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fMRI-based Static and Dynamic Functional Connectivity Analysis for Post-stroke Motor Dysfunction Patient: A Review

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ABSTRACT Functional magnetic resonance imaging (fMRI) has emerged as a prevalent tool for investigating motor deficits and rehabilitation in the context of stroke. Particularly, the exploration of functional connectivity (FC) through resting-state fMRI has the potential to unveil the neural connectivity mechanisms underlying post-stroke motor impairment and recovery. Despite the significance of this approach, there exists a gap in the literature where a comprehensive review dedicated to post-stroke functional connectivity analysis is lacking. In this paper, we undertake an extensive review of both static functional connectivity network analysis (SFC) and dynamic functional connectivity network analysis (DFC) in the context of post-stroke motor dysfunction. Our primary goal is to present comprehensive methodological insights and the latest research findings pertaining to motor function recovery after stroke. We commence by providing a succinct overview of SFC and DFC methods, elucidating the preprocessing and denoising techniques essential to these analyses. Subsequently, we summarize the application of two methods in stroke disease, mainly focusing on the extracted insight into post-stroke brain dysfunction and rehabilitation. Our review indicates a prevalence of SFC as the method of choice for post-stroke functional connectivity investigations. Specifically, SFC studies reveal a reduction in FC between motor areas due to stroke lesions, with increased FC correlating positively with functional recovery. Nevertheless, the DFC for post-stroke analysis has only begun to unveil its potential due to its ability in temporal dynamics. In summary, this review paper presents a thorough understanding of post-stroke functional connectivity analysis and its implications for the study of motor function recovery, offering valuable insights for future research and clinical applications.

INDEX TERMS Stroke, fMRI, Functional Connectivity, Static Functional Connectivity analysis, Dynamic Functional Connectivity analysis

I. INTRODUCTION

According to the report on Global Burden of Disease [1], stroke is the second leading cause of death and the second largest cause of disability. Across the globe, there were 101 million stroke cases and 13.7 million new stroke survivors in 2019 [2], which is nearly five times that of 2013. As more than 60% of the survivors are left with severe sequela, stroke has become the largest known cause of complex disability [3], and 77% of stroke survivors suffer from slow upper limb or hand movement disorder [4].

With the sharp growth of stroke survivors, various restorative therapies were proposed to assist stroke survivors in improving their motor function deficits [5], [6]. However, the effectiveness of the rehabilitation measures varies from individual to individual. Not every patient recovers their limbs to some extent after a stroke; even for individuals with identical levels of initial functional impairment, the rehabilitation effects vary greatly among people [7], [8]. Many unknown factors influence the outcome of recovery [9], [10]. Since the lesions that result in post-stroke disability are located in the brain, to gain insight into these factors, it is crucial to comprehend the processes in the brain when function recovery

occurs.

Emerging evidence has revealed that post-stroke recovery is a time-dependent process. The interrupted connectivity within the central nervous system reorganizes in structure and function over time to adapt to damage caused by a stroke. Hence, a number of cross-sectional [11]–[16] and longitudinal studies have been carried out recently to gain insight into this process [17]–[22]. By taking advantage of the dynamic alteration of the brain connectivity network, these studies can identify relevant behaviour of the brain system. For instance, how recovery adapts structurally and functionally over time and how this adaptation underpins functional recovery [23]. In addition, the structural or functional connectivity dynamics in brain network reorganization can help reveal what factors promote or impede the recovery process. Thus, informing more productive intervening therapies in accordance with this neural network modulation and ultimately facilitating greater rehabilitation programs.

Structurally, stroke lesions are considered one of the most important factors that cause network disconnection. Interestingly, after stroke, the lesion-surrounding regions can bypass the damage and rebuild connections to support the patient in relearning the lost function [10]. For example, one study [24] has demonstrated that a corticospinal tract (CST) connecting the cerebellum and the primary motor cortex will be generated after stroke, and these newly found physical connections are associated with skillful motor control. As a pathway connecting the motor cortex with motor neurons projecting from the spinal cord, CSTs play an essential role in the motor control system [25]. Once a CST is damaged due to lesions following stroke, alternative pathways will be recruited to compensate for the lost connections [24] and thus result in further change in structural connectivity [26].

Beyond impairing local physical connectivity, a stroke lesion can also alter the neural interaction between directly or indirectly connected brain areas [27]. This interaction (or communication) is shown with functional collaboration between brain regions, which is also referred to as functional connectivity (FC) [28]. Over the past few decades, the changes in functional network architecture during stroke recovery have been continually reported. A common finding in numerous studies looking at post-stroke FC is the decreased interhemispheric FC at the initial stage after stroke. Yet, this abnormal FC will develop normally two weeks after stroke onset and return to near ordinary levels with great possibility [29]–[31]. This gradually enhanced FC is demonstrated to favourably correlate with motor recovery in the subacute or chronic phase [18], [30], [32].

Since FC has become an essential metric in neuroscience related to stroke recovery, a variety of means of recording brain activity have been utilized to explore the brain FC patterns, including EEG (Electroencephalography), MEG (Magnetoencephalography), and fMRI (functional Magnetic Resonance Imaging). EEG and MEG measure the FC by recording the electromagnetic neural activity, whilst fMRI achieves this target by measuring the consistency of the blood oxygenation level-dependent (BOLD) signals across brain regions over time. Among these methods, fMRI is a well-liked non-invasive imaging method due to its high spatial-temporal resolution [10], [33]. However, whether the connection is evaluated at rest or when doing a task is a crucial factor that cannot be overlooked in post-stroke FC analysis with fMRI [34]. According to the observations across studies, these two approaches often produce variable results. Resting-state (rs)-fMRI has certain advantages compared with task-based fMRI. The primary advantage is that studies with rs-fMRI do not need to design the movement paradigm and quantify the motor executive performance, which is a difficulty with task-based fMRI studies and can be greatly diverse across studies. Measuring task performance in, for example, a hand grip task [35] and a hand movement task [36] are different. rs-fMRI, on the other hand, provides a unified manner for comparison between studies. Thus, rs-fMRI can facilitate further understanding of recovery mechanisms, while the recovery mechanisms discovered in a task-based fMRI study may only be effective for particular tasks. Therefore, this review concentrates on research employing resting-state fMRI to examine brain functional connectivity following stroke.

If we consider analyzing FC, from the perspective of the method of processing the rs-fMRI data, then there are also distinctions between the assumptions made regarding the time scales over which the brain functional connectivity evolves. Conventional methods assume that the FC measures are stationary over a full MRI scan, while it has been shown that the FC fluctuates even over a few seconds [37], [38] and the static FC network is too simplistic to capture the complete representation of FC evolution [39]–[41]. Recently, a growing number of methods have been introduced to explore dynamic functional connectivity following stroke and make an effort to bring an all-new perspective to investigate the recovery mechanism.

This review attempts to provide an overview of the latest progress in the changes to brain motor functional architecture following stroke from the perspective of static and dynamic functional connectivity (SFC and DFC) networks. While in 2011, the longitudinal changes of resting-state functional connectivity during motor recovery after stroke have been evaluated [28], and the dynamic development of brain connectivity after stroke has also been documented in 2018 [23], a review concentrating on post-stroke functional connectivity analysis from the standpoint of the techniques has not yet been provided. Hence, a summary of the most recent findings has been produced by synthesizing the present understanding of functional networks in the resting state from various viewpoints (see 1 for the overview). This review provides potential methodological guides and feasible references to map the post-stroke neuroplasticity of brain circuits. Additionally, the comprehension of resting-state functional networks under different analysis methods provides valuable guidance for designing dynamic neural rehabilitation interventions to benefit stroke patients.

TABLE 1. Notations used in this review.

Abbreviation	Definition	Abbreviation	Definition
AIS	Acute Ischemic Stroke	mRS	Modified Ranking Score
AN	Auditory Network	MTG	Middle Temporal Gyrus
ARAT	Action Research Arm Test	NIHSS	National Institutes of Health Stroke Scale
BOLD	Blood Oxygenation Level-Dependent	PCA	Principal Component Analysis
DFC	Dynamic Functional Connectivity	PCC	Posterior Cingulate Cortex
DLPFC	Dorsolateral Prefrontal Cortex	PMC	Premotor Cortex
DMN	Default Mode Network	PoCG	Postcentral Gyrus
FC	Functional Connectivity	PPC	Posterior Parietal Cortex
FCN	Functional Connectivity Network	PrG	Precentral Gyrus
FMA	Fugel-Mayer Assessment	ROI	Region of Interest
fMRI	Functional Magnetic Resonance Imaging	MPFC	Medial Prefrontal Cortex
FNC	Functional Network Connectivity	SFC	Static Functional Connectivity
HMM	Hidden Markov Model	SMA	Supplementary Motor Areas
ICA	Independent Component Analysis	SMN	Sensorimotor Network
M1	Primary Motor Cortex	TD	Tensor Decomposition
MFG	Middle Frontal Gyrus	WTC	Wavelet Transform Coherence

II. METHODOLOGY

A. LITERATURE SEARCH

The literature search was restricted to English-language articles published between January 2000 and May 2022 in the following electronic databases: PubMed, Web of Science, IEEE Xplore, ScienceDirect, MEDLINE (OvidSP), CDSR (Cochrane database of systematic reviews), Scopus, Compendex, Wiley Online Library, Academic Search Premier, and Springer Link. The electronic search terms were Stroke AND fMRI AND Functional Connectivity AND Motor deficit AND Rehabilitation. Studies that include task-related fMRI or involve effective connectivity or extend beyond motor function were excluded. This review included studies that explore the development of functional connectivity analysis methods, particularly, those studies that employ these approaches for post-stroke motor function impairment and rehabilitation.

B. TERMS AND DEFINITION

1) Notation

A list of notations is given in Table 1.

2) Post-stroke stage

Throughout this review, the terms: acute, subacute and chronic stages refer to the three phases of recovery after a stroke. The timeline of these phases, which spans from the time of the initial stroke to years afterwards, is summarized in Figure 2. Their definition is in accordance with the recommendation of [42] and previous studies in stroke rehabilitation programs [43], [44].

3) Functional connectivity, functional network connectivity and functional connectivity network

The terms Functional connectivity (FC), functional network connectivity (FNC), and functional connectivity network (FCN) are frequently used by authors in the studies reviewed in this paper. These nouns are so similar that the readers risk becoming confused if they are not attentive. Here, FC is defined as correlation (or other statistical dependencies) among spatially remote brain regions [45]. The process of inferring functional connectivity among multiple brain regions by calculating pairwise correlation is summarized in Figure 3(a). FNC can be seen as a higher level FC, which refers to a statistical dependency among large-scale functional networks (or functional domains) in the brain [46], for example, the default mode network (DMN) [47] and sensorimotor network (SMN) [48]. A representation of brain regions that are involved in the functional networks may be found in Figure 3(b). Unless otherwise stated, the FC and FNC refer to a pairwise Pearson's correlation in this review. By contrast, a Functional Connectivity Network (FCN) is a concept based on FC and FNC. It refers to a functional connectivity graph where the vertices represent the brain regions and the edges represent the strength of FC/FNC between these regions.

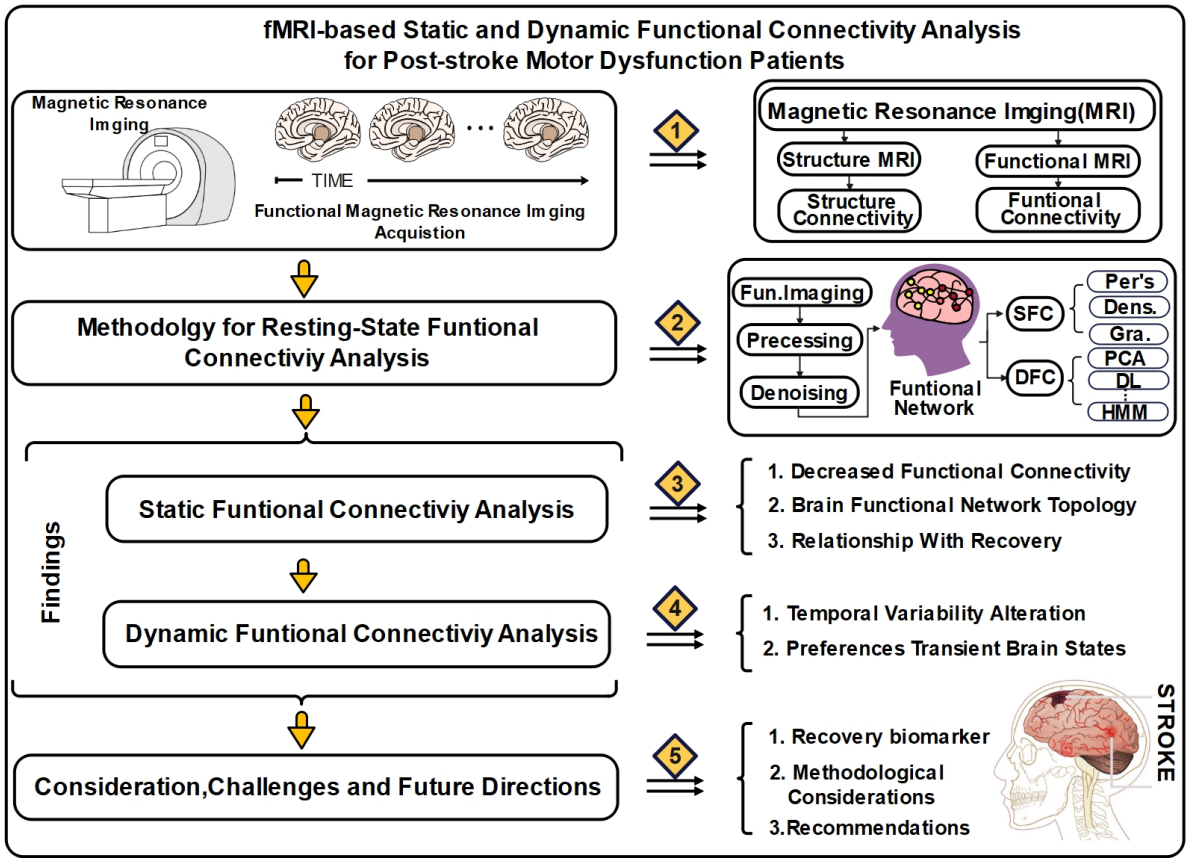

FIGURE 1. Overview of fMRI-based Static and Dynamic Functional Connectivity Analysis for Post-stroke Motor Dysfunction Patient.

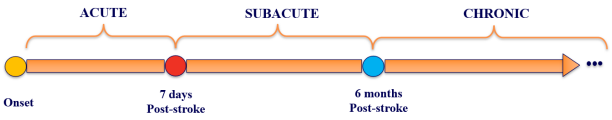

FIGURE 2. The phases of post-stroke recovery.

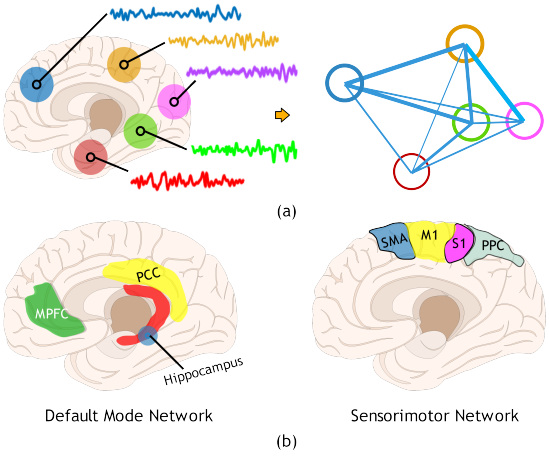

FIGURE 3. (a) Inferring functional connectivity among multiple brain regions by calculating pairwise correlation; FCN: a functional connectivity graph can be generated where the vertices represent the brain regions, and the edges represent the strength of FC/FNC between these regions. (b) The large-scale functional networks: the default mode network (DMN), which involves the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), bilateral hippocampus; and the sensorimotor network (SMN), which includes supplementary motor areas (SMA), primary motor cortex (M1), primary sensory area (S1), posterior parietal cortex (PPC).

4) Motor recovery measurement

Clinically, motor recovery after stroke is measured by the absolute difference between baseline and subsequent motor function scores [49]. This can be best achieved by comparing the motor function assessment at longitudinal time points. In the studies reviewed in this paper, there are several methods used by the authors to evaluate the post-stroke motor function, including the Fugl-Meyer assessment (FMA) scale [50], which evaluates patients' single-joint and multi-joint motor ability, loss of co-motor energy, finger individualization ability, movement speed, measurement impairment, ataxia, and motor reflex, and the paralysed hand function assessment scale [51] which measures the degree of paralysed hand for stroke patients. Other evaluation methods include the action research arm test (ARAT) [52], modified Rankin score (mRS) [53], etc.

Beyond motor function assessment, comparing the post-stroke recovery stage that the stroke patient is in at different time points can help demonstrate the motor recovery process. One of the most well-known methods of measuring the stroke

recovery stages is the Brunnstrom stages, also known as the Brunnstrom approach [54]. By classifying the assessment score into distinct zones, the National Institutes of Health stroke scale (NIHSS) or the evaluation scale indicated above are widely used to estimate the patient's stroke recovery stages. This partition can also be utilized to divide the patient sample into subgroups affected by stroke. Hence, in many cross-sectional studies, the relationship between the FC and motor recovery can be investigated by examining the FC alteration between different groups [55], [56].

III. FMRI PROCESSING FOR DFC AND SFC

A. PRE-PROCESSING AND DENOISING RS-FMRI

By sampling the brain's three-dimensional (3D) volume every 1-2 s (or faster), MRI scanning can obtain the brain landscape map at the millimetre spatial resolution. The BOLD signal contrast can be extracted within a full MRI scan, with the BOLD signal variance representing the resulting brain neural activity through multivariate time series. As the BOLD signal is weak and suffers from the noise of multiple sources, the raw fMRI data needs to undergo extensive pre-processing before further analysis. Pre-processing of rs-fMRI signals typically included the following steps:

1) removing a number of volumes from the beginning of the MRI scan in order to obtain a steady BOLD signal (typically, 3 [57] or 10 [13]);
2) slice timing correction;
3) realignment for head motion;
4) outlier detection for scrubbing;
5) registration to structural images, segmentation [58] and lesion-masked normalization [59];
6) spatial smoothing using a full-width at half-maximum (Gaussian kernel (4 or 8 mm recommendation).

Note that this is a general pre-processing pipeline. In the studies, the processing methods and their orders can vary according to specific applications and tasks.

Despite the capacity of the processes used in the pre-processing to remove the majority of brain activity disturbances, the BOLD signal often still contains considerable noise or non-neural variability. This can be the result of a combination of physiological, outlier, and residual subject-motion effects [60], [61]. These residual noise components in the BOLD signal will introduce strong and observable biases in all functional connectivity measures. Therefore, there are typically additional strategies to remove or at least minimize these underlying interferences in the context of functional connectivity. These strategies generally implement a denoising step, which can include linear regression of potential confounding effects in the BOLD signal (e.g. effects from the grey matter, white matter, and cerebrospinal fluid), linear detrending, and temporal band-pass filtering. As with the pre-processing, the denoising strategies have no gold standards, they are variable across the study methods and tasks.

Figure 4A and B illustrate various pre-processing steps and denoising strategies. One item to note is that while nearly all studies reviewed in this paper introduce the pre-processing step, the denoising step has not always been emphasised. The denoising step has been proven to benefit FC estimation by improving the signal quality and reducing the motion artefacts [60]. Hence, these additional denoising strategies should be encouraged to be gradually introduced into stroke studies. Doing this should enlarge the variability in FC alteration caused by stroke and then promote more reliable and accurate results.

Several existing open-source tools can perform the pre-processing and denoising steps to enable the fMRI data for analysis to be obtained reliably and rapidly, including the Statistical Parametric Mapping software package (SPM) [62], the FMRIB software library (FSL) [63], the Data Processing Assistant for Resting-State fMRI (DPARSF) [64], CONN toolbox [65], and the graph-theoretical network analysis toolbox (GRETNA) [66].

B. TIME SERIES EXTRACTION

After the raw rs-fMRI has been pre-processed and denoised, time series from the different brain areas during the fMRI scan have to be extracted for functional connectivity analysis. The methods for time series extraction are mainly divided into two categories: ROI-based and data-driven methods.

The ROI-based method relies on predefined regions of interest (ROI) to extract the time series for different brain areas. As the motor control region in the brain, nearly all investigations linked to post-stroke recovery of motor activity, include the primary motor cortex (M1) as one of their ROIs. Meanwhile, the supplementary motor area (SMA) is another region frequently investigated as an ROI. Decreased connectivity between M1 and SMA has been found across studies in stroke patients. Beyond M1 and SMA, other regions, including the premotor cortex, and inferior frontal gyrus, are also predefined as ROIs to investigate abnormal inter-regional connectivity following stroke. In addition, to manually set regions, the anatomical atlas is often used to identify ROIs. There are typically three anatomic atlases used to define brain regions: Destrieux [67], Harvard-Oxford [68] and AAL [69] atlas (see Figure 4C for the three anatomical atlases).

Data-driven methods, by contrast, do not pick brain areas beforehand and do not require prior knowledge of specific brain regions. Specifically, they use multivariate voxel-wise projection techniques such as independent component analysis (ICA) or its variants (e.g., group ICA) to decompose the raw fMRI data into multiple independent components (ICs). Each IC represents a brain area with independent brain activity. Figure 4C shows the diagram of the spatial ICA-based time series extraction method. Having obtained the ICs, these will then be visually inspected to identify if the brain areas they represent have brain activity because of a nerve action, or if this activity is just caused by noise. For instance, the spatial map of an IC with true brain activity can be matched with the previous anatomic brain function map. Meanwhile, their power-frequency curve has a specific fluctuating pattern (peak at low frequency, decrease rapidly, and then remain

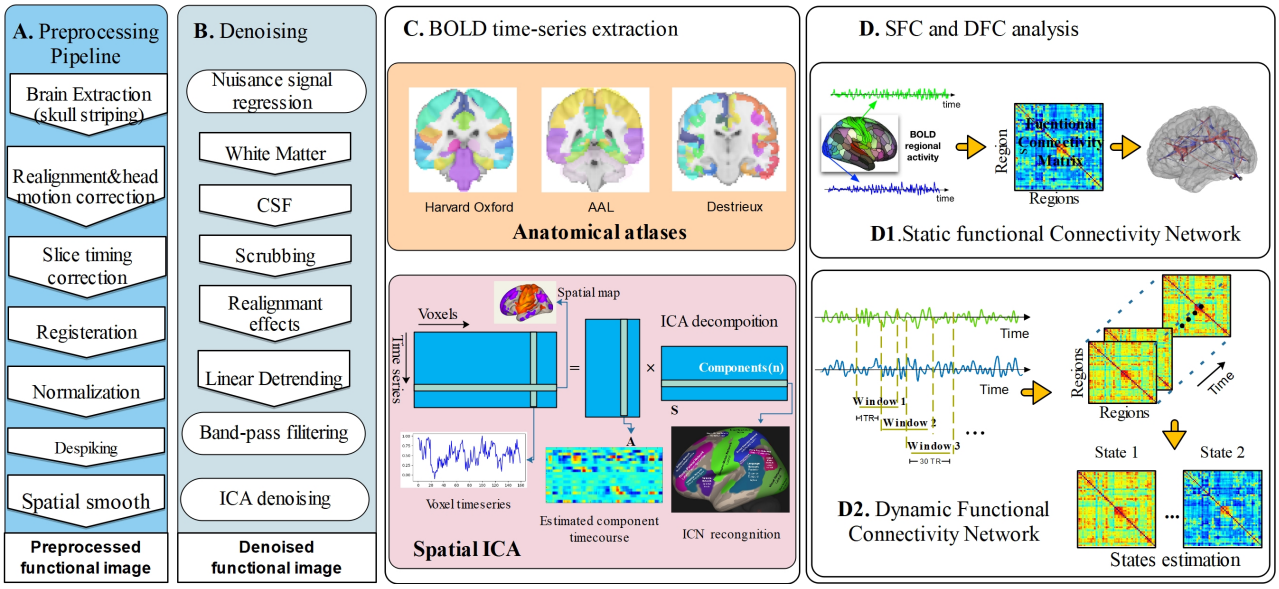

FIGURE 4. **The pipeline of fMRI processing for SFC and DFC analysis. A Preprocessing functional images. B Denoising functional images. C Atlases-based and Spatial ICA-based time series extraction. D1 SFC analysis. D2 Sliding window-based DFC analysis.**

relatively stable). The identified ICs are recognized as forming intrinsic connectivity networks (ICN). These ICN can be utilized for further functional connectivity analysis between functional areas or high-level functional connectivity between brain functional domains (e.g., the default mode, sensorimotor, subcortical, and cerebellar functional networks).

C. STATIC AND DYNAMIC FUNCTIONAL CONNECTIVITY ESTIMATION

1) Static functional connectivity estimation

Typically, SFC estimates functional connectivity between two brain regions by calculating the pairwise correlations between their time series. Mathematically, the static functional connectivity between two regions i and j can be expressed as

$$\mathrm{SFC}_{ij} = \frac{COV(X_i, X_j)}{\sigma_{X_i}\sigma_{X_j}} \tag{1}$$

where

- X_i and X_j represent the time series of brain activity for regions i and j, respectively.
- $COV(X_i, X_j)$ is the covariance between the time series of the two regions.
- σ_{X_i} and σ_{X_j} are the standard deviations of the time series X_i and X_j.

In the case of fMRI analysis, this correlation is frequently quantified with a canonical correlation coefficient [70]–[72], that measures the similarity of amplitudes of BOLD fluctuations. There are also studies using indices-based phase coupling measures, including the coherence [73] :

$$\mathrm{C}_{ij} = \frac{P(X_i, X_j)}{\sqrt{P_{X_i}} \cdot \sqrt{P_{X_j}}} \tag{2}$$

where

- P_{X_i} and P_{X_j} are power spectral densities of brain activity for regions i and j, respectively.
- $P(X_i, X_j)$ is the cross spectral densities of X_i and X_j.

or phase-locking relationships [74]:

$$\mathrm{PLV}_{ij} = \frac{1}{N}\sum_{1}^{n} e^{i(\phi(X_i)-\phi(X_j))} \tag{3}$$

here

- N is the number of time point of BOLD timeseries.
- $\phi(X_i)$ and $\phi(X_j)$ are the Hilbert transform of timecousre X_i and X_j

The pairwise correlations between region nodes or functional domains can construct a functional connectivity network (FCN) representing the brain's functional connectivity profile. Usually, before performing the group-level FC analysis, the individual correlation-based FC is transformed to a normally distributed Z-score using Fisher's r-to-Z transformation. Using the Z-score can be beneficial as it is not bounded by upper or lower limits, so it prevents the distribution of the results from becoming skewed close to the limits, which is helpful for further statistical analysis.

Based on the pairwise correlations, many SFC analysis methods exist, such as the FCN density analysis method [20], the Regional homogeneity (ReHo) based approach [75] and Kendall correlation coefficient (KCC) approach [76]. In addition, considering the investigated brain regions as nodes and the pairwise correlations as edges, the functional connectome can be viewed as an adjacency matrix or graph. Hence, the FCN can be naturally analysed with graph-based methods. For example, clustering coefficients, global efficiency and local efficiency of the FNC graph can be calculated with graph theory [77], and these graph-based measures can be integrated to analyze the functional connectivity of the brain.

2) Dynamic functional connectivity estimation

The development of DFC analysis for rs-fMRI was incited by the fact that the FC/FNC between regions or voxels may change in a short period [37]. There has been an accumulation of evidence demonstrating that the FC/FNC variation follows certain functional coupling patterns over time [78], [79], and these fluctuating coupling patterns support the brain regions in processing different functional requirements [79].

A multitude of approaches to quantify these dynamic patterns and their properties have been introduced (detailed reviews related to dynamic functional connectivity can be seen in [39], [79]–[81]). The most common and straightforward way to measure the DFC is by calculating the FC/FNC between regions/voxels in consecutive time periods (i.e. windows):

$$\mathrm{DFC}_{ij}(t) = \frac{\mathrm{cov}(X_i(t), X_j(t))}{\sigma_{X_i(t)}\sigma_{X_j(t)}} \tag{4}$$

where:

- $X_i(t)$ and $X_j(t)$ are the time series of brain activity for regions i and j within a specific time window centered at time t.
- $COV(X_i(t), X_j(t))$ is the covariance between the time series in this window.
- $\sigma_{X_i(t)}$ and $\sigma_{X_j(t)}$ are the standard deviations of the time series within this window.

The window length is usually constant across a sliding scheme spanning the full scan. The step size of the sliding window scheme is generally less than the window length; thus, two adjacent windows can partially overlap. With the sliding window method, thousands of FC/FNC matrices can be generated at the window length level. From these windows successive matrices which exhibit the dynamic evolution of the brain state within an MRI scan are obtained. Thus, the fluctuations in the time course of the connectivity can easily be assessed. The measurements to quantify the fluctuations include the temporal standard deviation(σ) [21], [22], coefficient of variation [82]:

$$\mathrm{CV}_{X(i)} = \frac{\sigma_{X(i)}}{\mu_{X(i)}} \tag{5}$$

where σ is temporal standard deviation and μ is mean of $X(t)$, or amplitude of low-frequency fluctuations (ALFF) [83]. In addition, matrix factorization techniques can summarise a series of FNC patterns into multiple FNC states. With recurrent or repeating connectivity patterns/states representing the underlying functional coupling patterns. The typical method used to summarize the connectivity patterns is K-means clustering [84], which has been widely used in fMRI studies for DFC analysis since a study by Allen et al [40]. The clustering approach reveals the reoccurring connectivity patterns from the windowed FC matrices and reflects the dynamic brain states corresponding to ongoing processing.

Another representative approach to summarising the brain state is the innovation-driven co-activation patterns (iCAPs) method [81]. ICAP method does not rely on the sliding window scheme but needs a clustering algorithm's assistance. It identifies BOLD signal transients (or innovation frames) and feeds them into clustering methods to obtain iCAPs [39], [85]. Besides these there are also several other DFC methods, such as principal component analysis (PCA) [86], dictionary learning (DL) [87], [88], the tensor decomposition (TD) methods [89], the dynamic community detection based method [90]–[93], the Hidden Markov Model (HMM) [94] and the wavelet transform coherence (WTC) [95]. However, in studies about post-stroke motor dysfunction, these methods are rarely investigated for DFC analysis.

3) SFC and DFC comparison

In principle, the SFC method assumes that FC/FNC is stationary over MRI scan time, and the functional connectivity is constant during an MRI scan. Nevertheless, SFC ignores that the human brain is a dynamic system that fluctuates even at the time scale of milliseconds [96]. Therefore, DFC analysis approaches have developed rapidly in the last decade to investigate the dynamic nature of the brain. In terms of the methodology, SFC analysis approaches are based on the average FC/FNC that aggregates over an entire fMRI scan. Despite SFC's methodological simplicity and ease, SFC approaches can clearly show disease-induced FC alterations. This is particularly important when investigating the impact of damage on specific brain functional areas. For example, many post-stroke studies have employed SFC to investigate the changes the stroke-lesion has caused in FC and to verify if the post-stroke FC reorganization can underpin functional recovery [55], [56], [97]. For that reason, the SFC can provide a valuable reference to functional rehabilitation programs. In clinical trials SFC has been used to identify regions with weakened FC. These regions can then be targeted using invasive or non-invasive tools (e.g. the transcranial magnetic stimulation [31], [98]) to restore the FC and help the affected brain motor function areas promote recovery [99].

By contrast, DFC analysis approaches employ time-resolving or signal decomposition methods to investigate a time-varying FC/FNC that spans the fMRI scan. DFC can extract relevant dynamic features to reflect functional network flexibility and brain state transition. However, despite this potential of DFC analysis, only a handful of studies have employed such time-resolved approaches to explore the dynamic neural mechanism following stroke. In contrast to the thriving research of DFC methods in other neurological diseases such as Parkinson's disease [100] and Huntington's disease [101], DFC analysis on rs-fMRI following stroke is still developing. Besides, compared with SFC analysis, DFC approaches typically have complicated mathematical/probability theories [49] (e.g., the HMM-based DFC analysis [94]). Hence, DFC is not as user-friendly to those clinicians without mathematical or engineering backgrounds. Furthermore, due to increased fMRI temporal-spatial resolution, the DFC is more sensitive to noise [39], [79]. Thus, the extra hyper-parameter setup (e.g., the window length and sliding window step size

TABLE 2. SFC and DFC comparison.

	Definition	Methods	Pros	Cons
SFC	FC remains static during fMRI scan	Pairwise correlation;	Mature application;	Overly simplistic methodology;
		FCN density [20];	Brain region focused;	Ignores brain FC dynamics;
		Regional homogeneity [75];	Clearly demonstrates FC alteration;	Exhaustively studied - may have reached limits.
		Graph theory [77];	Applied in clinical trials.	
DFC	FC continuously fluctuates	Sliding window [40];	Increased temporal-spatial resolution;	Complicated mathematics [49];
		PCA method [86];	Reflects network flexibility;	Sensitive to noise;
		DL method [87], [88]	Exhibits brain state transitions.	Long process to get to clinical trials.
		TD method [89];		
		DCD method [90], [91];		
		HMM [94];		
		WTC [72];		

in the sliding-window DFC method) needs to be fine-tuned to verify the validity of the results [79], [80].

Overall, SFC and DFC both have advantages and disadvantages (summarized in Table 2). Compared with DFC, SFC analysis is more mature and has more applications in post-stroke fMRI analysis; however, the DFC analysis can capture the intrinsic dynamic nature of the brain, which shows a potential promising prospect. Even though DFC models can rarely be seen in post-stroke studies currently, they are expected to boom in the future of post-stroke investigation.

IV. STATIC CONNECTIVITY ANALYSIS

A. DECREASED FUNCTIONAL CONNECTIVITY IS A COMMON FINDING

In numerous rehabilitation studies estimating resting-state FC, a comparison of results from stroke patients with those from healthy controls commonly found a decrease in interhemispheric FC in the functional network or at least between some regions. This reduction is caused by the disruptions in multiple large-scale functional brain networks, which have been viewed as one of the characteristics of motor impairment following stroke [29].

Looking at these results in detail, this decrease in interhemispheric connectivity is more distinct than in intrahemispheric connectivity. The lowest level of FC appears in the acute phase of stroke, and the earliest time this finding has been observed is within a few hours post-stroke [102]. Hence, interhemispheric FC reduction is often studied in AIS patients. For example, Liu et al. [20] observed disrupted interhemispheric FC between the motor cortices of acute stroke patients, which was associated with motor deficits. A recent study investigating dynamic structural and functional reorganizations following motor stroke reported a significantly lower interhemispheric FC in the first week [17]. In addition, Nai-Fang et al. [11] observed decreased interhemispheric FC within the cortical motor network in the first acute unilateral ischemic stroke patients. Specifically, the FC between the ipsilesional M1 and contralesional M1, contralesional postcentral gyrus (PoCG), dorsolateral premotor cortex (PMC) are significantly lower than that in controls. Besides the acute stage, interhemispheric FC reduction can also be observed in the post-stroke subacute and chronic stages. In [18], the FC between M1 and the contralateral cerebral cortex was reduced in stroke patients with unilateral ischemic motor neural network injury 2 weeks after onset. Additionally, the stroke participants recruited by [13] showed a decreased FC between the ipsilesional SMN and the contralesional SMN and auditory network (AN), which supports the early findings in [103] that the disruption of interhemispheric interactions between bilateral SMNs may result in motor deficits in patients with chronic stroke.

Beyond interhemispheric FC, the decreased contralesional M1 FC can be found in study [104]. The lowest FC levels in the contralateral sensorimotor cortex are 2 weeks after stroke. Results reported in [105] show reduced within-network FC in the contralesional precentral gyrus within the dorsal sensorimotor network and the contralesional superior parietal lobe.

B. BRAIN FUNCTIONAL CONNECTIVITY NETWORK TOPOLOGY SUPPORTS DECREASED FC

The brain FCN can be described as a set of nodes (ROIs or independent components) connected by edges (functional connectivity measure). Thus, graph theory analysis on FCNs can provide important information about the topological properties of the brain's functional network. When analyzing FC from the perspective of a brain graph, the various FC network topology measures also indicate reductions in FC in contrast to a healthy brain.

In terms of local topological measures of the FC graph, a study has proved the shortest path length to be lower than healthy controls in AIS [107] and the clustering coefficient was reported to decrease [108]–[110], though [107] suggested that stroke patients maintained the local clustering coefficient. In addition, another local measure, the weighted node degree

TABLE 3. Summary of studies using post-stroke rs-fMRI based static function connectivity for motor network analysis.

Study	Sub.	Stroke Info.	Ctrl.	Type	Timing	Func. Assessment	SFC Method	Findings
[17]	34	unilateral ischemic stroke	34	Longitudinal	1w; 4w; 12w	NIHSS; FMA	Seed-based: ROIs selected in SMN along the left and right M1	A significantly lower interhemispheric FC in the first week and a continual increase to week 12.
[11]	67	acute unilateral ischemic stoke	25	Cross-sectional	Within 7d	NIHSS; mRS (90d)	Seed-based: predefined ROIs (M1, SMA, PoCG, ventrolateral PMC, and dorsolateral PMC, PCC, anterior MPFC, inferior parietal lobule, retrosplenial cortex, and anterior hippocampus)	Significantly lower FC between iM1 & cM1, iM1 & cPCG, iM1 & cPMd, iPCG & cM1, iPCG & cPoCG, iP0CG & cPMd, and cM1 & cPCG; FC of iM11 & cM1, iM11 & cPoCG, iPCG1 & cM1,iM1 & cPMC was significantly lower in patients with unfavorable outcomes than in patients with favorable outcomes.
[13]	52	chronic subcortical stroke	52	Cross-sectional	> 3m	FMA	ICA based: 15 networks	Decreased FC between the ipsilesional SMN and the contralesional SMN and AN.
[18]	81	unilateral stroke	55	Longitudinal	2w; 3m	FMA	Seed-based: Predefined 24 ROIs	FC were weakened 2 weeks post-stroke and strengthened for 3 months.
[22]	76	unilateral stroke	55	Cross-sectional	from 7d to 1m	NIHSS; FMA	Seed-based: predefined 6 ROIs (left M1, right M1, left PMC, right PMC, left SMA, and right SMA)	Increased FC between cM1 & cPrG, iM1 & iPrG, precuneus & cPMC, iMFG & Precunesu, cCerebellar & cPoG, iPMC & cPrG, cIPL & I, cSMA & iPrG, cIFG & cMFG, iSMA & iMTG; No significant between SFC and clinical measure.
[12]	37	ischemic stroke	-	Cross-sectional	3d; 90d	NIHSS (at 3d); mRS (90d)	Atlas-based: Harvard-Oxford	Good functional outcome had greater functional connectivity right temporal lobe and left frontal lobe, between the left temporal lobe and right frontal lobe and between the right temporal and parietal lobes.
[14]	41	ischemic stroke	-	Cross-sectional	2-5d	NIHSS; mRS (90d)	Atlas-based: three atlases - Destrieux, Harvard-Oxford and AAL atlas	Worse outcomes showed higher values of characteristic path-length.
[106]	24	chronic supratentorial stroke	-	Cross-sectional	>2M	FMA	ICA based: 16 regions (SMA; left DLPFC; right FPN; left FPN; cerebellum)	The internetwork connectivity was significantly increased in the mild group for SMA–M1 in the affected hemisphere and SMA–DLPFC in the unaffected hemisphere and for lesion–M1 in the unaffected hemisphere compared with the severe group; Increased internetwork connectivity between remote brain regions may result in the reorganization associated with motor recovery.
[16]	42	chronic	-	Cross-sectional	>2w	NIHSS; FMA	Atlas-based;	Whole-brain interhemispheric homotopic functional connectivity, correlated with improvements in upper-extremity function.
[19]	65	Stroke	25	Longitudinal	2w; 3m; 1y	ARAT; Functional Independence Measures walk test	Atlas-based: 324 regions of interest	The degree of integration within networks and segregation between networks were significantly reduced sub-acutely but partially recovered by 3 months and 1 year; Network recovery not correlated with recovery from motor.
[20]	8	Stroke	10	Longitudinal	1w; 2w; 1m; 3m; 1y	Motricity Index; NIHSS	Seed-based: ROIs in sensorimotor regions and non-sensorimotor regions	Between the contralesional SMC and ipsilesional SMC, FC decreased in the first 2 weeks and followed by increases towards normal levels.

which measures the number of connections, has been found to decrease in the contralesional M1 of patients with limited recovery post-stroke [111]. There are no significant findings in topological measures between patients and controls reported in other studies following stroke [110].

Regarding the global topological measures of FCN, a reduction in network modularity was observed in an experiment including 25 patients with focal lesions because of stroke [15]. This finding was consistent with the decrease in interhemispheric function integration. Modularity is measured by the connection density within communities over that between communities and reflects the degree of functional integration and segregation [112]. A recent study [19] supported the findings in [15], with significantly lower modularity found in patients compared with controls, indicating decreased segregation in the FNC. Beyond modularity, other global measures of the FC network tended to decline. In [110], the FC concordance, which measures the network stability in time, was observed to decrease over time in contrast to intact networks. In addition, the small-worldness which reflects the ability of brain networks to satisfy the needs of local and global information processing, was significantly lower in patients than controls two weeks after stroke [113].

There is a great variety of graph theory-based topology measures, resulting in various dynamic patterns in the network topology being investigated in studies. In general, the graph topology alteration of FCN post-stroke can be interpreted in a concept of network randomization [15], the way the network reorganizes itself to adapt to the lost function, which also demonstrates the process of neuroplasticity that occurs in the brain post-stroke.

C. INCREASED FUNCTIONAL CONNECTIVITY IS POSITIVELY RELATED TO RECOVERY

Even though decreased FC relative to healthy controls is the dominant trend in patients following a stroke, many findings also include increased FC. Several longitudinal studies have demonstrated that the interhemispheric FC in the SMN first decreases in the early stages after stroke while increasing in the following weeks or months [30], [104], [114]. Other studies support this FC-increased finding as well. For example, in a systemic study [29], decreased FC was observed in stroke patients between the ipsilesional M1 and the sensorimotor cortex, the occipital cortex, the middle frontal gyrus (MFG) and the posterior parietal cortex (PPC), while the increased FC was also shown between ipsilesional M1 and cerebellum, the thalamus, the MFG and the PPC. Besides, in the study in [20], although the FC in the motor area decreased after stroke, the opposite occurred in cognitive networks. In addition, a recent study [22] reported that compared with healthy groups, the patients exhibit a significantly increased static FC between a large number of structures, including ipsilesional M1 and the contralesional precentral gyrus (PrG), contralesional M1 and the ipsilesional PrG, contralesional precuneus; ipsilesional MFG and precuneus, the contralesional cerebellar, PoCG, ipsilesional sub-gyral region; SMA and ipsilesional PrG, frontal-temporal space, MFG; ipsilesional SMA and the ipsilesional middle temporal gyrus (MTG).

The increased FC post-stroke seems to be restricted to between specific structures [23]. The highly consistent finding is that the increased FC occurred in connectivity with the cerebellum [29], [110], [115]. FC in the cerebellum has been reported to be crucial for recovery [116], [117]. Hence, the conclusion can be derived that FC in the cerebellum is a potential recovery mechanism. In fact, not limited to the cerebellum, many structures that found increased FC correlates with motor recovery. One commonly mentioned brain region is M1. Many studies have reported that FC increases between the ipsilesional M1 and contralesional M1 and between the ipsilesional SMC and contralesional SMC, and this increase is related to better recovery [20], [115], [118]. In addition, Ktena et al. [14] observed increased FC between lesion areas and M1 in the unaffected hemisphere of the chronic patient. They concluded that this phenomenon reveals the network reorganization process associated with motor recovery. Furthermore, the enhanced FC between M1 and SMA and other motion-related regions like the dorsolateral prefrontal cortex (DLPFC) has been be recorded and shown to be a potential mechanism for motor function recovery [14], [119].

In many studies related to the prediction of motor recovery or outcomes, increased FC is normally associated with minor severity or a better motor functional outcome. In a study that included 34 patients and healthy controls [17], the authors found a significantly lower interhemispheric FC in stroke patients compared to healthy controls in the first week. This result supports previous common findings, however, following this period, the FC continued to increase to week 12. Correlation analysis showed that the percentage of FC changes was significantly positively correlated with improved FMA scores from week 1 to week 4. In an early prediction study [12], 37 stroke patients were scanned on day 3 after stroke, and the fMRI data were used to predict 90-day outcomes. The results show that patients with good outcomes had higher FC than those with poor outcomes. Including the FC improved the model's accuracy to 94.7%, reflecting that increased FC plays an essential role in motor recovery. Stroke patients at the chronic stage have been shown to exhibit a similar increase in FC. In a study with a total of 107 participants, when compared to patients with a completely paralyzed hand, patients with a partially paralyzed hand had increased FC in the ipsilesional superior temporal gyrus, the ipsilesional middle occipital gyrus and the contralesional calcarine [13]. This finding is supported by findings in a larger cohort of patients with ischemic stroke at the acute stage. In a study with 85 AIS patients, the FC between ipsilesional M1 and contralesional PMD in patients with favourable outcomes was significantly greater than with unfavourable outcomes [11], which demonstrates that the increased FC can serve as an independent outcome predictor.

The findings related to SFC are summarized in Table 3. All studies agree the FC of the motor network is impaired after stroke onset, with decreased FC a consistent finding, but

TABLE 4. The summary of DFC analysis with fMRI for post-stroke recovery.

Studies	Sub.	Stroke Info.	Ctrl.	Type	Timing	Extraction Methods	DFC Method	Findings
[21]	19	Ischemic stroke	19	Longitudinal	7d; 2w; 3m	Seed-based: AAL 116 ROIs	Sliding window approach	FC temporal variability: Reduced temporal variability; Longitudinal increased over the stages.
[22]	75	Ischemic stroke	55	Longitudinal	7d-1m	Seed-based: six ROIs (bilateral M1, SMA and PMC)	Sliding window approach; Standard deviation	Increased dynamic FC between the ipsilesional M1 regions and contralesional PrG, and a negative correlation between DFC in the regions and FMA scores after stroke.
[57]	54	Ischemic stroke	-	Cross-sectional	<7d; >6m	Voxel-based: ICA (14 to 3 functional domain)	Sliding window approach; Sparse inverse covariance matrix; k-means clustering	Mild: lower variability values; Moderate-to-severe: higher dynamic connectivity variability fraction and dwell time improve the prediction performance.
[92]	15	Ischemic stroke	15	Cross-sectional	-	Voxel-based: ICA (32 to 8 functional domains)	Sliding window approach; multilayer temporal network	Mild patients were observed to have a significantly lower between-module interaction than severe patients as well as healthy controls. In contrast, severe patients showed remarkably lower within-module interaction and had a reduced overall interaction compared to healthy controls.
[93]	15	Ischemic stroke	15	Cross-sectional	-	Voxel-based: ICA (32 to 8 functional domains)	Sliding window approach; multilayer temporal network	Severe affect stroke patients have reduced recruitment and increased between-network integration; mild patients exhibited low network flexibility and less network integration
[41]	31	Ischemic stroke	17	Longitudinal	within 2 week	Voxel-based: spatially constrained ICA (13 network components)	Sliding window approach; k-means clustering	Severe subgroup: spatially segregated connectivity configuration; Regionally densely connected; Increased transition likelihood to the regionally densely connected state. Moderate: weakly connected configuration (low levels of connectivity) spent more time.
[120]	41	Ischemic stroke	-	Cross-sectional	<7d; >6m	Voxel-based: ICA (49 to 7 functional domain)	Sliding window approach; k-means clustering	NIHSS significantly correlated with fraction and dwell time of densely connected state.
[121]	47	Ischemic stroke	-	Longitudinal	2w; 3m; 12m	Seed-based: 324 ROIs and 19 subcortical ROIs	Sliding window approach; k-means clustering	The structure connection breaks induced by stroke lesions cause the abnormal fraction times, dwell times, and transitions between dynamic states, and this anomalies helps explain the post-stroke impairment and long-term outcome
[122]	15	Ischemic stroke	15	Longitudinal	1m; 2m; 3m; 4m; 5m	Voxel-based: ICA (32 to 8 functional domains)	Sliding window approach; multilayer temporal network	stroke lesions have significant and enduring alterations in dynamic behaviours within functional brain networks, resulting in distinct recovery trajectories for these groups. Whole-brain recruitment emerged as a robust and reliable feature, achieving an AUC of 85.93.

increased FC can also be observed. Increased FC is a form of neuroplasticity, which means that the lost FC has tended to increase to the normal level. From the perspective of neural activation, the decreased FC implies the existing pathways are disinhibited in the recruitment stage after stroke [10], and the increased FC shows that the damaged pathways surrounding the lesion area are newly built, thus improving motor function.

V. DYNAMIC CONNECTIVITY ANALYSIS

For patients with motor dysfunction following stroke, the number of examples of DFC analysis is not as high as SFC. However, from the existing investigations (summarized in Table 4), we can conclude the following findings.

A. TEMPORAL VARIABILITY OF FC IS ALTERED FOLLOWING STROKE

DFC analysis methods make use of the temporal variability of FC to reveal neural dynamic properties and recovery mechanisms of stroke. The temporal variability between specific regions illustrates the dynamic reconfiguration of the brain system over time in response to ongoing processing. At a global level, it reflects the degree of synchronization between functional areas in the brain. However, the definitions of temporal variability are not consistent across studies. The study in [21] calculated the temporal variability between specific regions as the average functional connectivity over different windows. By contrast, the temporal variability of FC in [22] was characterized as the standard deviation of time courses at predefined seed regions across a series of windows (note that this paper investigates the SFC and DFC at the same time).

In terms of the differences in temporal variability, Hu et al. [21] reported a significantly reduced temporal variability in stroke patients compared to the healthy group; however, the brain regions that exhibited decreased FC temporal variability were distinct between post-stroke stages. In the acute stage, the reduced regions cover the primary sensorimotor and DMN, while only the ipsilesional PoCG and ipsilesional anterior cingulate gyri (ACG) showed a declining trend in the subacute stage. Nevertheless, this finding is incompatible with the findings in [22], where an increased temporal variability in ipsilesional M1 and contralesional PrG was observed. This increase showed a longitudinal trend, which was exhibited across the stages post-stroke.

To take advantage of the information gained from the temporal variability, both studies investigated the relationship between dynamic FC and motor function recovery post-stroke. In [22], the authors detected a significantly negative correlation between FMA scores and FC variability in ipsilesional M1 and contralesional PrG. Whereas in [21], the increased FC variability from the acute to the subacute stage was reported to correlate positively with the increased FMA. The results across the studies appear to be different, even to some extent the opposite. However, this can be explained due to the studies being reported in these publications having different emphasises. Chen et al. [22] paid more attention to the variability of FC between the specific regions, while Hu et al. [21] focused on the trend of FC variability across the different post-stroke stages. In addition, the experimental methods and the investigated subjects vary between the studies, which partially leads to the diversity of results.

B. PREFERENCES IN TRANSIENT BRAIN STATES ARE ALTERED IN MOTOR FUNCTION AFFECTED PATIENTS

The transition between connectivity states in diseases with abnormalities in highly dynamic neural activity is an active research topic in DFC analysis. The so-called connectivity state is generally abstracted from the reoccurring BOLD signal using a sliding window scheme and a clustering algorithm. Thus, highly recurrent FC patterns within an MRI scan are identified as connectivity states. A successive list of these different states can vividly exhibit dynamic transitions between the multiple brain states. This dynamic transition globally reflects the FCN's flexibility and can be used to investigate the alteration or adaptation of dynamic interaction between brain functional networks after stroke. The flexibility and adaptation of connectivity states due to cognition or psychiatric disorders has been illustrated in other studies. In contrast, stroke-induced changes in brain states have rarely been investigated. Recently, the abnormal connectivity states in AIS has attracted the attention of researchers.

In a study that included 31 AIS patients [41], the authors outlined three different SMN connectivity states: the first is characterized by extremely strong intra-domain connectivity and extremely weak inter-domain connectivity; the second has remarkably weak intra-domain connectivity; and the third is compound state that combines the characteristics of states 1 and 2. These states do not differ too much from the states summarized in their further work in [57], [120], with all three studies revealing different aspects concerning post-stroke motor impairment. In [41] the authors provide details of the distinct configuration of FC connectivity states in stroke patients with various degrees of clinical symptoms. Moderately affected patients, for example, have significantly more dwell time in a weakly connected configuration, while severely affected patients prefer to stay in the state 1. This finding is consistent with the study [57], which included 41 AIS patients. This study also demonstrated that NIHSS significantly correlated with the fraction of the time a subject spent in state 1 over the scan and the time a subject spent in state 1 without switching to another state (the dwell time). Among the three studies [120] has the most AIS patients (54). In this study, the authors pay more attention to distinguishing the link between the SMN connectivity measure and the subgroups of patients either with or without the motor deficit. Results show that embedding the fraction of time and dwell time into the initial motor impairment-based model can improve the prediction performance (95% accuracy).

Note that this finding does not derive from multiple independent investigations. Hence, it needs to be validated in other stroke patient cohorts to ensure the results are reliable and reproducible. Additionally, only the SMN has so far shown

the preference shift in transitory brain states. If this variance is caused by changes in the globally dynamic interplay between distinct functional domains, this can be further investigated in the future.

C. TEMPORAL MODULATION OF FUNCTIONAL NETWORK REVEAL THE DYNAMIC RECONFIGURATION

Later, the multilayer temporal network was developed to examine the post-stroke dynamic reconfiguration in the brain function network. Multilayer temporal network analysis is an innovative approach that models the brain's functional connectivity as a series of interconnected layers, each representing different time points or temporal windows. This method allows us to examine how brain network connections evolve over time, and the network reconfigures itself to adapt to external function demands, providing a more granular view of the brain's dynamic processes. Wu's study [92], [93] employs this approach to investigate the temporal modulation of functional networks in stroke patients, offering new insights into the brain's neural rebuilding process during recovery. Besides, the dynamic reconfiguration process is closely related to the initial degree of clinical severity. The severe patients, for example, tend to have shown remarkably lower within-module interaction and had a reduced overall interaction compared to healthy controls [92], and tended to have reduced recruitment and increased between-network integration [93]. In the six-month follow-up investigation, the reduced recruitment can be a reliable predictor of motor function recovery with the help of machine learning methods(highest accuracy of 85%) [122] While Wu's study provides significant insights, it is important to consider its limitations, particularly the sample size. The study was conducted with a relatively small cohort of 15 stroke patients. This limited sample size may impact the generalizability of the findings and the statistical power of the conclusions.

VI. DISCUSSION

The literature search of studies in this review demonstrates that widespread changes in connectivity can be observed in post-stroke recovery. The exploration of alteration in functional connectivity, both static and dynamic, has significantly advanced our understanding of brain reorganization following a stroke.

Static functional connectivity analysis has laid the foundation by providing insights into the altered connectivity patterns between different brain regions post-stroke. This approach has revealed crucial information about the persistent disruptions in network connectivity associated with motor function impairments and the extent of damage sustained by specific brain regions. In a static brain functional network, decreased interhemispheric FC appears to be a common feature of resting-state network reorganization in stroke. This is accompanied by reduced network efficiency and modularity. Increased FC can also be observed, and a positive correlation exists between the increased FC of bilateral cerebral hemispheres and the degree of post-stroke functional recovery.

However, the limitations of static analysis, which assumes stable connectivity over time, have prompted the emergence of dynamic functional connectivity (DFC) methods. DFC offers a more nuanced perspective by capturing the temporal fluctuations in connectivity patterns, reflecting the brain's ongoing adaptive processes during recovery. The literature reviewed in this study underscores the potential of DFC to provide a comprehensive understanding of the recovery process by highlighting widespread changes in connectivity that static measures may overlook.

Current research demonstrates that DFC can identify critical periods of heightened neuroplasticity, monitor rehabilitation progress more effectively, and predict long-term outcomes with greater accuracy. These capabilities make DFC a promising tool for tailoring personalized rehabilitation strategies and enhancing the efficacy of therapeutic interventions. Moreover, DFC facilitates a deeper investigation into the brain's network flexibility and resilience, offering new avenues for optimizing neuromodulation techniques and fostering neuroplasticity.

In the following, we discuss two interesting aspects pertinent to SFC and DFC analysis following stroke: 1. whether static or dynamic functional connectivity can serve as a post-stroke recovery biomarker; 2. the methodological considerations relevant to functional connectivity analysis in stroke research.

A. FUNCTIONAL CONNECTIVITY AS A RECOVERY BIOMARKER FOLLOWING STROKE

Accurate prediction of motor function outcomes and treatment responses after stroke can benefit clinical and research settings, promoting effective delivery of rehabilitation care and the stratification of subjects in clinical trials. As a heterogeneous disease, stroke is characterized by varying lesion sizes and locations. Therefore, the demographic and clinical variables, such as age, sex, lesion volumes, etc., are naturally considered potential factors contributing to the post-stroke recovery prediction [123], [124]. Recently, there has been increasing interest in the role of functional connectivity measurements acquired from neuroimaging in predicting recovery performance. Hence, in this section, we discuss if SFC and DFC measurements can serve as a motor recovery biomarker following a stroke from the perspective of FC application.

An appropriate first step in investigating the role of FC measures in post-stroke motor recovery is to examine the strength of the association between connectivity and motor behaviour in different stroke populations. A correlation coefficient of 0.75 or greater usually indicates a strong correlation. Results from cross-sectional studies showed a moderate to strong association between measures of static functional connectivity and motor status after stroke ($r = 0.58 - 0.76$) [32], [56], [125]. The number of stroke patients participating in these studies ranged from 8 to 55. The motion assessment was measured using the upper extremity Fugl-Meyer assessment (UL-FMA) scores, the Motricity Index, and the Chedoke-McMaster Stroke Assessment.

Regarding DFC analysis, the dynamic FC measure – temporal variability, demonstrates a significant correlation with the UL-FMA scores at the chronic stage after stroke, showing the same effect as static FC analysis [21]. Another DFC study found a negative correlation between the differences in DFC measures in the motor execution network and FMA scores [22], however, the result did not pass through FDR correction. In addition, in a study with 31 AIS patients [41], dynamic functional connectivity patterns showed significant differences between stroke groups with varying motor status: patients with severely impaired mobility are more likely to have a regionally densely connected, highly segregated pattern; patients with mild motor impairment take more time to weakly connect the state with reduced segregation.

The results from the longitudinal studies also appear to underpin FC as a potential biomarker for post-stroke motor recovery. For example, in the longitudinal study of static FC in stroke patients, initial baseline measures of functional connectivity were strongly associated not only with longitudinal temporal assessment scores of motion status [29], [97], but also strongly correlated with changes in motor function recovery over time (motor function improvement, $r = 0.32 - 0.79$) [17], [118], [126], [127]. Dynamic analysis of FC at the longitudinal level further demonstrated the potential of FC alteration as a biological marker of rehabilitation (between bilateral intraparietal lobule and left angular gyrus, $r = -0.68$) [57].

The literature findings substantiate that FC can serve as a reliable biomarker for post-stroke motor recovery. However, it is advised to keep caution when assessing the causality relationship between functional connectivity and stroke recovery – the sample size and statistical reliability present challenges to using FC as a crucial factor in post-stroke recovery. On the one hand, sample sizes collected in clinical analyses typically range from 10 to 20 participants, with such small sample sizes results can be particularly to sensitive to outliers [128] and vulnerable to the effective size inflation [129], thus may not accurately represent the entire group. On the other hand, the operation of co-variables, such as age, sex, lesion size/location, baseline motor status/measure, etc., vary across studies, intensifying inconsistent FC recognition in stroke recovery. Nonetheless, we should not be too pessimistic. Despite these criticisms being fair, it does not change the strong or the strong versus weak FC effects observed in the recovery process [34]. In the future, longitudinal studies with more samples or demonstrating the clinical benefits of functional outcome prediction may underpin the role of FC in post-stroke recovery.

B. FUNCTIONAL CONNECTIVITY METHODOLOGICAL CONSIDERATIONS FOR STROKE RESEARCH

Generally, two experimental designs are used for FC analysis in stroke research: cross-sectional and longitudinal. These two study designs allow the investigation of different post-stroke effects on FC. Typically, a cross-sectional study examines the FC change between stroke and healthy controls (between-person effects); a longitudinal study can provide a snapshot of the FC changes in stroke patients over time (within-person effects) [130]. Due to intensive time and resource requirements, the majority of studies rely on cross-sectional designs. However, one of the defects of the cross-sectional study is the brain lesion-induced FC difference will be diluted by the cohort effects. For instance, since the lifestyle backgrounds vary in participants, FC differences between stroke patients and healthy will reflect not only the lesion-induced neural circuit reorganization but also differences in the environment the participants live in. To track the within-person FC changes in post-stroke recovery and to investigate the causality of FC and neuroplasticity, a longitudinal study is a potent method that can demonstrate the cross-sectional findings from the time dimension [17], [29], [114]. In the cross-sectional studies, static and dynamic FC analyses are present, while static accounts for the majority of longitudinal studies. Recently, dynamic connectivity analysis has been developed in multiple fields [87], [100], [120], [130], [131]. Since post-stroke recovery is time-dependent, investigating how the neural networks interact dynamically and to what extent dynamic connectivity patterns support motor function recovery and change deserves further study.

The Methodology section introduced general pre-processing methods. Although pre-processing steps involve choices between different analysis approaches (static vs dynamic), they vary only mildly across FC analysis investigations in post-stroke research. To the best of our knowledge, a systemic study of the effects of pre-processing choices has not been conducted. This can probably be attributed to the fact that the sample sizes for stroke patients are not large and, therefore, cannot support examining the pre-processing steps on the lesion-induced differences in functional connectivity. Hence, whether those pre-processing and denoising steps have a significant effect on the current findings could be explored in the future.

In terms of the brain parcellation methods they use, SFC and DFC studies have apparent preferences. Post-stroke studies with SFC analysis commonly use the atlas-based method to parcellate the whole brain. This brain map has been generated from massive brain investigations and can provide detailed brain information, allowing researchers to focus on the network or regions of interest. One of the biggest benefits of using the atlas-based method is that it provides a way to compare and obtain fairly consistent findings across studies; for example, lesions interrupt remote network connections, and the interhemispheric FC decreases, etc. By contrast, studies with DFC tend to use ICA since the DFC is more sensitive to noise due to increased temporal resolution. Hence, the results of DFC approaches can vary depending on the patient cohorts because the ICA is a data-driven approach and may isolate components belonging to different networks. Moreover, compared with the atlas-based method, ICA cannot examine changes in interhemispheric connections. Hence, how connections between hemispheres interact dynamically at the millisecond level may require combining SFC and DFC

results or new intervention approaches.

CONCLUSION

fMRI-based post-stroke functional connectivity analysis for post-stroke motor dysfunction patients has two branches: static functional connectivity (SFC) and dynamic functional connectivity (DFC). While SFC assumes that the FC/FNC is stationary during the fMRI scan, DFC maintains that the FC/FNC fluctuates even over short periods of time and has specific coupling patterns. A great many SFC and DFC analysis methods have been developed and successfully applied to investigate the alteration in functional interactions or communication which are behind post-stroke motor function deficit and recovery. In this context, this review summarized the current advances in SFC and DFC approaches and the latest findings for their application on post-stroke motor function research. The studies included in this review demonstrate that SFC is the predominant post-stroke functional connectivity analysis method in the last five fears. The results from SFC show that there is a reduction in FC between motor regions after a stroke, and that a rise in FC is highly associated with functional recovery. Meanwhile, DFC is developing rapidly. DFC's ability to provide a nuanced, time-sensitive understanding of brain connectivity changes, enabling the application of DFC methods has potential in post-stroke motor function impairment and recovery. With more DFC methods created and utilized to investigate the abnormal motor FC/FNC dynamics, DFC is expected to have far-reaching effects in terms of neural reorganization underlying stroke recovery and underpin understanding of the recovery mechanism.

Based on consideration of previous studies, recommendations from this review for future studies are:

1) Both SFC and DFC methodology needs to be validated on large cohorts to improve the reliability and robustness of their statistical results.
2) As a potent method for examining the stroke lesion-effect on alteration of FC/FNC dynamics within-person, DFC based longitudinal post-stroke investigations should be greatly encouraged in the future.
3) This variability in connectivity is thought to be closely linked to the brain's intrinsic neural timescales (INT), which represent the time windows over which neural populations integrate information [132]–[135]. The interplay between DFC and INT could provide insight into how the brain's functional architecture continuously adapts, allowing for the flexible coordination of neural processes that underlie loss functions after stroke.
4) The quantitative relationship between FC/FCN alteration and motor function improvement should be thoroughly investigated, particularly for dynamic FC/FNC alteration.
5) The post-stroke motor function research should not be limited to brain motor function areas. The interplay effect between the motor network and other functional networks, such as the cognitive network, should be considered.

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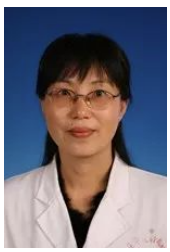

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