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Commentary

Electrophysiological Correlates of Virtual-Reality Applications in the Rehabilitation Setting: New Perspectives for Stroke Patients

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Abstract: Here we reviewed the last evidence on the application of electroencephalography (EEG) as a non-invasive and portable neuroimaging method useful to extract hallmarks of neuroplasticity induced by virtual reality (VR) rehabilitation approaches in stroke patients. In the neurorehabilitation context, VR training has been used extensively to hamper the effects of motor treatments on the stroke's brain. The concept underlying VR therapy is to improve brain plasticity by engaging users in multisensory training. In this narrative review, we present the key concepts of VR protocols applied to the rehabilitation of stroke patients and critically discuss challenges of EEG signal when applied as endophenotype to extract neurophysiological markers. When VR technology was applied to magnify the effects of treatments on motor recovery, significant EEG-related neural improvements were detected in the primary motor circuit either in terms of power spectral density or as time-frequency domains.

Keywords: virtual reality; EEG; rehabilitation; stroke

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1. Advanced Neurorehabilitation Systems for Recovering Patients with Stroke

Stroke is the third most frequent cause of worldwide death [1]. The great challenge of the survivors of stroke is to address the long-term consequences as sensory, motor, cognitive, and visual impairments. These neurological deficits are the main rehabilitation targets since these reduce the ability of individuals to perform activities of daily living (ADL) [1].

The International Classification of Functioning, Disability, and Health (ICF) [2] produced a transition from an exclusive neurophysiological focus to an inclusive rehabilitation perspective [3], based on the classification of three levels of human functions: (1) body level (physiological function and anatomical parts), (2) whole person (action and task execution by an individual), and (3) person in a social context (participation in a life situation) [4]. This approach ensures the improvement of quality of life (QOF) and the performance of ADL [5].

Advanced technology is increasingly being applied in neurorehabilitation to potentiate conventional treatments, reduce neurological disability, and improve global functions. A heavy limitation in conventional rehabilitation programs could be a reduced and inadequate dose of rehabilitation therapy, in terms of intensity and repetition of exercises. In stroke patients, lower-limb impairment impacts the mobility domain of QOF, whilst upper limb dysfunction negatively impairs all ADL activities.

Virtual Reality (VR) is one of the most utilized advanced neurorehabilitation technologies for increasing motor and cognitive abilities in stroke patients. VR is a computer-based technology that allows users to interact with a multisensory simulated environment, receiving ‘real-time’ feedback on specific performance (Figure 1). It is well recognized that feedback plays an important role in skill acquisition, mediating experience-dependent plasticity [6]. Especially in motor learning, feedback must be proposed not just at the end of the action but during movement performance. VR technologies promote this rehabilitation approach allowing a task-oriented training that maximizes frequency, intensity, and repetition of exercises, simultaneously enabling the immersive sensation [7]. This technology has emerged as a new approach to the treatment of stroke, since by simulating real-life activities, stroke patients can work on self-care skills in a setting that is usually impossible to create in a hospital environment [8].

Figure 1. Virtual Reality application on a neurological patient in a rehabilitation setting at Institute S’Anna.

As stated by Bowman and colleagues [9,10], a successful VR neurorehabilitation setting cannot be realized without the sense of presence and immersion, since the ultimate goal of the VS-related rehabilitation approach is to transfer abilities and skills acquired to real-world performance [11].

(a) The sense of presence is the most important component differentiating the VR from the other device [12,13]. VR allows the users to be in a virtual environment (VE) rather than in the place in which is located. Sanchez-Vives & Slater [14] claims that to be “present” means to transfer the consciousness in the VEs. It depends on different converging characteristics: the modality in which the user is represented in the VE, the number and quality of feedback, user’s characteristics (i.e., age, gender), and VE characteristics (how much realistic it is). In the simulation of a sensory-motor experience, the VEs recreate as close as possible a real situation, inducing the brain system to reactivate the underlying neural networks for the expected effect as in a real environment.

(b) Immersion is an objective property of the system that aims at generating a sense of presence as human subjective response. The degree of perceived immersion is dependent on technology. Finally, a high level of immersion does not guarantee a corresponding level of presence, while a higher sense of presence generates a deeper emotional response [15].

After applications in psychological treatments (i.e., exposure therapy for patients with phobia) and surgical training, VR expanded its borders acquiring a pivotal role in the rehabilitation fields (i.e., physical and cognitive treatments, ADL training, occupational therapy, speech therapy) and also in telerehabilitation [16]. About 20 years ago, VR began to be applied in rehabilitation, lying its rationale on the active learning provided by the immersion as a simulation of real life [17]. Additionally, it is worth noting that the learning of new motor tasks depends on the feedback originated from the performance. This concept has grounded the rationale of VR application [16]. The use of this technology represents an opportunity to reach a new, useful, and more aimed rehabilitation protocol, combining VR with conventional therapy [18]. In particular, the enriched environments of VR, encouraging and motivating a higher number of repetitions, train stroke patients to solve problems by learning new skills [19]. Furthermore, the continuous challenge provided by new modified tasks encourages and motivates the active participation of the patients to handle with VR equipment, reducing the therapist's supervision and assistance [16].

As reported by a Cochrane Review of Laver et al. [8], the post-stroke upper limb rehabilitation mediated by VR has a significantly better effect only when applied with conventional therapy. This claim has also been confirmed by Turolla et al. [16], who claimed that combining conventional treatment with VR is a more effective way to recover upper limb motor function with respect to conventional therapy alone. As concerns lower limbs, similar effectiveness was reported applying VR therapy [17]. Finally, Sarfo et al. [20] in a systematic review reported that telerehabilitation, when combined with virtual reality systems, has better (or similar) beneficial effects on motor and mood disorders of stroke patients compared with conventional face-to-face therapy. Finally, encouraging data were also reported by Agostini et al., [21] about VR application on anomia dysfunctions [22] in stroke patients. However, the full potential of VR applications in healthcare remains to be explored [14]. To stimulate and encourage VR applications as an alternative and/or complementary treatment in a rehabilitation setting, Tieri et al. [23] highlight the importance of VEs as a valid instrument to enhance implicit learning during robot-assisted rehabilitation and to increase the level of compliance in neurological patients [24], while the exploitation of the augmented feedback during motor/cognitive tasks can facilitate the reacquisition of motor abilities [16]. Moreover, it should be considered that the employment of VR applications may have a positive influence also on the Healthy System in terms of optimization of professional resources [16].

2. Looking for Endophenotypes of Recovery: *The Electroencephalography*

Endophenotypes are measurable subclinical heritable biological markers or behavioral traits that are internal phenotypic expressions of a genotype. Endophenotypes could be neuroanatomical, cognitive, or neurophysiological [25]. Identifying endophenotypes may be more useful in the identification of biological pathways related to those specific rehabilitation treatments, which might help to narrow the targets for potentially more effective interventions.

The concept underlying VR therapy is to improve brain plasticity by engaging users in multisensory training. Electroencephalography (EEG) is a non-invasive neuroimaging technique proposed as one of the most ecological tools useful to extract evidence of neuroplasticity in real-time [26,27]. Together with other techniques, such as functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS), EEG can provide different elements of neuronal information through VR rehabilitation programs.

EEG has several advantages especially in a VR environment since this neuroimaging tool is portable, relatively inexpensive, and easy to use with high temporal resolution [28]. Furthermore, new generation systems might also be wireless, which is ideal for the VR environment [28,29]. The optimal temporal information provided by EEG is strongly recommended, especially in protocols involving real-time neurofeedback and for monitoring of brain activities during VR tasks. Again, EEG is much less expensive, and its high temporal resolution (compared to other methods, such asfMRI and fNIRS) makes EEG ideal for real-time analysis and for monitoring brain oscillation during VR intervention. In this respect, EEG has overcome many of the fMRI and fNIRS limitations, becoming the best candidate for monitoring stroke patients in a VR setting.

Generally, EEG data can be used either for evaluating the presence of neural plasticity in stroke patients before and after neurobehavioral treatment or as neurofeedback for brain-computer interface (BCI) systems. Indeed, the most common brain signal activity (EEG rhythms) used with BCI paradigms in stroke patients is related to motor planning and execution [30]. During a motor attempt, the temporal pattern of the Alpha rhythm (8–12 Hz) over the sensorimotor cortices desynchronizes. This rhythm is considered an indirect indication of the action observation network and reflects the general sensorimotor activity. When these EEG signatures change in the Beta rhythm (12–30 Hz) in the form of event-related desynchronization, they indicate that motor action is executed [31].

It is well known that the preparation, the execution, and also the imagination of the movement produce an event-related desynchronization (ERD) on sensorimotor areas in the alpha and beta bands [31,32]. In particular, the ERD in the form of EEG power reduction [33] (the so-called mu-rhythm (8–13 Hz) or the value of the BOLD signal below the baseline level [34]) is observed on the contralateral sensorimotor areas during the preparation of the movement and extends bilaterally with the start of the movement. This phenomenon is similarly observed during hand motor imagery to the pre-movement ERD and seems to be locally restricted to the contralateral sensorimotor areas [32]. Recently, Porcaro and colleagues [33] have shown that higher desynchronization in both contralateral and ipsilateral sensorimotor areas is related to the performance of the movement during a visuomotor task. This effect was most evident in the ipsilateral component, suggesting the importance of the ipsilateral sensorimotor area during accurate movements.

Several reviews summarize the state-of-art of BCI combined with EEG technology for extracting neurofeedback useful to develop advanced neurorehabilitation approaches [35]. However, the present review is focused on the application of EEG signal as an endophenotype of neural changes induced by VR-related behavioral treatments on stroke patients.

3. EEG Reveals Neurophysiological Correlates of Neurorehabilitation with VR

Neurophysiological changes associated with VR neurorehabilitation is still relatively a new field of study, starting with preliminary evidence on behavioral tasks in healthy controls [36]. Today, the current usage of EEG in VR therapy is to monitor and provide augmented feedback regarding regions of cortical activation during motor and cognitive tasks [37,38].

As said before, VR can magnify the effects of several neurorehabilitation approaches [39], mainly those based on robotic devices. In a recent study, Calabrò et al. [40] investigated the neural basis of motor functional recovery of the lower limbs in 24 stroke patients who underwent Lokomat treatment with (experimental group) or without VR (control group). EEG signals were recorded using a Brain-Quick System from a standard 19 electrodes headset for 10 min while performing Lokomat training. EEG analysis consisted of the computation of the power spectral density (PSD) and the temporal frequency (TF) analysis to evaluate Event-related-spectral perturbations. Spectrum analysis was carried using a standard fast Fourier transform (FFT) algorithm within ϑ (4–7 Hz), μ (8–12 Hz), β (12–30 Hz), low-γ (Lγ) (31–45 Hz), and high-γ (Hγ) (46–70 Hz) bands and related to the phases of the gait cycle [41]. After an intervention period lasting 2 months, the experimental group underwent Lokomat rehabilitation with VR showing higher motor recovery of the lower limbs with respect to patients not using VR technology. This behavioral improvement was mirrored by underlying neural changes as detected by EEG. Indeed, the experimental group after treatment was characterized by stronger event-related spectral perturbations in the high-γ and β bands and more evident activation of premotor, precuneus, and associative visual areas with respect to the control group. Moreover, the authors also found that the magnitude of γ-band modulation was significantly correlated with the clinical improvement and the improvement in muscle strength, and it was paralleled by a more selective μ/β-band modulation concerning the temporal patterns of activation across the gait cycle.

Considering neurorehabilitation of upper limbs, Comani et al., [42,43] have tried to monitor the neural activity during a novel rehabilitation system based on the combination of a robotic device with VR. This is called Trackhold (PERCRO, Pisa, Italy), a passive robotic device [44] working in combination with a VR system and synchronized with high resolution EEG for the simultaneous recording of kinematic and functional data. This robotic system has seven degrees-of-freedom and is designed to improve the recovery of movements involving the wrist, the elbow, and the shoulder. The VR training applications simulate simple visuo-motor coordination tasks. Subjects interact online with the VR training applications by moving the Trackhold's end-effector and observe the changes occurring in the VEs in real time on a 22-in LCD monitor. EEG-related cortical activity was recorded using a head-cap with 128 Ag/AgCl electrodes concerning the execution of every task during rehabilitation training. The sampling frequency was set at 1024 Hz. Inverse source reconstruction was performed using the multiple sparse priors (MSP) algorithm, and the estimated source activity was summarized as 3D images using a TF contrast ranging from -2 to 2 seconds and from 8 to 30 Hz. The frequency range was chosen due to the characteristics of motor-related cortical activity to include both alpha and beta rhythms. In a first case-report study, Comani et al., [42] found that after the application of the Trackhold three times per week for 4 weeks, a significant recovery of the impaired upper limb was reported. EEG analysis revealed an initial bilateral over-recruitment of the sensorimotor network, which significantly tended to be reduced at the end of rehabilitation. The neural plasticity changes were mainly recorded in the primary motor circuit involving also the cerebellum. TF analysis revealed a similar pattern of recovery of normal oscillatory processing within the somatosensory network after neurorehabilitation. In a second study [44] the effectiveness of the Trackhold system was tested on a larger population of stroke patients, where the EEG-related functional re-organization was monitored in association with motor patterns replicating activities of ADL. After 13 rehabilitative sessions, researchers found very consistent motor recovery, although a large heterogeneity in neurophysiological data was also noted. This is due to the three "S" characterizing the stroke brain: the different Side, Size and Site of lesions, which may strongly determine the reliability of the detected neural activity.

4. Conclusions

VR programs for stroke neurorehabilitation are based on the potential of brain neuroplasticity that allows the acquisition of new motor skills despite neurological injuries. As stated by Saposnik et al., [45], the goal of VR therapy is to magnify these motor learning skills in stroke patients by improving neurorehabilitation principles, such as providing repetitive, graded intensity, and motivating task-specific training with real time multimodal feedback of movements and performance. Thus, VR systems are designed to enhance conventional rehabilitative treatments by providing a tool to deliver more specific, intensive, and enjoyable therapy.

However, it is possible to improve the potential and applications of VR systems by monitoring the effects of more targeted neurorehabilitation approaches with non-invasive and portable neuroimaging methods, such as EEG. As claimed by Teo et al., [37] EEG signals can be used to provide both feedback on location and level of brain activation, which can be used by clinicians to set intensity, progression, and type of therapy. In this narrative review, we have provided new insights on the brain neuroplasticity induced by these advanced systems applied to stroke patients. Future studies about neuroplasticity induced by different targeted and tailored neurorehabilitation approaches should be considered to define the best VR programs useful to increase motor and functional recovery.

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References

1. Katan, M.; Luft, A. Global Burden of Stroke. *Semin. Neurol.* **2018**, *38*, 208–211. [CrossRef]
2. Massetti, T.; da Silva, T.D.; Crocetta, T.B.; Guarnieri, R.; de Freitas, B.L.; Bianchi Lopes, P.; Watson, S.; Tonks, J.; de Mello Monteiro, C.B. The Clinical Utility of Virtual Reality in Neurorehabilitation: A Systematic Review. *J. Cent. Nerv. Syst. Dis.* **2018**, *27*, 1179573518813541. [CrossRef]
3. Palma, G.C.; Freitas, T.B.; Bonuzzi, G.M.; Soares, M.A.; Leite, P.H.; Mazzini, N.A.; Almeida, M.R.; Pompeu, J.E.; Torriani-Pasin, C. Effects of virtual reality for stroke individuals based on the International Classification of Functioning and Health: A systematic review. *Top. Stroke Rehabil.* **2017**, *24*, 269–278. [CrossRef] [PubMed]
4. Merians, A.S.; Fluet, G.G. Rehabilitation Applications Using Virtual Reality for Persons with Residual Impairments Following Stroke. In *Virtual Reality for Physical and Motor Rehabilitation. Virtual Reality Technologies for Health and Clinical Applications*; Weiss, P., Keshner, E., Levin, M., Eds.; Springer: New York, NY, USA, 2014. [CrossRef]
5. Barker, R.N.; Brauer, S.G. Upper limb recovery after stroke: The stroke survivors' perspective. *Disabil. Rehabil.* **2005**, *27*, 1213–1223. [CrossRef] [PubMed]
6. Kleim, J.A.; Jones, T.A. Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *J. Speech Lang. Hear. Res.* **2008**, *51*, S225–S239. [CrossRef]
7. Proffitt, R.; Lange, B. Considerations in the efficacy and effectiveness of virtual reality interventions for stroke rehabilitation: Moving the field forward. *Phys. Ther.* **2015**, *95*, 441–448. [CrossRef]
8. Laver, K.E.; Lange, B.; George, S. Virtual reality for stroke rehabilitation. *Cochrane Database Syst. Rev.* **2017**, *11*, CD008349. [CrossRef] [PubMed]
9. Bowman, D.A.; McMahan, R.P. Virtual Reality: How much immersion is enough? *Computer* **2007**, *40*, 36–43. [CrossRef]
10. Bowman, D.A.; Kruijff, E.; LaViola, J.J.; Poupyrev, I. *3D User Interfaces: Theory and Practice, Course Smart eTextbook*; Addison-Wesley: Boston, MA, USA, 2004; Available online: https://www.amazon.co.uk/3D-User-Interfaces-CourseSmart-eTextbook-ebook/dp/B00AU3JU9O (accessed on 2 March 2021).
11. Weiss, P.; Kizony, R.; Feintuch, U.; Rand, D.; Katz, N. Virtual Reality Applications in Neurorehabilitation. In *Textbook of Neural Repair and Rehabilitation*; Selzer, M., Clarke, S., Cohen, L., Kwakkel, G., Miller, R., Eds.; Cambridge University Press: Cambridge, UK, 2014; pp. 198–218. [CrossRef]
12. Schultheis, M.T.; Himelstein, J.; Rizzo, A.A. Virtual reality and neuropsychology: Upgrading the current tools. *J. Head Trauma Rehabil.* **2002**, *17*, 378–394. [CrossRef] [PubMed]
13. Riva, G. The neuroscience of body memory: From the self through the space to the others. *Cortex* **2018**, *104*, 241–260. [CrossRef] [PubMed]
14. Sanchez-Vives, M.V.; Slater, M. From presence to consciousness through virtual reality. *Nat. Rev. Neurosci.* **2005**, *6*, 332–339. [CrossRef] [PubMed]
15. Perez-Marcos, D.; Slater, M.; Sanchez-Vives, M.V. Inducing a virtual hand ownership illusion through a brain-computer interface. *Neuroreport* **2009**, *20*, 589–594. [CrossRef]
16. Turolla, A.; Dam, M.; Ventura, L.; Tonin, P.; Agostini, M.; Zucconi, C.; Kiper, P.; Cagnin, A.; Piron, L. Virtual Reality for the rehabilitation of the upper limb motor function after stroke: A prospective controlled trial. *J. Neuroeng. Rehabil.* **2013**, *10*, 85. [CrossRef]
17. Schiza, E.; Matsangidou, M.; Neokleous, K.; Pattichis, C.S. Virtual Reality Applications for Neurological Disease: A Review. *Front. Robot AI* **2019**, *6*, 100. [CrossRef]
18. Lang, C.E.; Macdonald, J.R.; Reisman, D.S.; Boyd, L.; Jacobson Kimberley, T.; Schindler-Ivens, S.M.; Hornby, T.G.; Ross, S.A.; Scheets, P.L. Observation of amounts of movement practice provided during stroke rehabilitation. *Arch. Phys. Med. Rehabil.* **2009**, *90*, 1692–1698. [CrossRef] [PubMed]
19. Lewis, G.N.; Rosie, J.A. Virtual reality games for movement rehabilitation in neurological conditions: How do we meet the needs and expectations of the users? *Disabil. Rehabil.* **2012**, *34*, 1880–1886. [CrossRef] [PubMed]
20. Sarfo, F.S.; Ulasavets, U.; Opare-Sem, O.K.; Ovbiagele, B. Tele-Rehabilitation after Stroke: An Updated Systematic Review of the Literature. *J. Stroke Cerebrovasc. Dis.* **2018**, *27*, 2306–2318. [CrossRef]
21. Agostini, M.; Garzon, M.; Benavides-Varela, S.; de Pellegrin, S.; Bencini, G.; Rossi, G.; Rosadoni, S.; Mancuso, M.; Turolla, A.; Meneghello, F.; et al. Telerehabilitation in poststroke anomia. *Biomed. Res. Int.* **2014**, *2014*, 706909. [CrossRef]
22. Piron, L.; Turolla, A.; Tonin, P.; Piccione, F.; Lain, L.; Dam, M. Satisfaction with care in post-stroke patients undergoing a telerehabilitation programme at home. *J. Telemed. Telecare* **2008**, *14*, 257–260. [CrossRef] [PubMed]
23. Tieri, G.; Morone, G.; Paolucci, S.; Iosa, M. Virtual reality in cognitive and motor rehabilitation: Facts, fiction and fallacies. *Expert Rev. Med. Devices* **2018**, *15*, 107–117. [CrossRef]

24. Bernardoni, F.; Ozen, O.; Buetler, K.; Marchal-Crespo, L. Virtual Reality Environments and Haptic Strategies to Enhance Implicit Learning and Motivation in Robot-Assisted Training. In Proceedings of the 2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR), Toronto, ON, Canada, 24–28 June 2019; pp. 760–765. [CrossRef]
25. Gottesman, I.I.; Shields, J.J. A polygenic theory of schizophrenia. *Proc. Natl. Acad. Sci. USA* **1967**, *58*, 199–205. [CrossRef]
26. Cottone, C.; Cancelli, A.; Pasqualetti, P.; Porcaro, C.; Salustri, C.; Tecchio, F. A New, High-Efficacy, Noninvasive Transcranial Electric Stimulation Tuned to Local Neurodynamics. *J. Neurosci.* **2018**, *38*, 586–594. [CrossRef] [PubMed]
27. Porcaro, C.; Cottone, C.; Cancelli, A.; Rossini, P.M.; Zito, G.; Tecchio, F. Cortical neurodynamics changes mediate the efficacy of a personalized neuromodulation against multiple sclerosis fatigue. *Sci. Rep.* **2019**, *3*, 18213. [CrossRef] [PubMed]
28. Ansado, J.; Chasen, C.; Bouchard, S.; Northoff, G. How brain imaging provides predictive biomarkers for therapeutic success in the context of virtual reality cognitive training. *Neurosci. Biobehav. Rev.* **2021**, *120*, 583–594. [CrossRef] [PubMed]
29. Ayaz, H.; Onaral, B.; Izzetoglu, K.; Shewokis, P.A.; Mckendrick, R.; Parasuraman, R. Continuous monitoring of brain dynamics with functional near infrared spectroscopy as a tool for neuroergonomic research: Empirical examples and a technological development. *Front. Hum. Neurosci.* **2013**, *7*, 871. [CrossRef]
30. Shih, J.J.; Krusienski, D.J.; Wolpaw, J.R. Brain-computer interfaces in medicine. *Mayo Clin. Proc.* **2012**, *87*, 268–279. [CrossRef]
31. Pfurtscheller, G.; da Silva, F.H.L. Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clin. Neurophysiol.* **1999**, *110*, 1842–1857. [CrossRef]
32. Neuper, C.; Schlögl, A.; Pfurtscheller, G. Enhancement of left-right sensorimotor EEG differences during feedback-regulated motor imagery. *J. Clin. Neurophysiol.* **1999**, *16*, 373–382. [CrossRef]
33. Porcaro, C.; Mayhew, S.D.; Bagshaw, A.P. Role of the Ipsilateral Primary Motor Cortex in the Visuo-Motor Network During Fine Contractions and Accurate Performance. *Int. J. Neural Syst.* **2021**, 2150011. [CrossRef]
34. Mayhew, S.D.; Porcaro, C.; Tecchio, F.; Bagshaw, A.P. fMRI characterization of widespread brain networks relevant for behavioural variability in fine hand motor control with and without visual feedback. *Neuroimage* **2017**, *148*, 330–342. [CrossRef] [PubMed]
35. Pichiorri, F.; Mattia, D. Brain-computer interfaces in neurologic rehabilitation practice. *Handb. Clin. Neurol.* **2020**, *168*, 101–116. [CrossRef] [PubMed]
36. Liu, M.; Wang, J.; Yan, N.; Yang, Q. Development of EEG Biofeedback System Based on Virtual Reality Environment. In Proceedings of the 27th Annual Conference on IEEE Engineering in Medicine and Biology, Shanghai, China, 1–4 September 2005; pp. 5362–5364. [CrossRef]
37. Teo, W.P.; Muthalib, M.; Yamin, S.; Hendy, A.M.; Bramstedt, K.; Kotsopoulos, E.; Perrey, S.; Ayaz, H. Does a combination of virtual reality, neuromodulation and neuroimaging provide a comprehensive platform for neurorehabilitation?—A narrative review of the literature. *Front. Hum. Neurosci.* **2016**, *10*, 284. [CrossRef]
38. Lin, C.T.; Chung, I.F.; Ko, L.W.; Chen, Y.C.; Liang, S.F.; Duann, J.R. EEG-based assessment of driver cognitive responses in a dynamic virtual-reality driving environment. *IEEE Trans. Biomed. Eng.* **2007**, *54*, 1349–1352. [PubMed]
39. Jäncke, L.; Cheetham, M.; Baumgartner, T. Virtual reality and the role of the prefrontal cortex in adults and children. *Front. Neurosci.* **2009**, *3*, 52–59. [CrossRef]
40. Calabrò, R.S.; Naro, A.; Russo, M.; Leo, A.; de Luca, R.; Balletta, T.; Buda, A.; La Rosa, G.; Bramanti, A.; Bramanti, P. The role of virtual reality in improving motor performance as revealed by EEG: A randomized clinical trial. *J. Neuroeng. Rehabil.* **2017**, *14*, 53. [CrossRef]
41. Castermans, T.; Duvinage, M.; Cheron, G.; Dutoit, T. Towards effective noninvasive brain-computer interfaces dedicated to gait rehabilitation systems. *Brain Sci.* **2014**, *4*, 1–48. [CrossRef]
42. Comani, S.; Velluto, L.; Schinaia, L. Monitoring neuro-motor recovery from stroke with high-resolution EEG, robotics and virtual reality: A proof of concept. *IEEE Trans. Neural. Syst. Rehabil. Eng.* **2015**, *23*, 1106–1116. [CrossRef]
43. Comani, S.; Schinaia, L.; Tamburro, G.; Velluto, L.; Sorbi, S.; Conforto, S.; Guarnieri, B. Assessing neuro-motor recovery in a stroke survivor with high-resolution EEG, robotics and Virtual Reality. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2015**, *2015*, 3925–3928.
44. Steinisch, M.; Tana, M.G.; Comani, S. A post-stroke rehabilitation system integrating robotics, VR and high-resolution EEG imaging. *IEEE Trans. Neural. Syst. Rehabil. Eng.* **2013**, *21*, 849–859. [CrossRef] [PubMed]
45. Saposnik, G.; Levin, M. Outcome Research Canada (SORCan) Working Group.Virtual reality in stroke rehabilitation: A meta-analysis and implications for clinicians. *Stroke* **2011**, *42*, 1380–1386. [CrossRef] [PubMed]