, fNIRS) will allow for such neuronally-based individualization of VR therapy.

In addition, it was recently proposed that the dynamics of time and space provides a “common currency” that connects neuronal and mental features (Northoff et al., 2019). Combining VR therapy with brain imaging in vivo may help to better understand how the brain’s spontaneous activity constructs its spatial and temporal relationships (Fig. 7).

One specific example of application for practical application and therapeutic use would be the sense of self. Recent studies in neuroscience showed that the resting state’s neuronal activity is closely related to our sense of self. Specifically, the resting states’ temporal dynamic, i.e., its scale-free properties in its power spectrum as measured by power law exponent (PLE) and autocorrelation window (ACW), has been related to self-consciousness in both fMRI and EEG: the larger the PLE and longer the ACW, with both indexing stronger power in slower frequencies and their long cycle durations, the higher the degree of private self-consciousness (Wolff et al., 2019, Huang et al. 2016, Kolvaart et al., 2020). This suggests that the resting state’s temporal dynamic is central in mediating our sense of self. Altered sense of self may then be related to altered resting state dynamic as it could indeed be shown in a recent study in schizophrenia showing abnormal PLE and ACW during self task (Northoff et al., 2020). VR too operates with a time series of changes; one could now design that time series in a scale-free way and a power spectral density that is slightly higher or lower than the one in the individual subject’s brain – exposing the subject to such VR should ultimately change its brain’s PLE and ACW in the direction as triggered by VR. The temporal features (and also spatial features) of VR could thus be exploited to manipulate corresponding temporal (and spatial) features in the brain – temporo-spatial dynamic would thus provide the « common currency » of VR, brain, and self (Northoff et al., 2019).

In context of psychiatry, to apply VR hypotheses about the specific relationships of VR-related measures, neuronal brain activity, and psychopathological symptoms are needed as they could guide the development of VR in diagnosis and treatment. As mentioned above, one potentially fruitful approach could be the recently developed «

Spatiotemporal Psychopathology » (Northoff 2016a and b, 2018) that conceives spatiotemporal changes in the brain’s dynamic to underly corresponding spatiotemporal changes on the psychological level which distort perceptual and cognitive function. Since VR manipulates spatiotemporal dynamical features, it may serve as ideal tool to remedy and « normalize » spatiotemporal changes on both neuronal and psychological levels.

What stems from the review of the literature is that cognitive and motor rehabilitation have been widely explored in post-stroke patients, but not as much in those who have suffered a debilitating TBI. Considering the prominent issue that TBIs, especially mild TBIs or concussions, have become in contemporary society, developing new methods to identify and treat any difficulties resulting from this type of trauma is imperative. Therefore, a more in-depth exploration of VR training coupled with neuroimaging in the case of TBI should be one objective of further research in the field.

Despite the increasing enthusiasm for combining VR with neuroimaging, and evidence of its use in clinical applications, the current literature review highlight several limitations:

First, larger clinical studies are required to identify neurobiomarkers for therapeutic success in the context of VR neurorehabilitation in different clinical populations. Much of the existing literature report mixed findings from small sample sizes (sometimes even single case studies), and often lack appropriate control comparisons or control conditions to differentiate neurofunctional spontaneous reorganization from neurofunctional reorganization induced by the VR training.

Secondly, there is little information about the relation between predictive neurobiomarkers of therapeutic success in the context of VR neurorehabilitation and optimal transfer to real-world functional improvements. These predictors and their impact on outcome are yet to be elucidated.

Thirdly, despite the full potential to identify predictive neurobiomarkers for therapeutic success using neuroimaging, the combination of both technologies is in early development. Further development is needed before VR rehabilitation can be guided by neurobiomarkers and be fully integrated into the routine rehabilitation. For example, multi-site, assessor-blinded randomized controlled trial might to be

conducted to validate predictive neurobiomarkers of therapeutic success of VR neurorehabilitation.

### Declarations of Competing Interest

Stéphane Bouchard is president of and own equity in Cliniques et Développement In Virtuo, a university spin-off that uses virtual reality as part of its clinical services and distributes virtual environments. The terms of these arrangements have been reviewed and approved by the Université du Québec en Outaouais in accordance with its conflict of interest policies. The remaining authors report no financial relationships with commercial interests.

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### References

- Ansado, J., Brulé, J., Chasen, C., Northoff, G., Bouchard, S., 2018. The virtual reality working-memory-training program (VR WORK M): description of an individualized, integrated program. *Annual Rev. Cybertherapy Telemedicine* 2018, 101.
- i Badia, S.B., Morgade, A.G., Samaha, H., Verschure, P.F.M.J., 2013. Using a hybrid brain computer interface and virtual reality system to monitor and promote cortical reorganization through motor activity and motor imagery training. *Ieee Trans. Neural Syst. Rehabil. Eng.* 21 (2), 174–181.
- Beck, L., Wolter, M., Mungard, N.F., Vohn, R., Staedtgen, M., Kuhlen, T., Sturm, W., 2010. Evaluation of spatial processing in virtual reality using functional magnetic resonance imaging (fMRI). *Cyberpsychol. Behav. Soc. Netw.* 13 (2), 211–215.
- Caglio, M., Latini-Corazzini, L., D'Agata, F., Cauda, F., Sacco, K., Monteverdi, S., et al., 2012. Virtual navigation for memory rehabilitation in a traumatic brain injured patient. *Neurocase* 18, 123–131. <https://doi.org/10.1080/13554794.2011.568499>.
- Cho, B.H., Kim, S., Shin, D.I., Lee, J.H., Min Lee, S., Young Kim, I., Kim, S.I., 2004. Neurofeedback training with virtual reality for inattention and impulsiveness. *Cyberpsychology Behav.* 7 (5), 519–526.
- Comani, S., Schinaia, L., Tamburro, G., Velluto, L., Sorbi, S., Conforto, S., Guarnieri, B., 2015. August). Assessing neuro-motor recovery in a stroke survivor with high-resolution EEG, robotics and virtual reality. In: *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE. IEEE.* pp. 3925–3928.
- Holper, L., Muehleemann, T., Scholkmann, F., Eng, K., Kiper, D., Wolf, M., 2010. Testing the potential of a virtual reality neurorehabilitation system during performance of observation, imagery and imitation of motor actions recorded by wireless functional near-infrared spectroscopy (fNIRS). *J. Neuroeng. Rehabil.* 7 (1), 57.
- Jang, S.H., You, S.H., Hallett, M., Cho, Y.W., Park, C.M., Cho, S.H., et al., 2005. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. *Arch. Phys. Med. Rehabil.* 86 (11), 2218–2223.
- Kolvaart, I., Wainio-Theberge, S., Wolff, A., Northoff, G., 2020. Temporal integration as the 'common currency' of brain and self – autocorrelation window correlates with tempora delay effects on self-relatedness. *Hum. Brain Mapp* in press.
- Laver, K., Lim, F., Reynolds, K., George, S., Ratcliffe, J., Sim, S., Crotty, M., 2012. Virtual reality grocery shopping simulator: development and usability in neurological rehabilitation. *Presence* 21 (1), 183–191.
- Merians, A.S., Tunik, E., Adamovich, S.V., 2009. Virtual reality to maximize function for hand and arm rehabilitation: exploration of neural mechanisms. *Stud. Health Technol. Inform.* 145, 109.
- Northoff, G., Wainio-Theberge, S., Evers, K., 2019. Is temporo-spatial dynamics the "common currency" of brain and mind? In *Quest of "Spatiotemporal Neuroscience"*. *Phys. Life Rev.* <https://doi.org/10.1016/j.plrev.2019.05.002>. pii: S1571-0645(19)30073-30079.
- Northoff, G., Sandsten, K.E., Nordgaard, J., Kjaer, T.W., Parnas, J., 2020. The self and its prolonged intrinsic neural time scale in schizophrenia. *Schizophr. Bull.* in press.
- Prochnow, D., Bermúdez i Badia, S., Schmidt, J., Duff, A., Brunheim, S., Kleiser, R., et al., 2013. A functional magnetic resonance imaging study of visuomotor processing in a virtual reality-based paradigm: rehabilitation gaming system. *Eur. J. Neurosci.* 37 (9), 1441–1447.
- Rizzo, A., Bouchard, S., 2019. *Virtual Reality for Psychological and Neurocognitive Interventions.* Springer Nature.
- Rizzo, A.A., Buckwalter, J.G., Bowerly, T., Van Der Zaag, C., Humphrey, L., Neumann, U., et al., 2000. The virtual classroom: a virtual reality environment for the assessment and rehabilitation of attention deficits. *Cyberpsychology Behav.* 3 (3), 483–499.
- Sangani, S., Lamontagne, A., Fung, J., 2015. Cortical mechanisms underlying sensorimotor enhancement promoted by walking with haptic inputs in a virtual environment. *Prog. Brain Res.* 218, 313–330 Elsevier.
- Schuster-Amft, C., Henneke, A., Hartog-Keisker, B., Holper, L., Siekierka, E., Chevrier, E., et al., 2015. Intensive virtual reality-based training for upper limb motor function in chronic stroke: A feasibility study using a single case experimental design and fMRI. *Disability and Rehabilitation. Assist. Technol.* 10 (5), 385–392 2015, P.385–392,10(5).
- Snider, J., Plank, M., Lee, D., Poizner, H., 2013. Simultaneous neural and movement recording in large-scale immersive virtual environments. *IEEE Trans. Biomed. Circuits Syst.* 7 (5), 713–721.
- Steinisch, M., Tana, M.G., Comani, S., 2013. A post-stroke rehabilitation system integrating robotics, VR and high-resolution EEG imaging. *Ieee Trans. Neural Syst. Rehabil. Eng.* 21 (5), 849–859.
- Teo, W.P., Muthalib, M., Yamin, S., Hendy, A.M., Bramstedt, K., Kotsopoulos, E., et al., 2016. Does a combination of virtual reality, neuromodulation and neuroimaging provide a comprehensive platform for neurorehabilitation?—a narrative review of the literature. *Front. Hum. Neurosci.* 10, 284.
- Wolff, A., Di Giovanni, D.A., Gómez-Pilar, J., Nakao, T., Huang, Z., Longtin, A., Northoff, G., 2019. The temporal signature of self: temporal measures of resting state EEG predict self consciousness. *Hum. Brain Mapp.* 40 (3), 789–803.