Chapter 2
Neuroplasticity and Virtual Reality

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Objective To present the key aspects of neuroplasticity and how VR technology can capitalise on and influence this phenomenon to promote motor rehabilitation.

2.1 Definition of Neuroplasticity

In this chapter we discuss neuroplasticity and consider how VR technology may be used to promote motor learning and rehabilitation. First, we discuss the nature of neuroplasticity and the physiological mechanisms involved in the induction of both short- and long-term changes that enable us to store and retrieve memories for later use. Second, we review how neuroplastic changes can be indexed using biological principles and the underlying tenets of learning. Third, we consider the fundamental

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elements of experience-dependent neuroplasticity and clinical interventions that have the potential to induce and affect neuroplasticity. Finally, we consider empirical evidence of the effects of VR on neuroplastic changes in the brain.

The incidence of brain trauma is significant across the globe, and the resultant brain damage of such traumas often carries significant social, economic and human (personal) implications. Fortunately, the brain is highly capable, even beyond its developmental years, to exhibit physiological, functional and structural changes over time; this is likely the substrate for recovery of lost function following an injury (Nudo, 2006). The ability of the nervous system to undergo physiological changes as a result of genetic, behavioural and environmental changes is referred to as neuroplasticity. The processes of development, ageing, learning, memory and neural response to trauma all involve the critical concept of neuroplasticity. (N.B. We will often discuss the concepts of this chapter in terms of the brain following insult or injury—oftentimes it is easier to demonstrate normal brain function by comparing and contrasting with pathological brain states.)

2.1.1 Short-Term Versus Long-Term Changes

Neuroplasticity can occur on multiple levels, meaning the nature and extent of neuroplasticity can vary. Relatively short-term cellular changes can occur as a result of a temporary alteration in excitability of a population of neurons whereas relatively long-term structural changes can occur following long-term practice of a skill or an insult to the brain such as a stroke (Johansen-Berg et al., 2002). For example, short-term neural excitability changes (on the scale of seconds to hours) can be observed by inducing voltage changes in cortical regions of the brain via single-pulsed transcranial magnetic stimulation (TMS); a technique that has been shown to induce only short-term transient effects on the excitability of the brain (Barker, 1999). An example of a longer-term change in the brain can be observed in individuals who have become proficient at certain tasks. For example, empirical evidence of expanded areas of the motor cortex associated with finger movement has been shown in pianists (e.g. Pascual-Leone, Cammarota, Wassermann, Brasil-Neto, Cohen & Hallett, 1993); this is a clear demonstration of how behaviour can result in a long-term physical change in brain regions over time. Long-lasting changes in the brain (on the scale of years to decades) can also be readily observed following insults to the brain such as stroke, which can cause significant tissue damage (Hallet, 2001). Given appropriate rehabilitation however, neuroplastic changes may occur over time that allow for full or partial recovery of any lost function after the insult. Indeed, the neuroplastic nature of the brain allows for it to restructure over time with training and practice. Later in this chapter we discuss ways in which the properties of brain plasticity can be exploited to create long-lasting changes in the brain using technology such as VR.

2.1.2 Changes in Neuronal Traffic

2.1.2.1 Synaptic Pruning and Hebbian Mechanisms

Individual connections between neurons in the brain are continuously being altered depending on environmental and behavioural stimulation and responses to bodily injury. A key component of the theory of neuroplasticity is this dynamic change in neural connectivity, which involves the interplay of two phenomena: synaptic pruning and Hebbian neural interactions. Although synaptic pruning was initially characterised in the visual system (for review, Tessier and Broadie, 2009), pruning can be considered more generally as a genetically programmed reduction in the number of physical synapses between neurons in all sensory–motor systems in the nervous system. This process of pruning is strongly influenced by stimulation from the environment and interactions between neurons during learning—a process termed Hebbian interaction (Hebb, 1949). For example, pairs of neurons that are often excited together will likely exhibit less pruning and perhaps strengthened mutual connectivity, whereas the connections of two neurons that fire independently of one another will become either pruned or weakened. This principle is known colloquially as: "neurons that fire together wire together; neurons that fire apart wire apart" (Bliss & Lomo, 1973). If connections between neurons are no longer being used, their level of connectivity may be reduced or eliminated to allow more room and resources for active connections to be strengthened. Effectively, the connections between neurons are constantly being altered and redefined. An understanding of the principles of synaptic pruning and Hebbian interactions is helpful when considering the design and implementation of technology geared towards altering the connectivity between neurons during the processes of learning and rehabilitation.

2.1.2.2 LTP and LTD Hypothesis of Learning and Memory

While much remains to be elucidated about the nature of learning and memory, the theory of long-term potentiation (LTP) is well documented and a strong candidate as a cellular correlate for learning and memory. LTP is defined as a long-lasting enhancement in signal transmission between neurons that occurs when two neurons are stimulated simultaneously (Bliss & Lomo, 1973); it is one of the ways by which chemical synapses are able to alter in strength. The counterpart of LTP, long-term depression (LTD), occurs when the postsynaptic effects of a given neuron on another are weakened. LTP and LTD are activity-dependent processes that result in an accentuation or a reduction, respectively, in the efficacy of synaptic transmission either through changes in the number of connections between neurons, the modulation of neurotransmitter exchange between neurons, or both (Mulkey & Malenka, 1992).

2.1.3 Gross Anatomical Changes

2.1.3.1 Changes in Connectivity

Changes in synaptic dynamics through pruning and Hebbian interactions are evidenced on a macroscopic brain level as connections between different brain regions that are strengthened or weakened over time and by experience. Importantly, the brain has the ability to form new functional connections after it has experienced an injury or perturbation (for review see Calautti & Baron, 2003). Clear evidence of this has been demonstrated in the human motor system. For example, work from Nudo and Milliken (1996) has shown that after a focal stroke in the area of motor cortex responsible for hand function, neurons adjacent to the stroke lesion take over some of the lost motor function. These data and others demonstrate that changes in connectivity within the brain underlie the ability of an individual to recover some of their lost motor function after injury. Despite potential benefits, however, changes in connectivity can also result in pathological consequences. For example, repeated consumption of an addictive substance may result in neural connectivity changes that lead to an increased desire to continue to seek the substance (for review, Alcantra et al., 2011; Thomas, Kalivas, & Shaham, 2008).

2.1.3.2 Changes in Brain Activity Patterns Over Time

There are many current methods that may be used to assess changes in brain activity over time. Although we provide an overview of functional magnetic resonance imaging (fMRI) as an assay tool in more detail below, it is helpful to introduce it here as one way in which global changes in brain activity have been measured. fMRI measures the blood-oxygen-level-dependent (BOLD) signal and, because of its high spatial resolution, is particularly well-suited to investigate whether shifts in brain activity patterns occur over time. Changes in both the location and level of the BOLD signal can reveal evidence of neuroplasticity. Motor learning, for instance, has been shown to change BOLD patterns across distributed brain circuits in both healthy and patient populations. For example, BOLD patterns in different brain regions were examined before and after participants learned a novel motor sequence task (Meehan et al., 2011). Learning the new task changed patterns of brain network activity in both healthy and stroke-damaged brains. Importantly, these data show that individuals after a stroke may compensate by relying on different brain regions than matched healthy controls (e.g. dorsolateral prefrontal cortex instead of dorsal premotor cortex) to support some forms of motor learning (Fig. 2.1).

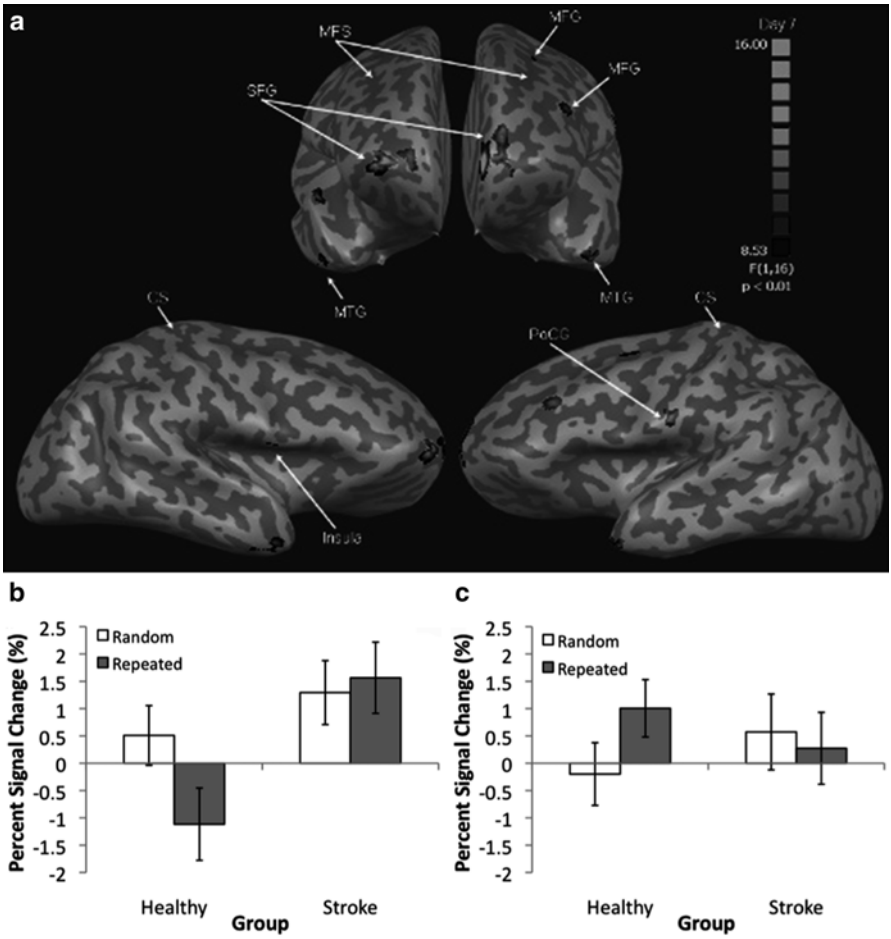

Fig. 2.1 (**a**) Sample fMRI showing the contrast in neural activity between individuals with stroke and matched healthy controls. Importantly, individuals with stroke rely on dorsolateral prefrontal cortex during motor sequence learning (**b**) while matched controls activate the premotor cortex to perform repeated sequences at a delayed retention test (**c**). Adapted from Meehan et al., 2011

2.2 How Can We Index Neuroplasticity?

There are several established methods of measuring neuroplastic changes in the nervous system. Here we discuss methods used to measure changes in excitability of different brain regions, methods to measure changes in metabolic demands in the brain, and methods of evaluating behaviour associated with neural changes.

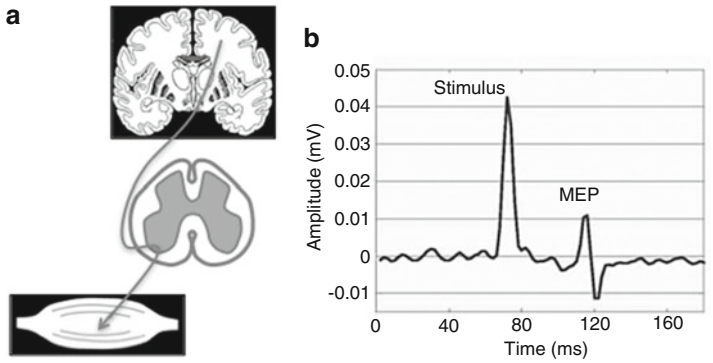

Fig. 2.2 Example of transcranial magnetic stimulation induced motor evoked potential. Stimulation over primary motor cortex induces depolarisation of pyramidal cells (**a**) and leads to an induced muscle response in the periphery (**b**)

2.2.1 Measuring Changes in Excitability of Brain Regions

2.2.1.1 Evoked Potentials

One common method of measuring changes in brain excitability is by presenting a stimulus to the nervous system and recording the electric potential that is evoked. This is called an evoked potential or response (Rothwell, 1997). Signals are typically recorded from the cerebral cortex, brainstem, spinal cord or peripheral nerves. For example, motor-evoked potentials (MEPs) can be recorded by stimulating the motor cortex of a subject and recording the electrical potential evoked in the muscle corresponding to the cortical area being stimulated (Pascual-Leone et al., 2002) (Fig. 2.2). The value of this technique is that differences in cortical excitability associated with disease, recovery or clinical intervention can be examined over time within the same individual. For example, measures of neural excitability could be obtained prior to, and following, a clinical intervention in order to examine the efficacy of the intervention (e.g. the effect of TMS applied to the motor cortex on general cortical excitability). While this technique provides a direct measure of the excitability state of the motor neurons in the brain and spinal cord, it is limited in its ability to assay the excitability of other brain regions, which do not have descending projections to muscles. For assessing more global brain areas, other measures are more appropriate.

2.2.1.2 Electroencephalography (EEG)

Electroencephalography (EEG) is used to measure electrical activity of the brain over time. More specifically, it measures the fluctuation of voltage between different areas in the brain as a result of changes in net ion flow across neuronal membranes

during synaptic transmission (Huang et al., 2007). EEG can be used as a diagnostic tool in clinical settings, for example, for the assessment of neural activity during epilepsy, encephalopathies and coma. Although EEG measures electrical activity across the entire surface of the head, the ability to pinpoint the source of the electrical signal using EEG methodology is limited (though more sophisticated source localisation algorithms are emerging (e.g. Koessler et al., 2007)). The main advantage of EEG arises from its outstanding temporal resolution that allows characterisation of changes in brain activity at the millisecond time scale.

2.2.1.3 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a technique used to examine magnetic fields produced by electrical currents in the brain. Like EEG, MEG signals are generated by net ion flow throughout neurons in the brain. The advantage of MEG is that it also offers millisecond scale temporal resolution as well as improved spatial resolution over EEG. Some source localisation algorithms show promise in identifying sub-cortical activity in addition to cortical activity (Hämäläinen et al., 1993). These acuity advantages arise because magnetic fields are less susceptible to distortion by the skull and scalp than are the electrical fields measured by EEG. However, MEG is only sensitive to tangential current sources (i.e. those which are parallel to the scalp), allowing it to mainly identify sources coming from depressions in the surface of the brain (sulci) while EEG is sensitive to both radial (directed towards or away from the scalp) and tangential sources (Huang et al., 2007), allowing it to be sensitive to both sulcal sources *and* sources from ridges surrounding the sulci (e.g. gyri). In this regard, MEG and EEG provide supplementary information concerning different parts of the brain and may be used in conjunction with each other to capture multiple physiological processes (Hämäläinen et al., 1993).

2.2.2 Measuring BOLD Contrast and Metabolic Changes

2.2.2.1 Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a non-invasive, indirect method of localising and measuring neural activity in the brain based on the relationship between neural activity and the metabolic demands associated with the increased neural activity. As stated earlier in this chapter, most fMRI experiments measure a blood-oxygen-level-dependent (BOLD) response. Changes in the BOLD signal result from changes in the blood deoxyhaemoglobin level in the brain. An increase in neuronal activity results in an increase in oxygen consumption, regional cerebral blood volume and regional cerebral blood flow, increasing the concentration of deoxyhaemoglobin and decreasing the concentration of oxyhaemoglobin (for review see Logothetis & Wandell, 2003; Norris, 2003). By comparing the BOLD

response across two or more test conditions (e.g. before and after learning a task), activation in a given brain area can be considered as increased or decreased relative to the control condition. Magnetic resonance imaging (MRI) is also used to acquire an anatomical scan of the brain prior to imaging with fMRI so that the location of any changes in the BOLD signal can be readily identified on a subject-specific basis.

The advantage of using fMRI lies in its unsurpassed spatial resolution (as much as 1 mm accuracy) and its ability to index the connectivity between functionally activated brain regions. This means that one is able to study how different brain areas interact with each other during certain tasks, or how brain activity in different areas changes following an insult to the brain. Studies have demonstrated that while neurological and behavioural tests may not be able to detect changes in brain function following traumatic brain injuries such as concussion, there is increasing evidence that advanced neuroimaging methods can provide more sensitive indications of the underlying brain pathology (e.g. Johnson et al., 2012). These findings suggest that fMRI may show promise as a prognostic tool to evaluate the neurological status of asymptomatic individuals who are suspected of injury (e.g. military personnel who are suspected of developing post-traumatic stress disorder). However, a significant limiting factor of fMRI is the relatively sluggish haemodynamics of blood flow, thus markedly limiting the temporal resolution of this approach. For example, while EEG and MEG allow one to characterise neural response at the millisecond time scale, fMRI operates on a multi-second time scale. Along the same vein, fMRI is only an indirect inference of neural activity (through changes in blood flow) while the other approaches measure neural activity more directly. Recently, new techniques have allowed for the measurement of brain activity via fMRI during interactions with virtual environments (VEs), thereby enabling one to examine whether or not exposure to VEs can influence a damaged brain's activity patterns and levels (e.g. Slobounov et al., 2010; Saleh et al., 2013).

2.2.2.2 Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging technique that uses the nuclear magnetic resonance properties of hydrogen to quantify brain metabolites in vivo. It can be used to study metabolic changes in neuropathies such as brain tumours, strokes and seizure disorders (Cirstea et al., 2011; Federico et al., 1998; Marino, Ciurleo, Bramanti, Federico, & De Stefano, 2011). The neurometabolites detectable by MRS often fluctuate in response to neuronal injury, hypoxia, cellular energy metabolism and membrane turnover (Brooks et al., 2001). These include: N-acetyl aspartate (a marker for neuronal integrity), lactate (a by-product of anaerobic metabolism during periods of hypoxia), creatine (related to the energy potential available in brain tissue), choline (an indicator of cell density and cell wall turnover), myo-inositol (an astrocytic marker and possibly a indicator of intracellular osmotic integrity) and glutamate (the main excitatory neurotransmitter in the central nervous system).

2.2.3 Measuring Changes in Behaviour

The neuroplastic nature of the brain enables the process of learning and re-learning to occur. Because the process of learning is supported by neuroplasticity, change in an individual's behaviour over time is an important index of cortical reorganisation. Indeed, all procedural and episodic learning, and relearning after injury to the brain, is supported by neuroplastic change. Motor learning is an ideal example to illustrate this concept. Motor learning is defined as the acquisition of a new behaviour through skilled practice and results in a relatively permanent change in the ability of an individual to perform a movement (Salmoni et al., 1984; Schmidt and Lee, 2011). Once a skilled movement is learned, the ability to perform the skill is robust and stable. Experience, practice or change in behaviour stimulates the brain to reorganise. Neuroplasticity, in the context of motor learning, refers to changes in neural organisation associated with skilled practice or modifications of movement patterns (Berlucchi and Buchtel, 2009). When a skill is repeatedly practised, neural changes occur as a result of functional reorganisation across many brain regions (Karni et al., 1998). As we will discuss later on (and in Chap. 3), technology such as virtual reality, which has the ability to enforce stereotyped, repeated practice of skills is an excellent method by which to promote learning and rehabilitation (e.g. by using sophisticated forms of feedback, practice schedules, engaging and rewarding practice environments, and the possibility of mass practice) to reinforce and perhaps even bolster neuroplasticity.

2.3 Experience-Dependent Neuroplasticity

2.3.1 Motor Learning and New Technology

Overall, learning and practising new motor skills is critical for inducing neuroplastic change and functional recovery after an insult to the nervous system. There is ample evidence to suggest that plasticity of the brain is dependent on use and that intensity, frequency and duration of practice are all important factors in determining the extent of neural reorganisation (for review see Adamovich, Fluet, Tunik, & Merians, 2009). Given the central role of practice for experience-dependent plasticity there is now acute interest in the development of new techniques, such as virtual reality interfaces, that enable the user to control or modify the task parameters to foster motor learning. These technologies may allow training to occur in a life-like enriching yet controlled environment, integrated into the clinical setting, and tailored to the specific needs of each individual.

2.3.2 Neuroplasticity in the Context of Motor Learning

Importantly, experience appears to be one of the main drivers of neuroplastic change. In fact, substantial short-term changes in the rate of both changes in skill and functional organisation can be observed even within a single training session. In the context of motor learning, "fast learning" (Doyon and Benali, 2005) is the rapid change often seen early in practice; however, this does not necessarily translate to sustained improvements in motor skill. With practice over multiple training sessions, improvement commonly plateaus and the slope of change associated with learning lessens (Karni et al., 1998). This characterises the "slow learning" phase (Doyon and Benali, 2005), which can continue for long periods of time. In addition, following the conclusion of a practice session, motor memories may be strengthened or enhanced by an offline process known as consolidation, which allows memories to stabilise and be available to be recalled at a later date (Brashers-Krug et al., 1996). A key question centres on why the speed of change associated with motor skill acquisition varies within and across practice sessions. Neurophysiology provides the answer. Rapid changes in the amount and location of neurotransmitters, within and between the neurons of the brain support fast learning (Nudo, 2006); while the structural modifications enabling new contacts between neurons underpin slow learning (Kleim et al., 2004). Because altering neuron structure requires more time than does reallocating neurotransmitters, rates of change in behaviour associated with learning vary between early and late learning (Karni et al., 1998).

Overall, an understanding of the mechanisms of neuroplasticity in the context of motor learning is important in designing and implementing tools to promote neuroplastic change. Notably, these properties can be particularly well exploited by technology such as VR to provide user experiences that promote the processes of both fast and slow learning.

2.4 What Is the Role of Virtual Reality in Neuroplasticity?

Generally, following damage to the brain an individual's ability to interact with the physical environment is diminished (Rose, Brooks, & Rizzo, 2005). New technology, such as VR, may potentially help reduce the burden of such physical limitations by providing an alternative, favourable environment in which to practice motor skills. VR can be defined as "an approach to user-computer interface that involves real-time simulation of an environment, scenario or activity that allows for user interaction via multiple sensory channels" (Adamovich, Fluet, et al., 2009).

New VR training approaches capitalise on recent technological advances including improved robotic design, the development of haptic interfaces and the advent of human–machine interactions in virtual reality (Merians, Poizner, Boian, Burdea, & Adamovich, 2006). There are many VR applications currently in use. For example, VR has been used in clinical settings as a training tool for surgeons and as a tool to deliver cognitive, post-traumatic stress disorder and pain therapy (Adamovich,

Fluet, et al., 2009; Bohil, Alicea, & Biocca, 2011). It also has the potential to aid in studying processes such as the dynamics of neurodevelopment and neuro-connectivity (Bohil et al., 2011) and to study the neural circuitry underlying certain animal behaviours (Dombeck & Reiser, 2012). VR allows for the possibility of delivering patient-specific opportunities for interaction with the environment via technology such as head-mounted displays or screens which require less set-up and effort than would be needed to provide a patient with an opportunity to interact with the real environment (Rose et al., 2005). It is this naturalistic environment allowing for interactive behaviour while being monitored and recorded that is the primary advantage of implementing VR technology (Bohil et al., 2011). This means VR technology can be used to deliver meaningful and relevant stimulation to an individual's nervous system and thereby capitalise on the plasticity of the brain to promote motor learning and rehabilitation (see Chap. 3).

2.4.1 VR Practice

As discussed above, learning and performing new skills is critical for inducing neuroplastic change and functional recovery after an insult to the nervous system. Virtual reality simulations are particularly effective tools that allow for monitoring of behaviour in three-dimensional space. VR set-ups allow for thorough analysis of the user's actions and the ability to provide guidelines and precise real-time feedback to promote the desired behavioural result. Research has shown, for example, that virtual-reality augmented robotically-facilitated repetitive movement training may potentially aid in improving motor control in patients with moderate to severe upper extremity impairment (who have difficulty performing unassisted movements) (Merians et al., 2006).

The majority of empirical data using VR paradigms has involved persons with chronic stroke or children with cerebral palsy (Chaps. 7 and 10). Virtual reality gaming and task simulations are becoming increasingly popular as a means of providing repetitive intensive practice to chronic stroke patients. This is posited to be a particularly effective form of rehabilitation due to its potential to promote increased interest of participants by virtue of task novelty. This may in turn lead to greater programme compliance, which may ultimately facilitate better clinical outcomes compared to traditional rehabilitation programmes (Adamovich, Fluet, et al., 2009; Merians et al., 2006; You et al., 2005).

2.4.2 Categorisation of VR Technology

Virtual environments (VEs) can be used to present complex, interactive multimodal sensory information to the user (Bohil et al., 2011). In fact, a major development in the use and clinical outcome efficacy of VR came with the addition of tactile

information and interaction forces into the visual experience of VR (Merians, Fluet, Qiu, Lafond, & Adamovich, 2011). This is important as the more relavant and realistic the training programme, the more easily it may be transferred into daily life. Further, fMRI data show that motor training that is specific to the task being learned induces larger neuroplastic change as compared to simply increasing arm use after stroke (Boyd, Randhawa, Vidoni, & Wessel, 2010). In general, VR systems are typically classified by the visual presentations they provide to a participant, the presence or absence of somatosensory feedback and the modality used to collect data from the participant (Chap. 5, Adamovich, Fluet, et al., 2009). In addition to providing visual–motor feedback, haptic technology allows virtual environments to provide force feedback. This refers to force and touch feedback provided to the user by the computer through specialised interfaces, which can simulate interactions with objects (Merians et al., 2006). This ability to provide visual–motor and somatosensory feedback to the user is paramount; the more relevant and realistic the input presented to the brain during training, the more valuable the training and the more likely this sensory information will be integrated and used to help re-organise the brain in a favourable manner.

2.4.3 Effects of VR on Neural Circuits

Embarking on a discussion of the potential neural processes that may be affected through VR interaction beckons a brief digression to the role that visual input has on the brain (see Chap. 4). Visual information can provide a potent signal for reorganisation of sensorimotor circuits. For example, visual errors can influence motor cortical areas during motor learning (Bray, Shimojo, & O'Doherty, 2007; Hadipour-Niktarash et al., 2007; Muellbacher et al., 2001, 2002; Richardson et al., 2006). Active and rewarded practice by which one learns to use feedback to reduce errors in movement shapes neural activity in motor and premotor areas (Bray et al., 2007; Wise et al., 1998). Moreover, repeated and intentional observation of actions can facilitate the magnitude of MEPs and influence cortico-cortical interactions (both intracortical facilitation and inhibition) in the motor and premotor areas (Leonard & Tremblay, 2007; Patuzzo, Fiaschi, & Manganotti, 2003; Stefan et al., 2005; Strafella & Paus, 2000). From retrograde tracer studies, it is also known that rich intra-hemispheric cortico-cortical connections link the occipital, parietal and frontal cortices which process visual, somatic and motor information (Dum & Strick, 2005; Fang, Stepniewska, & Kass, 2005; Lewis et al., 2005; Lewis & Van Essen, 2000a, 2000b; Mitchell & Cauller, 2001; Stepniewska, Fang, & Kaas, 2005). Likewise, single unit data show that a substantial number of neurons in motor, premotor and parietal areas are modulated by visual information (Graziano, 1999; Graziano & Gandhi, 2000; Graziano & Gross, 1998a, 1998b; Kakei, Hoffman, & Strick, 2003) thus providing direct modification of movement by visual information. Moreover, unlike proprioception, which is obligatorily coupled to active and/or passive limb movement, visual feedback of movement can be provided independent of the movement itself through

illusory manipulations. For example, patients with severe paresis or absence of volitional control can be asked to make an intention to move (or imagine movement) and this motor effort can be coupled with biological limb motion displayed through the VR interface (see Adamovich, August, Merians, & Tunik, 2009). Thus visual feedback offers a means to modulate the motor system without requiring overt movement. Indeed, the visual system is robust in that its influence over the brain often overrides other afferent modalities, such as proprioception, when a sensory conflict is introduced (Snijders, Holmes, & Spence, 2007). Finally, by virtue of the relatively distant location between the motor and visual systems and their largely separate vascular supply, the visual regions of the brain can often remain intact despite lesions to the motor system. These features of the visual brain position VR as a highly desirable tool to provide visual feedback to optimise motor learning in neurologically impaired individuals.

VR can provide sophisticated sensory information to users and elicit a feeling of real presence or immersion in the ongoing task (Riva, 1998; Riva, Castelnuovo, & Mantovani, 2006). Perhaps one of the strongest attributes of VR is that it enables sensory manipulations that are not possible in the real world (i.e. colour/brightness, location, form, auditory input, temporal/spatial distortions, presenting feedback in different vantage points, allow the user to playback movements for feedback or to freeze motion on the screen). Indeed these properties might maximise chances for feedback-induced neural reorganisation. For example, the clinician can control various parameters that cannot be controlled in the natural world—such as "freezing" motion of one of the virtual hands, or parts of a hand, to focus attention to salient aspects of feedback, or to augment the quality of movement observed in VR. Early evidence suggests that skills acquired after VR-based training may transfer to real-world functions (Chap. 6, Adamovich et al., 2004; Deutsch et al., 2004; Holden, 2005; Kenyon & Afenya, 1995; Merians et al., 2002; Merians et al., 2006). For example, training in virtual environments has been shown to lead to clinical and kinematic improvements that are attributed to mitigation of impairment rather than compensatory strategies (Subramanian, Lourenço, Chilingaryan, Sveistrup, & Levin, 2013). In two studies, functional improvements were paralleled by a shift from a predominantly contralesional sensorimotor activation pre-therapy to a predominantly ipsilesional activation post-therapy (Jang et al., 2005; You et al., 2005). Similar shifts in hemispheric lateralisation are observed after therapy performed in the real world (Carey et al., 2002, 2006; Small et al., 2002), which suggests that training an affected limb in VR with high-fidelity feedback may tap into similar neural reorganisation changes (e.g. neuroplastic changes) observed after training in the real world.

More recently, research has explored specific ways in which distortions can be introduced in VR to invoke neural plasticity. In this case, the neuroplastic change is generally measured as an increase or decrease in the excitability of the motor cortex. For example, in a study by Adamovich, et al. (Adamovich, Fluet, et al., 2009), healthy subjects and patients with chronic stroke performed a simple finger flexion task while observing their movement as a virtual reality doppleganger representation on an LCD display. The display was positioned over their hand such that the

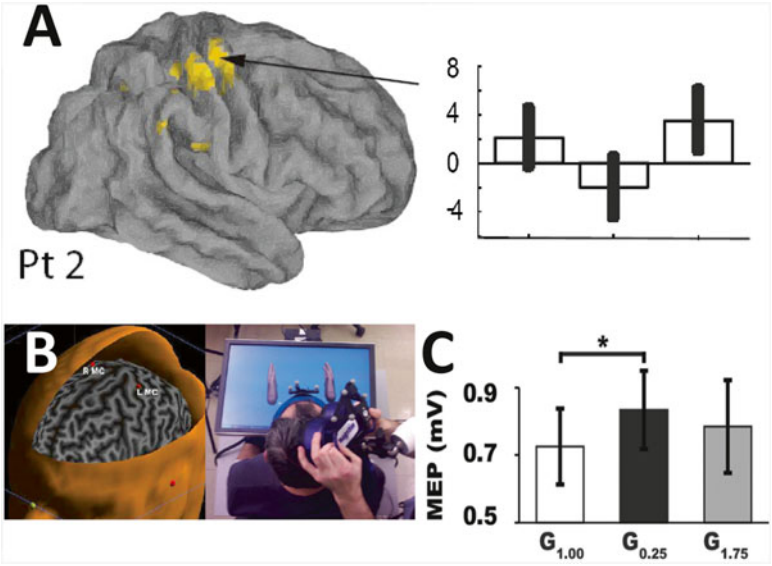

Fig. 2.3 (**a**) Adapted from Saleh, Adamovich, & Tunik, 2012. Significant activation in a chronic stroke subject performing a targeted finger flexion task with the affected hand. Feedback was presented in VR as either veridical (G1.00), scaled down (G0.25) or scaled up (G1.75) movement of a virtual hand model. The ipsilesional sensorimotor areas were significantly more activated in the G.25 and G1.75 conditions, compared to the veridical condition (betas for each condition shown in the right panel, error bars indicate 90 % confidence intervals). (**b**, **c**) Adapted from Bagce et al., 2012. The role of the corticospinal system in processing the gain discordance was tested with TMS. The task was as described above. Group mean MEPs were significantly increased in the G0.25 condition relative to the veridical condition

virtual hand was overlaid on the subject's actual hand. The VR hand model was actuated in real-time by the subjects' actual hand movement (recorded using a data glove). During the experiments, brain activity was assayed using fMRI and TMS measures. VR was used to manipulate the relationship between what the subjects did and what the subjects saw by scaling the amplitude of the VR hand motion (relative to their own movement) or by having subjects observe the virtual hand move without actually moving themselves. This work revealed a distributed parieto-frontal network involved in observation of movements performed by the virtual hand (Adamovich, Fluet, et al., 2009). Interestingly, the primary motor cortex (M1) seems particularly important for reconciling discrepancy between intended actions and discordant visual feedback ("visuomotor discordance") (Bagce, Saleh, Adamovich, & Tunik, 2011, 2012; Saleh et al., 2011, 2012).

Our preliminary data in healthy individuals (manuscript in preparation), reveal that activity of M1 can be facilitated by as much as 50 % after subjects had the opportunity to adapt to the discordant feedback and only by 12 % if subjects had not adapted. Figure 2.3 shows preliminary data for stroke patients who were exposed to similar gain discordance conditions. The observation that excitability can be

increased (even partially) in the affected motor cortex in individuals with stroke suggests that neuroplasticity may be harnessed in patients through VR-based interactions. In other words, what these findings suggest is that visual manipulations presented through VR may invoke similar responses, at least at the level of M1, in stroke and healthy subjects alike. However, what remains unclear is whether cumulative exposure to such visuomotor discordance, as typically occurs in learning paradigms, would translate to the same neural changes in the two groups. Given the unique advantages of VR that have been discussed (such as delivery of mass-practice and sophisticated feedback), this technology may be an important tool for clinicians to drive neuroplastic changes. The long-term clinical and neuroplastic outcome of VR training is currently under investigation. Nonetheless, these data illustrate how virtual reality manipulations may be used as a probe of neural function on the one hand, and as a training tool on the other.

2.4.4 Limitations of VR

While virtual reality environments offer many unique advantages to other approaches, limitations to their efficacy and practicality exist (Chap. 6). Firstly, larger clinical studies are required to establish the efficacy of using VR in sensorimotor rehabilitation in different clinical populations. Additionally, to date there is little information on the generalisability of the training effects of VR to the corresponding physical environment in general, and the VR training parameters associated with optimal transfer to real-world functional improvements remain yet to be elucidated. Furthermore, it is unclear whether advantages of VR over real-world training exist, and if so, precisely what these advantages are. It is important to investigate whether there is something unique to VR that can be exploited that cannot be with other types of therapies, or whether any benefits of VR can be attributed to the gaming platforms associated with VR themselves (i.e. are VR therapies only more effective therapeutics because they are more entertaining and therefore keep subjects more engaged and motivated throughout their training session? Is greater intervention adherence alone the cause of any discrepancies in VR treatments versus alternative ones?). While limitations in VR technology exist, the potential for favourable neuroplastic change afforded by such technology undoubtedly warrant further investigation.

2.5 Conclusion

Virtual reality allows for the observation of neural activity during realistic simulations using sensorimotor input. While much remains to be elucidated in the realm of VR and its clinical applications, the unique aspects of VR, which are not present in other therapies, have shown great potential in the field of rehabilitation therapy. A key component of the theory of neuroplasticity is the dynamic nature of change in

neural connectivity, and motor rehabilitation therapy implementing VR technology that can be tailored based on the specific needs of a particular subject may be particularly effective. The use of virtual reality technology in rehabilitation for brain damage in particular is becoming more prevalent in clinical settings. There is sufficient evidence demonstrating its efficacy to suggest it may become an integral part of cognitive assessment and rehabilitation treatments in the future. Given the unique elements virtual reality technology carries with it, significant effort into studying and refining rehabilitation approaches implementing virtual reality technology is well justified.

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