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Dynamics of brain connectivity after stroke

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Dynamics of brain connectivity after stroke

Running title: Connectivity after stroke

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Abstract

PURPOSE Recovery from a stroke is a dynamic time-dependent process with the central nervous system reorganizing to accommodate for the impact of the injury. The purpose of this paper is to review recent longitudinal studies of changes in brain connectivity after stroke.

METHOD A systematic review of research papers reporting functional or effective connectivity at two or more time points in stroke patients.

RESULTS Stroke leads to an early reduction of connectivity in the motor network. With recovery time, the connectivity increases and can reach the same levels as in healthy participants. The increase in connectivity is correlated with functional motor gains. A new, more randomized pattern of connectivity may then emerge in the longer term. In some instances, a pattern of increased connectivity even higher than in healthy controls can be observed, related either to a specific time point or to a specific neural structure. Rehabilitation interventions can help improve connectivity between specific regions.

CONCLUSIONS Motor network connectivity undergoes reorganization during recovery from a stroke and can be related to behavioural recovery. Detailed analysis of changes in connectivity pattern may enable a better understanding of adaptation to a stroke and how compensatory mechanisms in the brain may be supported by rehabilitation.

Keywords stroke; connectivity; EEG; fMRI; hand function;

1. Background

According to the Global Burden of Disease Study, stroke is the second most common cause of death and the third most common cause of disability worldwide with 25.7 million stroke survivors and 10.3 million new strokes in 2013 (Feigin et al., 2017). In the UK, there are 1.2 million stroke survivors and half of them are left with an impairment, which makes stroke the largest cause of complex disability (Adamson et al., 2004). The most frequent type of disability is upper limb weakness, which is found in 77% of disabled stroke survivors (Lawrence et al., 2001).

The number of stroke survivors has doubled during the last 23 years due to improved stroke care, aging and growth of the population as well as increased prevalence of stroke risk factors (Feigin et al., 2017), and this leads to a greater need for effective rehabilitation. The original insult resulting in motor disability occurs in the brain, so there is need for understanding the brain processes underlying recovery. Recovery is a dynamic process with the central nervous system reorganizing structurally and functionally to accommodate for the damage caused by the stroke. The insight into that process is best achieved by longitudinal studies. Ultimately it is the change in the functional architecture of the brain after an insult that can shed more light on the behaviour of this system, how it adapts over time and how this adaptation underpins recovery of function. A greater understanding of the changes in connectivity after stroke may inform more efficacious interventions for modulating neural network behaviour and ultimately better rehabilitation programmes. This review focusses on results of longitudinal studies in brain connectivity after stroke.

Motor dysfunction of the upper extremity has been extensively studied in stroke as it is the most frequent disability (Lawrence et al., 2001) and one that is genuinely debilitating in every-day life. Many innovative interventions have been designed to specifically target this

problem including robot-assisted training (Rodgers et al., 2017), constrained-induced movement therapy (Wolf et al., 2010), brain stimulation techniques (Fregni et al., 2006), neurofeedback (Mihara et al., 2013; Mottaz et al., 2015) and training with a brain-machine-interface (Bundy et al., 2017; Ramos-Murguialday et al., 2013). The effects of the therapies seem promising and hand function may show signs of recovery even in the chronic phase of recovery, although not in every patient (Ward, 2017). However, it has remained a mystery why patients with similar initial levels of motor impairment after a stroke can recover hand function to markedly different degrees (Stinear et al., 2017; Turner et al., 2012).

As a result of the high variability in recovery of motor function, more recent effort has focussed on not only recovery in terms of behavioural motor output, but also on possible recovery of affected brain networks (Ward, 2017). In terms of brain structure, the lesion location is an important factor that predicts motor function outcome (Park et al., 2016; Rondina et al., 2016). The corticospinal tract, connecting the primary motor cortex (M1) with the motor effectors, is one of the most crucial structures for hand function and thus corticospinal tract damage can lead to further changes in structural connectivity (Koch et al., 2016), even in the contralesional hemisphere (Lin et al., 2015), although there is still need for more large-scale longitudinal studies (Koch et al., 2016).

When analysed from the perspective of neural activation, the brain shows compensatory activity within the contralesional motor cortex in the days and weeks following a stroke that has affected hand function (Bajaj et al., 2016a). During recovery, a return to the ipsilesional M1 activation pattern is a typical result in classic fMRI activation studies utilising simple motor tasks (Ward and Frackowiak, 2006). However, brain activation accompanying other motor-related functions can still remain altered. For example, during the process of acquiring a new motor skill over time, a decrease of activation after training is present in healthy controls, whereas no change or even an increase in activation occurs in

stroke patients, notably in the areas that seem structurally disconnected before learning (Bosnell et al., 2011).

Even if the basic neural activation pattern related to hand movement may appear normal, there might still be changes of network functional architecture during recovery following a stroke (Pellegrino et al., 2012; Sharma et al., 2009). Studies analysing relations between activations in different regions employ typically two approaches: functional and effective connectivity. The first focuses on observing non-directional temporal associations between brain systems usually based on correlation or phase synchrony measures. The second focuses on tracking the causal influence that one region exerts on another, utilising different modelling measures such as Granger's causality or Dynamic Causal Modelling (DCM; Friston et al., 2013, Bajaj et al., 2016b).

A typical finding in stroke connectivity studies is decreased functional connectivity (FC) in the perilesional area observed shortly after the insult that slowly resolves with time; a process predicting recovery (Westlake et al., 2012). On the other hand, increased FC was observed after stroke expressed as an increase in small-world network efficiency in the gamma frequency band and an increase in the interhemispheric connectivity in stroke patients during a simple finger extension task (De Vico Fallani et al., 2016). There may be complex relationships between structural connectivity and FC following a stroke such as reduced M1 fractional anisotropy (structural connectivity) in the anatomical connection between M1 of both hemispheres, accompanied by increased resting state FC between the same two structures, suggesting that the activity is somewhat compensatory to structural damage (Liu et al., 2015). Further, there can be an increased neural activation *and* resting state FC in an intact ipsilesional M1 region, accompanied by reduced ipsilesional M1 cortical thickness (Zhang et al., 2014).

As connectivity emerges as an important measure in neuroscience, there has also been a wide range of methodologies developed to measure it. Another important division is whether the connectivity is probed at rest or during a task as this often produces different results. Finally, there is a multitude of methods to quantify the functional architecture on the brain, some common and some specific to the modality used (i.e. neuroimaging or neurophysiology). Whilst this may complicate interpretation, it is still worthwhile to review the time-dependent changes in connectivity following stroke, in line with the growing need of addressing complex questions using systematic reviews (Noyes et al., 2013).

Brain connectivity changes in the motor system after stroke were reviewed in 2013 (Jiang et al., 2013). There has been a large increase in studies employing connectivity measures in stroke recovery published since 2013 with a significant number of new studies describing time-related changes (18 out of 22 papers reviewed here). This review provides a systematic update with recent findings on time-related changes in connectivity following a stroke. The aim of the review is to synthesise current knowledge on connectivity changes after stroke and offer possible avenues towards targeting both location and timing of brain circuit modulation and designing neurorehabilitation interventions that take into account the dynamics of the adaptations in the neural system.

2. Method

2.1.Database search

The PubMed database was searched in 2016 and 2017 (last search May 2017) for English language articles with the following keywords: (1) population: stroke (2) function: motor and recovery or plasticity or reorganization (3) method: connectivity or coherence or mapping (4) tools: EEG or MRI. The intervention of brain-robot interface and brain stimulation were

excluded at the initial search level as external factors producing additional influence on the network.

The search was conducted by keywords and MeSH terms where available. The search yielded 206 articles screened subsequently using the exclusion criteria listed in Figure 1. The selection process led to a list of 22 articles. The reference lists of the selected articles were inspected, which lead to including additional two papers.

[Insert Figure 1 here]

2.2.Inclusion criteria

Further analysis of the search results led to inclusion of the papers written in English, reporting the time-related changes in brain connectivity accompanying hand function recovery and exercise programmes including simple training of a motor skill – motor learning – in humans post-stroke. A particular focus of this review was on repetitive measures of connectivity and how the change in time was quantified.

2.3.Exclusion criteria

In the process of further search results analysis, review papers, case series and pilot studies were excluded, as well as studies reviewing non-traditional motor therapy programmes, because these programmes involve brain networks broader than the motor network. To focus on functional architecture dynamics of the network adaptation, structural connectivity studies were also excluded. The additional therapy factors excluded from the review were medicine use (4 papers), music therapy (3 papers), acupuncture (2 papers), mirror therapy (1 paper), brain-computer interface (1 paper in the search results).

2.4. Division of the studies

There was a clear division among the included papers into publications describing recovery versus training effects. The first group included reports of connectivity changes over

the period of recovery, alongside possible standard rehabilitation. The second included studies that introduced a training or therapy programme specifically designed for the purpose of the study and observed the changes in connectivity pattern as a result of this programme. Therefore, the results of this review were analysed separately for the two groups.

3. Results

3.1. Methodology used

The summary of methodology of the reviewed papers are collated in Table 1 for the recovery studies and Table 2 for the training studies.

3.1.1. Recovery studies

[Insert Table 1 here]

Among the studies observing recovery without additional training, the dominant technique of connectivity measurement was fMRI (Cheng et al., 2012; Cheng et al., 2015; Golestani et al., 2013; Lee et al., 2015; Liu et al., 2016; Ovadia-Caro et al., 2013; Park et al., 2011; Rehme et al., 2011; Rosso et al., 2013; Wang et al., 2010; Xu et al., 2014; Yourganov et al., 2010). One study used MEG (Westlake et al., 2012) and one used EEG (Nicolo et al., 2015).

3.1.1.1.Reported measures

Five studies assessed connectivity during hand movement (Cheng et al., 2012; Cheng et al., 2015; Rehme et al., 2011; Rosso et al., 2013; Yourganov et al., 2010) and the remainder utilised the resting state paradigm (Golestani et al., 2013; Lee et al., 2015; Liu et al., 2016; Nicolo et al., 2015; Ovadia-Caro et al., 2013; Park et al., 2011; Wang et al., 2010; Westlake et al., 2012; Xu et al., 2014). The fMRI studies analysed FC based on the time series correlation matrix and reported specific regions, change, lateralization and FC density of regions connected with the region of interest (ROI) except Yourganov and colleagues

(2010), who assessed the complexity measures of a covariance matrix basing on principal component analysis (PCA). Five studies utilized graph theory to analyse the motor network characteristics in EEG (Nicolo et al., 2015) and fMRI (Cheng et al., 2012; Cheng et al., 2015; Lee et al., 2015; Wang et al., 2010). One of the studies described effective connectivity utilising the DCM approach (Rehme et al., 2011).

3.1.1.2.Regions of interest

All studies included M1 in their ROIs (Cheng et al., 2012; Cheng et al., 2015; Golestani et al., 2013; Lee et al., 2015; Liu et al., 2016; Nicolo et al., 2015; Ovadia-Caro et al., 2013; Park et al., 2011; Rehme et al., 2011; Rosso et al., 2013; Wang et al., 2010; Westlake et al., 2012; Xu et al., 2014), except for one study analysing only the perilesional activity (Westlake et al., 2012). The ROIs were defined a priori, except of studies which were based on measures derived from whole-brain analysis: 264 functional areas (Cheng et al., 2012); regions based on whole-brain automated segmentation (Lee et al., 2015); whole-brain FC density followed by FC strength analysis in selected ROIs (Liu et al., 2016); regions generated from activation maps of action versus rest data in half of the healthy voluneers group (Rosso et al., 2013) and whole-brain analysis (Yourganov et al., 2010). In one study (Ovadia-Caro et al., 2013), longitudinal changes of FC in resting state networks were derived from independent component analysis (ICA) and analysed based on an eight network template (Beckmann et al., 2005). A special focus of one study was FC of the contralesional sensorimotor area only (Xu et al., 2014).

3.1.2. Training studies

[Insert Table 2 here]

Of the training-related change studies, only one utilized EEG (Wu et al., 2015), whereas the remainder used the fMRI technique (Bajaj et al., 2015a, b; Fan et al., 2015;

Laney et al., 2015; Lazaridou et al., 2013; Varkuti et al., 2013; Wadden et al., 2015; Zhang et al., 2016; Zheng et al., 2016).

3.1.2.1.Intervention

All the training studies measured connectivity at two time points pre- and post-intervention (Bajaj et al., 2015a, b; Fan et al., 2015; Laney et al., 2015; Lazaridou et al., 2013; Varkuti et al., 2013; Wadden et al., 2015; Zhang et al., 2016; Zheng et al., 2016), except for one that monitored FC throughout the training period, obtaining four measurements per participant (Wu et al., 2015). The rehabilitation period ranged from 4 (Wu et al., 2015) to 8 weeks (Lazaridou et al., 2013). One study focused on training of a simple task for 5 days instead of a full rehabilitation programme (Wadden et al., 2015). Four studies compared two rehabilitation methods for stroke participants: robot-assisted versus robot-assisted paired with motor imagery brain-computer interface (BCI) (Varkuti et al., 2013); and motor imagery versus conventional physical therapy (Bajaj et al., 2015a, b; Zheng et al., 2016). Intensity of therapy varied from 3 hours a week (Laney et al., 2015; Varkuti et al., 2013) to 2 hours a day (Wu et al., 2015). Two of the studies assessed robot-assisted therapy (Fan et al., 2015; Varkuti et al., 2013), and one study used a robotic device for the evaluation task, although the training per se was performed at home without the use of a robot (Lazaridou et al., 2013).

3.1.2.2.Reported measures

The reported connectivity measures varied from a description of the areas involved in the motor network to regression model estimates. Alongside a classical time course correlation approach, FC was reported based on constrained principal component analysis (PCA) (Wadden et al., 2015), ICA (Varkuti et al., 2013), ICA-based independent vector analysis and graph theoretical measures (Laney et al., 2015). The causality was assessed using DCM (Bajaj et al., 2015a; Lazaridou et al., 2013) and a spectral version of Granger

causality (Bajaj et al., 2015b). Four studies focused on measuring connectivity during performance of a motor task (Bajaj et al., 2015a; Laney et al., 2015; Lazaridou et al., 2013; Wadden et al., 2015), whereas the main outcome measure in the remainder of the studies was resting state connectivity change induced by the training activity (Bajaj et al., 2015b; Fan et al., 2015; Varkuti et al., 2013; Wu et al., 2015; Zhang et al., 2016; Zheng et al., 2016).

3.1.2.3. Regions of interest

All of the studies included M1 in their ROIs (Bajaj et al., 2015a, b; Fan et al., 2015; Laney et al., 2015; Lazaridou et al., 2013; Varkuti et al., 2013; Wadden et al., 2015; Wu et al., 2015; Zhang et al., 2016; Zheng et al., 2016) and four of them only predefined M1 ROIs as seed regions (Fan et al., 2015; Wu et al., 2015; Zhang et al., 2016; Zheng et al., 2016). Four studies generated ROIs using data-based approaches: ICA-based independent vector analysis leading to obtaining components of interest encompassing meaningful networks (cerebellar, sensorimotor, frontal, frontoparietal, default mode network) (Laney et al., 2015); areas activated in all participants during a motor task (M1, supplementary motor area (SMA), cerebellum) (Lazaridou et al., 2013); ICA components reflecting the motor network system (M1, SMA, parietal) (Varkuti et al., 2013) and lastly, the motor network explaining the most variance in the whole-brain analysis (Wadden et al., 2015).

3.2 Critical appraisal

Critical appraisal has been conducted for methodology of the studies using self-developed criteria (Table 3 and Table 4). On a 3 point scale, a score of 3 for each appraisal criterion meant the reviewed study addressed the issue well, whereas a score of 1 suggested the issue was poorly addressed. The appraisal criteria included sample size, homogeneity of the group of patients, presence of a control group, description of ROI extraction for replicability purposes and description of connectivity measure used. For the training studies an additional criterion was added – description of the intervention used. Thus a total appraisal

score had a maximum value of 15 points for recovery studies and 18 points for training studies and reflected how well the study controlled for the known methodological issues and how well the intervention, ROI selection and connectivity measures were described for replicability purposes. Most of the studies addressed most of the issues well, with a median total score of 13 for recovery studies and a median total score of 14 for the training studies. The criteria that proved the most problematic were the homogeneity and size of the tested group – which is a known issue in testing clinical populations.

[Insert Table 3 and 4 here]

3.3 Reported Data

The results are collated in Table 5 for studies analysing recovery without training and Table 6 for studies analysing changes in connectivity accompanying training. Although all papers discuss connectivity after stroke, the diversity of techniques and methods used does not allow for a detailed meta-analysis. This is caused by use of different techniques, different measures and different approaches to ROI definition. Therefore, after critical appraisal of methods, the reported results allow only for a qualitative approach to the synthesis of findings. The results will be summarised separately for task-related and resting state connectivity.

3.3.1. Recovery studies

[Insert Table 5 here]

3.3.1.1.Resting-state connectivity

All recovery studies measuring resting state FC that compared the stroke participants' data to a control group reported decreases in FC or network efficiency measures at least in some nodes or networks analysed (Liu et al., 2016; Nicolo et al., 2015; Xu et al., 2014; Golestani et al., 2013; Westlake et al., 2012; Park et al., 2011; Wang et al., 2010).

The lowest level of FC was identified in the acute phase (Liu et al., 2016; Wang et al., 2010), as early as within a few hours post stroke (Golestani et al., 2013). The nadir for FC at 1 month post stroke was accompanied by the highest FC asymmetry (Park et al., 2011). The lowest level of FC for the contralesional sensorimotor cortex was found at two weeks post-stroke (Xu et al., 2014).

The sensorimotor resting state network characteristic for the healthy brain was disrupted after stroke, showing more asymmetry and employing additional nodes not present in healthy participants (Park et al., 2011). A decrease in FC was observed in the perilesional area, relative to the homotopic region (Westlake et al., 2012), although there was an increase of FC in a small number of voxels of the perilesional area as well. However, the reduction of the increased FC with time was not associated with hand function recovery, whereas it was associated with the reduction of the decreased FC (Westlake et al., 2012). When compared to healthy individuals, stroke patients presented with a general reduction of both short-range and long-range FC density in the bilateral sensorimotor areas (Liu et al., 2016). Specifically, decreased FC was demonstrated in stroke patients between the ipsilesional M1 and the sensorimotor cortex, occipital cortex, middle frontal gyrus, posterior parietal cortex (Park et al., 2011). A decrease in contralesional M1 FC was noted in one report (Xu et al., 2014). Reduced interhemispheric connectivity and absent SM1 connectivity to the bilateral subcortical regions was reported in non-recovered stroke patients as compared with both healthy controls and the patients that presented with non-motor deficits (Golestani et al., 2013).

Increases in FC were observed between ipsilesional M1 connectivity and cerebellum, thalamus, middle frontal gyrus and posterior parietal cortex (Park et al., 2011). Finally, although the FC of motor areas decreased after stroke, the opposite occurred in cognitive networks, defined as the dorsolateral prefrontal cortex bilaterally (associated with higher-

order cognitive processes) and the contralesional temporal cortex (assumed to be part of the default-mode network) (Liu et al., 2016). The cognitive network FC increased initially after the insult and then gradually decreased and reached normal levels later in recovery.

Network topology measures also revealed reductions in FC. Reductions in the contralesional M1 Weighted Node Degree (WND) – a measure of number of connections – has been found in a 'bad recovery group' at 2-3 weeks post stroke (Nicolo et al., 2015). In other studies, however, no differences between the stroke patients and healthy controls were found in topological measures at the first time point post-stroke (Wang et al., 2010).

The general dynamics of changes in FC with time was the reduction of both decreased and increased FC towards the levels observed in healthy population (Golestani et al., 2013; Liu et al., 2016; Park et al., 2011; Xu et al., 2014). An index of FC concordance - a measure of stability of the network in time - decreased over time in the functional networks affected by the lesion as compared with the intact networks (Ovadia-Caro et al., 2013). Importantly, the results suggest that the affected networks became less similar to the initial state even in locations distant, but functionally connected to the lesioned structures.

In the first study that systematically focused on network topology changes after stroke, the average of the clustering coefficient of all nodes in the network decreased over time, whereas no differences were observed in the shortest path length (Wang et al., 2010). The authors interpreted these findings as a sign of motor execution network randomization during recovery from stroke, especially since no differences in both measures were visible between healthy controls and stroke patients at the first session after stroke. Similar changes were not observed in other systems, such as the motor-imagery network. When specific nodes were taken into account, ipsilesional M1 and contralesional cerebellum showed an increase in the

centrality over the period of the recovery, whereas ipsilesional cerebellum and thalamus showed a decrease.

The network topology dynamics pattern varied in other studies, although the results were still interpreted in line with the concept of network randomization: the characteristic path length decreased over time whereas clustering coefficient and small-worldness index remained stable over time (Lee et al., 2015).

All recovery studies reported an association between different measures of connectivity and hand function measures. Positive correlations with hand function measures were observed for FC between the following structures: ipsilesional M1-thalamus (Park et al., 2011), M1-contralesional cerebellum (Wang et al., 2010; Westlake et al., 2012), M1-SMA (Park et al., 2011; Westlake et al., 2012), M1-premotor cortex (PM) (Park et al., 2011), M1-ipsilesional somatosensory cortex, M1-inferior frontal gyrus (Westlake et al., 2012) and finally interhemispheric, but not intrahemispheric contralesional SM1 (Xu et al., 2014). Functional connectivity density (FCD) and strength (FCS) of motor hub regions (Liu et al., 2016) and reduction of decreased FC in the perilesional area (Westlake et al., 2012) were also related to hand function recovery. Restoration of decreased FC was noted in patients with recovered motor deficit, as opposed to non-recovered patients, whose interhemispheric FC remained lower even at 90 days post-stroke (Golestani et al., 2013).

In terms of network topology, there were positive correlations with hand function for the clustering coefficient of the motor execution network, and centrality of M1, SMA, thalamus and cerebellum (Wang et al., 2010), weighted node degree (WND) in the ipsilesional ROIs in beta band and in theta band in the contralesional areas at the first time point post stroke (Nicolo et al., 2015). Although high WND at the first time point was related

to better recovery, high WND later on was related to worse recovery. This process thus seems only adaptive at the acute stages of stroke recovery (Nicolo et al., 2015).

Negative correlations with hand function measures were observed for the FC between the following structures: M1-ipsilesional thalamus, M1-ipsilesional cerebellum (Wang et al., 2010), PM-cerebellum, M1-contralesional sensorimotor cortex and posterior parietal cortex (Westlake et al., 2012). Characteristic path length (Lee et al., 2015), high WND in beta band in the ipsilesional and theta in contralesional nodes at the second time point (Nicolo et al., 2015) were also negatively correlated with hand function measures.

3.3.1.2.Task-related connectivity

Similarly to the resting state analysis, a decrease in task-related connectivity was reported as a dominant trend in stroke patients compared with healthy controls (Rosso et al., 2014; Rehme et al., 2012), however one of the task-related studies reported the increase in FC in 10 out of 11 functional connections (Cheng et al., 2015). The increases included 6 cortico-subcortical connections, one intra – cerebellar and 3 cortico-cortical connections (between contralateral PM and: M1, postcentral gyrus and ipsilateral PM) (Cheng et al., 2015). One study did not report direction of changes in FC, focusing on classification potential of the chosen network parameters instead (Yourganov et al., 2010).

Decreased FC was demonstrated in stroke patients between the ipsilesional M1 and the middle frontal gyrus, SMA, cerebellum, as well as interhemispheric M1 connectivity (Rosso et al., 2013). Increases in FC were reported only in the contralesional hemisphere, between PM and SMA in all stroke patients and additionally - in the severely motor impaired group - increases in FC between the contralesional M1 and the ipsilesional cerebellum (Rosso et al., 2013). Causality flow was reduced between SMA-M1, PM-M1 and a weaker inhibitory

coupling between the ipsilesional motor areas and contralesional M1 was observed at the first time point (Rehme et al., 2011).

Importantly, an appearance of transient positive effective connectivity coupling from contralateral M1 to ipsilateral M1 was reported in the second time point at 2 weeks (Rehme et al., 2011). The connection was additional to the pattern of decreased connectivity observed in the first time point in stroke participants and was not present in healthy controls. In another study, transient cortico-cortical network abnormalities – increased interaction between bilateral PFC – was reported only in severely impaired patients at 3 months post stroke and interpreted as a result of increased cognitive effort to meet the demands of the task (Rosso et al., 2013).

With time, the decreased and increased connectivity normalized to the levels seen in the healthy population (Cheng et al., 2015; Rehme et al., 2011; Rosso et al., 2013; Westlake et al., 2012), except of the severely impaired group that showed persistently reduced FC between ipsilesional hemisphere with cerebellum and ipsilesional M1 with SMA (Rosso et al., 2013).

Network topology dynamics varied: in one study the clustering coefficient remained stable over time, but the characteristic path length increased (Cheng et al., 2012), whereas in another the characteristic path length decreased over time, with the clustering coefficient and small-worldness index stable over time (Cheng et al., 2015).

Positive correlations with hand function measures were observed for connectivity between the following structures: M1-contralesional cerebellum, M1-PM (Cheng et al., 2015), M1-SMA, PM-thalamus (Rehme et al., 2011). Also the clustering coefficient of the motor execution network, small-worldness at T1 (Cheng et al., 2015) and sphericity and

dimensionality of the network (Yourganov et al., 2010) were all positively associated with hand function measures.

Negative correlations with hand function measures were observed for the connectivity between the following structures: PM-thalamus, characteristic path length and clustering coefficient in the affected hand network (Cheng et al., 2015); and for the inhibitory coupling from contralesional M1 to ipsilesional M1 and additional transient positive coupling from contralesional M1 to ipsilesional M1 (Rehme et al., 2011).

The ipsilesional FC of M1 was associated with hand motor strength, but after removing the impact of corticospinal tract injury, the significance remained only for ipsi- to contralesional M1 and cortico-cerebellar connectivity (Rosso et al., 2013).

3.3.2. Training studies

[Insert Table 6 here]

3.3.2.1.Resting-state connectivity

The training studies comparing resting state connectivity in stroke patients with control participants reported significant decreases in connectivity measures before the training (Zhang et al., 2016, Zheng et al., 2016, Bajaj et al., 2015b), however one of them reported increases as a dominant trend (Zhang et al., 2016). One study reported a disconnection of the healthy connectivity pattern into three independent components; however no healthy controls were tested (Varkuti et al., 2013).

Decreased FC was demonstrated in stroke patients between the ipsilesional M1 and the SMA, middle occipital gyrus, bilateral inferior parietal lobule, cerebellum, posterior cingulate gyrus (Zheng et al., 2016) and sensorimotor cortex (Zheng et al., 2016, Zhang et al., 2016). Increases in FC were observed between ipsilesional M1 connectivity and thalamus, middle frontal gyrus, middle temporal gyrus, and basal ganglia (Zheng et al., 2016), ipsilesional

prefrontal cortex, inferior parietal cortex, SMA and contralesional angular gyrus (Zhang et al., 2016). Causality flow at the first time point post-stroke was reduced from SMA-M1, PM-M1, SMA-PM (Bajaj et al., 2015b).

A pattern of FC normalization has been observed for both decreased and increased FC as a result of training (Zhang et al., 2016; Zheng et al., 2016). Increments in the decreased FC reaching levels even higher than in control participants have also been noted, for example in M1 connectivity with the ipsilesional superior and inferior frontal gyrus, middle temporal gyrus, basal ganglia and thalamus (Zheng et al., 2016). Increments in M1 FC were also seen as a result of robot-assisted therapy with numerous cortical and subcortical regions in both hemispheres (including bilateral: medial prefrontal cortex, cerebellum and superior temporal gyrus, ipsilesional: middle temporal gyrus, inferior parietal lobule, SMA, posterior cingulate cortex, SI/SII, caudate nucleus and contralesional: M1, ACC, insula, middle occipital gyrus) (Fan et al., 2015). The lateralization index (Zheng et al., 2016, Fan et al., 2015) and the causality measures (Bajaj et al., 2015b) also followed the trend of normalization as a result of training.

All the studies without a control group reported changes in FC as a result of training, however it is not possible to interpret these results as showing a tendency to resemble the connectivity pattern of a healthy population with time (Fan et al., 2015; Varkuti et al., 2013; Wu et al., 2015).

A positive relationship between FC and hand function was reported (Wu et al., 2015; Fan et al., 2015; Varkuti et al., 2013; Zhang et al., 2016; Zheng et al., 2016). Motor gains during therapy were positively correlated to the connectivity between ipsilesional M1 and contralesional medial superior frontal gyrus at baseline (Zheng et al., 2016).

The FC M1 in EEG beta band at baseline was found to be a robust biomarker of hand function status of the participants (Wu et al., 2015). Specifically, higher FC of ipsilesional M1 with the ipsilesional PM predicted better hand function. Addition of structural variables to the regression model increased the explained variance of the hand function score, with two crucial although uncorrelated predictors – ipsilesional M1-PM FC and the extent of the cortricospinal tract damage (Wu et al., 2015).

3.3.2.2.Task-related connectivity

Only one training study testing task-related FC compared the stroke data with healthy controls and reported that the motor task related network was randomized, illustrated by greater variance in the motor network (Wadden et al., 2015).

Causality flow at the first time point post-stroke was reduced between SMA-cerebellum and SMA-M1 (Lazaridou et al., 2013). Increases in connectivity were observed between ipsilesional M1 connectivity and cerebellum (Lazaridou et al., 2013).

A pattern of connectivity normalization after training was observed for both decreased and increased connections (Lazaridou et al., 2013). Interestingly, different types of tasks influenced the direction of changes: after motor imagery training, the SMA exerted a negative influence over the M1, which was in turn positive after motor execution training. Motor imagery tasks showed strongest connectivity between PM and M1 bidirectionally, whereas motor execution task revealed strongest connections from PM to M1 and SMA to M1 (Bajaj et al., 2015a). As a result of training, small-worldness and centrality of the motor related ROIs increased (Laney et al., 2015).

All the training studies without a control group reported changes in connectivity as a result of training, however it is not possible to interpret these results as showing a tendency to

resemble the connectivity pattern of a healthy population with time (Bajaj et al., 2015a; Laney et al., 2015).

A positive relationship between connectivity and hand function in training studies was reported (Bajaj et al., 2015a; Wadden et al., 2015), specifically for sensorimotor and cerebellar networks and the association was greater for responders than non-responders to the intervention (Laney et al., 2015).

4. Discussion

The main findings of the systematic review suggest firstly that stroke initially leads to reductions in connectivity in the motor network system. Secondly, connectivity increases with time, both during spontaneous recovery or supported by therapy or training. Thirdly, this increase in connectivity is positively correlated with motor gains. However, a new pattern of connectivity may emerge, as the motor network becomes more randomized. In summary, training, even in the chronic phase, can improve connectivity between specific nodes.

4.1. Decrease of connectivity as a dominant trend

At the first time point of measurement (days to weeks after a stroke), the dominant trend was a decrease in connectivity after stroke in both spontaneous recovery and training studies, in resting state and task-related connectivity, in EEG and fMRI measures, expressed by simple FC, causality and network topology measures. All recovery studies with a control group reported decreases in connectivity or network efficiency measures at least in some nodes or networks analysed (for references of predominant findings see tables). There were only two studies reporting increases in FC as a dominant trend (Cheng et al., 2015; Zhang et al., 2016). All the training studies that used healthy controls reported significant decreases in connectivity measures before training.

4.2. The role of increased connectivity

Higher FC in some structures after stroke has been observed, but when analysed further, it was accompanied by a decrease in clustering coefficient of the network, a result that leads to a conclusion that the motor network becomes 'more scattered' with recovery (Wang et al., 2010). This observation is in line with the concept of randomization of the network, which was also reported in other studies (Cheng et al., 2012; Cheng et al., 2015; Ovadia-Caro et al., 2013; Park et al., 2011; Wadden et al., 2015).

A transient additional connectivity path between ipsilesional and contralesional M1 in stroke patients has been observed at two weeks post stroke and it resolved in later recovery (Rehme et al., 2011). An additional inhibitory pathway leading from the contralesional to the ipsilesional M1 has also been found in another study in stroke patients, and correlated with worse motor function (Grefkes et al., 2008). Connectivity increases between the ipsilesional M1 and contralesional M1 have been noted in many studies (De Vico Fallani et al., 2016; Li et al., 2014; Liu et al., 2016; Zhang et al., 2016) and were interpreted as a proof for the contralateral disinhibition theory (Volz et al., 2015; von Carlowitz-Ghori et al., 2014). Analysing the connectivity in different time points may suggest that the imbalance of inhibition is a dynamic restorative mechanism that may play an adaptive role at a specific moment during recovery. However, the results of this review suggest it may be related to worse recovery if it leads to establishing an inhibitory overactivity of contralesional M1 on the lesioned hemisphere (Rehme et al., 2011).

The common finding of the reviewed papers is that connectivity is more asymmetrical across hemispheres after a stroke compared to healthy controls. Cross-sectional studies also showed a shift of connectivity towards the contralesional hemisphere (Gerloff et al., 2006) and found it to be a correlate of poor recovery (Strens et al., 2004) differentiating well recovered from not well recovered patients even when they performed a movement of the

unaffected hand (Serrien et al., 2004). The asymmetry, however, can be reduced as a result of therapy (Zheng et al., 2016). The connectivity asymmetry could therefore be another expression of compensatory activity after stroke.

The increase in FC at the first time point post stroke noted in some studies seems to be restricted to connections between specific structures (Park et al., 2011; Wang et al., 2010; Zheng et al., 2016). Of the subcortical structures, the most consistent increases in connectivity after stroke has been noted among the connections to the cerebellum (Lazaridou et al., 2013; Park et al., 2011; Wang et al., 2010) (however the opposite – decreases in FC – has also been found by Zheng et al. (2016)). Cerebellar FC has been found crucial for the recovery process (Cheng et al., 2015). The cerebellum is also a crucial structure for motor adaptation (Debas et al., 2010; Hikosaka et al., 2002; Krebs et al., 1998; Lohse et al., 2014). The enhancement of cerebellar FC as a result of training was seen also in the healthy control group by Wadden et al. (2015), which is in line with the fact that the process of recovery and rehabilitation of motor function can been modelled on motor adaptation and motor learning (Dipietro et al., 2012).

Another region found crucial for motor learning is the PM (Lefebvre et al., 2015; Meehan et al., 2011; Wadden et al., 2015). The activation in dorsal PM in the affected hemisphere has been found to correlate with motor learning in stroke patients (Lefebvre et al., 2015) and in healthy participants (Meehan et al., 2011; Shadmehr and Holcomb, 1997). Premotor cortex has been also previously found to play a role in motor recovery from brain insult (Carey et al., 2002). An increase of connectivity has been noted in one cross-sectional study on subacute stroke patients (James et al., 2009) between the ipsilesional PM and contralesional PM and interpreted as a proof of functional reorganization of the motor network following stroke. This increase in connectivity has not been observed in any studies covered by this review, however the reduction in connectivity between ipsilesional M1 and

ipsilesional PM has been noted in stroke patients and was associated with worse motor function (Rehme et al., 2011; Wu et al., 2015).

4.3. Limitations

Connectivity is an emerging neuroscientific measure and a wide range of methodologies have been developed, including functional and effective connectivity, measured at rest and during task, in neuroimaging and neurophysiological studies. Different approaches have been adopted to quantify change in time in connectivity, from simple notes on appearance of different connections to developing concordance measures. This is reflected in the studies incorporated into this review and thus our interpretations are a generalised viewpoint and the nature of the data did not allow for a specific meta-analysis at this stage. Connectivity is however a very promising measure in the field of neurorehabilitation, since it allows observation of subtle functional changes after an insult often not reflected in anatomical alterations in the brain. Therefore the authors believe that this review can be useful for a better understanding of recovery processes and further the design of more efficacious interventions.

4.4. Conclusions

Widespread changes in connectivity have been observed both in spontaneous recovery and as a result of training both at rest and during a motor task. In some cases, the changes could not have been observed using the activation-based type of analysis. Generally, stroke patients have an early decrease in connectivity, as compared with healthy controls, that is ameliorates with recovery time. The changes in connectivity correlate with changes in motor status in stroke patients.

The rare incidence of increased connectivity developing after stroke can be grouped and interpreted as transient increases in connectivity that appear up to a month post stroke

between *specific* structures. The M1 seems to be supported more by subcortical structures during this period. The enhanced cortico-cortical connectivity between the bilateral M1 also appears to be a transient compensatory mechanism, playing a role in re-establishing the M1-M1 inhibition, although not always successfully. In the later stages of recovery, the motor network stabilizes and the reduced connectivity patterns improve, whereas the increased connectivity patterns are diminished, with values resembling those of healthy controls. The network characteristics, however, suggest that the motor system remains more randomized.

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Table 1

Methodology of recovery studies

Authors	Stroke participants	Stroke participants characteristics	Healthy controls	Timing	Techni-que	ROI and how were they defined	Reported measures of connectivity
Liu et al., 2016	8	left internal capsule and neighbouring regions; right handed	10	5 time points: 1w, 2w, 1m, 3m, 1y	rs fMRI	whole-brain for FCD, then then selected ROIs based on FCD analysis to analyse FCS	FCD (functional connectivity density = number of connected voxels) for each grey matter voxel both short-range and long-range; FCS (functional connectivity strength = correlation between timecourse of two voxels)
Cheng et al., 2015	12	both left and right hemisphere, right handed, motor deficits	16	4 time points: less than 10d, ~2w, 1m, 3m	fMRI during finger tapping	task-state motor execution networks, 21 ROIs	FC (correlation matrix) and graph theory: characteristic path length, clustering coefficient, small-worldness, nodal betweenness
Lee et al., 2015	12	moderate to severe motor deficit	0	4 time points: 2w, 1m, 4m, 6m	rs fMRI	whole-brain automated segmentation	FC (correlations) and graph theory: characteristic path length, clustering coefficient
Nicolo et al., 2015	24 (of which 21 in motor analysis)	MCA stroke, both left and right hemisphere	18 stroke just motor assessment (EEG only at T0); 26 healthy	2 time points: 2-3 w, 3m	rs EEG (128/eyes closed)	motor areas, M1 defined a priori based on the human motor area template (Mayka et al., 2006)	FC graph theory; reported - weighted node degree (= index of region importance, calculated as a sum of imaginary coherence of motor voxels with all other brain voxels) at each frequency band

Rosso et al., 2013	22 (12 patients failed to complete all testing sessions)	both left and right hemisphere, 2 groups: severe and mild motor deficit	28	3 time points: 3w, 3m, 6m	fMRI during hand grip	cortical and cerebellar network M1 connectivity ROIs based action-rest activation in 14 healthy volunteers	FC Correlations between homologous regions, intrahemispheric connectivity between cortical regions and cerebellum connectivity
Xu et al., 2014	13	both left and right hemisphere, right handed, motor deficits	13	5 time points: 1w, 2w, 1m, 3m, 1y	rs fMRI	contralesional SM1 based on previous work with hand-grasping task (peak coordinate +9mm)	FC contralesional SM1 connectivity with whole brain voxelwise correlations, Morticity index interhemispheric connectivity calculated relative to the SM1 connectivity to itself (temporal correlation between all voxel pairs); also whole brain connectivity maps
Golestani et al., 2013	31	both left and right hemisphere	15, 20 non-motor deficits	3 time points: <24h, 7d, 90d	rs fMRI	ipsilesional SM1 - contralesional SM1 outlined on anatomical images	
Ovadia-Caro et al., 2013	12	ischemic stroke	0	3 time points: 1d, 7d, 90d	rs fMRI	8-network template	FC spatial concordance (similarity over time) of affected and unaffected networks
Cheng et al., 2012	12	both left and right hemisphere, right handed, motor deficits	0	4 time points: less than 10d, ~2w, 1m, 3m	fMRI during finger tapping	Whole-brain networks (264 functional areas)	FC graph theory: characteristic path length, clustering coefficient
Rehme et al., 2012	12 in first 2 time points, 10 in all 3 (data loss of 2 patients)	both left and right hemisphere, ischemic MCA, lesions affecting the CST, but not elements of the motor network outlined for the analysis, unilateral deficit at time point 1, right handed	12	3 time points: less than 72h, 2 w, 3-6 m	fMRI during hand movement	bilateral motor network (M1, PM, SMA)	EC DCM: coupling parameters for all 30 possible connections in affected hand movement condition; parameters which were significantly enhanced or reduced in patients compared to controls were then analysed between sessions with t tests

Westlake et al., 2012	14	first MCA stroke, lesions in the corticospinal pathway, both left and right hemisphere; different time since stroke (1-52wk) but taken into account in the analyses	20, tested 2-8 weeks	2 time points: 8-12 w between visits	rs MEG	perilesional (+ 2 cm around the margin of the lesion), compared with the homotopic region	FC alpha band coherence of each VOI=averaged strengths of imaginary coherence of the voxel with any other voxels in the brain; baselined to the homotopic region (t-test); % voxels showing difference; change in time index = (fc2-fc1)/fc1;
Park et al., 2011	12	within 2 weeks after stroke, both left and right hemisphere, motor deficits	11 age matched	4 time points: <2 w, 1,3,6 m	rs fMRI	ipsilesional M1 outlined on images	FC M1 correlation matrix with every voxel timecourse; lateralization index for each correlation map
Yourganov et al., 2010	9	acute stroke, motor deficit, ability to move the affected hand in 1m post stroke	0	4 time points: 1m, 2m, 3m, 6m	fMRI during finger tapping and wrist flexion	whole brain	FC Complexity measures of the covariance matrix based on PCA to classify MRI sessions to early vs late: sphericity index, dimensionality of PCs
Wang et al., 2010	10	left motor pathway subcortical stroke	9 at 2 wk; 36 cross-sectional; 12 longitudinal	5 time points: 1w, 2w, 1m, 3 m, 1y	rs fMRI	motor execution network (21 regions) based on previous work with a simple motor task (Jiang et al., 2004)	FC (correlation coefficient matrix of all pairs of the ROIs); turned into a graph (network sparsity threshold 0.5); small world measures: clustering coefficient, shortest path length, betweenness centrality= influence of a node on information flow between other nodes; reporting p values for linear mixed model estimation for each parameter change over time

rs = resting state; h= hour; d = day; w = week; m = month; y = year; FC = functional connectivity; EC = effective connectivity

Table 2

Methodology of training studies

Authors	Stroke participants	Stroke participants characteristics	Healthy controls	Intervention	Technique	ROI and how were they defined	Reported measures of connectivity
Zhang et al., 2016	17	left and right hemisphere, motor deficit, 40-77d post stroke	15	pre and post 30d therapy: conventional rehabilitation or motor imagery	rs fMRI	M1 whole brain connectivity	FC (correlation matrix) FC = correlation of time series of each ROI voxel with each voxel of the rest of the brain; t test comparisons between groups and time points: reporting locations of connected regions; laterality index (based on the number of connected voxels of M1 with ipsilateral/contralateral sensorimotor cortex)
Zheng et al., 2016	12	chronic; left motor pathway lesion resulting in hemiplegia; previously right handed	12	pre and post 4w intervention: 6 participants with a motor imagery training, 6 without	rs fMRI	ipsilesional M1, based on coordinates from previous studies (6 mm radius)	
Bajaj et al., 2015a	10	left and right hemisphere, hemiparesis, 1-54m post stroke	0	pre and post 60h therapy (14-51d): motor imagery or motor imagery+standard rehabilitation	fMRI during pinching or motor imagery task	M1 PM SMA	EC DCM: optimal model parameters
Bajaj et al., 2015b	13	left and right hemisphere, hemiparesis, 1-54m post stroke	17	pre and post 60h therapy (14-51d): motor imagery or motor imagery+standard rehabilitation	rs fMRI	5 areas of motor execution network: lM1, rM1, lPM, rPM, SMA	EC Spectral version of Granger causality: total interdependence, one-way directional influence and instantaneous causal flow derived from spectral density matrix

Fan et al., 2015	10	left and right hemisphere, post acute (mean: 48 days post stroke), mild and moderate paresis	0	pre and post 4w bimanual robot assisted therapy	rs fMRI	Ipsi- to contralesional M1 ROI based analysis, M1 to whole brain voxel-by-voxel analysis	FC (correlation matrix)
Laney et al., 2015	10 (divided into responders and non-responders)	chronic, moderate to severe impairment	0	Pre and post 6w of 3h/w therapy	fMRI during finger flexion	Components of interest encompassing meaningful networks (cerebellar, sensorimotor, frontal, frontoparietal, default mode) obtained by independent vector analysis	FC graph theory: small-worldness, centrality
Wu et al., 2015	12	left or right hemisphere affected; chronic motor deficit	0	4 time points during 28 d therapy	rs EEG (128 ch)	M1 defined at sensor level (electrodes overlying the ROI: C3 or C4+ 6 surrounding electrodes in 256 system)	FC mean coherence of high beta reported regression coefficients of the Partial Least Square model of M1 EEG coherence
Wadden et al., 2015	9	chronic; right hemisphere subcortical lesions; right handed	9	2 time points: visuomotor tracking task trained for 5 d	fMRI	motor network was the target: 1. whole-brain analysis, 2. motor network (obtained in 1st step as the one explaining the most variance) analysis only in stroke participants to reveal compensatory network	FC ANOVA on fMRI constrained principal component analyses (CPCA) predictor weights; reporting a) coordinates of clusters involved in the network b) subject and condition specific predictor weights for each component -> component/network chosen for explaining the most variance
Lazaridou et al., 2013	5	chronic	12	2 time points: 8 w simple motor task training	fMRI	areas activated in all participants during a motor task (M1, SMA, Ce)	EC % change in connectivity between selected regions

Varkuti et al., 2013	9	more than 1 month after stroke, motor deficit, both left and right hemisphere, mainly subcortical location around basal ganglia	0	2 time points: 12 rehabilitation sessions in approx. 1 m; 2 types of interventions compared	rs fMRI	4 ICA components reflecting motor network system (centres in ipsilesional M1, contralesional M1, SMA, visuospatial system - bilateral parietal)	FC change based on ICA (subtracting IC image timepoint1 from timepoint2 for each participant and each component)

rs = resting state; h= hour; d = day; w = week; m = month; y = year; FC = functional connectivity; EC = effective connectivity

Table 3

Critical appraisal of recovery studies

Authors	Sample size	Homogeneity	Controls	ROI definition	Connectivity definition	Appraisal total
Liu et al., 2016	1	3	3	3	3	13
Cheng et al., 2015	2	2	3	3	3	13
Lee et al., 2015	2	2	1	3	3	11
Nicolo et al., 2015	3	2	3	3	3	14
Rosso et al., 2014	3	2	3	3	3	14
Xu et al., 2014	2	2	3	3	3	13
Golestani et al., 2013	3	2	3	3	3	14
Ovadia-Caro et al., 2013	2	1	1	3	3	10
Cheng et al., 2012	2	1	1	3	3	10
Rehme et al., 2012	2	2	3	3	3	13
Westlake et al., 2012	2	2	1	3	3	11
Park et al., 2011	2	2	3	3	3	13
Yourganov et al., 2010	1	1	1	3	3	9
Wang et al., 2010	1	3	3	3	3	13
Criterion total	28	27	32	42	42	

Table 4

Critical appraisal of training studies

Authors	Sample size	Homogeneity	Controls	Intervention	ROI definition	Connectivity definition	Appraisal total
Zhang et al., 2016	2	2	3	3	3	3	16
Zheng et al., 2016	2	3	3	3	3	3	17
Bajaj et al., 2015a	2	1	1	3	3	3	13
Bajaj et al., 2015b	2	1	3	3	3	3	15
Fan et al., 2015	2	2	1	3	3	3	14
Laney et al., 2015	2	2	1	3	3	3	14
Wu et al., 2015	2	2	1	3	1	3	12
Wadden et al., 2015	1	1	3	3	3	3	14
Lazaridou et al., 2013	1	1	3	3	3	3	14
Varkuti et al., 2013	1	1	1	3	3	3	12
Criterion total	17	16	20	30	28	30	

Table 5

Results of recovery studies

Authors	Connectivity in stroke as compared to controls	Increase/decrease in time	Correlation of connectivity to function
Liu et al., 2016	reduced in sensorimotor, increased in cognitive areas	increase in sensorimotor, decrease in cognitive -> return to normal levels	both FCD and FCS in the hub regions correlated with clinical scores
Cheng et al., 2015	increased in 10/11 connections, reduced in 1/11; no change in the topological configuration	characteristic path length decrease over recovery time	positive and negative correlations of FC in different structures, increase in connectivity - positive correlation; clustering coefficient and shortest path length - negative correlation
Lee et al., 2015	no controls	characteristic path length decreased up till 3 m then stabilised; no change in clustering coefficient	CPL at T1 negatively correlated with recovery at T3
Nicolo et al., 2015	reduced beta WND in contralesional M1in 'bad recovery' group	higher WND at T0 in 'good' versus 'bad recovery' group non significant at T1	ipsilesional beta WND at T0 - positive, at T1- negative
Rosso et al., 2014	reduced mostly, increased in PM-SMA and additionally M1-Ce in severely impaired patients	correlation values returned to normal values, except for that of the IL M1-SMA correlation, which remained decreased	ipsilesional connectivity correlated with function but after accounting for CST injury only M1-M1 connectivity and M1-cerebellum connectivity correlations with function remained significant
Xu et al., 2014	reduced	Increase	positive with connectivity between bilateral SM1, no association with contralesional SM1 Connectivity
Golestani et al., 2013	reduced	Increase	positive
Ovadia-Caro et al., 2013	no controls	concordance decreased in networks affected by lesions	positive correlation between the clinical change and concordance

Cheng et al., 2012	no controls	global decrease as illustrated by longer characteristic path length of ipsilateral tapping network for right hemisphere lesions only and no change in clustering coefficient, but local clustering coefficients changed (decreases and increases for specific nodes) -> network randomization	no report
Rehme et al., 2012	reduced: positive SMA-M1, PM-M1; negative M1-M1	increase of SMA-M1; transient additional positive M1-M1 connectivity	positive SMA-M1, negative M1-M1
Westlake et al., 2012	decreased and increased FC as compared to the homotopic region in contralesional hemisphere	Increase	positive with S1 and IFG, negative with posterior parietal and contralesional SM1
Park et al., 2011	decreased to cortical areas, increased to subcortical and MFG and parietal	Increase	positive
Yourganov et al., 2010	no controls	sensitivity maps indicate that at least some of the brain regions are involved in changes in functional connectivity over time	sphericity correlated with functional improvement, dimensionality (both) with final functional measure but not improvement
Wang et al., 2010	no difference at T0 in the network graph theoretical parameters, FC increase (ipsilesional thalamus and cerebellum) and decrease (ipsilesional M1)	clustering coefficient decrease; connectivity increase (ipsilesional M1, contralesional cerebellum) and decrease (ipsilesional cerebellum and thalamus),	positive for clustering coefficient and centralities of several structures; positive and negative for FC in different structures

Table 6

Results of training studies

Authors	Connectivity in stroke as compared to controls	Increase/decrease in time	correlation of connectivity to function
Zhang et al., 2016	most connections increased, decreased between the ipsilesional M1 and bilateral M1.	decrease; M1-M1 increase	positive correlation between M1-M1 connectivity increase and function change
Zheng et al., 2016	decrease M1 to cortical structures and Ce, increase with subcortical and middle frontal and middle temporal gyrus; asymmetrical	Increase	positiveM1 - contra medial superior frontal gyrus at T0
Bajaj et al., 2015a	no controls	reorganization of connectivity pattern in motor execution network	positive for function change and connectivity
Bajaj et al., 2015b	causal flow in connections of the motor execution network was not present in stroke participants	three causal connections for the mental practice with physical therapy group	correlation between causality and hand function in the physical therapy group
Fan et al., 2015	no controls	decrease between ipsilesional M1 and contralateral regions.; increases in other regions	positive correlation for M1-M1 connectivity
Laney et al., 2015	no controls	smallwordness increase	Increased centrality of sensorimotor and cerebellar network correlated positively with hand function, greater in respondents as compared with non-responders
Wu et al., 2015	no controls	increase PM-M1 decrease M1-parietal as predictors of motor gain	positive with the increase of M1-PM connectivity and decrease of the M1-parietal
Wadden et al., 2015	randomized	no differences in network activity as a result of training contrasted with increased activity in healthy participants	positive

Lazaridou et al., 2013	decrease SMA-M1 SMA-Ce /increase M1-Ce	Increase	not reported
Varkuti et al., 2013	no controls but report disconnection	Increase	positive with increases

Figure 1

Paper selection process – flowchart

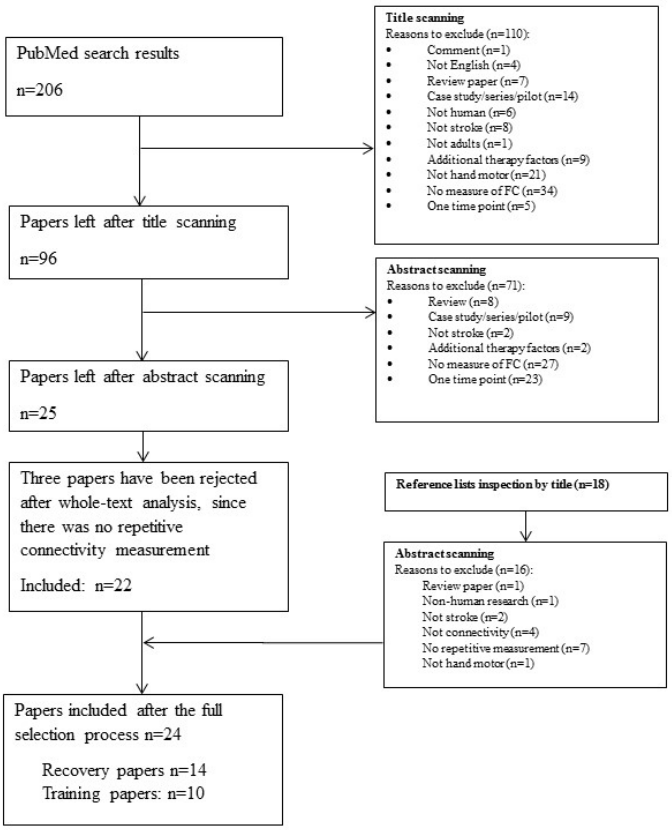

Figure 1
Paper selection process – flowchart

190x275mm (96 x 96 DPI)