Chapter 9
Cognitive Rehabilitation and Neuroimaging in Stroke

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Abstract Stroke is a neurological condition, which may result in long-lasting deficits on both cognitive and motor functions. Despite the increase in cognitive rehabilitation (CR) studies in stroke, most have focused on behavioral outcomes. As such, the interaction between improvement in cognitive processes following CR and their underlying neural systems remains limited.

This chapter provides an overview of cognitive impairment after stroke, its rehabilitation, and the underlying mechanisms of post-stroke neuroplasticity. Because individual differences in post-stroke neuroplasticity may explain often observed heterogeneities in cognitive recovery, this underscores the importance of understanding the underlying neural mechanisms in recovery as well as deploying more integrated rehabilitation approaches to enhance treatment outcomes.

A major focus of the chapter is on how neuroimaging studies lead to a better understanding of functional and structural changes in the brain after CR following a stroke. The chapter reviews how neuroimaging techniques can provide insight into the effectiveness of various rehabilitation approaches and in the development of future interventions. The major methodological issues confounding CR effectiveness are reviewed, and recommendations for improved CR studies in the future using neuroimaging are discussed.

Keywords Stroke · Cognition · Cognitive rehabilitation · Neuroimaging Plasticity

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Stroke and Cognitive Impairment

Stroke is the major cause of long-term disability and the second leading cause of vascular dementia (Kalaria, Akinyemi, & Ihara, 2016). Improvements in health care have led to a considerable increase in stroke survival rate, which, in turn, results in more people living with disabilities and neuropsychological deficits following stroke (Nichols-Larsen, Clark, Zeringue, Greenspan, & Blanton, 2005). Vascular cognitive impairment (VCI), a term introduced to refer to the role of vascular risk factors in cognitive impairment (van der Flier et al., 2018), occurs in 20–80% of the stroke patients, and current diagnostic criteria may even underestimate its prevalence (Bour, Rasquin, Boreas, Limburg, & Verhey, 2010; Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010; Sun, Tan, & Yu, 2014). Stroke lesions, cerebral microbleeds, and other pathologies sometimes at microscopic level may occur in various strategic brain areas including both gray and white matter (WM). Therefore, resultant cognitive symptoms can be very heterogeneous, affecting executive functions, memory, language, and orientation in particular (Sachdev et al., 2004). Executive dysfunction and memory disorders are the most prevalent deficits after stroke (Kramer, Reed, Mungas, Weiner, & Chui, 2002; Loewenstein et al., 2006) and are considered the main cause that precludes patients from achieving a complete recovery (Sachdev et al., 2004). These deficits are present in around 61% of patients after acute ischemic stroke (Ballard, Rowan, Stephens, Kalaria, & Kenny, 2003). Of these patients, 30% manifest a certain degree of cognitive impairment within a period between 3 and 15 months (Ballard et al., 2003).

Post Stroke Plasticity

After a stroke, the brain experiences changes to restitute the lost functions (Loubinoux, Brihmat, Castel-Lacanal, & Marque, 2017). In restitution, the impaired function is restored, and it is usually based on neurological and/or muscular redundancy. Compensation, on the other hand, involves behavioral changes and compensatory mechanisms, and it is based on the recruitment of both perilesional and distant areas (Jones, 2017). Restitution can be complete and has been shown to benefit from utilizing functional cognitive reserve (Di Pino et al., 2014). Compensation, however, often leads to incomplete recovery, and the often-occurring maladaptive plasticity can even worsen deficits (Hommel, Detante, Favre, Touzé, & Jaillard, 2016). The complexity of these processes may also explain the lack of an efficient treatment (Sarraj & Grotta, 2014), and it implies the existence of a time window in which rehabilitative therapies should be administered to optimize outcome. Therefore, the key question is when should (cognitive) rehabilitation (CR) begin after stroke when considering endogenous brain protection versus brain repair (Detante et al., 2014; Gutiérrez, Merino, Alonso De Leciñana, & Díez-Tejedor, 2009). This question is still under debate due to both the different phases in brain recovery and the substantial heterogeneity in the post-stroke population. Results from studies conducted with animals and, lately, human suggest that rehabilitation displayed permaturely (within the first 24 h after stroke) or too intensively may be harmful. On the other hand, rehabilitation within the first 2 weeks might be beneficial (Coleman et al., 2017). Research on rehabilitation in the acute stage is quite scant, and the marked discrepancy between the time when rehabilitation should be conducted (acute-to-subacute) and the time when the most part of rehabilitation in stroke is really addressed (chronic) has also been highlighted (Stinear, Ackerley, & Byblow, 2013).

Post-stroke VCI is frequently underestimated in comparison to motor impairments because cognitive impairment after stroke can be confused with age-related mild cognitive impariments (Corriveau et al., 2016; Sun et al., 2014). Furthermore, VCI is often related to poor motor recovery (Leśniak, Bak, Czepiel, Seniów, & Członkowska, 2008; Rand, Eng, Liu-Ambrose, & Tawashy, 2010), which means that motor and cognitive recovery are somewhat interrelated (Constans, Pin-Barre, Temprado, Decherchi, & Laurin, 2016; Leisman, Moustafa, & Shafir, 2016) and that an effective intervention should target both motor and cognitive improvement after the stroke (Constans et al., 2016).

Stroke and Cognitive Rehabilitation

During stroke rehabilitation, patients are helped to regain skills lost due to brain damage, and the main goal is to achieve the highest possible level of independence (Belagaje, 2017; Jokinen-Salmela et al., 2015). Current approaches include individual remediation therapy, group-based training, and computerized cognitive rehabilitation (CCR) (Cicerone et al., 2019).

Previous Cochrane reviews reported that the information available on CR is insufficient to provide specific guidelines for clinical practice (Bowen, Hazelton, Pollock, & Lincoln, 2013; Loetscher & Lincoln, 2013), even when certain treatments have showed large effects. Based on the definition of classes of evidence, the latest evidence-based review on CR (Cicerone et al., 2019) found significant support for treatment of attention *(Practice Standard)*, visuospatial deficits (*Practice Guideline*), memory deficits (*Practice Standard*), language deficits (*Practice Guideline*), and executive deficits (*Practice Standard and Practice Option*). Additionally, in the case of CCR, a recent review (Sigmundsdottir, Longley, & Tate, 2016) reported that the methodological quality of the reseach conducted is low, with marginal studies achieving Level I evidence. Furthermore, there are limitations with the generalizability of the results for TBI and stroke. The only evidence that exists is in MS and brain tumor populations (Sigmundsdottir et al., 2016). Cicerone et al. (2019) also indicates that CCR should be coupled with a therapist administration, adapted to the level the patient needs, and the incorporation of metacognitive strategies.

Despite these improvements, there is still an uncertainty about the effectivity of CR in stroke patients (Kalron & Zeilig, 2015). This situation is partially due to the fact that the biological mechanisms underlying the benefit of CR are not fully understood which poses a problem for the design of effective cognitive interventions (Greenwood & Parasuraman, 2015). Further, none of the stroke studies cited in the review of Cicerone et al. (2019) used fMRI to examine potential changes in the brain of patients receiving CR. Moreover, randomized controlled studies conducted thus far often suffer from methodological issues that should be addressed. These methodological issues include, for example, the use of suitable control groups (i.e., including a control group treated with a control intervention versus including only a passive, nontreated control group) (Higgins & Green, 2011), discrepancies in outcome measures (Bogdanova, Yee, Ho, & Cicerone, 2016), duration of the cognitive intervention (Stinear et al., 2013), ignoring effects related to practice (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010), un-assessed test–retest reliability of the questionnaires (Baird, Tombaugh, & Francis, 2007; Buck, Atkinson, & Ryan, 2008), usage of tests unable to detect specific cognitive impairments (McDonnell, Bryan, Smith, & Esterman, 2011), lack of adjustment for primary outcomes (Saquib, Saquib, & Ioannidis, 2013), heterogeneity in treatment effects (Gabler et al., 2009), large variance patient age (Gaynor, Geoghegan, & O'Neill, 2014), lack of control to distinguish whether cognitive improvements are due to restitution or the use of implicitly learned approaches (van de Ven et al., 2017), and lack of long-term follow-up assessments including ecologically valid outcome measures (Cicerone et al., 2005). The lack of guidelines and standardized protocols, as well as the lack of differentiation between the severity of the injury and the chronicity, often leads to heterogeneity in the sample, which makes the interpretation of the results more difficult (Bogdanova et al., 2016).

Finally, there are some methodological issues, which are specific for CCR which should be addressed. These include the relatively short training periods; the lack of report of the rate of adherence to the protocol, as well as the role of supervision in CCR (i.e., the exact amount of interaction between the therapist and the participant); the intensity of training programs (massed versus distributed); and the familiarity of the participants with computers and computer games in general (for a list of available softwares used in stroke population see (Rabipour & Raz, 2012)).

Neuroimaging and Stroke: The Use of Neuroimaging in Cognitive Rehabilitation

Routine clinical measurements applied in CR, such as neuropsychological assessment, structured observation, clinical interviews, and self-report questionnaires may not provide specific information about what is happening in the brain in response to treatment. The application of various neuroimaging techniques allows us to monitor rehabilitation-induced plastic changes and to assess treatment effectiveness. Most importantly, it can also help to explain why some patients response better to a certain treatment while others exhibit little or no response.

Neuroimaging techniques can investigate both structure and function of the human brain; however, we should keep in mind that the timescale of different changes is also quite distinct. Functional MRI (fMRI) has been clearly demonstrated to capture plastic changes even after a relively *short intervention period* for instance in persons with multiple sclerosis (MS) (Chiaravalloti, Dobryakova, Wylie, & DeLuca, 2015; Chiaravalloti, Wylie, Leavitt, & DeLuca, 2012). Changes in structural connectivity, however, have been seen reported after motor and aphasic rehabilitation in *longitudinal intensive intervention studies* in motor and aphasia rehabilitation. For example, in the case of motor rehabilitation, the use of constraint-induced movement therapy (CIMT) has proved to increase gray matter volume in parietal areas associated with motor and sensory functions, in frontal areas as well as in the hippocampus in frontal and parietal sensory–motor areas and the hippocampus (Gauthier et al., 2008).

Aphasia

The number of fMRI studies reporting changes in the activity of the brain after therapy for aphasia is scarce. The three main rehabilitation techniques being used are (1) *constraint-induced language therapy* (CILT), (2) *melodic intonation therapy* (MIT), and (3) *speech and language therapy* (SLT). The CILT (Pulvermuller et al., 2001), also called intensive language action therapy (ILAT), has demonstrated its clinical effectiveness in several randomized clinical trials (RCTs) (Pulvermuller et al., 2001; Stahl, Mohr, Dreyer, Lucchese, & Pulvermüller, 2016). (1) It is based on massed practice to promote neuroplastic changes boosted by Hebb's correlation learning law, (2) it draws upon the functional links between the brain's language and motor systems, and (c) it guides the patients to use utterances that are still within their grasp (Pulvermuller & Berthier, 2008). Richter, Miltner, and Straube (2008) analyzed the connection between brain changes and therapy effects using fMRI in 16 chronic motor aphasic patients and 8 healthy controls. Brain functional activity was assessed during the completion of word-reading and word-stem tasks. Before treatment, the functional activity in the right inferior frontal gyrus/insula was more pronounced in aphasic patients in comparison to healthy participants. While the therapeutic approach did not change the brain functional activity in neither of the two tasks in the group of chronic aphasic patients, the success of the treatment was associated with a small decrease of the functional activity in the right hemispheric regions, involving the inferior frontal gyrus and the insula. The authors reported that functional activation in the right hemisphere before aphasia therapy was a predictor of the therapeutic achievement.

In another study carried out by Breier, Maher, Novak, and Papanicolaou (2006), patients with chronic aphasia received CILT therapy and magneto encephalograpy (MEG) before and after treatment. Patients/responders to the therapy showed more functional activity both in posterior areas of the left hemisphere and in homologous areas of the right hemisphere before the therapy than those for whom the treatment did not have any effect. Parallel to the study conducted by Richter et al. (2008), it was the right hemisphere but not the left, the determinant in the recovery of aphasia.

The MIT (Sparks, Helm, & Albert, 1974) is a structured aphasia therapy that uses features of language such as intonation, rhythm, and stress to enhance language production after stroke. Patients repeat melodically intoned functional relevant sentences which increase in complexity. Several studies using this therapy have reported the enhancement of WM integrity of the arcuate fasciculus, which connects the right and left frontal and temporal regions (Breier, Juranek, & Papanicolaou, 2011; Schlaug, Marchina, & Norton, 2009).

Finally, in the case of SLT (Brady, Kelly, Godwin, Enderby, & Campbell, 2016), in a study conducted by Bonilha, Gleichgerrcht, Nesland, Rorden, and Fridriksson (2016) in 24 patients with post-stroke chronic aphasia, the authors concluded that favorable naming resulted from the spared connections between healthy cortical areas in the left impaired hemisphere and its connections with homologous areas in the right hemisphere.

Despite the encouraging results, several limitations should be considered. First, the vast majority of studies conducted using fMRI and structural MRI have been conducted with small samples (Breier et al., 2011; Breier, Randle, Maher, & Papanicolaou, 2010; Crosson et al., 2005; Kakuda, Abo, Kaito, Watanabe, & Senoo, 2010; Kurland, Pulvermüller, Silva, Burke, & Andrianopoulosa, 2012; Mohr, Difrancesco, Harrington, Evans, & Pulvermüller, 2014; Tabei et al., 2016), which prevents the generalization of the results to the stroke population. Second, stroke is characterized by the heterogeneity of its samples (i.e., lesion type, lesion size, lesion localization, post-stroke severity, time after stroke) which, in the case of small samples, hampers the generalizability and representativeness of the results to the stroke population. Additionally, the studies conducted ignore singular differences such as the individual baseline activation, or the timing after stroke, factors that are relevant for the efficacy of intervention. As an example, whereas in the study conducted by Bonilha et al. (2016), with chronic aphasic stroke patients, favorable outcomes resulted from preserved connections between spared cortical areas in the left impaired hemisphere and its connections with homotopic areas in the right hemisphere; in the study conducted by Mattioli et al. (2014) with a small sample of acute stroke patients (2 days after stroke), they found that favorable outcomes in aphasia recovery were related with brain activations in the left hemisphere, concretely in the left inferior frontal gyrus (Mattioli et al., 2014). As stated previously, the timing in which a therapy begins is of extremly relevance, as it is not the same to modulate and boost spontaneous recovery after stroke, that is, trying to counteract for the loss of function in chronic stroke, when most of the changes have already occurred. Lastly, the function of the right hemisphere in aphasia recovery is controversial. Some authors state that the disinhibition of the right hemisphere (transcallosal disinhibition) is maladaptive, and it leads to the persistence of the language deficits rather to their recovery (Heiss & Thiel, 2006; Naeser et al., 2004; Perani et al., 2003), whereas other authors maintain that the recovery of language production is related with an increase in the functional activity of anatomical areas located in the right hemisphere (Crinion & Leff, 2007; Fridriksson, Baker, & Moser, 2009; Schlaug et al., 2009). Future studies with larger samples should be conducted in order to compare the effects of aphasia therapy in the acute stage in comparison with its effects when the therapy is administered in the chronic phase to discern the function of the right hemisphere in aphasia recovery.

Spatial Neglect

Unilateral neglect, hemineglect, and spatial neglect are interchangeable, pointing to the same concept: the incapacity to notice, relate, and orient toward a stimuli placed in the side of the space contralateral to the side of the damage. Even when a large proportion of patients recover from their deficit spontaneoulsly, there is evidence that points out that patients who have seemengly recovered could still show deficits of attention when they are assessed with more sensitive tasks (Bonato, Priftis, Umiltà, & Zorzi, 2013) and problems in activities of daily living (Chen, Chen, Hreha, Goedert, & Barrett, 2015; Chen, Hreha, Kong, & Barrett, 2015). An anatomo-functional model for neglect has been proposed based on healthy subjects (Corbetta & Shulman, 2002). This model is composed by the dorsal attentional network (DAN) and the ventral attentional network (VAN). The DAN is comprised by the superior parietal lobules, the intraparietal sulcus, the precuneus, and the frontal eye field, which shows increased functional activity when an individual directs his/her attention toward a visual target. The VAN includes the temporoparietal junction and the middle and inferior frontal gyri and shows an increased functional activity when the individual tries to process a stimulus in an unanticipated spatial emplacement (Singh-Curry & Husain, 2009) (Table 9.1).

Two main rehabilitation techniques have been proposed for the rehabilitation of neglect: (1) motor imaginery (MI) and (2) virtual reality (VR). MI consists of the mental representation of an activity without participating in the real activity (Simon, Welfringer, Leifert-Fiebach, & Brandt, 2018).

Only a handful of studies have tested MI as an approach to treat visuospatial neglect deficits in stroke patients (Leifert-Fiebach, Welfringer, Babinsky, & Brandt,

Table 9.1 Attentional domains and definitions

Domain	Definition
Alertness/arousal	Ability to be prepared to reply
Selective attention	Ability to concentrate on a stimulus while disregarding irrelevant stimuli
Sustained attention	Ability to hold the attention along an extended period of time
Spatial attention	Ability to locate the attention to all sides of space
Divided attention	Ability to divide the attention between different tasks

Adapted from Loetscher T, Lincoln NB. 2013. Cognitive rehabilitation for attention deficits following stroke. Cochrane Database of Systematic Reviews, (5), CD002842

2013; McCarthy, Graham Beaumont, Thompson, & Pringle, 2002; Park, Choi, Kim, Jung, & Chang, 2015; Park & Lee, 2015; Welfringer, Leifert-Fiebach, Babinsky, & Brandt, 2011). None of them, however, have used structural or functional MRI to study the effects of MI in the brain, which prevents the understanding of the effects of MI therapy in the brain. Furthermore, research suggests that the implementation of MI to treat patients with neglect has limitations as the parietal lobe, a key region for MI (Hétu et al., 2013), is frequently impaired in patients with neglect (Karnath, Berger, Küker, & Rorden, 2004).

VR is a new innovative technique in neglect. Few studies have been conducted either using the record of eye movements or behavioral outcomes, respectively (Cameirão, Faria, Paulino, Alves, & BermúdezBadia, 2016; Yasuda, Muroi, Ohira, & Iwata, 2017). Only one study has applied fMRI to test the effects of VR in patients with neglect (Ekman et al., 2018). In this study, the authors employed the RehAtt®, a training system that incorporates visual, audio, and tactile stimulation to address the attention to the contralesional space while executing the task in the scanner (Fordell, Bodin, Eklund, & Malm, 2016). This system boosts the underlying mechanisms related to neglect in the attention networks. The authors assessed task-fMRI activity changes before and after RehAtt® employing the Posner cueing task (See Fig. 9.1). In this study, patients improved their execution in the Posner cueing fMRI task, and their functional brain activity was increased after the VR internventions in a widespread network involving the pre-frontal and temporal lobes during attentional cueing. The authors concluded that, as the strongest effects were found in

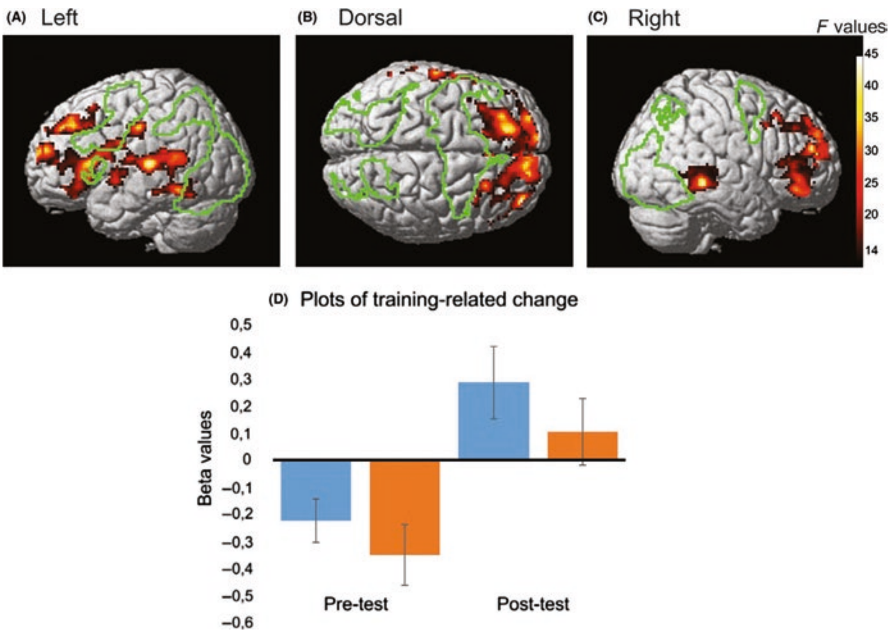

Fig. 9.1 Increased fMRI activity before and after the Posner cueing condition task. A training-related fMRI increase in the ACC, the DLPFC, and the bilateral temporal cortex is observed in comparison with the baseline. (From Ekman et al., 2018)

prefrontal regions associated with goal-directed behavior and in guiding attention. Their results indicated that changes related to the training in neglect patients mainly occured outside the anatomical regions related to guiding attention toward a visual stimulus (DAN), and to the process of a stimulus in an unexpected location (VAN). Further studies with larger samples and different attention paradigms should be conducted to compare the acute versus the chronic phase in order to conclude, if the recovery of neglect involves areas outside or inside the proposed anatomo-functional substrates.

Attention

Attentional deficits are highly prevalent in stroke patients both in the acute phase and in the chronic phase (Hyndman, Pickering, & Ashburn, 2008; Stapleton, Ashburn, & Stack, 2001). Deficits in attention involve broad assortments such as: a drop in concentration, disminished error control, difficulties in multitasking, and mental slowness. Those deficits have, in turn, consequences on other cognitive domains such as memory and language (Lezak, Howieson, Loring, Hannay, & Fischer, 2004; Loetscher & Lincoln, 2013).

In relation to the neuroanatomical correlates associated with attention deficits after stroke, right hemispheric lesions have been correlated with visuo-spatial attentional deficits, whereas left hemipsheric lesions placed in regions involving the thalamus and the basal ganglia have been associated with nonspatial attentional deficits (sustained, divided, and selective attention) (Murakami et al., 2014).

To increase one's understanding of the different attentional components, (Loetscher & Lincoln, 2013) describe the different domains of attention in Cochrane review. These include alertness/arousal (ability to be prepared to reply), selective attention (the ability to concentrate on a stimulus while disregarding irrelevant stimuli), sustained attention (the ability to hold the attention along an extended period of time), spatial attention (the ability to locate the attention to all sides of space), and divided attention (the ability to divide the attention between different tasks).

Only two systematic reviews in relation to the rehabilitation of attentional deficits following stroke have been published (Loetscher & Lincoln, 2013; Virk, Williams, Brunsdon, Suh, & Morrow, 2015). Both reviews cited the same six studies (Barker-Collo et al., 2009; Rohring, Kulke, Reulbach, Peetz, & Schupp, 2004; Schöttke, 1997; Sturm & Willmes, 1991; Westerberg et al., 2007; Winkens, Van Heugten, Wade, Habets, & Fasotti, 2009), and the most recent of which is dated 2009. From all these studies, only divided attention showed significant medium-to-large treatment effects (Virk et al., 2015). None of these studies have used neuroimaging as a proof of concept, though. Due to the impact that attentional deficits have in other cognitive domains (Lezak et al., 2004; Loetscher & Lincoln, 2013), further studies focused on the rehabilitation of attention should be considered adding neuroimaging to study the neuronal plastic changes associated with the rehabilitation of attention.

Memory and Executive Function

Compared to the vast amount of neuroimaging studies on the rehabilitation of motor dysfunction, aphasia and neglect, there is a paucity of studies focused on executive dysfunction and memory impairment. To date, only two group-based studies have assessed the brain effects of CR on memory and executive function in patients with stroke (Lin et al., 2014; Nyberg et al., 2018). In the study conducted by Lin and colleages (Lin et al., 2014), the authors used a computer-assisted cognitive training combined with rs-fMRI to study the effects of CR on memory and executive function on the brain. Patients in the treatment group improved on the measures of memory and executive function. This improvement was positively correlated with the increased functional connectivity (FC) in the hippocampus and the frontal and parietal lobes (see Fig. 9.2).

Nyberg and colleagues conducted a longitudinal study with 22 stroke patients evaluated at three time points: at baseline, after a period of 6 weeks in which the participants were followed without intervention, and after a 6-week training (≥18/25 sessions) on working memory with Cogmed QM, an online program designed for training working memory. Diffusion tensor imaging (DTI) was acquired at baseline and after the training (Nyberg et al., 2018). The authors did not find any change on cognitive functions or WM integrity after treatment.

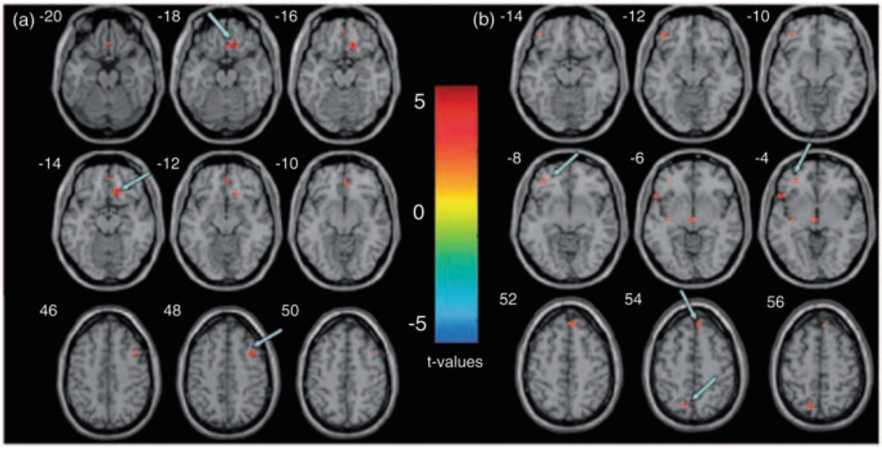

Fig. 9.2 Significant fMRI increase in the FC of the patients after treatment in different anatomical regions indicated by the arrows. The changes in activation were between (**a**) the left hippocampus-right inferior frontal gyrus and the left hippocampus-right middle frontal gyrus and (**b**) right hippocampus-left middle frontal gryus, right hippocampus-left inferior frontal gyrus, right hippocampus-left superior frontal gyrus and right hippocampus-left parietal lobe. (From Lin et al., 2014)

The Use of Music Therapy in Stroke

Brain is an experience-dependent structure that changes in response to the environment. In experimental studies with rats, context enrichment (CE, auditory, visual, and olfactory) has been shown to play an important role in the the recovery of cognition and motor functions and reducing lesion volume (Maegele et al., 2005; Maegele et al., 2005).

Neuroimaging studies conducted with healthy participants have reported that the processing of music can result in recruitment of temporal, frontal, parietal, cerebellar, and limbic/paralimbic areas related to the processing of the acoustic aspects of music (Herdener et al., 2014; Zatorre, 2013). Voxel-based morphometry (VBM) and DTI studies indicate that the constant involvement in musical activities can lead to GM (increased volume) and WM (larger tract volume) changes (Halwani, Loui, Rüber, & Schlaug, 2011; James et al., 2014).

Recent clinical studies have shown that music can be effective in improving the connectivity of temporal auditory and frontal motor areas (Grau-Sánchez et al., 2013; Rodriguez-Fornells et al., 2012). In the study carried out by Särkämö and colleages (Sarkamo et al., 2014), a group of 49 stroke patients were randomly assigned to the music group (MG, listening to their favorite music 1 h/day during 6 months), the audiobook group (ABG, listening verbal material 1 h/day during 6 months), or to the control group (CG, did not receive any material). All three groups received standard care and rehabiliation. After treatment, the MG group showed an increase in GM volume (GMV) in different anatomical regions in the frontal and limbic areas in the contralesional hemispere and around the lesioned area in the damaged hemisphere (See Fig. 9.3). The observed GMV increases in frontal and limbic areas were associated with improvemmnets in cognition and mood (attention, memory, and language for the frontal areas; mood for the limbic areas). Particularly, left hemisphere-damaged patients showed an increase in the left and right superior frontal gyrus (SFG) and in the right medial SFG. This increase was related to the enhancement of verbal memory, language function, and focused attention after 6-month follow-up.

Implications for Cognitive Rehabilitation Practice and Future Directions

In this chapter, we have provided an overview of the use of CR in combination with functional and structural neuroimaging to assess the neural mechanisms underlying the effects of CR in stroke. It is important to emphasize that neuroimaging in CR helps to (1) better understand the impact of our therapies in terms of the neural changes produced in the brain after our treatment (whether they occur in the targeted brain areas and they have the expected effect) and (2) potentially improve our therapeutic interventions.

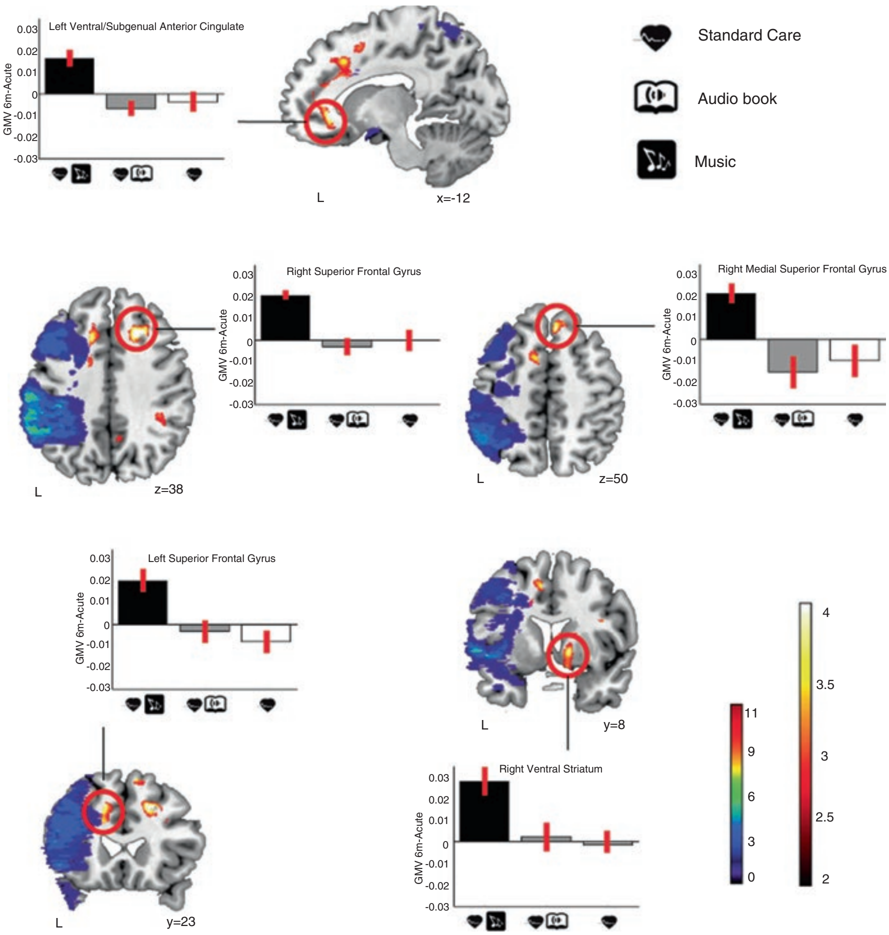

Fig. 9.3 This figure shows the changes in GVM from the acute to 6 months after treatment. The blue/red/green regions show the lesion overlap in the group of patients. The red-yellow colors show areas of GMV increase in the MG group in comparison with the ABG and CG groups in the frontal (left and right superior frontal gyrus (SFG) and in the right medial (SFG)) and limbic areas in the contralesional hemisphere and around the lesioned area in the damaged hemisphere. (Reprinted with permission from Sarkamo et al., 2014)

In comparison with other neurological conditions such as MS, the number of studies combining CR and neuroimaging in stroke is surprisingly low. The vast majority of studies with stroke patients investigate biomarkers with the aim of predicting clinical outcome, as well as to study the neural substrates underlying the spontaneous recovery of various cognitive functions in the first months after stroke. These studies have been critical in the advancement of our knowledge of the neural mechanisms ocurring after a stroke, whether they are adaptive or maladaptive. However, this knowledge does not seem to be applied in relation to the study of the changes in the brain neural mechanisms followed after the use of CR. Furthermore, the CR studies carried out, regardless of whether they used neuroimaging or not as a proof of concept, suffer from the aforementiond methodological problems (e.g., heterogeneity of the sample, lack of a proprer randomization, lack of an active control group), which not only prevents the generalization of the results but also represents a barrier to achieve the level of evidence needed to guide future directions in the development of effective CR therapies in the stroke population. This situation, also highlighted by the corresponding Cochrane's reviews, hinders transferring scientific results into everyday practice. Therefore, there is a clear need of improving the design of CR studies in order to overcome the aforementioned barriers in future studies. In this improvement, the time in which the therapy is applied as well as the heterogeneity of the sample should be considered closely. First, the effect of the CR therapy may not be the same when applied after a few weeks than when applied after several months after the stroke. With the application of CR therapy after a few weeks, we can take the advantage of the spontaneous changes ocurring after the stroke stimulating the adaptive changes whereas preventing the maladaptive ones. In the case of chronic stroke patients, the effectiveness of the CR therapy will be more difficult to achieve considering the fact that maladaptive changes may have already occurred. Second, the heterogeneity of the sample is something that should also be considered. Heterogeneity does refer not only to the site and the volume of the lesion but also to the individual response to CR. One should consider the fact that even in a well-designed study, we are going to find interindividual differences in relation to the effectiveness of the CR therapy applied. There are several factors that can be exerting their influence in how an individual respond to a single treatment. Therefore, the ability to identify good responders to the treatment is as important as the identification of the nonresponders, as the nonresponders may need another CR approach.

As highlighted in the present chapter, studies focused on the rehabilitation of attention, memory, and executive functions after stroke using neuroimaging to test the neural effects of the rehabilitation in the brain are scarce. These cognitive functions can have the same detrimental effects on the activities of daily living as other impairments such as aphasia or neglect. Given that attention, memory, and executive problems are prevalent following stroke, additional studies using neuroimaging parameters should be the focus of future research.

Finally, any treatment will be the most effective when optimized based on the specific deficit of the patient in the context of his/her degree of spared cognition and cerebral reserve. Optimization of such treatment effects also remains neglected in stroke CR research to date and represents an important area for future research.

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