Neuroengineering Approaches Assessing Structural and Functional Changes of Motor Descending Pathways in Stroke

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Abstract

Stroke is a leading cause of adult disability worldwide, with approximately 101 million survivors globally. Over 60% of these individuals suffer from long-term, often lifelong, movement impairments that significantly hinder their ability to perform essential daily activities and maintain independence. Post-stroke movement disabilities are highly associated with structural and functional changes in motor descending pathways, particularly the corticospinal tract (CST) and other indirect motor pathways via the brainstem. For decades, neuroengineers have been working to quantitively evaluate the post-stroke changes of motor descending pathways, aiming to establish a precision prognosis and tailoring treatments to post-stroke motor impairment. However, a clear and practicable technique has not yet been established as a breakthrough to change the standard of care for current clinical practice. In this review, we outline recent progress in neuroimaging, neuromodulation, and electrophysiological approaches for assessing structural and functional changes of motor descending pathways in stroke. We also discuss their limitations and challenges, arguing the need of artificial intelligence and large multi-modal data registry for a groundbreaking advance to this important topic.

Keywords: Stroke, Motor Descending Pathways, MRI, Transcranial Magnetic Stimulation (TMS), Cortico-muscular connectivity

1. Introduction

Stroke is a leading cause of adult long term disability worldwide[1]. There are approximately 101 million stroke survivors in the world with over 60% of them experiencing long-term movement disabilities[2]. These impairments are often life-long and lead to difficulty with activities of daily living and returning to work[3]. A stroke lesion results in focal damage to motor or sensory cortices and their descending or ascending pathways. Recovery outcomes are highly variable, influenced by the lesion's location and size, associated white matter alterations (e.g., fiber loss or degeneration), and the effectiveness of therapeutic interventions and rehabilitation strategies. These factors determine the degree of functional restoration, highlighting the importance of precise lesion characterization and individualized rehabilitation plans to optimize recovery outcomes[4].

The somatic motor system is organized into two major descending pathway systems: direct and indirect pathways. The direct pathways, including the corticospinal tract (CST), are primarily responsible for voluntary motor control. In contrast, the indirect pathways, such as the corticoreticulospinal tract (CRST), which is composed of the corticoreticular tract (CRT) and the reticulospinal tract (RST) with synaptic connections in nuclei at the brainstem, focus on reflexive and postural control of musculature[5]. Post-stroke movement disabilities are highly associated with structural and functional changes in these motor control pathways. Reduced CST fiber density severely compromises precise, individuated control of single joints[6, 7]. CST damage also triggers secondary adaptive changes in the brain and spinal cord, including maladaptive hyperexcitability of the CRST, a key factor in severe post-stroke motor impairments[8, 9]. This leads to stereotyped, coarse, multi-joint movements, known as pathological limb synergies[10]. In the upper limb, this manifests as "flexion synergy," where increased shoulder abduction causes involuntary activation of elbow, wrist, and finger flexors, a hallmark of post-stroke motor dysfunction[11, 12].

The mechanisms underlying these motor impairments are closely linked to damage in motor pathways and the plasticity of the nervous system following a stroke. The RST consists of two components: the dorsal and medial RST. The dorsal RST originates from the medullary reticular formation, receives input from the contralateral primary motor cortex, and provides inhibitory input to spinal reflex circuits, descending ipsilaterally to the spinal cord[13]. The medial RST, originating from the pontine reticular formation, receives input from the ipsilateral premotor cortex and supplementary motor areas, descending ipsilaterally to the spinal cord and providing excitatory input to the spinal motor network[8]. Post-stroke, damage to the ipsilesional motor cortex, CST and/or CRT leads to significant motor deficits. CST damage impairs voluntary limb movement, while CRT damage reduces input to the contralesional medullary reticular formation, resulting in hypoactivity of the contralesional dorsal RST's inhibitory effects on spinal stretch reflexes[14]. Concurrently, inputs from the contralesional premotor cortex and supplementary motor areas to the contralesional pontine reticular formation become hyperexcitable, driving spasticity and abnormal flexion synergy[15, 16]. Spasticity, characterized by hyperactive stretch reflexes, affects up to 65% of stroke patients and is associated with poor motor function[17, 18].

Due to the critical role of motor descending pathways in post-stroke movement impairments, specifically flexion synergy and spasticity, neuroengineers are developing methods to quantify changes in these pathways. Techniques such as neuroimaging, neuromodulation, and electrophysiological approaches are being explored to assess these changes. This review discusses the recent advancements in these methods, highlighting current limitations, challenges, and future research directions.

2. Imaging-based approach for detecting and evaluating structural changes of motor descending motor pathways post stroke

2.1 Lesion load on the corticospinal tract using structural imaging

The CST, extending from the motor cortex through the internal capsule and cerebral peduncles and decussating at the medulla into the spinal cord, is frequently affected in both ischemic and hemorrhagic strokes. This leads to lasting motor deficits due to disruption of signal transmission between the brain and the extremities[19]. Structural magnetic resonance imaging (MRI), particularly T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) are utilized (**Figure 1**) because these allow for detailed assessment of ischemic and hemorrhagic lesions in cortical and subcortical areas where CST fibers are located[20, 21]. T1WI is a powerful imaging modality providing high-resolution anatomical details and is particularly useful for detecting primary ischemic or hemorrhagic lesions, as well as assessing atrophy and secondary degeneration. This allows for precise localization of stroke lesions and their relationship to motor pathways. T2WI is highly sensitive to changes in water content and is particularly effective in identifying edema, gliosis, and other pathological changes associated with CST damage[22]. Each phase of stroke - acute, subacute, and chronic—presents unique structural changes in the CST[23]. T1WI and T2WI offer distinct advantages in visualizing these changes, helping clinicians evaluate lesion load, secondary degeneration, and the likelihood of functional

improvement[21].

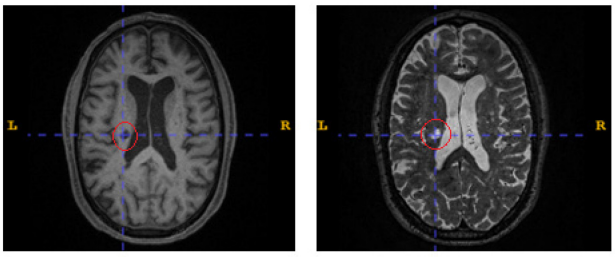

Figure 1. Lesion appears dark on T1-weighted (left) and bright on T2-weighted MRI images (right).

In the acute stage of ischemic stroke, T1WI and T2WI help identify the immediate effects of injury in the CST[24]. T1WI shows early hypointensity in the infarcted area, allowing for lesion localization. T2WI is especially useful for detecting edema, which appears as hyperintensity in the affected CST[25, 26]. Edema in the acute stage can expand into surrounding motor-related areas, increasing lesion load and the risk of additional motor deficits[27]. T1WI and T2WI also help identify the risk of midline shift or compression on the CST, which can worsen motor outcomes. During the subacute stage of ischemic stroke, MRI changes become more pronounced as edema subsides and gliosis begins. T1WI can reveal hypointense regions as the infarcted tissue undergoes necrosis and volume loss. Detecting this degeneration is crucial for assessing prognosis, as it often correlates with motor impairment severity[28].

In chronic stages, Wallerian degeneration, gliosis and scarring become prominent, and the CST develops persistent atrophy. Wallerian degeneration is a process of progressive axonal degeneration that occurs following injury to a neuron, often due to stroke, traumatic injury, or demyelinating disease. This degeneration involves the breakdown of the distal portion of the axon and its myelin sheath after a disconnection from the neuron's cell body[29-31]. The process is primarily observed in the CST, especially in regions distal to the primary lesion, such as the cerebral peduncle and pons. T1WI reveals hypointense signals and associated atrophy, while T2WI shows hyperintense signal corresponding to ongoing gliosis[32, 33]. These signal changes and degree of atrophy along the CST indicate sites of irreversible axonal loss and reduced plasticity potential. Identifying these changes can aid in assessing long-term outcomes for motor function in affected patients[34, 35].

Quantitative analyses of post stroke lesion on MRI can be predictive of motor outcomes, as larger lesions within or near the CST often correlate with more significant motor impairment[36, 37]. A study indicated that lesion load to both the primary motor cortex (M1) and ventral premotor cortex derived from T1WI were strongly related to stroke motor severity indexed by Fugl-Meyer Assessment cut-off scores[38]. A meta-analysis assessed the correlation between MRI-based lesion size and functional outcomes in patients with stroke. This research included various studies using different techniques to estimate acute lesion size, such as structural MRI, diffusion-weighted imaging (DWI), and perfusion-weighted imaging (PWI)[39]. Notably, the analysis found that T2WI was more reliable for estimating lesion volume compared to other sequences[39]. Consequently, T2WI is a preferred modality to approximate final infarct size, offering valuable insights into the relationships between infarct size, functional outcomes, and prognosis[40].

In recent years, algorithms driven by artificial intelligence (AI) have leveraged structural MRI to improve lesion detection, segmentation, and quantification, thereby aiding in accurate stroke severity assessment and outcome prediction[41].Guo et al. used machine learning algorithms in combination with support vector machine (SVM) classifiers, achieving a Dice coefficient of 0.73 for detecting ischemic stroke lesions on T1WI[42, 43]. Other studies have illustrated that the Hybrid UNet Transformer (HUT) excelled in single-modality segmentation on the Anatomical Tracings of Lesions After Stroke (ATLAS) dataset, demonstrating an increase of 4.84% in the Dice score and a notable 41% improvement in the Hausdorff Distance score[44]. Classification models have also been developed utilizing decision tree and k-nearest neighbors (kNN) algorithms. A recent study revealed that the decision tree algorithm surpassed kNN in distinguishing between thrombotic, hemorrhagic, and embolic strokes, demonstrating high classification accuracy[45]. With the advancement of novel AI technologies such as SAM, large language models (LLMs), and VMamba, future AI-assisted acute stroke diagnosis is expected to achieve higher levels of accuracy and reliability[46].

2.2 Integrity assessment of motor pathways using diffusion imaging

To localize the damaged pathways within the CST, diffusion tensor imaging (DTI)—calculated from diffusion-weighted MRI (DWI)—provides a method to examine the integrity of white matter through tractography[47]. By quantifying anisotropic diffusion levels of white matter via fractional anisotropy (FA) values, DTI can assess brain microstructures and white matter integrity in various neurological conditions[48]. FA is sensitive to the relative magnitude of the eigenvalues of the diffusion tensor, which reflect the directionality and extent of water diffusion[49]. Axial diffusivity, the first eigenvalue of the diffusion tensor, reflects the magnitude of diffusivity parallel to the direction of maximal diffusion. In the white matter, axial diffusivity is oriented along the direction of axons, and is thought to primarily relate to axonal integrity.

Given that lesions from stroke often disrupt white matter, lower FA values, especially on the ipsilesional side, are

associated with significant motor deficits[7]. Recent studies have shown that lesion load in the CST can better predict motor impairment on the Fugl-Meyer Assessment, particularly in severely impaired stroke patients. Furthermore, analyzing MRI of the brainstem and spinal cord has revealed that damage to the CST and other sensorimotor pathways, e.g., the reticulospinal and rubrospinal tracts with an increased FA, contributes to motor impairment following stroke[50, 51]. Changes in white matter integrity in these pathways correlate with the severity of motor deficits, suggesting that abnormal motor synergies and hand impairments may be related to neuroplastic changes in bulbospinal pathways. This suggests that alterations in both FA and diffusivity can provide valuable insight into how motor pathways may be affected by stroke[46]. This process of tracking water diffusion, which reflects the orientation of neural fibers, is known as tractography. FA values are typically used with two main types of tractography algorithms, deterministic and probabilistic, to improve the accuracy of fiber tracking[52-56]. However, deterministic tractography has the limitation of assuming a fixed fiber direction at each voxel, without accounting for the inherent uncertainty in fiber orientation. In contrast, probabilistic tractography samples a wider range of possible fiber orientations, generating multiple potential pathways to better capture uncertainty. While this approach is more accurate, it requires more computational resources. Some studies also use CST masks, calculated from probabilistic CST tractography either in healthy control subjects or individually for stroke patients, and overlay them onto the FA images of stroke patients. However, there are growing concerns about the accuracy of overlaying FA images by directly applying only the masks of CST tracts from either controls or stroke patients, due to variability in lesion location and size. In recent years, more detailed subsegments of the motor cortex have been explored, which improve the accuracy of tractography. For example, Derek B. Archer et al. (2018)[57] proposed a high-resolution sensorimotor area tract template (SMATT) that segments corticofugal tracts by setting seed points at six key cortical regions (HMAT) within the specific sensorimotor areas proposed by Mayka et al. (2006)[58], using DTI of 100 subjects[57]. The SMATT, along with a probabilistic version that quantifies tract overlap, offers new tools for segmenting and labeling sensorimotor tracts at higher spatial resolution (**Figure 2**). However, concerns remain about the accuracy of directly applying these outcome masks to stroke cases for extracting FA values. To address the potential inaccuracies in fiber tracking in the presence of brain lesions, Qiurong Yu et al. (2023) combined the six subregional masks from SMATT with a transcallosal tract template (TCATT) for frontal tracts, allowing for more precise fiber projections (**Figure 3**)[59, 60].

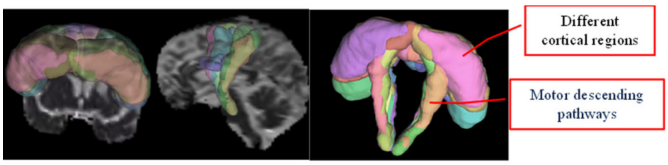

Figure 2. Different cortical regions (HMAT; left) and their underlying motor descending pathways (SMATT; middle).

They also integrated resting-state fMRI to enhance functional connectivity assessments, further improving the accuracy of their approach. Tractography is also highly sensitive to factors such as image quality, scanning parameters, and settings (e.g., diffusion modes, number of directions, and isotropic voxel size). These variables can impact the tractography process, including the step sizes used for tracking, potentially introducing bias and making it more difficult to accurately predict changes in specific motor pathways. From a practical perspective, increasing the number of diffusion directions leads to longer scan times, especially when patients require urgent care. For example, scanning with 90 diffusion directions can take up to 20 minutes[61]. Traditionally, clinical practice has used only three directions, though more recently, 6 to 12 directions have become common in neuroimaging. For research purposes, however, more directions are typically used. However, even this increase may still limit the accuracy of fiber tracking, as the eigenvectors and eigenvalues derived from water molecule diffusion may not fully capture the complexity of the white matter pathways.

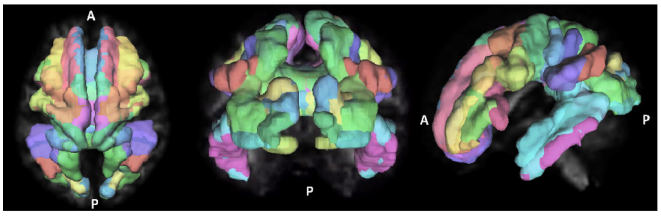

Figure 3. TCATT atlas in transverse, sagittal, and coronal views visualize the neural pathways that connect the left and right hemispheres of the brain through the corpus callosum.

As computational technology has developed, several software programs and algorithms for automatic tractography have been introduced, including DSI Studio (**Figure 4**) and MRtrix[62]. These programs utilize DWI images along with tracking parameters (e.g., angles, minimal step sizes) and predefined atlas regions for seed placement and ROIs. This facilitates the visualization and projection of motor pathway fibers easier by setting the ROI based on the default atlas, including CST and CRST areas. One the other hand, some studies have even adopted AI for fiber tractography, such as DeepDTI. Later, Hongyu Li et al. (2021) proposed SuperDTI, model trained on healthy control data that shows a quantification error of less than 5% in white-matter and gray-matter regions and has even been applied for lesion detection in stroke patients[63].

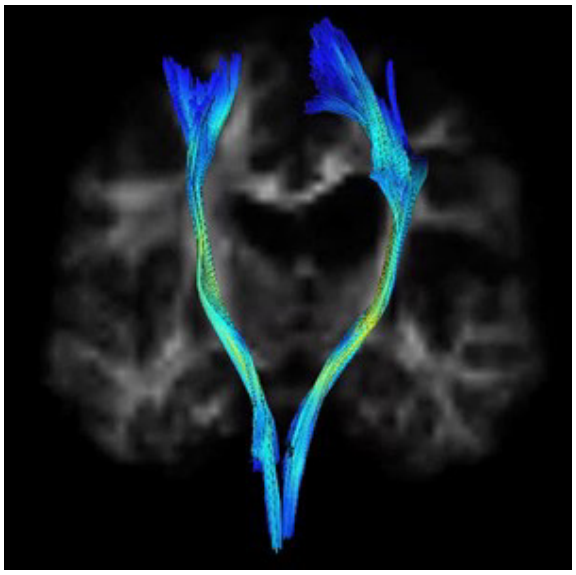

Figure 4. Automatic tractography of the corticospinal tract using the DSI Studio.

In summary, imaging-based approaches such as structural MRI provide detailed anatomical information for clinical and research purposes, helping to identify stroke lesions. Meanwhile, DWI offers a method for assessing white matter integrity through the orientation of water molecules, which is crucial for understanding the status of motor pathways following a stroke. With advancements in technology, AI now assists in lesion delineation and even performs tractography under limited conditions, enhancing our ability to analyze complex neural structures. These developments are paving the way for personalized rehabilitation strategies that are tailored to individual patient needs, ultimately improving functional outcomes.

3. TMS Motor Evoked Potential for assessing functional changes of motor descending motor pathways post stroke

3.1 Motor evoked potential on lesioned corticospinal tract

Transcranial magnetic stimulation (TMS) is a safe, non-invasive, and painless technique that can be used to investigate the excitability of the cortex and motor descending pathways[64]. With TMS, a magnetic stimulus is applied via coil, the effects of the stimulation are dependent on coil shape, size, orientation[64]. Motor-evoked potential (MEP) is a biphasic electromyography (EMG) response to TMS in the target muscles. In humans, the functional integrity of the CST can be assessed after stroke using TMS over ipsilesional M1 to elicit contralateral motor evoked potentials (cMEPs) in paretic upper limb muscles[65, 66]. The simplest method for evaluation is presence or absence of cMEPs early after stroke to gain information on functional integrity of the CST[34, 67]. Previous studies have found that the presence of cMEPs correlated with greater strength and higher FMA scores[68]. Further, if present, the features of the cMEP have gained important scientific and clinical relevance, as they have been associated to motor cortex excitability, and integrity and conduction velocity of the activated fibers of the motor pathway[69]. Specifically, the peak-to-peak amplitude provides insights into cortico-spinal excitability and the latency (or onset) provides information on the conduction within triggered neuronal pathways. Both latency and amplitude of cMEPs have been shown to be significantly correlated with clinical motor assessments post stroke[70-73]. This is shown in **Figure 5.**

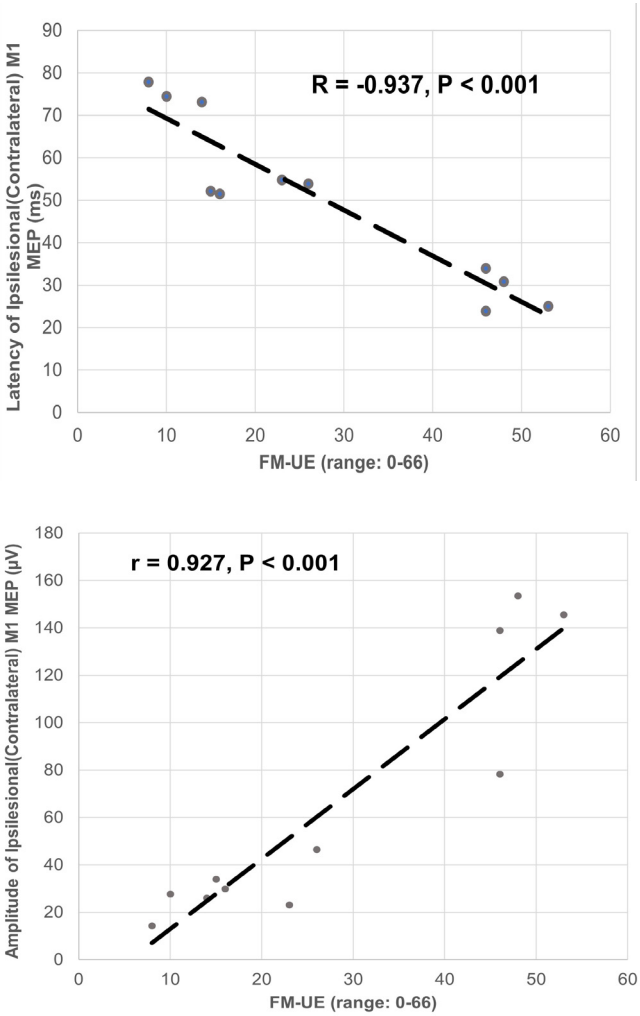

Figure 5. Correlation between the latency and amplitude of ipsilesional (contralateral) M1 MEP and FM-UE. *Adopted from [63], authors received permission from the primary author and colleagues, CC by 4.0*

However, the extraction of features from cMEPs elicited by TMS is performed manually, increasing variability due to observer-dependent subjectivity. To eliminate trials without MEPs, or with poor signal-to-noise ratio, several studies use manual protocols comprising a visual inspection of the EMG

trace from each trial, either during MEP acquisition or in posterior offline processing[74-76]. Further, the methodology employed for MEP signal processing is heterogeneous throughout the literature[77, 78]. Therefore, recent research in this field is focused on unbiased methods to automate amplitude and latency detection. Many algorisms have been presented that can accurately detect MEP amplitude and latency in healthy controls[79-81]. However, due to neurological lesion in stroke subjects, there is an increase in the variability of the extracted features[82]. This makes automation of MEP difficult and can cause unreliability even with good signal-to-noise ratio[83]. A recent method has been proposed by Tecuapetla-Trejo et al (2021). Their algorithm was able to successfully automate MEP selection and feature extraction for stroke subject in the acute phase, with no significant differences from manual measurement performed by three experts[84].

Another cause of variability in the MEP measures is the activation of the target muscle, a pre- activation will decrease the threshold required to produce a MEP, and the MEP amplitude will be larger than that of a muscle at rest[85]. This can cause intra- and inter-subject MEP variability, as subject-related parameters such as anticipation of stimulation, active thinking about body movements, or action observations have shown to effect MEP characteristics[86]. Due to the high variability of MEPs from stimulation pulse to pulse, definitions of intensity thresholds have been established as an attempt to individualize and standardize the stimulation intensity applied during TMS[87]. The conventional criteria for resting motor threshold (RMT) is the lowest stimulation intensity required to elicit an MEP of 50 μV in ≥5 of 10 trials[88] and for activated motor threshold (AMT) is defined as the lowest intensity to produce a 200 μV *MEP in ≥5 of 10 trials*[89]. However, recently, with the advancement of TMS technologies, MEPs that fall below the conventional RMT criteria (responses <50 μV) have been shown to be informative and reliable[90]. This is especially important for stroke participants as they have a lower amplitude in the paretic limb, compared to the non-paretic limb and healthy controls[91, 92].

3.2 Motor evoked potential on contralesional cortico-reticulospinal tract

Post-stroke movement disorders are not only linked to decreased function in the ipsilateral M1 and its descending CST but are also associated with enhanced activity in the contralesional premotor and supplementary motor areas[93, 94]. This suggests that post-stroke motor dysfunction involves complex interactions between both hemispheres, impacting motor control and requiring a more comprehensive approach to understanding stroke recovery mechanisms[95-97]. Most studies aiming to activate the contralesional CRST use previously published methodology for targeting the premotor cortex, by starting at M1 and moving the coil 1-3 cm medial and 2.5-3 cm anterior of the contralesional M1 and using an anterior-posterior coil orientation[98-100]. This is shown visually in **Figure 6**.

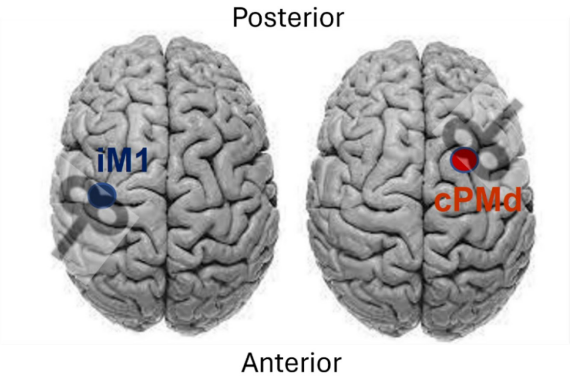

Figure 6. Coil orientation for stimulating ipsilesional primary motor cortex (iM1) and contralesional dorsal premotor area (cPMd), assuming the lesion on the left side. *Adapted from [63], authors received permission from the primary author and colleagues, CC by 4.0*

Recent research indicates post-stroke changes of CRST innervation in upper limb muscles, particularly biceps muscles, underscoring its significance in upper limb rehabilitation[101]. In stroke patients, TMS of the contralesional hemisphere (at the premotor cortex and at M1) can elicit responses in ipsilateral muscles of the paretic arm, attributed to the activation of oligosynaptic cortico-bulbospinal pathways. This response likely reflects hyperexcitability of the CRST[102-105]. While TMS is used to assess CRST excitability, the literature shows variability in stimulation targets, with inconsistent locations and frequent use of anterior-posterior coil orientation[106].

The presence of ipsilateral motor-evoked potentials (iMEPs) from contralesional motor cortex is associated with motor and neurophysiological impairments, with more frequent iMEPs observed in individuals with greater impairment, suggesting maladaptive role of contralesional CRST hyperexcitability. A study found that iMEP occurrence is higher in stroke patients with severe CST damage compared to those with milder damage[93, 107]. Stronger contralesional CRST projections (reflected by higher iMEP amplitudes) correlate with increased upper limb strength, while stronger ipsilesional CST projections are linked to better motor control and improved muscle individuation[108]. The differences in excitatory and inhibitory capacities of the contralesional CRST and ipsilesional CST provide insight into their roles: CST terminals are predominantly excitatory, while CRST terminals include both excitatory and a significant minority of inhibitory connections[109, 110]. This dual role of the CRST may mediate the muscle suppression needed to support strength, offering a potential mechanism for its contribution to motor recovery[108].

4. Cortico-muscular connectivity and inter-muscular connectivity for brain-muscular communication post stroke

4.1 Cortico-muscular connectivity

Corticomuscular techniques investigate the connections of the cerebral cortex and muscle activation using functional corticomuscular coherence (fCMC)[111, 112] and corticomuscular coherence (CMC)[113]. CMC, first presented by Conway in 1995, emphasizes the importance of cortical neurons in coordinating motor unit output and demonstrates how cortical activation directly affects muscle movements[114-116]. Additionally, these measurements capture the synchronization and coordination required for controlled movement, reflecting both efferent and afferent motor pathways[117-119].

CMC is most commonly measured by monitoring electroencephalography (EEG) signals and corresponding surface electromyography (EMG), simultaneously. This allows for visualization of real-time motor command projections and sensory feedback during voluntary activities, allowing for the identification of pathway-specific corticomuscular interactions[120-124]. Large advancement has been made in the field of CMC analysis, methods such as extended partial directed coherence (ePDC)[125], multiscale transfer entropy (MSTSE)[126, 127], multi-spectral phase coherence[128], wavelet-based coherence[129-131], and generalized cortico-muscular-cortical network (gCMCN)[132] have emerged. These methods improve causal coupling assessments across brain signals and can show complicated connections between the motor cortex and peripheral muscles[126, 128, 133, 134]. Collectively, these new results highlight the importance of fCMC in understanding motor control processes, particularly after stroke, while also emphasizing the need for enhanced techniques that go beyond typical coherence analyses to account for cortical specialization[125, 126, 135].

Linear neural connection mostly reflects direct corticospinal tracts and frequently decreases in the ipsilesional hemisphere following a stroke[119, 136-138]. However, no studies have found a substantial increase in CMC in the contralesional hemisphere during flexion synergy expression[139, 140]. This finding raises questions about the usefulness of linear coherence for studying contralesional indirect motor pathways, which may operate on a nonlinear basis. Nonlinear connectivity, defined as coupling across different frequencies, is thought to result from the nonlinear characteristic of synaptic connections, which can aggregate across several synapses in indirect motor pathways[141, 142]. In contrast, the direct corticospinal pathways have fewer synapses[143]. Cross-spectral coherence (CSC) is a method for identifying various nonlinear interactions, including harmonic and intermodulation couplings, which can be observed in both static and dynamic nonlinearities[114, 119]. Additionally, the creation of the n:m coherence analysis approach enables a comprehensive measurement of cross-frequency coupling between different frequency components approach[144, 145]. In chronic hemiparetic stroke, the recruitment of contralesional indirect motor pathways, such as the corticoreticulospinal tract (CRST), has been linked to the expression of flexion synergy, as evidenced by cross-spectral connectivity analyses that show increased nonlinear connectivity during shoulder abduction tasks[16], as shown in **Figure 7**.

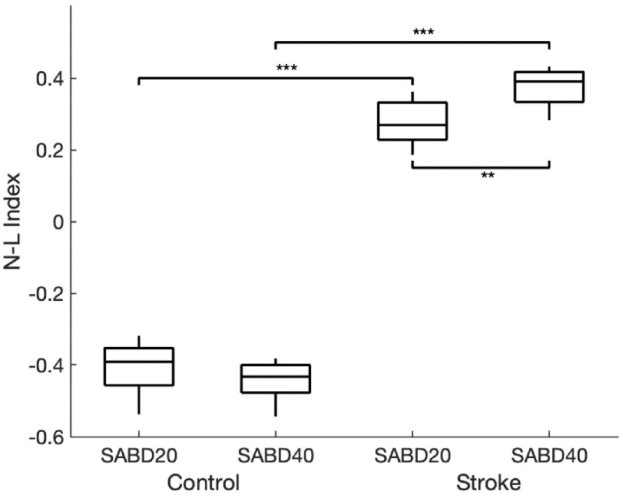

Figure 7. N-L index (nonlinear-over linear connectivity index): N-L Index = (SN-SL) / (SN+SL), where SL is the sum of linear connectivity and SN is sum of nonlinear connectivity for control and stroke subjects with different level of shoulder abduction (SABD). Two-sample t-test was applied across groups with same level of SABD, and paired t-test was applied among groups with different levels of SABD. ** for p-value < 0.01 and *** for p-value < 0.001. *Adapted from [16], authors received permission from the corresponding author and colleagues, CC by 4.0*

Cortical oscillations between the cortex and the muscle are also direction-dependent[133, 144, 145]. Previous research has demonstrated that information flow between cortico-cortical regions is directed, and similar directional viewpoints are recognized while analyzing corticomuscular interactions[119, 133, 141]. The strength of this oscillatory component of the cortical drive can serve as an index of cortical excitability and corticospinal tract integrity[139, 140, 146, 147], as a primary cause of movement difficulties in stroke patients is irregular nerve oscillation transmission due to the reduction in the brain's neurological control over muscle movements[148]. Additionally, assessing alterations in CMC time delays may also give insight into changes in motor descending pathways post stroke. Stroke participants have been shown to have significantly longer nerve conduction delays between the EEG signal from the ipsilesional motor cortex and the EMG signal from the tested muscles, suggesting the increased delay caused by the absence of direct corticospinal projections[149]. One could also asses CMC time delays

between contralesional cortex and the muscles of the paretic limb to evaluate both corticospinal tract's damage and signal transmission in the contralesional cortico-reticulospinal pathway[15, 150].

Following a stroke, it is important to highlight that patients have considerably lower mean beta CMC values than healthy controls[151]. Beta oscillations help to maintain stable load during muscular contractions and relate to higher force output in dynamic tasks[152]. Beta-CMC is a significant measure of motor system performance as it is essential for connecting motor cortex activity to muscle function during hand movements, indicating integration and coordination[112, 120, 146]. Recently, Beta-CMC has been found to be considerably disrupted between ipsilesional motor cortex and the paretic side deltoid muscle in stroke patients, as seen by an increased nerve conduction delay from the motor cortex to the deltoid[149]. Chronic stroke patients have also been shown to exhibit significantly lower Beta-CMC during stable force contraction tasks compared to healthy persons, implying that proprioceptive disruptions may reduce beta oscillations, decreasing fCMC and motor control precision[128, 135, 153]. Measuring Beta-CMC is an effective method for evaluating motor descending pathways and evaluating both linear and nonlinear brain-muscle connection can reveal information about the participation of ipsilesional CST and contralesional CRST. For example, more linearity in Beta-CMC indicates increased contralateral corticospinal activity, whereas higher nonlinearity indicates increased ipsilateral corticoreticulospinal activity, offering a holistic picture of motor pathway functionality[143].

4.2 Inter-muscular connectivity

Stroke-induced motor impairments disrupt not only the direct brain-muscle pathways but also the coordination among various muscles that are crucial for performing complex and coordinated movements[16]. This occurs because the patients' intermuscular coordination abilities, or muscle synergy, become altered or weakened[154]. Previous research, using EMG patterns, found that the specific altered upper limb muscle synergies of stroke involve the abnormal coupling of shoulder and elbow muscles during dynamic reaching[155]. Further, flexion of paretic wrist and fingers is involuntarily coupled with certain shoulder and elbow movements[11]. Abnormal coactivation of the three heads of the deltoid muscle has also been observed in stroke[156]. These abnormal muscle synergies are associated with motor impairment; the incidence of abnormal muscle co-activation increases as the severity of motor impairment increases[157, 158]. From this perspective, while traditional stroke rehabilitation often focuses on the strength and recovery of individual muscles, since actual movement occurs through the cooperation of various muscles, the importance of investigating abnormal muscle coactivation should be emphasized in the stroke neurorehabilitation.

A representative method used to evaluate intermuscular interactions is inter-muscular coherence (IMC). This analytical technique is an effective way to observe neural synchronization between muscles[159], serving as a metric that quantifies the correlation between pairs of electromyographic (EMG) signals across frequency bands[160, 161]. IMC explains the extent of shared contributions of descending neural activity among the motor neuron pools located in the spinal cord and the strength of neural synchronization at different frequency bands[162], and it signifies the functional relationships between muscles that are activated together in specific patterns or synergies to effectively complete motor tasks[152, 159]. IMC can be calculated using the following equation:

$$|C_{xy}(f)|^2 = \frac{|P_{xy}(f)|^2}{P_{xx}(f) \cdot P_{yy}(f)}$$

where f denotes the frequency of each EMG signal, $P_{xx}(f)$ and $P_{yy}(f)$ are auto-spectra of the rectified EMG signals of any muscle pair at a given frequency and $P_{xy}(f)$ is the cross-spectrum between them. To measure the importance of the coherence between muscles, a metric known as confidence level (CL) is implemented[163]:

$$CL = 1 - (1 - \alpha)^{\frac{1}{L-1}}$$

Where α signifies the degree of significance (α = 0.95) and L indicates the number of data segments utilized for spectrum estimation. The coherence between two muscles is recognized as significant if its value surpasses the confidence level (CL)[164].

A review of previous studies reveals that IMC analysis found significantly lower coherence in the alpha frequency band between the anterior deltoid and triceps brachii muscles in stroke patients compared to healthy controls[165]. Watanabe et al. found that using beta-band IMC, which reflects CST activity, intermuscular coherence increased with rising difficulty in postural tasks among young and elderly adults[166]. Further, IMC in the beta frequency band can serve as a synchronization index for assessing upper limb motor dysfunction in stroke patients[167]. In this way, IMC across each frequency band can serve as a synchronization index for evaluating motor dysfunction in stroke patients, helping to understand patient characteristics.

In the context of motor descending pathways, IMC can serve as a critical indicator of the flexion synergy that results from increased reliance on the corticoreticulospinal tract. As IMC reflects the shared descending neural drive among

motor neuron pools in the spinal cord. IMC plays an essential role in understanding and analyzing these symptoms, providing insights that can inform the development of more sophisticated rehabilitation protocols. Such research is crucial for enhancing the recovery process in stroke patients.

5. Limitation and challenges

Although much work has been done in the field, several challenges remain for accurately quantifying changes in motor descending pathways post stroke. Many of the techniques described use manual processes that are labor-intensive, time consuming, and have inter-observer variability. The analysis highly depends on the experience of the observer, leading to inconsistencies and potential errors. AI-based software is being developed to streamline these processes, but it is not yet widely adopted in clinical practice[168]. There are also unique challenges in improving these AI-based methods for stroke. Data quality and availability complicate the development of reliable AI tools. Moreover, the "black box" nature of many AI algorithms, where the decision-making process is not easily interpretable, creates hesitation among clinicians to fully trust AI-based tools. The integration of AI models into clinical workflows remains challenging due to concerns the accuracy.

While there is a large number of randomized control trials evaluating stroke rehabilitation of the upper extremity, research quality continues to be a challenge. Only a small percentage of have multi-center trials and many have limited sample sizes[169]. In a recent review of randomized controlled trails for rehabilitation of the upper limb post stroke, the median sample size (start/finish) was found to be 30 (IQR 20-48)/29 (IQR 19-44)[169]. Sample size is further hindered by difficulty in recruitment. Recruitment and retention for stroke rehabilitation trials have barriers such as lack of understanding of the trial, burdensome time commitment (work or lack of childcare), and transportation[170]. Neither recruitment rate or recruitment efficiency has increased in stroke trials over the past 25 years; if anything, they have decreased[171]. The small sample sizes within these trials affect the accuracy and hinder the creation of objective methods for assessing motor descending pathways post stroke.

6. Future direction: artificial intelligence and large multi-modal data registry

As mentioned in the previous section, there are significant challenges in the field of neuroengineering; however, the techniques are still evolving. With more publicly available datasets related to stroke, such as The Ischemic Stroke Lesion Segmentation (ISLES), which includes FLAIR, DWI, and Apparent diffusion coefficient (ADC) images, and Anatomical Tracings of Lesions After Stroke (ATLAS), which provides T1 images from patients at various stages (acute, subacute, and chronic), researchers can now utilize multi-modal MR images[172, 173]. These images come from different disease stages and even different scanners (e.g., GE, Philips, and Siemens). Despite potential challenges with co-registration and the fact that some images may have only undergone preliminary preprocessing, these datasets reflect conditions that are much closer to real-life scenarios.

Additionally, recently the American Heart Association/American Stroke Association hosted a challenge to merge stroke registry data, which includes patient-level and inpatient data from hospitals across the US[174]. This initiative has gained attention from the public, hospitals, and academic institutions, and is forming a trend of integrating multi-modal imaging with non-imaging datasets. Once such comprehensive datasets are established, AI models can be trained with both imaging data and clinical assessments, such as stroke outcomes, complications from treatment, or even muscle assessments. With the integration of non-imaging data, such as functional movement assessments, AI models can be further trained to predict the effectiveness of rehabilitation interventions. These models could identify patterns that link muscle function recovery with brain lesion characteristics, enabling personalized rehabilitation plans that optimize recovery for each patient. Furthermore, AI could help track progress over time, offering real-time feedback to clinicians and patients, improving rehabilitation protocols and outcomes.

With this richer, more holistic dataset, AI models can be developed to be more objective and accurate. These models may even be able to predict patient outcomes based on lesion characteristics, functional impairments, and muscle rehabilitation progress, offering the potential for personalized treatment in clinical practice in the future.

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