MRI markers of functional connectivity and tissue microstructure in stroke-related motor rehabilitation: A systematic review

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ABSTRACT

Background: Stroke-related disability is a major problem at individual and socio-economic levels. Neuromotor rehabilitation has a key role for its dual action on affected body segment and brain reorganization. Despite its known efficacy in clinical practice, the extent and type of effect at a brain level, mediated by neuroplasticity, are still under question.

Objective: To analyze studies applying MRI markers of functional and structural connectivity in patients affected with stroke undergoing motor rehabilitation, and to evaluate the effect of rehabilitation on brain reorganization.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were applied to select studies applying quantitative non-conventional MRI techniques on patients undergoing motor rehabilitation, both physical and virtual (virtual reality, mental imagery). Literature search was conducted using MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE from inception to 30th June 2020.

Results: Forty-one out of 6983 papers were included in the current review. Selected studies are heterogeneous in terms of patient characteristics as well as type, duration and frequency of rehabilitative approach. Neuromotor rehabilitation promotes neuroplasticity, favoring functional recovery of the ipsilesional hemisphere and activation of anatomically and functionally related brain areas in both hemispheres, to compensate for damaged tissue.

Conclusions: The evidence derived from the analyzed studies supports the positive impact of rehabilitation on brain reorganization, despite the high data heterogeneity. Advanced MRI techniques provide reliable markers of structural and functional connectivity that may potentially aid in helping to implement the most appropriate rehabilitation intervention.

1. Introduction

Neurological diseases are the second leading death cause and the first of disability-adjusted life years (DALYs) according to the last available report of the Global Burden of Disease (GBD) (Collaborators GBDN). Among the non-communicable neurological diseases causing physical disability, stroke was the largest contributor to DALYS (Collaborators GBDN), and although age-standardized mortality rate has sharply decreased in the last two decades, the incidence did not show the same trend, resulting in an overall increased GBD for stroke survivors (Collaborators GBDS, 2019; Rajsic et al., 2019).

Motor rehabilitation impacts the clinical evolution of post-stroke phase both allowing functional recovery of the affected body segment and enhancing neuroplasticity (Dimyan and Cohen, 2011). Despite its advantages, there are some fundamental unanswered questions: is there an optimal time to start physiotherapy? What is more effective in terms of rehabilitation approach, frequency, duration, setting? Are there categories of patients more suitable for physiotherapy than others? Literature data in this regard are considerably heterogenous, and as such, not easily comparable. A recent review focused on motor rehabilitation in stroke analyzed 15 randomized controlled trials (RCTs), all but one yielding similar results in the intervention group and in the control group in terms of rehabilitation efficacy (Stinear et al., 2020). Conversely, several other smaller RCTs focusing on the same topic...
reported significantly positive results only in the active group (You et al., 2005; James et al., 2009; Whitall et al., 2011).

These apparently contradictory results might be related to the different rehabilitative treatments, but more likely are due to challenges in the design and realization of the clinical trials.

A better understanding of the underlying physiopathogenic mechanisms as well as the identification of biomarkers able to capture brain changes in response to rehabilitative treatment and to predict the clinical outcome in an early phase would help solve this quandary. Advanced MRI techniques might have a prominent role as they are non-invasive, reproducible, and allow to investigate both structural and functional aspects of the same pathogenic phenomenon. Indeed, the use of non-conventional MRI techniques have broadened the field’s knowledge about brain plasticity from a microstructural and functional point of view, and the derived quantitative markers have been recently included in studies evaluating the efficacy of rehabilitative treatments (Sun et al., 2020). Namely, functional MRI provides information about brain regional activity, based on blood oxygen level changes. This technique can provide both the level of activity during rest (resting state fMRI) and activation maps triggered by specific tasks (Fig. 1). On the other hand, structural changes can be measured both in terms of grey matter (GM) or white matter (WM) volume, through techniques such as voxel-based morphometry (VBM), or tissue integrity, evaluating the mobility and directionality of water molecules within the brain, using diffusion tensor imaging (DTI) (Fig. 1).

The advent of advanced MRI techniques has provided insight into how neuroplasticity occurs at a functional level, in terms of activation pattern or functional connectivity (FC) changes and at a structural level, which can translate in volumetric modifications or altered diffusivity profiles of the tissue. While some of these adaptive dynamic processes lead to an improvement of motor or cognitive performances, in some cases they are associated to a worse clinical outcome, a phenomenon called ‘maladaptive plasticity’ (Jang and Gordon, 2013; Lee et al., 2009).

In the last decades, a better understanding of disease-related pathogenic mechanisms, as well as the possibility to observe a more prolonged period of disease evolution in large cohorts of patients, have facilitated the development of a broader spectrum of rehabilitative approaches (Levard et al., 2021; Liu et al., 2020).

Despite these advances, the efficacy of rehabilitation on recovery is still under question, mostly due to the lack of robust markers, and the use of different variables (rehabilitative settings, type of treatment, inclusion criteria) that make literature studies difficult to compare. With this background, the aim of this systematic review is to summarize and critically analyze the available data on MRI markers and motor rehabilitation applied to stroke and to describe the current state of the art with respect to the effects of neuromotor rehabilitation on brain plasticity.

Fig. 1. Examples of images derived from task-based fMRI (upper left), resting-state fMRI (upper right), voxel based-morphometry (lower left) and diffusion tensor imaging (lower right).
2. Methods

Literature search, data selection and scientific writing were performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria (Liberati et al., 2009). The protocol for the review was not registered before the literature search began.

2.1. PICOS eligibility criteria:

Participants: the only eligibility criterion was the recruitment of adult patients (≥18 years old) affected by ischemic or hemorrhagic stroke.

Interventions: studies applying quantitative non-conventional MRI techniques on patients undergoing motor rehabilitation, both physical (physical exercise, resistance training, aerobic exercise, endurance training, motor rehabilitation using robotic devices for upper or lower limbs) and virtual (virtual reality, motor imagery), were selected. Motor rehabilitation was defined as multiple training sessions of the selected physiotherapy approach. As such, studies reporting MRI results after single rehabilitative sessions or task training that was not part of rehabilitative treatments were excluded. Moreover, studies using exclusively brain stimulation to enhance brain plasticity, as well as studies on cognitive rehabilitation, or aiming at improving cognitive functions, were excluded.

Comparisons: Both studies with an active group of patients (i.e. patients undergoing motor rehabilitation of any sort) and a control group of patients not undergoing any treatment, studies comparing groups of patients undergoing different rehabilitative treatments and studies comparing patients undergoing rehabilitative treatment and healthy subjects.

Outcomes: The outcome considered in the review was to evaluate the effect of motor rehabilitation on surrogate MRI markers representative of functional and/or tissue microstructure.

Study designs: Peer-reviewed Randomized and non-RCTs, including ≥5 subjects and case studies were included in the analysis. Conference proceedings, reviews, book chapters, case reports and editorials were excluded.

2.2. Information sources, search and study selection

Literature search was conducted using MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE from inception to 30th June 2020. The MeSH terms “stroke” AND (“rehabilitation” OR “physiotherapy” OR “exercise” OR “virtual reality” OR “robotics”) AND (“MRI” OR “brain plasticity” OR “connectivity”). Papers written in languages other than English were excluded. References from the selected articles were then screened for further records. Three researchers (E.T, A.P, M.C.) independently assessed the selected articles to evaluate their eligibility, and disagreements were solved by discussion.

2.3. Data extraction

For each study, the study design, number of subject, rehabilitative setting (i.e. inpatient, outpatient, home-based), MRI markers pre- and post-intervention were extracted and reported.

3. Results

The literature search retrieved, as of June 30th, 2020, 6983 papers using the abovementioned MeSH terms, to which we added 4 papers retrieved from references. Six-thousand nine-hundred forty-four papers were eliminated for the following reasons: duplicates (2257), not fitting with the topic of the review after reading the title/abstract or the entire manuscript (3694), editorials (12), reviews (539), case reports (181), not written in English language (145), case series <4 patients (116). A total of 43 papers were discussed in details in this review (Fig. 2).

3.1. Characteristics of the studies

The key features of the studies are depicted in Table 1 for studies applying structural techniques and Table 2 for studies applying fMRI. The study designs were as follows: 20 RCTs (You et al., 2005; Whitall et al., 2011; Luft et al., 2004; Deng et al., 2012; Wu et al., 2019; Várkuti et al., 2013; Ramos-Murguialday et al., 2013; Ramos-Murguialday et al., 2019; Gauthier et al., 2008; Lin et al., 2010; Bajaj et al., 2015; Jang et al., 2005; Liu et al., 2014; Wang et al., 2019; Sun et al., 2013; Dechaumont-Palacin et al., 2008; Kim et al., 2020; Carey et al., 2007; Luft et al., 2008; Ertelt et al., 2007), 23 non-RCTs (1 semi-RCT (Takahashi et al., 2008), 5 case-control studies (CC) (James et al., 2009; Horn et al., 2016; Schaechter et al., 2002; Murayama et al., 2011; Dong et al., 2007), 15 case series (CS) (Johansen-Berg et al., 2002; Enzinger et al., 2009; Könönen et al., 2012; Page et al., 2009; Hamzei et al., 2008; Hamzei et al., 2006; Fan et al., 2015; Page et al., 2010; Szafarski et al., 2006; Askim et al., 2009; Zheng et al., 2016; Fan et al., 2015; Pinter et al., 2013; Landsmann et al., 2016; Koganemaru et al., 2015), 1 open label study (Yang et al., 2017), 1 not specifying the study design other than non-RCT (Saleh et al., 2017).

With respect to patients’ characteristics, the diagnosis was either subacute (12 studies (James et al., 2009; Wu et al., 2019; Liu et al., 2014; Dechaumont-Palacin et al., 2008; Kim et al., 2020; Horn et al., 2016; Murayama et al., 2011; Fan et al., 2015; Askim et al., 2009; Fan et al., 2015; Pinter et al., 2013; Yang et al., 2017)) or chronic (27 studies (You et al., 2005; Whitall et al., 2011; Luft et al., 2004; Deng et al., 2012; Ramos-Murguialday et al., 2013; Ramos-Murguialday et al., 2019; Gauthier et al., 2008; Jang et al., 2005; Sun et al., 2013; Carey et al., 2007; Luft et al., 2008; Ertelt et al., 2007; Takahashi et al., 2008; Schaechter et al., 2002; Dong et al., 2007; Johansen-Berg et al., 2002; Enzinger et al., 2009; Könönen et al., 2012; Page et al., 2009; Hamzei et al., 2008; Hamzei et al., 2006; Fan et al., 2015; Page et al., 2010; Szafarski et al., 2006; Askim et al., 2009; Zheng et al., 2016; Fan et al., 2015; Pinter et al., 2013; Landsmann et al., 2016; Koganemaru et al., 2015)) stroke, or both (4 studies (Várkuti et al., 2013; Lin et al., 2010; Bajaj et al., 2015; Wang et al., 2019)), even though the definition of “subacute” and “chronic” varied among studies, with 3 or 6 months as temporal thresholds between the two stages.

With respect to the rehabilitative treatment, the setting was as follows: inpatient (IP, 6 (Wu et al., 2019; Wang et al., 2019; Kim et al., 2020; Horn et al., 2016; Murayama et al., 2011; Askim et al., 2009)), outpatient (OP, 1 (Whitall et al., 2011), physiotherapist supervised

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Fig. 2. Flow-chart of the papers selection process.

| Papers identified through literature search (6983) | References after duplicates removed (4759) |
|-------------------------------------------------|-------------------------------------------|
| Studies stayed in the screening process for their title/abstract (112) | References excluded Not fitting with the topic (3582) |
| Studies included in the review for their title/abstract (43) | Editorials (12) |
|                                                  | Reviews (539) |
|                                                  | Case reports (181) |
|                                                  | Not written in English language (145) |
|                                                  | Case series <4 patients (116) |
without further information on the setting (28 (You et al., 2005; James et al., 2009; Luft et al., 2004; Värkuti et al., 2013; Gauthier et al., 2008; Lin et al., 2010; Bajaj et al., 2015; Jiang et al., 2005; Liu et al., 2014; Sun et al., 2013; Dechaumont-Palacin et al., 2008; Luft et al., 2008; Ertelt et al., 2007; Takahashi et al., 2008; Schaechter et al., 2002; Enzinger et al., 2009; König et al., 2012; Page et al., 2009; Hamzei et al., 2008; Hamzei et al., 2006; Fan et al., 2015; Szafarski et al., 2006; Fan et al., 2015; Pinter et al., 2013; Landsmann et al., 2016; Koganemaru et al., 2015; Yang et al., 2017; Saleh et al., 2017), home-based (1 (Johansen-Berg et al., 2008), mixed (OP + home-based 4 (Ramos-Murguialday et al., 2013; Ramos-Murguialday et al., 2019; Dong et al., 2007; Page et al., 2010), OP + IP 1 (Zheng et al., 2016), telerehabilitation (TR, 2 (Deng et al., 2012; Carey et al., 2007). The mean duration of each rehabilitative session was 130.6 min (standard deviation 15–360 min), with constraint induced motor therapy (CIMT) sessions being the longest. The weekly frequency of the physiotherapy sessions ranged from 3 to 5 days/week, and the total duration of the rehabilitative cycle ranged from 10 days to 6 months.

MRI was always acquired both before and at the end of the rehabilitative cycle, whereas in 6 studies there was also a second MRI timepoint, either within the cycle (Kim et al., 2020) or after 2 weeks (Koganemaru et al., 2015), 3 months (Murayama et al., 2011), 4 months (Whitall et al., 2011), or 6 months (Ramos-Murguialday et al., 2019; Schaechter et al., 2002). Among the 43 selected studies, 4 applied structural MRI (3 diffusion tensor imaging (DTI) (Kim et al., 2020; Fan et al., 2015; Yang et al., 2017), 1 voxel-based morphometry (VBM (Gauthier et al., 2008)), whereas the remaining 39 performed functional MRI (fMRI) (32 task-related fMRI (You et al., 2005; Whitall et al., 2011; Luft et al., 2004; Deng et al., 2012; Ramos-Murguialday et al., 2013; Ramos-Murguialday et al., 2019; Lin et al., 2010; Bajaj et al., 2015; Jiang et al., 2005; Liu et al., 2014; Sun et al., 2013; Dechaumont-Palacin et al., 2008; Carey et al., 2007; Luft et al., 2008; Ertelt et al., 2007; Takahashi et al., 2008; Horn et al., 2016; Schaechter et al., 2002; Murayama et al., 2011; Dong et al., 2007; Johansen-Berg et al., 2002; Enzinger et al., 2009; König et al., 2012; Page et al., 2009; Hamzei et al., 2008; Page et al., 2010; Szafarski et al., 2006; Askim et al., 2009; Pinter et al., 2013; Landsmann et al., 2016; Koganemaru et al., 2015; Saleh et al., 2017), 7 resting state-fMRI (James et al., 2009; Wu et al., 2019; Värkuti et al., 2013; Wang et al., 2019; Hamzei et al., 2006; Zheng et al., 2016; Fan et al., 2015).

4. Discussion

In this review, the search for studies that incorporated MRI markers to analyze FC/tissue microstructure in stroke patients and monitor their evolution in response to rehabilitation led to 43 results, here discussed based on the type of MRI connectivity markers (Table 3-4).

4.1. Tissue microstructure

Only 4 out of 43 studies applied structural MRI imaging (Gauthier et al., 2008; Kim et al., 2020; Fan et al., 2015; Yang et al., 2017). The paucity of structural data might be related to the short study duration, intrinsic to the nature of the studies itself, temporally linked to the few weeks of a rehabilitative cycle. Structural brain modifications have been described in response to motor tasks in healthy subjects, involving both GM and WM (Draganski et al., 2004; Scholz et al., 2009; Taubert et al., 2010), with plenty of histological data confirming it (Xu et al., 2009; Sampaio-Baptista et al., 2018). However, to detect such changes occurring over a brief period, in a population of older people in whom brain tissue is partially compromised by the ischemic insult, might present some challenges. Overall, the analyzed studies showed structural changes in treated patients (Gauthier et al., 2008; Kim et al., 2020; Fan et al., 2015; Yang et al., 2017), even though only 2 studies had a control group (Gauthier et al., 2008; Kim et al., 2020). Finally, future studies might benefit by utilizing graph theory-based analysis to better characterize structural connectivity, rather than just investigating tissue microstructure.

4.2. Lower limb rehabilitation

The 2 robot-assisted gait training studies showed higher fractional anisotropy (FA), a marker of tissue integrity, in the contralateral sensorimotor cortex (SMC) paralleled by improved locomotor function (Kim et al., 2020; Yang et al., 2017). Some evidence shows that increased functional and/or structural FC/SC of the contralateral hemisphere correlate with poorer recovery, as it might indicate that the ipsilesional hemisphere is beyond recovery for intensity and extent of damage (Enzinger et al., 2009; Cramer et al., 2007). On the contrary, gait function seems to be controlled by both hemispheres (MacKay-Lyons, 2002), and as such the dominance of the contralateral hemisphere might just represent a positive adaptive change in which functions of lesioned hemisphere are compensated by the activation of previously quiescent areas of the contralateral one.

4.3. Upper limb rehabilitation

The 2 studies that focused on the upper limb reported better clinical outcomes after rehabilitation, paralleled by higher FA in the ipsilesional cortico-spinal tract (CST) as well as in the transcallosal motor fibers in the bilateral arm training study (Fan et al., 2015), and increased GM volume in bilateral SMC and hippocampus in the constraint-induced (CI) therapy study (Gauthier et al., 2008). Interestingly, the former study performed on subacute stroke patients, showed an initial reduction of FA of both ipsilesional CST and transcallosal M1-M1 fibers in the early post-stroke phase (Kim et al., 2020).

Taken together, these results suggest that the clinical improvement of the affected limb/function is related to the restoration of an inter-hemispheric balance, represented by functional recovery of the ipsilesional hemisphere and activation of compensatory areas of the contralesional one.
| Authors                     | Study design | Subjects with MRI results | Training mode | Setting | Disease phenotype | Session duration (min) | Total duration | Imaging |
|-----------------------------|--------------|---------------------------|---------------|---------|-------------------|------------------------|----------------|---------|
| Dechaumont-Palacin et al. (2008) | RCT          | Tot = 13 Int = 7 Con = 6 | Passive proprioceptive training vs CPT | PT       | Subacute          | 4 weeks (5d/w)         |                | Task fMRI |
| Askim et al. (2009)         | CS           | Tot = 12                 | TSP           | IP      | Subacute          | NA                     | NA             |  Task fMRI |
| James et al. (2009)         | CC           | Tot = 8 Int = 5 Con = 3  | TSP vs CPT    | PT      | Subacute          | 120                    | 3 weeks (5d/w) | Re-fMRI  |
| Murayama et al. (2011)      | CC           | Tot = 15 Int = 7 Con = 8 | CIMT          | IP      | Subacute          | 300                    | 2 weeks       | Task fMRI |
| Finter et al. (2013)        | CS           | Tot = 7                 | RAT           | PT      | Subacute          | 20 min                 | 3 weeks (5d/w) | Task fMRI |
| Liu et al. (2014)           | RCT          | Tot = 15 Int = 10 Con = 5| MI + CPT vs CPT| PT     | Subacute          | 45                     | 4 weeks (5d/w) | Task fMRI |
| Fan et al. (2015)           | CS           | Tot = 10                | RAT           | PT      | Subacute          | 90                     | 4 weeks (5d/w) | Re-fMRI  |
| Horn et al. (2016)          | CC           | Tot = 26 Int = 12 Con = 14| CPT + AAT    | IP      | Subacute          | 60                     | 3 weeks (5d/w) | Task fMRI |
| Wu et al. (2019)            | RCT          | Tot = 25 Int = 14 Con = 11| BCI          | IP      | Subacute          | 60                     | 4 weeks (5d/w) | Res-fMRI*|
| Johansen-Berg et al. (2002) | CS           | Tot = 7                 | CIMT          | Home based | Chronic          | 360                    | 2 weeks       | Task-MRI |
| Schaechter et al. (2002)    | CC           | Tot = 9 Int = 4 Con = 5 | CIMT          | PT      | Chronic           | 240                    |                | Task fMRI |
| Luft et al. (2004)          | RCT          | Tot = 21 Int = 9 Con = 12| Bilateral arm training vs CPT| PT     | Chronic           | 60                     | 6 weeks (3d/w) | Task-MRI |
| Jang et al. (2005)          | RCT          | Tot = 10 Int = 5 Con = 5 | VR            | PT      | Chronic           | 60                     | 4 weeks (5d/w) | Task fMRI |
| Hamzei et al. (2006)        | CS           | Tot = 6 Int = 4 Con = 10| CIMT          | mcCIMT  | Chronic           | 360                    | NA            | Re-fMRI  |
| Szaflarski et al. (2006)    | CS           | Tot = 14 Int = 4 Con = 10| CIMT          | PT      | Chronic           | 30                     | 10 weeks (3d/w)| Task fMRI |
| Carey et al. (2007)         | RCT          | Tot = 20 Group 1 = 10 Group 2 = 10| Finger tracking vs simple finger training| TR     | Chronic           | variable              | 10 days       | Task fMRI |
| Dong et al. (2007)          | CC           | Tot = 16 Int = 4 Con = 12| CIMT          | OP + home based| Chronic       | 360                    | 2 weeks       | Task fMRI |
| Ertelt et al. (2007)        | RCT          | Tot = 7 Int = 6 Con = 13| AOT vs TSP    | PT      | Chronic           | 90                     | 3 weeks (5d/w) | Task fMRI |
| Hamzei et al. (2008)        | CS           | Tot = 8                 | CIMT          | PT      | Chronic           | 180                    | 4 weeks (5d/w) | Task fMRI |
| Takahashi et al. (2008)     | semiRCT      | Tot = 13 Group 1 = 6 Group 2 = 7| RAT          | PT      | Chronic           | 90                     | 3 weeks (5d/w) | Task fMRI |
| Page et al. (2009)          | CS           | Tot = 10                | MI + TSP      | PT      | Chronic           | 30                     | 10 weeks (3d/w)| Task fMRI |
| Lin et al. (2010)           | RCT          | Tot = 13 Int = 5 Con = 8 | CIMT          | PT      | Subacute/chronic  | 120                    | 3 weeks       | Task fMRI |
| Page et al. (2010)          | CS           | Tot = 8                 | TSP with neuromusculature OP + home based| OP     | Chronic           | 30                     | 8 weeks (5d/w) | Task fMRI |
| Whitall et al. (2011)       | RCT          | Tot = 38 Int = 17 Con = 21| Bilateral vs monolateral arm training| OP     | Chronic           | 60                     | 6 weeks (3d/w) | Task fMRI |
| Kornon et al. (2012)        | CS           | Tot = 11                | CIMT          | PT      | Chronic           | 360                    | 3 weeks (5d/w) | Task fMRI |
| Vinkuti et al. (2013)       | RCT          | Tot = 9 Group 1 = 6 Group 2 = 3| MI-BCI vs RAT| PT     | Subacute/chronic  | NA                     | 4 weeks       | Task fMRI |
| Ramos-Murguialday et al. (2013); Ramos-Murguialday et al. (2019) | RCT | Tot = 32 Int = 16 Con = 16| BCI          | OP + home based| Chronic       | 120                    | 4 weeks       | Task fMRI |

(continued on next page)
4.4. Functional connectivity

Thirty-nine studies described FC changes after rehabilitation. Functional changes within different brain areas happen constantly as adaptive mechanisms to different stimuli or environmental situations. The abrupt onset of an imbalance between energy demand and blood supply caused by stroke leads to a functional rearrangement, with the aim to compensate for the damaged tissue, and often involves different brain areas in both hemispheres. The functional response to rehabilitation is complex and depends upon several factors, ranging from the lesion location, to the damage extent and also to the specific rehabilitation approach.

4.5. Lower limb rehabilitation

Among the 39 fMRI studies, only 5 were performed on lower limb-related rehabilitation (You et al., 2005; Deng et al., 2012; Luft et al., 2008; Enzinger et al., 2009; Landsmann et al., 2016). This might be due to technical challenges related to the motor task during MRI acquisition and to the abovementioned complex bihemispheric control on lower limb movements and gait function that would render challenging interpretation of results. Overall, these studies seem to confirm the previously mentioned structural data, showing both an increased activation of bilateral cortical areas and a functional recovery of the ipsilesional one, when possible, paralleling the clinical improvement of locomotor function (You et al., 2005; Deng et al., 2012; Enzinger et al., 2009; Landsmann et al., 2016). Notably, 2 studies highlighted the prominent role of brain structures, such as thalamus (Enzinger et al., 2009), cerebellum and midbrain (Luft et al., 2008), in gait function.

Table 3
Main structural MRI results post-rehabilitation treatment.

| Authors               | Disease phenotype | Imaging technique | Results |
|-----------------------|-------------------|-------------------|---------|
| Fan et al. (2015)     | Subacute          | DTI               | ¶FA iCST, transcortical motor fibers ¶volume b1 SMC, SMA and hippocampus |
| Gauthier et al. (2008)| Chronic           | VBM               |         |
| Yang et al. (2017)    | Subacute          | DTI               | ¶FA a-posterior cingulate cortex ¶FA dientral capsule, pedunculopontine nucleus and substantia nigra ¶FA chupramaginal gyrus and SMA ¶FA cl superior temporal, cingulate and postcentral giri |
| Kim et al. (2020)     | Subacute          | DTI               |         |

VBM-voxel based morphometry; DTI-diffusion tensor imaging; FA-fractional anisotropy; bl-bilateral; il-ipsilesional; cl-contralesional; SMC-sensorimotor cortex; SMA-supplemental motor area; CST-corticospinal tract.
### Table 4
Main functional MRI results post-rehabilitation treatment.

| Authors | Disease phenotype | Imaging | Results |
|---------|-------------------|---------|---------|
| **Upper limb rehabilitation** | | | |
| Dechaumont-Palacin et al. (2008) | Subacute | Task fMRI | ↑ cf SMA, PMC, S2 |
| Askim et al. (2009) | Subacute | Task fMRI | ↑ if S1M1, M1, cf S2 |
| James et al. (2009) | Subacute | Rs-fMRI | ↑ EC if PMC → cf PMC |
| Murayama et al. (2011) | Subacute | Task fMRI | ↑ if S1M1, cerebellum |
| Pinter et al. (2013) | Subacute | Task fMRI | ↑ if S1M1, cerebellum; ↓ cl M1 |
| Liu et al. (2014) | Subacute | Task fMRI | ↑ if S1M1, cerebellum |
| Fan et al. (2015) | Subacute | Rs-fMRI | ↑ if S1M1-M1 |
| Horn et al. (2016) | Subacute | Task fMRI | ↑ if S1M1 |
| Wu et al. (2019) | Subacute | Rs-fMRI* | ↑ diffuse bilateral activation |
| Johansen-Berg et al. (2002) | Chronic | Task fMRI | ↑ if PMC, S2 |
| Schaechter et al. (2002) | Chronic | Task fMRI | ↑ if PMC, SMA, M1 |
| Luft et al. (2004) | Chronic | Task fMRI | ↑ if S1M1 |
| Hamzei et al. (2006) | Chronic | Rs-fMRI | Δ if S1M1* |
| Jang et al. (2005) | Chronic | Task fMRI | ↑ if S1M1 |
| Szafiarski et al. (2006) | Chronic | Task fMRI | NS at a group level |
| Carey et al. (2007) | Chronic | Task fMRI | NS at a group level |
| Dong et al. (2007) | Chronic | Task fMRI** | ↑ il M1, cerebellum |
| Ertelt et al. (2007) | Chronic | Task fMRI | ↑ il ventral PMC, SMA, STG, IP areas |
| Hamzei et al. (2008) | Chronic | Task fMRI | Δ if S1M1* |
| Takahashi et al. (2008) | Chronic | Task fMRI | ↑ if S1M1 |
| Page et al. (2009) | Chronic | Task fMRI | ↑ if PMC, M1, cl PMC |
| Lin et al. (2010) | Subacute / chronic | Task fMRI | ↑ if PMC |
| Page et al. (2010) | Chronic | Task fMRI | ↑ if S1M1, IPL |
| Whitall et al. (2011) | Chronic | Task fMRI | ↑ if S1M1, SMA |
| Körösen et al. (2012) | Chronic | Task fMRI | ↑ if S1M1 |
| Várkuti et al. (2013) | Subacute / chronic | Rs-fMRI | ↑ if FC M1-M1, S1M1, cerebellum |
| (Ramos-Murguialday et al., 2013; Ramos-Murguialday et al., 2019) | Chronic | Task fMRI | ↑ if PMC, M1 |
| Sun et al. (2013) | Chronic | Task fMRI | ↑ if S1M1 (few pts showed ↓ if S1M1) |
| Bajaj et al. (2015) | Subacute / chronic | Task fMRI | ↑ if FC M1-SMA |
| Koganemaru et al. (2015) | Chronic | Task fMRI | ↑ if S1M1, cl PMC |
| Zheng et al. (2016) | Chronic | Rs-fMRI | ↑ if FC M1-M1, il M1-cl msFG |
| Saleh et al. (2017) | Chronic | Task fMRI | ↑ if il S1M1, il thalamus |

| Authors | Disease phenotype | Imaging | Results |
|---------|-------------------|---------|---------|
| **Lower limb rehabilitation** | | | |
| You et al. (2005) | Chronic | Task fMRI | ↑ il motor network |
| Luft et al. (2008) | Chronic | Task fMRI | ↑ cerebellum, midbrain, cl IPL, S1, SPG |
| Enzinger et al. (2009) | Chronic | Task fMRI | ↑ il S1M1, il thalamus |
| Deng et al. (2012) | Chronic | Task fMRI | NS |

### 4.6. Upper limb rehabilitation

Functional MRI changes in response to upper limb rehabilitation are very variable, ranging from an increased activation of ipsilesional sensorimotor areas (Whittal et al., 2011; Ramos-Murguialday et al., 2013; Jang et al., 2005; Sun et al., 2013; Dechaumont-Palacin et al., 2008; Takahashi et al., 2008; Dong et al., 2007; Johansen-Berg et al., 2002; Askim et al., 2009; Pinter et al., 2013; Saleh et al., 2017) or contralesional areas of the unaffected hemisphere (Luft et al., 2004; Lin et al., 2010; Schaechter et al., 2002; Page et al., 2010) or both (Ertelt et al., 2007; Page et al., 2009; Fan et al., 2015). Moreover, some studies reported a reduced activation of the ipsilesional hemisphere in the post-rehabilitation phase, usually associated with clinical improvement and as such interpreted as more efficient and focused activation of the interested areas (Sun et al., 2013; Zheng et al., 2016; Koganemaru et al., 2015; Ward et al., 2003).

An univocal interpretation of these heterogeneous and apparently contradictory result is difficult, partly because many variables need to be taken into consideration, such as the individual disability level, the type of rehabilitative approach, the extent of tissue damage and the involvement of cortical and/or subcortical regions.

The type of rehabilitative approach adopted in the studies has a crucial role, determining what brain areas are functionally activated and potentially reorganized. In general, CIMT is associated with activation of SMC (Gauthier et al., 2008; Lin et al., 2010; Schaechter et al., 2002; Dong et al., 2007; Johansen-Berg et al., 2002; Hamzei et al., 2008; Hamzei et al., 2006; Szafiarski et al., 2006) and cerebellum (Murayama et al., 2011), bilateral limb training seems to facilitate the activation of bilateral areas (Whittal et al., 2011; Luft et al., 2004), action-observation therapy leads to an increased mirror neuron system (ventral PMC, inferior parietal areas)activation (Ertelt et al., 2007), passive proprioceptive training triggers the activation of secondary somatosensory areas (Dechaumont-Palacin et al., 2008), rehabilitation approaches using virtual reality, robotic therapy or brain-computer interface induce often the activation not only of motor areas but also of visuomotor or associative ones (Wu et al., 2019; Várkuti et al., 2013; Ramos-Murguialday et al., 2015; Ramos-Murguialday et al., 2019; Fan et al., 2015).

These latter rehabilitative treatments are not only associated with a widespread activation of different functional brain areas, but also to a...
more significant clinical improvement, when directly compared to other rehabilitative approaches (You et al., 2005; Wu et al., 2019; Takahashi et al., 2008; Saleh et al., 2017). Therefore, more cognitively challenging tasks, such as the ones involving the visuo-motor loop, in some patients promote neuroplastic changes more effectively, through the recruitment of motor as well as other areas involved in different functions such as motor learning, executive and visuospatial functions, as previously hypothesized (Gauthier et al., 2008; Landsmann et al., 2016; Pascual-Leone et al., 1995; Carey et al., 2005). Some studies have also tested the relationship between FC and the impact of MI, or mental practice, intended as the cognitive rehearsal of simple movements or more complex activities, usually part of the daily life activities (Bajaj et al., 2015; Liu et al., 2014; Wang et al., 2019; Sun et al., 2013; Page et al., 2009). Whereas a recent Cochrane review has reported no evidence of efficacy of such a rehabilitative approach (Silva et al., 2020), some studies show that it has an impact of brain reorganization, and seems to reinforce the effect of physical therapy (Bajaj et al., 2015; Liu et al., 2014).

The integrity of structures anatomically related to stroke areas is also relevant in the process of brain reorganization, as demonstrated by 2 studies on the relationship between ipsilesional SMC and the pyramidal tract (primary motor cortex and CST) (Hamzei et al., 2008; Hamzei et al., 2006). The integrity of the pyramidal tract is associated with a reduced, more focused activation of the ipsilesional SMC, likely due to increased synaptic efficiency. Conversely, damage to the former structure results in increased activation of the latter one, as a higher efficiency and number of activated neurons is necessary to maintain the same level of motor performance. Moreover, several studies have also described functional changes of thalamus (Askim et al., 2009; Fan et al., 2015) and cerebellum (Várkuti et al., 2013; Liu et al., 2014; Murayama et al., 2011; Askim et al., 2009; Fan et al., 2015) associated with functional gain of the affected body segment, as the first is the main relay center of cortico-subcortical pathways and the second plays a key role in motor learning and sensorimotor input/output integrations.

Interestingly, few studies have analyzed not only FC (i.e., the strength of connectivity between regions) (Fan et al., 2015) but also effective connectivity (James et al., 2009; Saleh et al., 2017), intended as the directionality of functional interaction between brain regions. In both studies, rehabilitation strengthened the connectivity of the ipsilesional hemisphere, enhancing its influence on the contralateral one (James et al., 2009), as well as the influence of the ipsilesional primary somatosensory cortex on primary motor cortex (Saleh et al., 2017). In both studies, the rerouted connectivity was significantly associated with a clinical improvement.

Another important yet unanswered question concerns whether the clinical, structural and functional changes gained during rehabilitation last over time or fade away in the subsequent period. This is a relevant issue, as it allows to define whether the skills acquired during rehabilitation, as well as the functional and structural brain reorganization, are just a mere response to the intensive physical activity or they are consolidated acquisitions that the patient will be able to exploit in a real-life setting. Only 4 studies have included longer follow-ups and MRI results are quite heterogenous, ranging from a more focused activation of the ipsilesional motor cortex paralleling the functional gain (Dong et al., 2007), to maintenance of the gains observed immediately after training (Murayama et al., 2011), to a partial (Schaechter et al., 2002) or complete loss of the functional changes obtained with rehabilitation (Ramos-Murguialday et al., 2019).

Altogether, the findings of all the aforementioned studies suggest that although neuroplastic changes occur spontaneously after stroke, with the aim to functionally compensate the damaged area, rehabilitation has a crucial role in promoting and addressing functional and structural reorganization. The overall impact of rehabilitation on brain connectivity seems to be positive, reducing the risk of maladaptive changes and facilitating the recovery of an interhemispheric balance. This is usually reflected by a better quantitative and/or qualitative activation of the ipsilesional hemisphere, when possible, sometimes associated to the activation of other compensatory, functionally and anatomically related brain regions. Unfortunately though, the available data do not support a prolonged effect of rehabilitation over time, but further larger studies are needed to elucidate this question.

Notably, all the studies here analyzed underline the paramount importance of MRI markers in monitoring structural and functional brain response to rehabilitation and allowing to understand the pathophysiological mechanisms underlying neuroplasticity.

4.7. Adaptive vs maladaptive plasticity

As previously stated, the main aim of neuromotor rehabilitation is to promote functional recovery, and all the studies included in the current review describe a causal relationship between clinical improvement obtained through physiotherapy and pro-adaptive plastic brain reorganization. Maladaptive plasticity refers to aberrant brain changes resulting in limited clinical recovery and appearance of abnormal compensatory motor patterns (Jang and Gordon, 2013). There is some evidence of a relationship between poorer clinical outcome and a more widespread cortical activation (Lee et al., 2009), or a higher recruitment of the contralateral hemisphere (Schwerin et al., 2008; Calautti et al., 2007), leading to define these two latter compensatory mechanisms as “maladaptive”. Some studies indirectly support this theory, associating the improvement of clinical outcomes with reduced cortical activation, interpreted as increased neuronal efficiency (Sun et al., 2013; Dong et al., 2007; Zheng et al., 2016; Kogamemuro et al., 2015; Ward et al., 2003). However, some other studies report an association between contralesional activation and clinical recovery (Luf et al., 2004; Lin et al., 2010; Schaechter et al., 2002; Page et al., 2010). This apparent discrepancy can be explained considering that the border between adaptive and maladaptive plasticity is thin and different pathophysiological mechanisms within the brain might underlie the same clinical symptom. Indeed, the lesion location and extent, as well as the degree of involvement of other components of the ipsilesional motor pathways are key factors addressing the neuroplastic changes able to effectively favor the functional recovery.

As a consequence, an accurate MRI assessment of patients eligible for neurorehabilitation with a functional and structural characterization of the lesion and the connected brain areas, can add valuable information and facilitate the choice of the most appropriate rehabilitation treatment.

4.8. Methodological considerations

Some methodological observations have to be considered, when interpreting studies results (Table 5). In general, the studies are difficult to compare because of an extreme heterogeneity in patient demographics, lesion size/location, time since stroke (even the temporal thresholds used to define “chronic” and “subacute” differ across studies), clinical scales applied to measure disability, rehabilitation duration and frequency, fMRI approach (region of interest vs global analysis), task.

| Homogeneity of patient characteristics | Timing since stroke (subacute/chronic) |
|----------------------------------------|--------------------------------------|
| Control group                          | Stroke etiology (hemorrhagic/ischemic) |
| MRI                                    | Comparable exposure time to physical activity |
| Structural and functional characterization of lesion (cortical/subcortical) | ipsilesional motor pathway other brain regions anatomically and functionally related to stroke site Long term follow-up |

Table 5

Key points to improve interpretation and reproducibility of MRI results in future studies.

- Standardization of task frequency and amplitude
- Possible other confounding factors (head movements, mirror movements)
This aspect, together with the small sample size of most studies, renders it difficult to extrapolate and adapt results to the clinical practice, especially at an individual level.

4.9. Timing of rehabilitation treatment

The timing of the rehabilitative intervention with respect to stroke onset is highly relevant for different reasons. The brain undergoes spontaneous changes at a cellular and tissue level after stroke. Experimental and clinical evidence describes different reparative mechanisms including synaptogenesis, neurogenesis, neuroaxonal growth, angiogenesis, and rerouting of surviving networks (Alia et al., 2017; Dąbrowski et al., 2019). This network rewiring involves both hemispheres: on one hand, the small part of ipsilesional motor pathways residing in the contralesional hemisphere becomes active (Caramia et al., 2000), and on the other, the inhibitory influence of the lesioned hemisphere on the contralateral is significantly less effective (Askim et al., 2009; Valone et al., 2016). Therefore, the contralesional hemisphere plays a dominant role in the first post-stroke phase, and the amount of its activation depends on lesion location and extension. However, whether the hyperactivation of contralesional brain areas is beneficial or detrimental is still controversial, as some studies associate it with clinical recovery (Lin et al., 2010; Schaechter et al., 2002; Page et al., 2010), others with maladaptive plasticity and a worse prognosis (Enzinger et al., 2008), and others have reported a positive relationship between lateralized activation towards the ipsilesional hemisphere and clinical improvement (Loubinoux et al., 2007). Environmental stimuli, such as life-related activities and rehabilitation, heavily influence brain reorganization, and consequently the timing of rehabilitative intervention is an important issue. Some animal studies have shown that earlier rehabilitation intervention is related to a greater extent of functional recovery, but whether this is applicable to humans remains a matter of debate (Lotze et al., 2019). Whereas it might be difficult to precisely quantify the contribution of rehabilitation in brain reorganization in the subacute stroke patients, as its effects overlap the spontaneous mechanisms of recovery, the potential efficacy of rehabilitative treatments might also be greater, as neuroplastic changes are still ongoing and more easily addressable than in the chronic phase.

4.10. Rehabilitation setting

Another aspect that needs to be taken into consideration concerns the rehabilitation setting. Only few studies have been carried out during hospitalization (Wu et al., 2019; Wang et al., 2019; Kim et al., 2020; Horn et al., 2016; Murayama et al., 2011; Askim et al., 2009; Zheng et al., 2016), whereas most of them have been performed in an outpatient setting, which is more economically sustainable and feasible. However, the results of these latter studies might be influenced by the global level of the patients’ physical activity that depends on disability, social/familial environment, working situation and educational level. Moreover, very frequently outpatient rehabilitation requires access to the rehabilitation center 3–5 times a week, with a possible selection bias of patients that have either lower disability or higher familial support. However, results derived by the few studies exploring the effects of home-based physiotherapy and telerehabilitation are generally positive and in support of it (Deng et al., 2012; Ramos-Murgualday et al., 2013; Johansen-Berg et al., 2002; Page et al., 2009). Considering the current widespread accessibility of technological devices and the significant reduction of related economic costs, telerehabilitation might be more widely exploited in the future, as a complementary approach able to strengthen the results obtained with therapist-supervised treatments.

4.11. Control group

Another possible confounding factor concerns the type of treatment performed by the control group. Sometimes, the control group is either “passive” (You et al., 2005; Jang et al., 2005) or receive the same kind of “conventional treatment” than the intervention group, but the latter is also performing the experimental activity (Gauthier et al., 2008; Bajaj et al., 2015; Liu et al., 2014; Kim et al., 2020). If this translates into more exposure time for the treatment group, the results might reflect the higher level of physical activity/motor stimulus instead of being specifically related to motor skills acquired during the rehabilitative treatment.

4.12. MRI

The last aspect worth discussing is related to the imaging techniques. First, structural data derived from diffusion imaging markers applied to GM, as well as functional data applied to cerebellum and brainstem, might need to be interpreted cautiously due to technical challenges of the MRI techniques in those specific brain regions (Scucco et al., 2018). Second, motor tasks during MRI acquisitions might present some issues related to the potential presence of head movements, mirror movements and the variability of motor task performance in terms of amplitude and frequency. Most of the studies describe effective ways to eliminate or control for these possible confounding factors. Resting state fMRI overcome task-related challenges as the use of a specific stimulus is not required and the patient simply remains still while being imaged.

4.13. Methodological considerations and bias assessment

Quantitative MRI typically requires a fair amount of post-processing to go from the original acquisition as it comes from the scanner to the final result. This naturally calls into question to what extent these measures are reproducible. One way to assess this is via scan-rescan experiments or by assessing how similar measures are across different scanning platforms. In this case, it has been shown in healthy individuals that measures of functional connectivity and DTI-derived indices are in fact reproducible (Huang et al., 2012; Prohl et al., 2019). However, this is typically the case only under carefully controlled conditions where acquisitions are kept homogenous and the post-processing is performed in the same manner. The fact that vastly different results can be obtained based on exactly how the post-processing was performed represents a potential source of bias in the studies that have been included in this systematic review of the literature. For example, several different software packages can be utilized, which in turn also allow for different processing options. It is often the case that authors do not extensively describe exactly what was done when describing the methodology utilized in a given study. Overall, these aspects render direct comparisons of data between studies quite difficult. One possible way to remediate this problem in the future is by encouraging authors to register their exact analysis plans ahead of time. Not only will this provide an accurate record of what will be done, it will also avoid the possibility of authors trying to analyze their data in many different ways and only picking the one that shows the “best” results. Although several of the RCTs included in our review were registered ahead of time (e.g., on clinicaltrials.gov), this is still not necessarily sufficient to overcome potential risks of bias as the detailed analysis plans were not also registered. As such, there is an unknown level of bias in nearly all of the studies that have been included in the current review.

5. Conclusions

In conclusion, all the studies analyzed in this review have provided useful information on the impact of different rehabilitation approaches on SC and FC in subacute and chronic stroke patients. The overall evidence suggests that rehabilitation-induced clinical improvement is paralleled by brain reorganization tending towards the recovery of an interhemispheric balance and of ipsilesional hemisphere activity, together with the activation of functionally related contralateral areas. Future clinical trials on the effects of neuromotor rehabilitation might be
improved by the inclusion of more homogeneous populations, as well as MRI measures analyzing structural integrity of areas that are not directly damaged by the stroke but that are part of the motor pathways. Structural and functional MRI markers can be useful in capturing brain changes in response to rehabilitation, giving reliable and reproducible quantitative information useful to monitor treatment efficacy. However, there is still a clear gap in translating findings from group-based studies to the individual patient. In this regard, future work is needed to properly validate MRI markers derived from either functional connectivity and/or structural properties. It will only then be possible to incorporate MRI markers from rehabilitation-related research into a clinical setting. The advent of such studies that can better inform on neuroplasticity might then subsequently help lead to tailored rehabilitation strategies according to individual patient’s level of physical disability and entity of brain tissue damage. In turn, it could then potentially be possible to identify those patients that are more suitable for specific rehabilitative approaches.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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