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# Near-infrared spectroscopy as a promising tool in stroke: Current applications and future perspectives

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Stroke is caused by an acute focal disruption of the vasculature in the central nervous system. Neurological-related functional deficits are the most devastating consequences for stroke survivors. Neural signals from stroke patients can reflect the functional statuses of patients and provide insights into the neuronal recovery mechanism for functioning, which could be used as the basis for designing optimal treatment strategies. Near-infrared spectroscopy (NIRS) is a low-cost, noninvasive, easily operated neuroimage method and it is compatible with various rehabilitative programs. These advantages make NIRS an excellent candidate in research for stroke recovery. Here, we focused on the brain functions and recovery for stroke patients at stable status, conducted a systematic literature review about NIRS applications in stroke since 2000 and identified a total of 72 references through ScienceDirect and PubMed database retrieval. The NIRS studies in stroke include resting-state function and its recovery, motor function and its

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recovery, motor and cognition interference, cognitive function and its recovery, language function and its recovery, emotional function and its recovery and other applications. Based on the results of the quality assessment, we identified some study gaps from the previous research and provided suggestions for some methodological improvement in the future. The trend of NIRS gives a boost to its application in stroke, and the potential research directions for NIRS in stroke are prospected, including multi-center clinical research, treatment efficacy prediction research and brain–muscle coupling research. Finally, limitations of NIRS are discussed.

*Keywords*: Near-infrared spectroscopy; stroke; function deficits; recovery.



## 1. Introduction

Stroke is a neurovascular disease caused by insufficient brain blood supply due to the sudden rupture of blood vessels (cerebral hemorrhage) or blood vessel blockage (cerebral infarction) in the brain. It is a global disease burden, characterized by high morbidity, mortality, and disability. Stroke was ranked as the second largest cause of death and disability-adjusted life-years globally reported in 2016.[1] The consequences of stroke include hemiparesis, sensory and motor impairment, perception impairment, cognitive impairment, aphasia, dysphagia, etc.[2] The function impairment caused by stroke seriously affects patients' quality of life and their return to society.

The function recovery after stroke has been attributed to plasticity and reorganization of the brain.[3] Monitoring neural signals can be an effective way to study the functional status and recovery for stroke patients, and can be used as the basis for treatment strategies development. Nowadays, the most used imaging techniques in stroke prognosis are functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), electroencephalography (EEG), magnetoencephalography (MEG) and electromyography (EMG).[4–6] Among these techniques, NIRS can provide a reasonable spatial and temporal resolution that was between fMRI and EEG. NIRS has less constraint for subjects during measurement and could obtain results with high ecological validity. This characteristic makes NIRS and has a unique advantage when investigating motor function as well as physical rehabilitation training in stroke. Furthermore, NIRS is low-cost, easily operated, and noninvasive.

Because of these merits, NIRS has excellent potentials for widespread applications in stroke.[5,7,8] A recent review by Yang *et al.* has systematically reviewed the use of NIRS in stroke.[5] Their review covered a wide range of studies, including studies using NIRS in bedside or intraoperative monitoring, studies about patients at risk of stroke, and studies on brain function and recovery after stroke. They concluded that previous research provided preliminary evidence of NIRS in stroke as a monitoring, therapeutic, and research tool.

The ongoing development of NIRS technology gives a boost to research on stroke applications. Here, we focused on the brain functions and recovery for stroke patients at stable status and performed a systematic review from the previous studies. We assessed and discussed the quality of the published studies including experimental design, data processing and statistical analysis, discussed the latest trend of NIRS and its impact on stroke studies, finally prospected the potential research directions for NIRS in stroke.

## 2. Basics of Near-Infrared Spectroscopy

NIRS has been a promising and noninvasive optical functional neuroimaging method since it was first described by Jöbsis 40 years ago.[9] Its measurement is based on the tissues' optical properties of high scattering and low absorption to near-infrared light (700–900 nm). The scattering is about 100 times more probable than absorption,[10] which makes that the light could penetrate the brain cortex (or the muscle tissue) and then be scattered back to the measurement surface with sufficient photons for detection. The absorption is mainly associated with the interaction between photons and chromophores in the tissue.

NIRS techniques can be classified as continuous wave (CW), time-resolved spectroscopy (TRS), and frequency domain spectroscopy (FDS). The CW system emits CW light and measures the change of light intensity. According to Lambert–Beer's law,

the change in light attenuation due to absorption is proportional to chromophore concentration. Because of scattering, the pathlength of photons in the tissue remains unknown. Hence, the CW system could only measure concentration changes of oxyhemoglobin ($\Delta$ [$HbO_2$]), deoxyhemoglobin ($\Delta$ [Hb]) and total-hemoglobin ($\Delta$ [tHb]). The TRS system illuminates the tissue with a short ($\sim 100$ ps) light pulse and obtains light's time point spread function. The FDS system emits intensity-modulated light and detects both attenuation and phase delay of emerging light. TRS and FDS can identify the optical properties of tissues, including the reduced scattering and absorption coefficients, and get absolute concentrations for $HbO_2$ and Hb.[11,12] Nowadays, the CW system is mostly used in cognitive and clinical research.[13–16]

For NIRS measurements, each source-detector channel's sensitivity exhibits a banana-shaped profile resulting from light diffusion in all directions inside the tissue. The maximum detection depth is about half of source-detector separation.[17] With a proper source-detector separation (e.g., 3 cm), NIRS can measure brain activation from the gray matter (Fig. 1). For CW-NIRS, the modified Lambert–Beer's law relates the light attenuation change to chromophore concentration change under the assumption of constant light scattering and homogeneous light absorption (Eq. (1))[18]:

$$\Delta \mathrm{OD} = \alpha \times \Delta c \times \mathrm{DPF} \times d, \tag{1}$$

where OD is the light attenuation, $\alpha$ is the specific absorption coefficient, $c$ is the chromophore concentration. DPF is the differential pathlength factor that can be obtained from the previous references,[19]

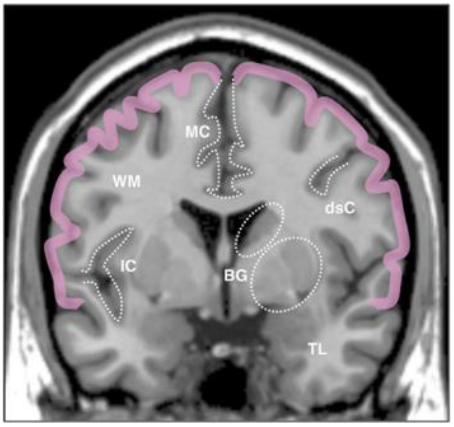


Fig. 1. Coronal slice illustrating brain structures accessible with NIRS (pink ribbon).[20] Reproduced with permission from Ref. 18.

and $d$ is the source-detector separation. Usually, at least two different wavelengths are used in CW-NIRS. One is sensitive to $HbO_2$, and the other is sensitive to Hb. Thus, the concentration changes of $HbO_2$ and Hb can be obtained according to the following equation

$$\begin{aligned}\Delta \mathrm{OD}^{\lambda 1} &= (\alpha^{\lambda 1}_{\mathrm{Hb}} \Delta_{C_{\mathrm{Hb}}} + \alpha^{\lambda 1}_{\mathrm{HbO_2}} \Delta_{C_{\mathrm{HbO_2}}}) \times \mathrm{DPF}^{\lambda 1} \times d \\ \Delta \mathrm{OD}^{\lambda 2} &= (\alpha^{\lambda 2}_{\mathrm{Hb}} \Delta_{C_{\mathrm{Hb}}} + \alpha^{\lambda 2}_{\mathrm{HbO_2}} \Delta_{C_{\mathrm{HbO_2}}}) \times \mathrm{DPF}^{\lambda 2} \times d\end{aligned}. \tag{2}$$

## 3. Method

### 3.1. *Search strategy*

We searched the ScienceDirect and PubMed databases to systematically review all original published research using NIRS in stroke patients since 2000. The initial search was conducted in the ScienceDirect database by using the following search terms: "stroke" and ("NIRS" or "near-infrared spectroscopy" or "optical methods"), and yielded 903 papers. After initial title selection and abstract screening, we eliminated abstract articles, theoretical articles, review articles, case reports, animal studies, and bedside or intraoperative monitoring studies. Then we searched the PubMed database, and finally identified a total of 72 stroke studies with NIRS (Fig. 2). Among these studies, 10 are on the resting-state function and its recovery (Table 1), 39 are about motor function and its recovery (Table 2), seven are on motor and cognition interference (Table 3), three are on cognitive function and its recovery, two are about language function and its recovery, two are about emotional function and its recovery and nine are for other applications in stroke.

### 3.2. *Assessment of study quality*

Referring to the National Institutes of Health's Quality Assessment tool for Observational cohort and Cross-sectional studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) and the Joanna Briggs Institute critical appraisal tools for Quasi-Experimental Studies (https://jbi.global/critical-appraisal-tools), we evaluated the quality of 68 included studies (four studies about the NIRS method were excluded) including experimental design, data processing and statistical analysis. We used the following questions as criteria: (1) Was

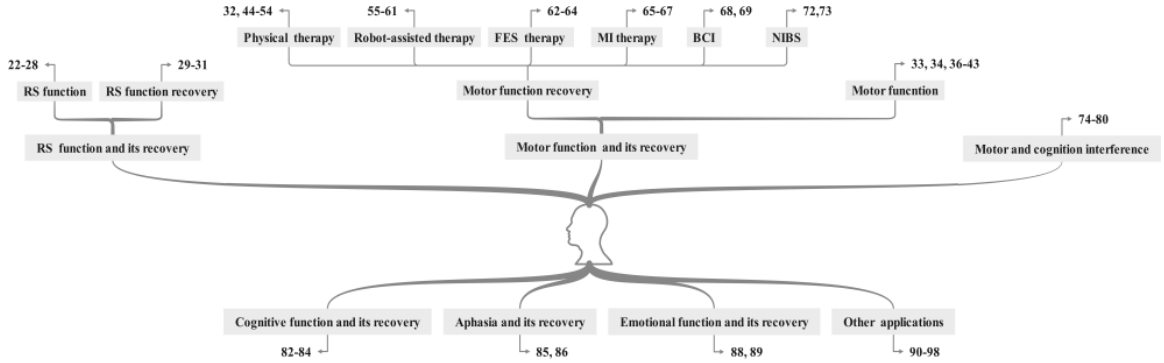


Fig. 2. Summary of NIRS application in stroke. The number represents the reference number.

the research objective clearly stated? (2) Was the study population clearly specified and defined? (3) Were the inclusion and exclusion criteria prespecified and uniformly applied to all participants? (4) Was sample size justification, power description or variance and effect estimated provided? (5) Were the exposure(s) of interest measured prior to the outcome(s)? (6) Were the exposure measures clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Was there a control group? (8) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? (9) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

## 4. NIRS In Stroke Studies

### 4.1. *Resting-state function and its recovery*

#### 4.1.1. *Resting-state function*

Resting state (RS) is an organized baseline default mode of the brain. The RS function has been an important method to investigate brain diseases, including stroke.[21] Table 1 summarizes RS studies in stroke with NIRS. Li *et al.* investigated the cerebral spontaneous oscillations with NIRS during RS, and identified five oscillations from different frequency intervals representing various physiological activities.[22] The oscillations from frequency intervals of $0.4 \sim 2$ Hz and $0.15 \sim 0.4$ Hz mainly reflected the cardiac and respiratory activities. Oscillations of $0.06 \sim 0.15$ Hz, $0.02 \sim 0.06$ Hz and $0.005 \sim 0.02$ Hz reflected myogenic activities, neurogenic activities of the vessel wall and endothelial related metabolic activities, respectively. Afterward, they conducted a series of studies to assess the amplitude and connectivity characteristics for different RS oscillations in stroke patients. They found that patients with cerebral infarction (CI) had significantly lower oscillation amplitudes in I ($0.005 \sim 0.02$ Hz), II ($0.02 \sim 0.06$ Hz), III ($0.06 \sim 0.15$ Hz), and V ($0.4 \sim 2$ Hz) frequency intervals.[22] The RS oscillation amplitude also reduced in subjects at risk for stroke.[23]

Stroke patients showed abnormal functional connectivity (FC) in different RS oscillations. Han *et al.* found that elderly patients with CI had a significant reduction of wavelet coherence and wavelet phase coherence in the prefrontal cortex (PFC) at the 0.052–0.145 Hz frequency interval, indicating reduced RS functional connectivity (RSFC) between the left and right PFC and disruption of neurovascular coupling.[24] Hypertension could aggravate the PFC phase synchronization changes in stroke patients.[25] Tan *et al.* further showed that elderly patients with CI had more extended RSFC abnormalities in different frequency intervals.[26] Su *et al.* analyzed the coupling between cerebral oxyhemoglobin and mean arterial pressure (MAP) signals in different frequency intervals. The increased coupling from MAP to cerebral oxyhemoglobin indicated the impaired cerebral autoregulation in patients.[27] As to effective connectivity (EC), Liu *et al.* demonstrated a significant reduction of coupling strength of EC in CI patients. The coupling direction changed from the motor cortex (MC) driving PFC to PFC driving MC, which is different from the healthy subjects. These findings indicated that information transmission was blocked in patients resulting in coupling strength decrease and connectivity loss.[28]

Table 1. Summary of NIRS studies in RS function and its recovery.

| Reference | Subjects | Type of stroke | Time since stroke | Device | Measured regions (channels) | Clinical applications |
|---|---|---|---|---|---|---|
| Li *et al.*[22] | PT: 10 (7 M) age = 65 ± 7 years NS: 10 (7 M) age = 63.5 ± 6.4 years | CI | >12 months | TSAH-100 | forehead (1) | assess the cerebral oxygenation oscillations in PT |
| Li *et al.*[23] | PT: 12 (10 M) age = 60.3 ± 10.1 years NS: 20 (14 M) age = 59.6 ± 10.2 years | CIA | | TSAH-100 | forehead (1) | assess the cerebral oscillations in subjects at risk for stroke |
| Han *et al.*[24] | PT: 10 (7 M) age = 74.4 ± 9.0 years NS: 18 (7 M) age = 69.9 ± 7.3 years | CI | >12 months | TH200 | forehead (2) | assess the prefrontal RSFC for PT |
| Han *et al.*[25] | PT: 21 (12 M) age = 76.6 ± 8.5 years NS: 21 (9 M) age = 69 ± 7.4 years | CI | >12 months | TH-200 | forehead (2) | assess the phase relationship of PFC oscillations in PT |
| Tan *et al.*[26] | SP: 12 (6 M) age = 79.0 ± 7.2 years NS: 16 (8 M) age = 68.7 ± 8.6 years | CI | >12 months | TH200, OXYMON MK III | PFC, SMC (10) | assess the frequency-specific RSFC in PT |
| Su *et al.*[27] | PT: 17 (14 M) age = 55.4 ± 10.7 years NS:17 (9 M) age = 51.8 ± 7.9 years | CI | 2 ∼ 6 months | NirScan | PFC, PL, OL (24) | analyze coupling between cerebral oscillations and MAP |
| Liu *et al.*[28] | PT: 11 (6 M) age = 72 ± 7.6 years NS:11 (5 M) age = 65 ± 6.3 years | CI | >12 months | NirScan | PFC, MC (10) | assess the frequency-specific EC in PT |
| Huo *et al.*[29] | PT: 20 (20 M) age = 62.5 ± 7.3 years | CI | 1 ∼ 5.5 months | NirSmart | PFC, MC, OL (32) | investigate MNES-related changes in RS EC |
| Xie *et al.*[30] | PT: 27 (24 M) age = 64.7 ± 9.9 years | CI:17 CH:10 | 1 ∼ 6 months | NirSmart | PFC, MC, TLC (32) | investigate how intermittent sequential pneumatic compression affected brain function |
| Arun *et al.*[31] | PT: 20 NS: 20 | | 4 ∼ 8 weeks | NIRSport | MC (20) | identify the RSFC change during recovery |

*Notes*: PT: patients; NS: normal subjects; M: male; PL, parietal lobe; TLC, temporal lobe cortex; CIA: cerebral ischaemia.

#### 4.1.2. *RS function recovery*

Along with recovery, the RSFS for stroke patients reorganized. Huo *et al.* found that stroke patients showed significantly increased connectivity from PFC to the occipital lobe (OL) in the median nerve electrical stimulation state (MNES) compared with the RS. This connectivity changed from bilateral to ipsilateral. The connectivities between right PFC and left PFC, between right PFC and left MC, between right PFC and right MC changed from ipsilateral in RS to bilateral in MNES.[29] The intermittent sequential pneumatic compression could induce increase of oscillation amplitude in bilateral MCs.[30] Arun *et al.* observed significantly decreased ipsilesional connectivity, increased contralesional connectivity, and decreased connectivity between the left and right MCs in patients with left hemispheric stroke. For patients with right hemispheric stroke, there was an obvious increase in the ipsilesional connectivity and connectivity between the left and right MCs. During recovery, connectivity normalization was observed in the ipsilesional

MC and between bilateral MCs.[31] This means that RSFC reorganization could reflect recovery after stroke.

### 4.2. *Motor function and its recovery*

Motor dysfunction is the most common function deficit after stroke. NIRS was useful for investigating the cerebral blood volume and oxygenation during different rehabilitation tasks in stroke patients.[32] Nowadays, NIRS has been used in motor recovery with physical therapy, robot-assisted therapy, electrical stimulation, motor imagery (MI), brain–computer interface (BCI) and noninvasive brain stimulation (NIBS). NIRS studies about motor function and its recovery are listed in Table 2.

#### 4.2.1. *Motor function*

There are six studies investigating the upper limb (UL) motor function in stroke patients with cerebral oxyhemoglobin. NIRS was proved to be an alternative and effective way to assess the cerebral activation in spite of patients' baseline circulatory status.[33,34] Both the contralateral and ipsilateral MC activation contributed to the motor function recovery after stroke.[35] Kato observed an extended activation in both the contralateral and ipsilateral MCs (primary motor cortex, PMC, and supplementary motor areas, SMA) for chronic stroke patients during hand movement.[36] Similarly, Lim *et al.* found that chronic stroke patients had more activation of ipsilesional sensorimotor cortex (SMC) during the reaching and gripping task but with worse performance compared with healthy controls. The bilateral SMC activation was significantly correlated with the gripping performance when using the weaker arm or both arms for patients.[37] Bilateral SMC activated during affected hand movements early after stroke ($< 25$ days), and then the activation returned to normal pattern at later stage ($> 35$ days).[38] Sakurada *et al.* found that internal focus dominant participants showed significantly higher activation in left PFC than external focus dominant participants during rhythmic hand movements. This result means that for stroke patients, there are individual differences for strategies to improve motor function. Thus, the rehabilitation and training programs should be personalized.[39]

One study reported the hemodynamic changes of forearm extensor muscles during flexion and extension of the fingers for patients.[40] The oxygenation and blood volume showed no evident difference between dominant and nondominant muscles for control subjects, while $\Delta$ [$HbO_2$] in the paretic muscle is significantly lower than that in the nonparetic muscle for patients. Results supported a shift toward more anaerobic metabolism in affected muscles after stroke.

Three papers were found for gait and postural balance, and confirmed the critical role of MC and PFC in gait and balance control after stroke. Miyai *et al.* found that the bodyweight support lowered SMC activation for patients, and the improvement of gait correlated with the improvement of asymmetry in SMC activation.[41] Mihara *et al.* found that for infratentorial stroke patients with ataxia, PFC activation was sustained throughout the whole gait period, reflecting the compensatory mechanisms for locomotor control.[42] They also observed postural perturbation-related activation in the bilateral PFC, the contralesional premotor area (PMA) and parietal association cortical areas for stroke patients.[43]

#### 4.2.2. *Motor function recovery*

**Physical therapy**

Four studies are about recovery of UL motor function. Hatakenaka *et al.* observed that UL performance gains in the pursuit rotor (PR) task were significantly lower for patients compared to healthy subjects, indicating their motor learning deficit. The PFC activation in the PR task shifted from the pre-SMA to SMA with task repetitions in healthy subjects but not in patients.[44] It was found that along with the two-month rehabilitation training, SMC activation related to the paretic-arm movement shifted from the contralesional to ipsilesional hemisphere, and this progressive lateralization changed concomitantly with increase in the Fugl-Meyer assessment (FMA).[45] Kinoshita *et al.* also found that after two-month physical and occupational therapy, the improvement in UL motor function was negatively correlated with the change of laterality index (LI) in Brodmann Area 4 for stroke patients with moderate-to-severe UL hemiparesis.[46] Bai *et al.* used the hand grasp-and-release task and demonstrated that Remind-to-Move treatment enhanced the recruitment of contralateral PMC and is useful for recovery.[47]

For motor function of lower limb (LL), Lin *et al.* demonstrated that active cycling with speed

Table 2. Summary of NIRS studies in motor function and its recovery.

| References | Subjects | Type of stroke | Time since stroke | Device | Measured regions (channels) | Clinical applications |
|---|---|---|---|---|---|---|
| Saitou *et al.*[32] | PT: 44 (31 M)<br>age = 66.0 ± 9.3 years<br>NS: 24 (2 M)<br>age = 22.6 ± 4.1 years | CI: 33<br>CH: 11 | > 3 months | HEO-200 | forehead | measure PFC activation under rehabilitation tasks |
| Murata *et al.*[33] | PT: 6 (4 M)<br>age: 42 ∼ 68 years<br>NS: 6<br>age: 28 ∼ 68 years | CIA | 3 ∼ 12 months | NIRO-300 | PSMC<br>(2) | compared NIRS and fMRI activation during a motor task |
| Murata *et al.*[34] | PT: 10 (7 M)<br>age = 58.2 ± 9.6 years<br>NS: 10 (8 M)<br>age = 52.5 ± 9.9 years | TIA: 9<br>CI: 1 | < 1 month | NIRO-300 | PSMC<br>(2) | evaluate mechanisms for failure of BOLD imaging in PT |
| Kato *et al.*[36] | PT: 6 (4 M)<br>age = 72.3 ± 7.3 years<br>NS: 5 (3M)<br>mean age = 64 years | CI | > 2 months | a optical system (Hitachi) | MC<br>(24) | evaluate the compensatory motor activation |
| Lim and Eng[37] | PT: 11 (10 M)<br>age = 68 ± 5.9 years<br>NS:11 (6 M)<br>age = 27 ± 3.4 years | CI: 4<br>CH: 7 | > 6 months | NIRSport | SMC<br>(20) | determine the SMC activation during the unrestrained motor task |
| Takeda *et al.*[38] | PT: 5 (1 M)<br>age = 63.2 ± 9.0 years<br>NS: 5 (2 M)<br>age = 54 ± 11.7 years | CI | > 3 days | ETG-4000 | ROI: PSMC<br>(26) | investigate longitudinal changes of PSMC activation during recovery |
| Sakurada *et al.*[39] | PT: 18 (15M)<br>age = 65.1 ± 13.9 years<br>Yong NS: 23 (10M)<br>age = 21.4 ± 2.3 years<br>Elderly NS: 23 (16M)<br>age = 72.1 ± 5.0 years | CI: 14<br>CH: 4 | 10.7 ± 8.8 days | ETG-7100 | ROI: PFC<br>(15) | identify neurological basis for individual optimal attentional strategy |
| Msoudi Motlagh *et al.*[40] | PT: 6<br>age = 64.6 ± 12 years<br>NS: 6<br>age = 30.3 ± 5 years | CI<br>CH | > 6 months | Custom made oximetry | two forearm muscles: extensor, flexor (2) | test if hemodynamic activity in paretic muscles is suppressed |
| Miyai *et al.*[41] | PT: 6 (5 M)<br>age = 57 ± 6 years<br>NS: 5 (3 M)<br>age = 53 ± 11 years | CI: 4<br>CH: 2 | 75 ± 27 days | OMM-2001 | frontoparietal regions<br>(36) | investigate whether BWS affected cortical activation during gait |

Table 2. (*Continued*)

| References | Subjects | Type of stroke | Time since stroke | Device | Measured regions (channels) | Clinical applications |
|---|---|---|---|---|---|---|
| Mihara *et al.*[42] | PT: 12 (11M)<br>age = 52.7 ± 16.9 years<br>NS:11<br>age = 42.6 ± 11.6 years | CI: 6<br>CH: 6 | 88.3 ± 44.8 days | OMM-3000 | frontoparietal regions (42) | investigate cortical activations during ataxic gait in PT |
| Mihara *et al.*[43] | PT: 20 (15 M)<br>age = 61.6 ± 11.9 years | CI: 11<br>CH: 9 | 111.4 ± 89 days | OMM-3000 | frontoparietal regions (50) | investigate postural perturbation-related brain activation |
| Hatakenaka *et al.*[44] | PT: 12 (10 M)<br>age = 56 ± 16 years<br>NS: 6 (3 M)<br>age = 53 ± 9 years | CI: 6<br>CH: 6 | > 2 months | OMM-2001 | frontoparietal regions (42) | study how motor learning capacity affects rehabilitation |
| Delorme *et al.*[45] | PT: 10 (6 M)<br>age = 61 ± 7 years<br>NS: 8 (5 M)<br>age = 56 ± 6 years | CI: 7<br>CH: 3 | 23.7 ± 5.4 days | Oxymon | MC (SM1) (16) | assess the time course of SMC activation and motor recovery |
| Kinoshita *et al.*[46] | PT: 8 (1 M)<br>age = 68.8 ± 7.1 years | CI: 4<br>CH: 4 | > 1 month | FOIRE-3000 | frontoparietal regions (49) | study the association between motor recovery and interhemispheric imbalance |
| Bai and Fong[47] | PT: 12 (6 M)<br>age = 63.3 ± 6.9 years<br>NS:15 (12 M)<br>age = 55.0 ± 7.3 years | | ≥ 6 months | ETG-4000 | MC, DLPFC (34) | investigate the brain activation for PT receiving RTM |
| Lin *et al.*[48] | PT: 17 (16 M)<br>age = 55.5 ± 12.1 years | CI: 8<br>CH: 9 | 18.7 ± 30 months | Imagent | MC (20) | study brain activation during active and passive cycling in PT |
| Miyara *et al.*[49] | PT: 11 (11 M)<br>age = 52.6 ± 15.4 years<br>NS: 6 (6 M)<br>age = 32.5 ± 3.9 years | | median time: 3 months | FOIRE-3000 | frontoparietal regions (50) | examine whether WBV induces acute changes in SMC activation |
| Jigjid *et al.*[50] | PT: 15<br>age = 63.1 ± 7.7 years | CI<br>CH | 6.9 ± 4.2 years | NIRO-300 | gastrocnemius muscle (2) | assess how passive leg movements affect muscle oxygenation and EMG activity |
| Miyai *et al.*[51] | PT: 8 (5 M)<br>age = 57 ± 12 years | CI: 4<br>CH: 4 | > 1 month | an optical imaging system (Shimadzu) | frontoparietal regions (36) | investigate neural mechanisms for locomotor recovery |

Table 2. (*Continued*)

| References | Subjects | Type of stroke | Time since stroke | Device | Measured regions (channels) | Clinical applications |
|---|---|---|---|---|---|---|
| Fujimoto *et al.*[52] | PT: 20 (17 M)<br>age = 60.2 ± 9.5 years | CI: 5<br>CH: 15 | 37 ∼ 229 days | OMM-3000 | frontoparietal regions<br>(50) | examine the cortical involvement in balance recovery |
| Huo *et al.*[53] | PT: 13 (12 M)<br>age = 50.3 ± 16 years<br>NS:16 (9 M)<br>age = 55.9 ± 8.1 years | CIA | > 2 weeks | NirScan | PFC, MC, OL<br>(24) | study limb linkage rehabilitation-related brain activity and EC |
| Lu *et al.*[54] | PT: 18 (15 M)<br>age = 46.8 ± 16.3 years<br>NS:16 (9 M)<br>age = 55.9 ± 8.1 years | | 0.5 ∼ 12 months | NirScan | PFC, MC, OL<br>(24) | investigate brain network under four-limb linkage rehabilitation in PT |
| Saita *et al.*[55] | PT: 10 (8 M)<br>age = 66.8 ± 12.0 years<br>NS: 6 (4 M)<br>age = 58.7 ± 7.1 years | CI: 8<br>CH: 2 | 23.9 ± 15 days | FOIRE-3000 | frontoparietal regions<br>(48) | study mechanisms for the rehabilitation effect using HAL-SJ |
| Massimiliano *et al.*[56] | PT: 23 (13 M)<br>age = 60.4 ± 13.2 years | CI: 15<br>CH: 8 | 3–508 months | NIMO | forearm flexor muscles | study acute effects of hand passive motion on forearm perfusion and spasticity |
| Bae *et al.*[57] | PT: 9 (8 M)<br>age = 45.3 ± 10.2 years | CI: 1<br>CH: 8 | 65 ∼ 205.6 months | LABNIRS | frontoparietal regions<br>(40) | study the optimal speed for passive wrist movements by a robot for PT |
| Song *et al.*[58] | PT:<br>Experiment: 18 (12)<br>age = 61.2 ± 12.8 years<br>Control: 18 (9)<br>age = 60.4 ± 14 years | | experiment:<br>3.4 ± 3.6 months<br>Control:<br>3.6 ± 5.4 months | NIRScout | PMC<br>(12) | study effect of robot-assisted gait training on brain activation |
| Miyai *et al.*[59] | PT: 6 (4 M)<br>age = 57 ± 13 years | CI: 2<br>CH: 4 | 81 ± 31 days | an optical imaging system (Shimadzu) | frontoparietal regions<br>(36) | assess the cortical activation during hemiplegic gait |
| Lee *et al.*[60] | PT: 20 (13 M)<br>age = 61.7 ± 6.9 years | CI: 6<br>CH: 14 | 36.7 ± 26.6 months | NIRScout | PFC, MC<br>(49) | investigate the effect of GEMS-H on cortical activation |
| Caliandr *et al.*[61] | PT: 22 (13 M)<br>age = 59.5 ± 7.9 years<br>NS: 15 (9 M)<br>age: 43 ∼ 69 years | CI | 1 ∼ 11 years | NIRO-200 | forehead<br>(2) | assess exoskeleton assisted gait |
| Hara *et al.*[62] | PT: 16 (13 M)<br>age = 18 ∼ 73“eqno −“rm ″ years | CI: 10<br>CH: 6 | 12 ∼ 24 months | ETG-4000 | PSMC<br>(24) | investigate effects of EMG-controlled FES |

Table 2. (*Continued*)

| References | Subjects | Type of stroke | Time since stroke | Device | Measured regions (channels) | Clinical applications |
|---|---|---|---|---|---|---|
| Ferrante *et al.*[63] | PT: 9 (9 M)<br>mean age = 56 years<br>NS: 7 (7 M)<br>mean age = 53 years | CI: 5<br>CH: 4 | 4 ∼ 40 days | A TRS system | rectus femoris (1) | verify whether stroke altered muscular metabolism |
| Lo *et al.*[64] | PT: 9 (5 M)<br>age = 62.9 ± 7.7 years<br>NS: 7 (2 M) | CI | 1 ∼ 53 months | NIRScout | MC (28) | study the effects of FES with different intensity during passive cycling |
| Mihara *et al.*[65] | PT: 20<br>REAL group: 10 (8 M)<br>age = 56 ± 7.9 years<br>SHAM group: 10 (4 M)<br>age = 60.1 ± 8.5 years | CI: 12<br>CH: 8 | 89 ∼ 194 days | OMM-3000 | frontoparietal regions (50) | investigate whether neuro feedback could enhance MI efficacy |
| Mihara *et al.*[66] | PT: 54<br>REAL group: 28 (21 M)<br>age = 62.3 ± 10.4 years<br>SHAM group: 26 (19 M)<br>age = 60.1 ± 12.3 years | CI<br>CH | REAL:<br>315.5 ± 535 days<br>SHAM:<br>463 ± 764.7 days | OMM-3000 | frontoparietal regions (50) | test that NIRS-NFB with SMA activation could promote gait and balance recovery |
| Brunetti *et al.*[67] | PT: 11 (7 M)<br>mean age = 62 years | CIA | 15–92 days | NIRScout | OPA and precentral areas (24) | identify factors determining MT recovery variability |
| Rea *et al.*[68] | PT: 7 (4 M)<br>age = 54.7 ± 14.1 years | | > 12 months | ETG-4000 | frontoparietal regions (48) | assess if LL motor preparation in PT can be measured and classified |
| Matarasso *et al.*[69] | PT: 4 (1 M)<br>age = 55.8 ± 7.8 years | CI: 3<br>CH: 1 | > 23 months | ETG-400<br>NIRSport | MC | conduct a pilot test of a BCI protocol |
| Tamashiro *et al.*[72] | PT: 59 (39 M)<br>mean age = 61 years | CI<br>CH | 9.5 ∼ 33 months | FOIRE-3000 | frontoparietal regions (49) | investigate the LF-rTMS/ occupational therapy effect |
| Rezaee *et al.*[73] | PT: 12 (12 M)<br>age = 46 ± 13 years | | 1 ∼ 6 years | OctaMon+ | PFC, SMC (8) | evaluate the feasibility of combined NIRS and EEG to identify responders to tDCS |

*Notes*: CH: cerebral hemorrhage; TIA: transient ischemic attack; ROI: region of interest; OPA: occipito-parietal areas.

feedback induced better cycling performance as well as increased activation in unaffected PMC compared to active cycling without feedback.[48] A study from Miyara *et al.* found that the whole-body vibration improved the spasticity in stroke patients and evoked increased bilateral SMC activation, especially the contralesional SMC.[49] Jigjid *et al.* found that the EMG activity and muscle oxygenation in both paretic and nonparetic lower limbs increased in passive leg movements. Patients with better motor function recovery showed less difference in the $HbO_2$ level between the affected and unaffected muscle. This study shows that even passive leg movement is effective to prevent metabolic deterioration in LL after stroke.[50]

Gait function is an important factor that determines the ability to complete activities of daily living independently. Miyai *et al.* investigated MC activation changes in stroke patients before and after two-month of inpatient rehabilitation. After rehabilitation, the motor function improved, the PMC activation in the affected hemisphere increased, and the asymmetry in SMA activation significantly improved which was correlated with gait improvement.[51] Fujimoto *et al.* found that after intensive rehabilitation, postural perturbation-related activations in PFC and bilateral SMA were observed in patients. Bilateral SMA activation was significantly increased after rehabilitation, and the SMA activation increment of the unaffected hemisphere was positively correlated with the gain in balance function.[52] This means that SMA plays an important role in the control of postural balance and gait function recovery for stroke patients.

Two studies investigated the influence of four-limb linkage rehabilitation training on brain connectivity in stroke patients. Huo *et al.* found that patients had more activation in the contralesional MC than that in the ipsilesional MC during the rehabilitation task state (RTS), while healthy controls showed similar activation in bilateral MCs. For patients, the coupling strength from the MC and OL to the contralateral PFC in the low frequency interval was significantly higher.[53] The wavelet phase coherence was also modulated during RTS for patients.[54] These results indicate that four-limb linkage rehabilitation may induce plastic reorganization of cognitive resource to compensate the impaired function.

**Robot-assisted therapy**

Robot-assisted therapy can improve the recovery of UL motor function. Its effect manifests in both the UL perfusion and the brain activation. Saita *et al.* found that after treatment with single-joint hybrid assistive limb (HAL-SJ) robot, the number of elbow flexion/extension movements within 15 s and the ipsilesional PMC activation prominently increased for patients.[55] Gobbo *et al.* evaluated the acute effects of robot-assisted hand passive motion on forearm local perfusion and UL spasticity in patients with hemiparesis. They found evident improvements in forearm perfusion and decreased UL heaviness and stiffness.[56] Researchers also evaluated the optimal parameter setting under robot-assisted therapy. Bae *et al.* found that compared with 0.25 Hz and 0.5 Hz, passive wrist movements at 0.75 Hz by a rehabilitation robot gave rise to the greatest activation in the contralateral SMA, PMA and somatosensory association cortex for stroke patients, suggesting an optimal speed for the robot to arouse sufficient proprioceptive input to MC.[57]

For gait recovery, robot-assisted training not only improved behavioral outcomes but also reorganization brain activation.[58,59] Miyai *et al.* investigated the brain activation during treadmill walking in patients with severe stroke either with mechanical assistance in swinging the paretic leg control (CON) or with facilitation technique that enhanced swinging of the paretic leg (FT).[59] The gait performance and overall cortical activations were greater under the FT condition. PMC was mainly activated in the affected hemisphere, and its activation might reflect adaptive locomotion control, compensation, or cortical network reorganization. Lee *et al.* found that walking with Motivating System-Hip (GEMS-H) induced more stronger and more balanced activation in the primary sensorimotor cortex (PSMC) to promote gait recovery at the early phase in chronic stroke patients. During the late phase, there were less activation in SMC and SMA indicating that GEMS-H produced a more coordinate and efficient gait pattern by the rhythmic hip flexion and extension movement.[60] Caliandro *et al.* found that the PFC activation was stronger in walking with Ekso than that in walking without Ekso, indicating an extra attention and executive effort in Ekso walking. Meanwhile, it was found that muscle hypo-activation and coactivation

of nonparetic limb are associated to a high prefrontal metabolism.[61]

**Electrical stimulation therapy**

As to UL motor function, Hara *et al.* found that five-month electromyography-controlled functional electrical stimulation (EMG-FES) therapy improved arm function in most chronic stroke patients. EMG-FES induced greater brain cortical perfusion in the ipsilesional SMC than the voluntary muscle contraction condition or FES condition, and caused a shift in the cortical perfusion from the contralesional to ipsilesional SMC.[62] For LL motor function, Ferrante *et al.* studied the muscle metabolic indexes during knee flex-extension induced by FES, and found the local and unilateral muscle metabolic dysfunction for patients.[63] Lo *et al.* showed that passive cycling with low-intensity FES promoted more bilateral S2 activation than passive cycling without FES and passive cycling with high-intensity FES, indicating its better facilitation of cortical excitability.[64]

**MI therapy**

MI refers to the repeated imagination of a certain action or movement situation in the mind without actual muscle activity. Mihara *et al.* used NIRS–mediated neurofeedback (NIRS-NFB) as an adjuvant treatment way in MI training. They found that neurofeedback with hemoglobin signals detected by NIRS could enhance the MI-related ipsilesional PMA activation and facilitate the motor function recovery in patients compared with neurofeedback with irrelevant randomized signals. This cortical activation change was correlated with the hand function recovery.[65] Recently, they published another randomized controlled trial, and observed greater gait and balance function improvement in the intervention group with SMA activation as NIRS-NFB compared with the sham group.[66] Only the intervention group exhibited increased MI-related SMA activation and enhancement of RSFC between SMA and ventrolateral PMA. Mirror therapy (MT) belongs to the MI therapy. In the study of Brunetti *et al.*, they showed that the initial motor function and the activity shift in both precunei could discriminate between MT responders and MT nonresponders.[67]

**BCI**

Rea *et al.* conducted a pilot study about NIRS-BCI in stroke. Using the single-trial linear discriminant analysis, they found that the MC activation could discriminate the ipsilesional and contralesional hip movement preparation in most patients. This study provides insight for BCI applications with NIRS in the motor rehabilitation after stroke.[68] Another pilot study supported that real-time fMRI and real-time NIRS as BCI neurofeedback systems combined with motor learning could gain motor recovery commensurate with prior studies with longer-duration motor learning (without BCI). The brain activity was successfully modulated during NIRS-NFB training. This study indicates that BCI holds the potential for reducing training time for recovery.[69]

**NIBS**

NIBS techniques, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), have been proved to be effective approaches to promote motor recovery.[70,71] Tamashiro *et al.* demonstrated that low-frequency rTMS combined with intensive occupational therapy allowed more pronounced motor recovery for patients with unaffected hemisphere dominance than those with affected hemisphere dominance. Patients' LI before treatment negatively correlated with the recovery of UL motor function.[72] The efficacy of NIBS varies among patients, and combined NIRS and EEG can be used to identify chronic stroke responders to cerebellar tDCS.[73]

### 4.3. *Motor and cognition interference (dual task)*

Dual-task walking (DTW) (i.e., performing a secondary task while walking) is essential for people's daily activities. However, DTW is challenging for most stroke survivors. The investigation of neural mechanisms of DTW could help to understand the DTW performance in stroke survivors.

Seven studies investigate DTW in stroke patients and are listed in Table 3. All these studies focus on the participation of PFC in DTW and show that motor abilities regulate PFC activation in DTW. Al-Yahya *et al.* found that PFC activation was more extensive during treadmill walking under the DTW (walking while counting) condition than under the single-walking (SW) condition in both patient and control groups. However, under the simulated walking, the stroke group showed more increased PFC activation in DTW than SW

Table 3. Summary of NIRS studies in motor and cognition interference, cognitive function and its recovery, and aphasia and its recovery.

| References | Subjects | Type of stroke | Time since stroke | Device | Measured regions (channels) | Clinical applications |
|---|---|---|---|---|---|---|
| Al-Yahya *et al.*[74] | PT: 28 (26 M)<br>NS: 30 (18 M) | | $>6$ months | Oxymon Mk III system | forehead (8) | investigate PFC activation and its relationship to gait under SW and DTW |
| Mori *et al.*[75] | PT: 14 (12 M)<br>age $= 61.1 \pm 9.3$ years<br>NS: 14 (11 M)<br>age $= 66.3 \pm 13.3$ years | CI: 5<br>CH: 9 | $>6$ months | a NIRS system (WOT™) | forehead (16) | study the association between PFC activation and dual-task interference |
| Hawkins *et al.*[76] | PT: 24 (16 M)<br>age $= 58.0 \pm 9.3$ years<br>Elderly NS: 15 (7 M)<br>age $= 77.2 \pm 5.6$ years<br>Young NS: 9 (4M)<br>age $= 22.4 \pm 3.2$ years | | $18.3 \pm 9.3$ months | Niro 200NX | forehead (2) | investigate group differences in PFC control of walking |
| Hermand *et al.*[77] | PT: 11 (6 M)<br>age $= 71.4 \pm 10.1$ years | CI: 9<br>CH: 2 | $45.5 \pm 34.5$ days | Portalite | forehead (2) | assess effects of N-back tasks on cerebral activity, gait and cognition |
| Chatterjee *et al.*[78] | PT: 33 (22 M)<br>age $= 59.6 \pm 9.7$ years | | $19.2 \pm 10.4$ months | Niro 200NX | forehead (2) | investigate whether individual differences affected PFC activity |
| Liu *et al.*[79] | PT: 23 (21 M)<br>age $= 51.5 \pm 10.7$ years | CI: 12<br>CH: 12 | $>6$ months | NIRSport | PFC, MC (14) | investigate effects of cognitive DTW |
| Clark *et al.*[80] | PT: 31<br>SS group: 14<br>ACC Group: 17 | | $5 \sim 47$ months | Niro 200NX | PFC (2) | assess changes in walking function and PFC activation following two interventions |

*Notes*: FC: frontal cortex; TL, temporal lobe.

compared to the control group.[74] It was observed that there were more physical and cognitive costs during DTW for chronic stroke patients than normal subjects. The PFC might prioritize stroke patients' physical demands but prioritize cognitive demands for normal subjects.[75] Hawkins *et al.* found that the PFC activation was lowest for young healthy adults during walking and increased significantly in the verbal fluency DTW. However, for chronic stroke patients and older adults with mild gait deficits, PFC was activated more during walking than young adults, and showed no difference between DTW and SW. The over-activation of PFC was a beneficial compensation to preserve walking speed in stroke patients.[76] The over-activation of PFC was also seen under SW in subacute stroke patients.[77] The PFC recruitment was affected by individual differences.[78] Chatterjee *et al.* showed that patients with low balance confidence exhibited higher PFC activation during walking than patients with high balance confidence. Besides, patients with poor cognitive performance showed similar cognitive performance and PFC activations in the single cognitive task (serial-7 subtraction) and DWT (walking with serial-7 removal), implying that the single cognitive task already reached the ceiling of resource recruitment. Liu *et al.* found that the gait performance cost existed in both the walking while performing cognitive task (WCT) condition and walking while performing motor task (WMT) condition for stroke patients. There were no obvious differences between these two conditions. Activation in bilateral PMC and nonlesioned SMA in WCT and WMT was more substantial than

that in SW, and negatively correlated with gait performance. This study suggested that SMA and PMC were crucial in the cognitive and motor dual task walking after stroke.[79] After multiple sessions of accurate adaptability walking intervention, PFC activation reduced in the DWT indicating a more automatic control of walking.[80]

These seven studies demonstrated that motor abilities regulated PFC activation during walking. SW could approach the ceiling of available PFC resources for patients with apparent locomotion deficit, leaving no extra resource. The over-activation of PFC might be involved as a compensatory mechanism to ensure the preferential control of walking in patients.[76,77] The MC also plays a vital role in DTW, but it needs more research.

### 4.4. *Cognitive function and its recovery*

Three papers are about cognitive function and its recovery. The PFC plays a predominant role in cognitive control,[81] and hyper-frontal activity might compensate for cognitive impairment in stroke patients.[82] Moriya *et al.* investigated the acute effect of physical exercise on working memory for stroke patients. They found that aerobic exercise at moderate intensity could improve working memory and increase PFC activation, especially the right PFC.[83] Besides, cluster needling of scalp acupuncture therapy combined with pharmacological treatment could significantly improve the cerebral hemoglobin levels and cognitive performance in stroke patients.[84]

### 4.5. *Aphasia and its recovery*

Aphasia is one of function deficits after stroke, which seriously affects patients' communication ability. Obayashi showed that language impairment after thalamic stroke was attributed to inferior frontal gyrus (IFG), SMA, and language-related brain areas. SMA may contribute to the recovery of word retrieval difficulty and aphasia.[85] Hara *et al.* investigated the effect of rTMS and intensive speech therapy on aphasia in chronic stroke patients. rTMS was guided by the dominant activated hemisphere in a language task. Those with left hemisphere activation received low-frequency rTMS to the right IFG, while those with right hemisphere activation received high-frequency rTMS to the right IFG. They found that both interventions similarly improved language function.[86]

### 4.6. *Emotional function and its recovery*

Two studies are about emotional function and its recovery. Mood disorders after stroke are common, especially post-stroke depression (PSD).[87] Koyanagi *et al.* observed that the frontal $HbO_2$ activation in the verbal fluency task negatively correlated with patients' Hamilton rating scale for depression scores.[88] Li *et al.* found that the PFC activation was significantly increased after tDCS treatment than that before treatment when patients processed negative faces.[89]

### 4.7. *Other applications*

Five studies are on how different factors influence cerebral blood oxygenation. It was found that both head-of-bed positioning and an ipsilateral infarct significantly altered cerebral blood flow, $HbO_2$ and tHb concentrations for acute stroke patients.[90] The infusion of vinpocetine also influences the cerebral blood flow in acute stroke patients.[91] Pizza *et al.* investigated the brain hypoxia caused by sleep-disordered breathing (SDB, obstructive and central apneas) in stroke patients.[92] The brain activation in PFC could be enhanced by increasing standing load for patients with a consciousness disorder.[93,94]

There are four studies about the NIRS method. Motion artifact is a confounding factor in oscillation-based NIRS studies that must be considered.[95] NIRS combined with DC-MEG, or EEG, show great potential in assessing neurovascular coupling by simultaneously monitoring vascular and neuronal signal changes in stroke patients.[96,97] Sato *et al.* used the TRS system and showed difference in optical characteristics between normal and abnormal brain tissues.[98]

### 4.8. *Results of quality assessment*

Table 4 shows the results of quality assessment, and the assessment for each study is provided in the supplementary materials. Studies in this review scored 6.1 out of 9 on average and range from 4 to 8. All studies clearly stated the research objective, and 14 studies failed to prespecify the inclusion and exclusion criteria for participants. All studies clearly

Table 4. Quality assessment for 68 included studies.

| | Question | Mean score |
|---|---|---|
| 1 | Was the research objective clearly stated? | 1 |
| 2 | Was the study population clearly specified and defined? | 0.94 |
| 3 | Were the inclusion and exclusion criteria prespecified and uniformly applied to all participants? | 0.79 |
| 4 | Was sample size justification, power description or variance and effect estimated provided? | 0.01 |
| 5 | Were the exposure(s) of interest measured prior to the outcome(s)? | 0.63 |
| 6 | Were the exposure measures clearly defined, valid, reliable, and implemented consistently across all study participants? | 0.99 |
| 7 | Was there a control group? | 0.66 |
| 8 | Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | 1 |
| 9 | Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | 0.10 |



defined the exposure(s) and outcome(s), and exposure(s) in 25 studies was not prior to the outcome (s). There was not an independent control group in 23 studies. Nearly all studies did not conduct sample size justification or provide power description except one study. Most studies did not correct systemic interference from superficial layers of the head, leaving key potential confounding variables unadjusted.

## 5. Discussion and Conclusions

This review focuses on NIRS applications in stroke. The existing literatures indicated that NIRS plays an important role in studying the resting-state function and its recovery, motor function and its recovery, motor and cognition interference, cognitive function and its recovery, language function and its recovery, emotional function and its recovery, and other applications for stroke. These studies have enhanced our comprehensive knowledge about post-stroke functional deficits and their recovery. Indeed, these studies pointed a very important direction for personalized rehabilitative intervention development.

More than 50% of the included studies are focused on the motor function recovery in stroke. NIRS was used as a measurement method to evaluate the brain (or muscle) function and the neural mechanism of recovery in stroke patients, and also as a therapeutic tool to increase the effectiveness of stroke recovery. There are also many studies about RS, especially RS connectivity. The RS brain networks can reflect the anatomical structure and relate to the task-state brain networks.[99] Boyd *et al.* concluded that RS brain network biomarkers have significant potential in clinical application for motor recovery after stroke,[100] reflecting the important research and clinical value for RS in stroke.

The quality assessment results indicated that there are some methodological limitations from the previous studies. First, most studies did not conduct sample size analysis before their study nor provide the statistical power in the results. The subject number in the experimental group varied from 4 to 59 (median: 12; mean: 14.9). 45 studies included the independent control group with subject number ranging from 4 to 32 (median: 11; mean: 13.7). Based on the statistical results of these studies, it is not feasible to calculate the statistical power. Kohl *et al.* proposed that the median sample size ($N = 20$) is relatively small for published NIRS-NFB studies by estimating the statistical power in a recent review.[101] Thus, it can be seen that the sample size for many included studies in this review is also small, and this might cause low statistical power and the exposure effect overestimated. The small sample size is not a specific but general problem for neuroscientific research, and Button *et al.* provided recommendations on how to improve this problem.[102] In the future, it is better for a study to follow some study quality assessment tools and perform *a priori* analysis of sample size which can control both type-1 error probability and type-2 error probability.[103] Otherwise, it is convincing and useful to give statistical power or statistical sensitivity in the results, favoring subsequent review studies or meta-analysis.

Second, extracerebral systematic component is a main confounding factor in NIRS signals, but most included studies did not employ a particular approach to remove this confounder. Although there were studies combining NIRS and fMRI which have proved that NIRS signals were correlated with the BOLD signal,[104,105] such systemic interference might cause false positive or false negative results.[106] Moreover, it should be noted that the absence of functional contrast in resting state studies increases the risk of contaminating results by extracerebral systematic signals.[106] Thus, it is quite necessary to verify the important work with systemic interference being removed in the future. At present, short-distance measurements as regressors in a General Linear Model (GLM) and GLM with temporally embedded Canonical Correlation Analysis (tCCA) method has been proved to be efficient in removing systemic interference.[107,108] When the device is not configured for short-distance measurement, additional system physiology (e.g., heart rate) can be measured to help clear the signal.[109] It is also better to combine NIRS and fMRI to validate the correlation of NIRS signals with the BOLD signal, which is instructive for the placement of optodes, selection of data processing methods and explanation of results. In addition, it is also important to design the optimal baseline condition in the experiment to deduct "spurious" activity from the experimental condition. Following the guidelines according to the recently proposed best practices for NIRS publications will undoubtedly help to enhance reliability and repeatability of NIRS studies.[109]

Third, three were some limitations about the control condition in the previous studies. For example, the experimental condition and control condition had inequivalent elements. Some studies differed in age[32,40,49] or physiological characteristics.[24,25] between the patient and control groups, introducing extra causes to affect the outcomes. Some studies added the treatment of interest on top of the treatment in the control group.[84] This might confuse results as to whether the exposure effect was due to a longer-duration treatment or a specific treatment. Some studies did not design an independent control group. A well-designed control condition can strengthen the validity of causal inferences between exposure and outcome. Thus, it is necessary to follow guidelines for designing suitable control conditions.[110,111]

Although these weaknesses existed, previous studies have provided insights into stroke function and recovery. With rigorous research practices, there are still many limitations needed to be investigated. First, most studies are single center. It is necessary to conduct multi-center clinical research to make sure the results have universal significance. Second, various rehabilitation methods (such as MT[67] and NIBS[112,113]) can help recovery from stroke, but the efficacy varies among individuals. It is quite necessary to make use of machine learning techniques to identify neural markers predicting responders and nonresponders to these rehabilitation methods, which can better formulate personalized treatment plans. Third, the brain–muscle coupling is important in stroke recovery process.[114] NIRS can collect hemodynamic responses from the central nervous system and peripheral muscles, providing a possible approach to study the brain–muscle coupling in stroke patients. The advantages of NIRS make it valuable in these future potential research fields.

Ongoing development of NIRS technology provides new possibilities in stroke applications. Portable, wearable and wireless NIRS devices have been developed recently.[115,116] These devices can be used in naturalistic environment and make it possible to continuously track patients in the real-world. This will help to understand patients' functional status of and adjust the personalized rehabilitation strategies in time. Of course, standard protocols must be developed before these devices used in the naturalistic settings. In addition, a portable time-domain NIRS system has recently been developed which broke through the limitations of high cost and complexity of TRS.[117] The time-domain NIRS system can differentiate the difference in optical parameters between normal and stroke-induced abnormal brain tissues, separate cerebral activity and extracerebral activity, and provide absolute values of blood oxygen parameters.[118] This will promote the comparability and generalizability of NIRS results and provide new biomarkers with optical parameters which can characterize brain tissue structure.

NIRS has also been developed into a promising tool in the neurofeedback and the BCI applications.[101,119] Researchers have conducted double-blinded randomized sham-controlled studies and proved that NIRS-NFB is an effective tool for promoting motor rehabilitation after stroke.[65,66]

Optical BCI has also been demonstrated to be useful in restoration of movement after stroke.[119] Due to the advantages of NIRS, it is easier to conduct much training to promote the NIRS-NFB or BCI performance. Moreover, it is possible to carry out neurofeedback and BCI treatment for chronic stroke patients in daily life with portable NIRS system. However, NIRS measures brain hemodynamic response which lags several seconds after the neural activity. This will have an adverse impact on neurofeedback and BCI application performance based on real-time neural signals. One promising way is the hybrid system (such as NIRS-EEG).[120] By broadening the use reliability of such hybrid system, it can extend the scope of NIRS towards broader clinical application.

There are some shortcomings for NIRS that should be mentioned. NIRS cannot detect activation from deep brain structures. However, focal lesions after stroke could result in disruption across the entire network due to diaschisis.[4,121] Patients with subcortical lesion might show abnormal brain activity not only in deep-brain regions but also in cerebral regions. From this perspective, NIRS can measure cerebral activation to study patients with subcortical lesion. Besides, cortical measurement with NIRS is contaminated by systemic interference from superficial layers of the head. This systemic interference must be removed with a verified method, such as the short-distance measurements as regressors in a GLM method,[107] the GLM with tCCA method,[108] the adaptive filtering,[122] the wavelet-based method,[123] the common average reference spatial filtering approach,[124] etc. In the future, NIRS can be better applied in clinical research with the development of processing methods.[125–129]

In conclusion, we reviewed an important role of NIRS in stroke studies, especially about resting-state function and recovery, motor function and recovery, and motor and cognition interference. Together with rigorous research and reporting practices, NIRS would continue to leverage its unique strengths in stroke research, such as in multi-center studies, and treatment efficacy prediction studies. Although NIRS has some limitations, its application can be expanded by combining with other neuroimaging techniques, such as EEG,[130,131] and advancing the signal processing techniques for NIRS.

## Conflict of Interest

The authors declare no conflict of interest.

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