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"Remind-to-Move" treatment enhanced activation of the primary motor cortex in patients with stroke

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Abstract

"Remind-to-Move" (RTM) has been developed and used as a new treatment for rehabilitation of upper extremity functions in patients with hemiplegia. This study aimed to investigate the cortical activation patterns using functional near-infrared spectroscopic topography (fNIRS) for patients with chronic stroke receiving RTM by comparing with their healthy counterparts. Twelve patients with right hemispheric stroke and 15 healthy adults participated in this study. All participants were instructed to completed three experimental conditions - RTM, Move without reminding (Sham), and Remind with No-move (RNoM). In patients with stroke, RTM elicited higher level of activation than the Sham in the contralateral somatosensory association cortex, primary motor cortex, primary somatosensory cortex and the dorsolateral prefrontal cortex, which has been found in healthy participants. However, effects of RTM were robust and more widely distributed in healthy participants, comparing to patients with stroke, comparatively RNoM showed no significant higher activation than the baseline in those areas in both populations. RTM enhances the recruitment of contralateral primary motor cortex and this effect appears to be associated with increased attention allocation towards moving hands upon tactile stimulation in the form of vibration. The RTM treatment is useful to patients with stroke.

(**Words:** 194)

Keywords: stroke; movements with reminder; hemiparetic upper extremity; primary motor cortex; fNIRS

Introduction

Hemiparetic upper extremity is one of the common consequences among stroke survivors, with 70% of patients after stroke experiencing permanent upper extremity hemiplegia (Henrik Stig Jørgense. 2000). Patients with stroke tend to perform activities of daily living with their unaffected arms without using or involving their paretic arms, although the paretic arms still retain some voluntary motor control. One of the explanations for this phenomenon is due to a behavioral suppression of movements which is called learned nonuse (Andrews and Stewart 1979; Taub et al, 2006). Other neurological factors may also contribute to the development of the learned nonuse, such as pain, limited voluntary motor control, sensation deficits, and difficulties in movement initiation (Sunderland and Tuke 2005).

Constraint-Induced Movement Therapy (CIMT) has been developed to reduce disability caused by learned nonuse for eligible stroke survivors (Winstein et al., 2016). The key successful constituents of CIMT include: repetitive and task-oriented training, adherence-enhancing behavioral strategies, and constraining the use of the unaffected arm (Morris et al. 2006). However, CIMT can only apply to patients with higher functioning hemiparetic upper extremity (i.e., have sufficient ability to grasp and release small objects), and that a substantial number of patients cannot comply with the high-intensity of CIMT (i.e., six-hour of restraint per day for 3 weeks) and meet the safety criteria such as mobilization without risks of fall (Leung et al. 2009). Therefore, we developed a new treatment alternative – Remind-to-Move (RTM), instead of restraining the unaffected hand, this treatment focus on reminding the individual to move/use their hemiparetic arms in daily life according to a set series of simple customized movements tailored by therapists upon a vibration signal generated from a sensory cueing wristwatch device tied to the paretic arm, which aims to increase the amount of movement as well as enhancing the awareness towards their paretic arms (Fong et al. 2013b). In a few subsequent studies, RTM was found that to be useful to improve upper extremity motor functions in patients with subacute and chronic stroke (Fong et al. 2013b; Yang et al. 2017) and children with unilateral cerebral palsy (Fong et al. 2013a; Dong et al. 2017; Wei et al. 2019). We also found that both RTM and CIMT resulted in similar effects on their upper extremities, therefore, the RTM treatment could be used as an alternative or supplement to CIMT for children with hemiplegic arm impairment (Dong et al., 2017).

We hypothesized that therapeutic effects of RTM may be two-fold – the effect of sensory stimulation in terms of strong vibration prior to movements, and the effect of intense repetitive customized movement

upon prompting by the vibration cue emitted at a fixed interval. The reason of using vibration for cueing is that most of the somatosensory functions are impaired in stroke patients, even though their muscle power remains unaffected (Bolognini et al. 2016). Dean et al.'s study (2012) suggested that the problem of motor preparation was a crucial factor contributing to hemiparetic motor deficits, and motor cueing could be a promising intervention with priming effects for movement initiation, and that sensory cues prior to movements can facilitate patients with stroke increasing efforts and attention in preparing and initiating motor responses. A meta-analysis also indicated that attention can be selectively allocated to particular objects or tasks by external central reminders, and that the dorsolateral prefrontal cortex (DLPFC) performs an important role in this process (Wager et al. 2004).

To conclude, we hypothesized that the neural mechanism behind RTM is that the external signals emitted from the sensory cueing device would improve patients' awareness of their paretic limbs by reminding them to engage in repetitive standardized task practice and participate in real-life activities by modulating their attention towards the ipsilesional primary motor cortex (M1), and that by priming the motor system with sensory stimulation and using movement-based strategies, it might be possible to increase the extent in activating the DLPFC to which they initiated movements in their paretic arms to achieve better recovery of motor function. Therefore, the current cross-sectional study aimed to investigate the cortical activation patterns using functional near-infrared spectroscopic topography (fNIRS) in the contralateral hemisphere (contralateral to the moving hand; ipsilesional hemisphere in stroke) during RTM, and compared with the 'Remind with No-move' and the Sham conditions in patients with stroke and their healthy counterparts.

Methods

Participants

We recruited by convenience sampling 12 patients with right hemispheric stroke (6 males and 6 females; mean age = 63.3, SD = 6.9) in the self-help groups and 15 healthy adults (12 males and 3 females; mean age = 55.0, SD = 7.3) in the community. All patients met the following inclusion criteria: (1) with right hemispherical involvement; (2) with period of stroke onset prior to the study ≥ 6 months; (3) had normal cognitive function (full scores in the Abbreviated Mental Test) (Chu et al. 1995); and (4) had mild to moderate impairment in hemiparetic (left) upper extremities measured using the upper extremity score of the Fugl-Meyer Assessment (mean = 46.6, SD = 12.6) (Gladstone et al. 2002).

This study was conducted following the ethical principles regarding human experiments (Helsinki Declaration) (Christie 2000). Written informed consent was obtained from all participants. This study was approved by the Humans Research Ethics Committee of the Hong Kong Polytechnic University (Ref. No.: HSEARS20181212006).

Experimental Paradigm

Participants were required to sit comfortably on an adjustable chair in front of a table in a quiet room except for the consistent noise made by an fNIRS machine. A computer monitor, with a white cross on a black background, was placed on the table 70 cm away from participants. All participants wore the sensory cueing wristwatch device – SCW-V2 (Fig. 1), on their left wrists, and performed three conditions - RTM, Move without reminding (Sham), and Remind with No-move (RNoM). The current experiment was event-based design and each condition included 5 events. In each event, participants could look at their left hands during motor task performance, otherwise, they focused on the white cross on the table in front of them. The SCW-V2 looks like a small pager in size (6.5×6.0×2.5cm) with 70g in weight and was easy to secure comfortably to the wrist using non-allergenic neoprene straps with a Velcro™ closure. The device emitted a vibration cue in the form of a rhythmic vibration (196Hz, similar to the vibration mode of a mobile phone) upon a customized time interval. The signal would not stop until the acknowledgment button on the device was pressed (Wei et al. 2019).

In the RTM condition, once the participant felt a vibration sensory cue on the affected (left) hand as emitted by the SCW-V2, once every minute, they were asked to press the acknowledgement button on the top of the device with their right hands (Fong et al. 2013b; Wei et al. 2019), and perform 10 repetitions of hand grasp-and-release movements at a frequency of 0.5 Hz with left hands subsequently, that took about 20 seconds in total. In other words, participants in each event of the RTM condition had nearly 20 seconds for movements and 40 seconds for rest. To familiarize with the pace of movements, participants were asked to practice with a metronome for 5 minutes before using the wristwatch device. If patients had difficulty in making a full hand grasp, they could try the best to perform the movements as they could.

In the Sham condition, the SCW-V2 was turned off, i.e. there was no sensory cueing before every movement. Participants were told to perform the hand grasping with left hands spontaneously at their own pace with an interval between 40 seconds to 120 seconds. Therefore, the period for the movements

was relatively fixed, while the rest period was various across participants. To match with similar amount of movements as found in the RTM condition, participants in the Sham also needed to press the acknowledgement button before starting in order to perform about 10 repetitions of hand grasping.

In the RNoM condition, the setup was the similar as in the RTM condition. Once the participants felt the vibration sensory cue, they needed to press the acknowledgement button as well, but they did not need to perform any movements after the cue. We measured the concentration changes of oxyhemoglobin (ΔHbO) during movements using the fNIRS. Although the vibration sensory stimulation was very short, we were interested in whether a pure vibration cue with no-movements could still induce significant cortical activation in follow-up period.

fNIRS Data Acquisition

We used a continuous-wave optical system (ETG-4000, Hitachi Medical Co., Japan) to measure the ΔHbO at the cerebral cortex. The sources of this system generated two wavelengths of near-infrared light at 690 nm and 830 nm with a fixed sampling rate at 10 Hz. A total of 34 channels (CH) were constituted by a 3 × 3 holder and a 3 × 5 holder. The 3 × 3 holder covered the top of head and its middle line was along the line between Nasion and Inion. The 3 × 5 holder was placed horizontally and covered the right hemisphere. Moreover, the middle point of CH6 and CH7 was located at the Cz and CH19 was located at the C4 in accordance with the international 10/20 system. A 3D digitizer (PARTIOT, Polhemus, Colchester, Vermont, USA) was used to acquire the coordinates of channels. The acquired coordinates were transformed to the MNI coordinates (Lancaster et al. 2000) and further projected to the MNI standard brain template by using NIRS_SPM toolbox (available at: https://www.nitrc.org/projects/nirs_spm/) (Ye et al. 2009). Fig. 2 shows the channels projected on the MNI standard brain template and the MNI coordinates are available in Table 1 of our supplementary material. Using the above configuration, the channels could cover the supplementary motor area (SMA), premotor cortex (PMC), M1, Primary sensory cortex (S1), and the DLPFC, etc. In all conditions, we also marked the onset of event manually once participants pressed the acknowledgement button of the wristwatch device SCW-V2.

Preprocessing of fNIRS Data

In this study, we adopted ΔHbO signals as the indicator of hemodynamic response because it is more

sensitive than deoxyhemoglobin on regional cerebral blood flow (Strangman et al. 2002; Hoshi et al. 2001). We preprocessed the fNIRS data offline using HomER2 toolbox in Matlab 2014a (The MathWorks Inc., USA) (Huppert et al. 2009). After raw intensity data was converted to optical density changes, the Spline interpolation algorithm was used to correct motion artifacts caused by head movements during data acquisition. Then, a bandpass filter between 0.01 Hz and 0.2 Hz was carried out to remove the effect of physiological noises and drifts. Finally, the optical density was converted to ΔHbO based on the modified Beer–Lambert law. The mean time for completing 10 repetitions in healthy participants was 16.1 (SD = 3.2) seconds, while 18.3 (SD = 4.6) seconds for patients with stroke. Although participants practiced the pace of hand grasp before the experiment, they still completed 10 repetitions of movements 20 seconds earlier. Therefore, we cut a temporal window from -2 s to 16 s relative to the onset of movements (t = 0 s) for event averaging for healthy participants, while -2 s to 18 s for patients with stroke.

Statistical Analysis

Statistical analysis was carried out by using Matlab 2014a and SPSS23. A p-value of <0.05 (two-tailed) was set as significant. Both one-sample Kolmogorov-Smirnov tests and histogram plots were applied to check for the normality of variables prior to parametric tests. First, we performed paired *t*-test to investigate the effects of the three conditions on ΔHbO in all channels for patients with stroke and healthy participants. Because the short sensory cue in the RNoM could not elicit significant higher level of activation on ΔHbO than baseline in all channels in patients with stroke, and 33 out of 34 channels in the healthy participant, therefore, we excluded the RNoM condition in subsequent analyses to minimize the number of comparisons. Second, to evaluate the overall differential effect on ΔHbO between the RTM and Sham conditions across populations (healthy vs stroke) in all the channels (34 channels). We used a three-way repeated measure analysis of variance (rmANOVA), with a between-subject factor (populations) and two within-subject factors (conditions and channels). Third, we performed two-way rmANOVAs for all channels in order to explore in which brain regions the activation pattern of RTM significantly differed from that of the Sham across populations. The Dubey/Armitage-Parmar (D/A-P) correction was applied to avoid the inflation of type I error caused by multiple comparisons (34 channels) (Sankoh et al. 1997; Metzger et al. 2017). The adjusted p value (p_{adj}) was calculated using the following formulas (Sankoh et al. 1997):

$$g(k) = M^{1-r(k)} \quad (1)$$

$$p_{adj}(k) = 1 - (1 - p(k))^{g(k)} \quad (2)$$

Where M, r(k) and p(k) is the number of outcomes (i.e. 34 channels), mean correlation between the k^{th} outcome and the remaining M - 1 outcomes, and the k^{th} unadjusted p value, respectively. The correlation was indexed by means of Pearson correlation coefficients using all the data samples ((12 patients with stroke +15 healthy participants) × 3 conditions). Last, we compared the ΔHbO between the RTM and Sham in the two populations using paired t-tests and the D/A-P correction was applied again. Statistical results were visualized by using the BrainNet View toolbox (Xia et al. 2013).

Results

Activation compared with baseline

Fig. 3 shows ΔHbO induced by the three conditions in both populations. Regarding the activation induced by the RNoM condition (Fig. 3 - upper panel), only one channel, CH34 (retrosubicular area, PMC) was found to have a significant higher level of ΔHbO than the baseline in healthy participants ($t(14) = 3.00$; $p = 0.001$), but there were no channels showing higher activation than baseline in patients with stroke. On the contrary, the RTM induced a significant higher level of ΔHbO than baseline in 23 and 17 channels in the healthy participants and the patients with stroke, respectively (middle panels of Fig. 3). The Sham conditions induced a significant higher level of ΔHbO than baseline in 11 and 10 channels in the healthy participants and the patients with stroke, respectively (lower panels of Fig. 3).

ANOVA analyses

A three-way ANOVA demonstrated significant main effects of conditions ($F(1, 25) = 11.7$; $p = 0.002$) and channels ($F(5.3, 130.7) = 5.9$, $p < 0.01$), and a marginally significant main effect of populations ($F(1, 25) = 3.6$, $p = 0.069$). The interaction effects of conditions×populations ($F(1, 25) = 0.9$, $p = 0.361$) and channels × populations ($F(5.3, 130.7) = 1.3$, $p = 0.274$) were not significant, but the interaction of conditions×channels was significant ($F(7.1, 176.9) = 2.3$, $p = 0.031$), suggesting that the RTM and Sham conditions had differential effects in some brain regions. The interaction of conditions × channels × populations was not significant ($F(7.1, 176.9) = 0.7$, $p = 0.646$).

Fig. 4 shows the main effects of populations and conditions calculated by using two-way rmANOVA tests. The main effect of populations was significant in only one channel (CH1, SMA) after the D/A-P correction ($F(1, 25) = 11.5$, corrected $p = 0.008$), suggesting a higher level of ΔHbO in patients with stroke than healthy participants. In addition, we found similar main effects of populations in other brain regions ($F(1, 25)$ values ranging from 4.9 to 6.5, uncorrected p values < 0.05, corrected p values > 0.05), mainly in the SMA (CH2, CH4 and CH7) Broca's area (CH25 and CH30) and the superior temporal gyrus (CH32). There were no channels in which healthy participants showing a higher level of ΔHbO than patients with stroke. Regarding the main effect of conditions, the RTM showed a higher level of ΔHbO than the Sham in most of the 34 channels. After the D/A-P correction was applied, we still found 18 channels showing significant differences ($F(1, 25)$ values ranging from 10.1 to 20.5, corrected p values < 0.05), mainly distributed in the SMA (CH2 – CH7), M1 (CH15), S1 (CH14 and CH19) and the DLPFC (CH21). We did not find any channels that the Sham showed a higher level of ΔHbO than the RTM condition. There were no channels showing significant interaction effects after the D/A-P correction was applied.

Paired t-tests

Fig. 5 shows the *t* value of comparisons between the RTM and the Sham conditions in healthy participants and patients with stroke. In healthy participants, the RTM condition had a significant higher level of ΔHbO in 12 out of 34 channels ($t(14)$ values ranging from 2.3 to 4.7, corrected p values < 0.05), mainly covering the SMA (CH2 to CH7), S1 (CH19) and the supramarginal gyrus part of Wernicke's area (CH18). In addition, the RTM also tended to show superior effects than the Sham ($t(14)$ values ranging from 2.3 to 2.8, uncorrected p values < 0.05, corrected p values > 0.05) in the somatosensory association cortex (CH13), M1 (CH15), PMC (CH20; BA6) and the DLPFC (CH16 and CH21).

In patients with stroke, a smaller number of channels were found to have significant differences with that of the healthy participants between the RTM and Sham conditions on the level of ΔHbO ($t(11)$ values ranging from 2.8 to 3.6, corrected p values < 0.05), in the somatosensory association cortex (CH12) and S1(CH19). Similar to healthy participants, the RTM tended to show superior effects than the Sham in patients with stroke ($t(11)$ values ranging from 2.3 to 2.8, uncorrected p values < 0.05, corrected p values > 0.05) in activating the somatosensory association cortex (CH13), M1 (CH15), and the DLPFC (CH21).

Discussion

The present study was the first one to explore the mechanism underlying the RTM treatment which was developed as a new rehabilitation treatment for upper extremity functions in patients with hemiplegia. We investigated the cortical activation over contralateral hemisphere during the RTM and Sham conditions by using fNIRS. In addition, one more condition, RNoM, was included to rule out the effects of pure sensory cueing without subsequent movements. Our findings showed that, during the period of hand movements, the RTM can induce a higher level of cortical activation in the SMA, and contralateral M1, S1 and the DLPFC than the Sham. However, the effect of facilitating cortical recruitment in healthy participants was larger and more widely distributed than that in patients with stroke during the RTM condition.

As noted earlier in the literature, we hypothesized two therapeutic effects of RTM - the effect of attention modulation as a result of sensory cueing in the form of vibration prior movements and another is the priming effect of movement initiation and repetitive movements subsequently. Our findings indicated that the reminding cue for movements demonstrated enhanced activation of the M1, S1, SMA, somatosensory association cortex and the DLPFC. Anatomically, peripheral somatosensory receptors can detect external stimulus very quickly and this information is conveyed to contralateral S1 and the secondary somatosensory cortex (Kaas 1993). A previous study showed that activation of the S1 had a significant positive correlation with hand motor function recovery in patients with stroke (Laible et al. 2012). The S1 had enriched corticocortical projection to other regions in ipsilateral hemisphere, for example, the M1 and posterior parietal areas (Kaas 1993; McIntyre et al. 1984). A recent study found that the projection to pyramidal cells of M1 from the S1 had a “driver” role to the M1 (Petrof et al. 2015), which indicated the essential role of somatosensory information in the production of high-quality motor outputs (Fink et al. 2014; Asai 2015). While our present finding echoes the prerequisite anatomic foundation and establishes the possibility of activating the M1 via somatosensory stimulation, we should consider the difference in experimental designs - the somatosensory stimulation was used as a reminder in our study, and participants have to perform motor tasks immediately after receiving the stimulation, which was different from other studies of using somatosensory stimulation as training first, then performed motor tasks afterwards.

With regard to the DLPFC, it plays an important role in cognitive functions, such as working memory

and executive control including attention shitting, attention allocation and dual-task interference (Kane and Engle 2002). Many previous studies showed the DLPFC has an essential role in voluntary attention allocation process and external reminder can direct the attention to particular objects and tasks. Luks et al. (2007) used cued Flanker task to test the process of allocation of attention and their results showed that the DLPFC and intraparietal sulcus showed significantly a higher level of activation during the process of allocation of attention towards external cues. In the current study, the RTM demonstrated a higher level of activation over the DLPFC during movements than the Sham, which was likely to be attributed to attention allocation towards the hand. Our findings supported that the effect of RTM could enhance participants' awareness towards their left arms and modulate higher level top-down attention allocation towards the moving hands during movements (Katsuki and Constantinidis 2014).

We also found that the RTM had a specific effect in recruiting the SMA in subsequent movements compared with the Sham condition. Anatomically, the SMA and pre-SMA are subdivisions of the supplementary motor complex, located on the medial region of the brain (Nachev et al. 2008). However, these two regions could not be well separated by fNIRS due to the low spatial resolution. The SMA has reciprocal connection with the M1 and it was found that this connection could facilitate the excitability of the M1 (Matsunaga et al. 2005; Arai et al. 2012). On the other hand, the pre-SMA receives projection from the DLPFC and this connectivity is believed to mediate high-order cognitive control (Wang et al. 2005; Nachev et al. 2008). Our findings underpin the role of the supplementary motor complex in mediating cognition-action process and also support the mechanism of RTM as a top-down motor control treatment.

Another interesting finding was that patients with stroke generated significantly larger ΔHbO than healthy participants, particularly in the SMA, whilst healthy participants showed more robust difference between the RTM and Sham conditions. A meta-analysis based on neuroimaging studies in patients with stroke demonstrated that there was over-activation in contralesional M1, and bilateral SMA and PMC during movements of their affected hands (Rehme et al. 2012).

Our results may be argued that the higher level of activation in the RTM than the Sham was due to the delayed hemodynamic response of vibration sensory stimulation which mixed up with the hemodynamic response of movements (Haigh et al. 2015). In this study, the onset of movements took place after the vibration stimulation immediately, and the peak amplitude of hemodynamic response to this stimulus

was highly possible to be in the time window of movements which we cut for event averaging. However, in the RNoM condition, participants were required to press the acknowledgement button of the wristwatch device once they felt the vibration, and they did not perform any movements afterwards. Our results showed that the RNoM condition did not induce any significant increase of ΔHbO over the somatosensory association cortex, M1, and S1 after the sensory stimulus. Here, we believe that sensory modality in terms of vibration itself cannot significantly induce a hemodynamic change in the cortex because of the following reasons. First, the vibration in our experiment was very short, and it usually lasted approximately one second from onset to stopping. Therefore, such a short stimulus could not produce a huge and prominent hemodynamic response that could be captured by fNIRS. Second, we performed the event averaging from -2 to 16 seconds relative to the onset of events for healthy participants and -2 to 18 seconds for patients with stoke. Therefore, such a long time-window for averaging may hide a small hemodynamic response elicited by the short vibration stimulus. Taken together, we were confident that activation changes measured in the RTM was likely due to the hemodynamic response of subsequent movements, without significant confounding from the delayed hemodynamic response of the sensory stimulus.

Our study has the following limitations. First, we employed a 3D digitizer to acquire the coordinates of each channel, however, this could not provide very precise estimation of the channel location compared with individual structural MRI-based channel location estimation which has a better spatial resolution. Second, we had not matched the age of healthy participants with patients with stroke in the study population which might limit the results' interpretation. Finally, the overall higher ΔHbO in stroke patients than healthy participants at resting might confound the effect of RTM in the levels of ΔHbO.

Conclusions

Our findings supported our hypotheses that the RTM treatment can enhance the activity of the M1 and the DLPFC in patients with stroke. The neural mechanisms of the RTM treatment may be attributed to the increase of attention allocation towards the moving hands and the recruitment of contralateral M1. Our study established a preliminary understanding of the mechanism underlying clinical effects of the RTM treatment in patients with stroke.

(**Words:** 4121)

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Declaration Conflicting Interest

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References

Andrews K, Stewart, J (1979) Stroke recovery: he can but does he? Rheumatol Rehabil, 18:43-38. https://doi.org/10.1093/rheumatology/18.1.43

Arai N, Lu MK, Ugawa Y et al (2012) Effective connectivity between human supplementary motor area and primary motor cortex: a paired-coil TMS study. Exp Brain Res, 220:79-87. https://doi.org/10.1007/s00221-012-3117-5

Asai T (2015) Feedback control of one's own action: self-other sensory attribution in motor control. Conscious Cogn, 38:118-129. https://doi.org/10.1016/j.concog.2015.11.002

Bolognini N, Russo C, Edwards DJ (2016) The sensory side of post-stroke motor rehabilitation. Restor Neurol Neurosci, 34:571-586. https://doi.org/10.3233/rnn-150606

Christie B (2000) Doctors revise declaration of Helsinki. Bmj, 321:913. https://doi.org/10.1136/bmj.321.7266.913

Chu L, Pei C, Ho M et al (1995) Validation of the Abbreviated Mental Test (Hong Kong version) in the elderly medical patient. Hong Kong Med J, 1:207-211.

Dean PJ, Seiss E, Sterr A (2012) Motor planning in chronic upper-limb hemiparesis: evidence from movement-related potentials. PLoS One, 7:e44558. https://doi.org/10.1371/journal.pone.0044558

Dong VA, Fong KN, Chen YF, et al (2017) 'Remind-to-move' treatment versus constraint-induced movement therapy for children with hemiplegic cerebral palsy: a randomized controlled trial. Dev Med Child Neurol, 59:160-167. https://doi.org/10.1111/dmcn.13216

Fink AJ, Croce KR, Huang ZJ, et al (2014) Presynaptic inhibition of spinal sensory feedback ensures smooth movement. Nature, 509:43-48. https://doi.org/10.1038/nature13276

Fong KN, Jim ES, Dong VA et al (2013a) 'Remind to move': a pilot study on the effects of sensory cueing treatment on hemiplegic upper limb functions in children with unilateral cerebral palsy. Clin Rehabil, 27:82-89. https://doi.org/10.1177/0269215512448199

Fong KN, Yang NY, Chan MK et al (2013b) Combined effects of sensory cueing and limb activation on unilateral neglect in subacute left hemiplegic stroke patients: a randomized controlled pilot study. Clin Rehabil, 27:628-637. https://doi.org/10.1177/0269215512471959

Gladstone DJ, Danells CJ, Black SE (2002) The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. Neurorehabil Neural Repair, 16:232-240. https://doi.org/10.1177/154596802401105171

Haigh SM, Cooper NR, Wilkins AJ (2015) Cortical excitability and the shape of the haemodynamic response. Neuroimage, 111:379-384. https://doi.org/10.1016/j.neuroimage.2015.02.034

Jørgense HS, Nakayama H, Raaschou HO et al (2000) Functional and neurological outcome of stroke and the relation to stroke severity and type, stroke unit treatment, body temperature, age, and other risk factors: the Copenhagen stroke study. Top Stroke Rehabil, 6:1-19. https://doi.org/10.1310/BT7J-2N6U-VD53-E1QU

Hoshi Y, Kobayashi N, Tamura M (2001) Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model. J Appl Physiol , 90:1657-1662. https://doi.org/10.1152/jappl.2001.90.5.1657

Huppert TJ, Diamond SG, Franceschini MA et al (2009) HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt, 48:D280-D298. https://doi.org/10.1364/ao.48.00d280

Kaas JH (1993) The functional organization of somatosensory cortex in primates. Ann Anat, 175:509-518. https://doi.org/10.1016/s0940-9602(11)80212-8

Kane MJ, Engle RW (2002) The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. Psychon Bull Rev, 9:637-671. https://doi.org/10.3758/bf03196323

Katsuki F, Constantinidis C (2014) Bottom-up and top-down atention: different processes and overlapping neural systems. Neuroscientist, 20:509-521. https://doi.org/10.1177/1073858413514136

Laible M, Grieshammer S, Seidel G et al (2012) Association of activity changes in the primary sensory cortex with successful motor rehabilitation of the hand following stroke. Neurorehabil Neural Repair, 26:881-888. https://doi.org/10.1177/1545968312437939

Lancaster JL, Woldorff MG, Parsons LM et al (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp, 10:120-131. https://doi.org/10.1002/1097-0193(200007)10:3<120::aid-hbm30>3.0.co;2-8

Leung DP, Ng AK, Fong KN (2009) Effect of small group treatment of the modified constraint induced movement therapy for clients with chronic stroke in a community setting. Hum Mov Sci, 28:798-808. https://doi.org/10.1016/j.humov.2009.04.006

Luks TL, Simpson GV, Dale CL et al (2007) Preparatory allocation of attention and adjustments in conflict processing. NeuroImage, 35:949-958. https://doi.org/10.1016/j.neuroimage.2006.11.041

Matsunaga K, Maruyama A, Fujiwara T et al (2005) Increased corticospinal excitability after 5 Hz rTMS over the human supplementary motor area. J Physiol, 562:295-306. https://doi.org/10.1113/jphysiol.2004.070755

McIntyre AK, Proske U, Rawson JA (1984). Cortical projection of afferent information from tendon organs in the cat. J Physiol, 354:395-406. https://doi.org/10.1113/jphysiol.1984.sp015383

Metzger FG, Ehlis AC, Haeussinger FB et al (2017) Functional brain imaging of walking while talking - an fNIRS study. Neuroscience, 343:85-93. https://doi.org/10.1016/j.neuroscience.2016.11.032

Morris DM, Taub E, Mark VW (2006) Constraint-induced movement therapy: characterizing the intervention protocol. Eura Medicophys, 42:257-268.

Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. Nat Rev Neurosci, 9:856-869. https://doi.org/10.1038/nrn2478

Petrof I, Viaene AN, Sherman SM (2015) Properties of the primary somatosensory cortex projection to the primary motor cortex in the mouse. J Neurophysiol, 113:2400-2407. https://doi.org/10.1152/jn.00949.2014

Rehme AK, Eickhoff SB, Rottschy C et al (2012) Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. Neuroimage, 59:2771-2782. https://doi.org/10.1016/j.neuroimage.2011.10.023

Sankoh AJ, Huque MF, Dubey SD (1997) Some comments on frequently used multiple endpoint adjustment methods in clinical trials. Stat Med, 16:2529-2542. https://doi.org/10.1002/(sici)1097-

0258(19971130)16:22<2529::aid-sim692>3.0.co;2-j

Strangman G, Culver JP, Thompson JH et al (2002) A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage, 17:719-731

Sunderland A, Tuke A (2005) Neuroplasticity, learning and recovery after stroke: a critical evaluation of constraint-induced therapy. Neuropsychol Rehabil, 15:81-96. https://doi.org/10.1080/09602010443000047

Taub E, Uswatte G, Mark VW et al (2006) The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys, 42:241-256

Wager TD, Jonides J, Reading S (2004) Neuroimaging studies of shifting attention: a meta-analysis. NeuroImage, 22(4):1679-1693. https://doi.org/https://doi.org/10.1016/j.neuroimage.2004.03.052

Wang Y, Isoda M, Matsuzaka Y et al (2005) Prefrontal cortical cells projecting to the supplementary eye field and presupplementary motor area in the monkey. Neurosci Res, 53:1-7. https://doi.org/10.1016/j.neures.2005.05.005

Wei WXJ, Fong KNK, Chung RCK et al (2019) "Remind-to-move" for promoting upper extremity recovery using wearable devices in subacute stroke: a multi-center randomized controlled study. IEEE Trans Neural Syst Rehabil Eng, 27:51-59. https://doi.org/10.1109/TNSRE.2018.2882235

Winstein CJ, Stein J, Arena R et al (2016) Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 47:e98-e169. https://doi.org/10.1161/str.0000000000000098

Xia M, Wang J, He Y (2013) BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One, 8:e68910. https://doi.org/10.1371/journal.pone.0068910

Yang NY, Fong KN, Li-Tsang CW et al (2017) Effects of repetitive transcranial magnetic stimulation combined with sensory cueing on unilateral neglect in subacute patients with right hemispheric stroke: a randomized controlled study. Clin Rehabil, 31:1154-1163. https://doi.org/10.1177/0269215516679712

Ye JC, Tak S, Jang KE et al (2009) NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. Neuroimage, 44: 428-447. https://doi.org/10.1016/j.neuroimage.2008.08.036

Figure Captions

Fig. 1 Sensory cueing wristwatch device (SCW-V2).

Fig. 2 Top (a) and right-lateral (b) views of the locations of channels in the MNI brain template.

Fig. 3 Concentration changes of oxyhemoglobin (ΔHbO) in the three conditions in both healthy and patients with stroke. *RNoM* reminding with no-movements; *RTM* "Remind-to-Move"; *Sham* movements without reminding.

Fig. 4 The main effects of populations and conditions reflected by F values from the two two-way ANOVA analysis. Numbers in black colour represent the channels that remained after the D/A-P correction was applied, the numbers in grey colour represent the channels which had significant F values but did not pass the D/A-P correction.

Fig. 5 The comparison between the RTM and the Sham conditions in both healthy participants and patients with stroke. The colour map is the t value of each channel (RTM > Sham). Numbers in black colour represent the channels that remained after the D/A-P correction, the numbers in grey colour represent the channels which had significant t values but did not pass the D/A-P correction. *RTM* "Remind-to-Move"; *Sham* movements without reminding.

Fig. 1

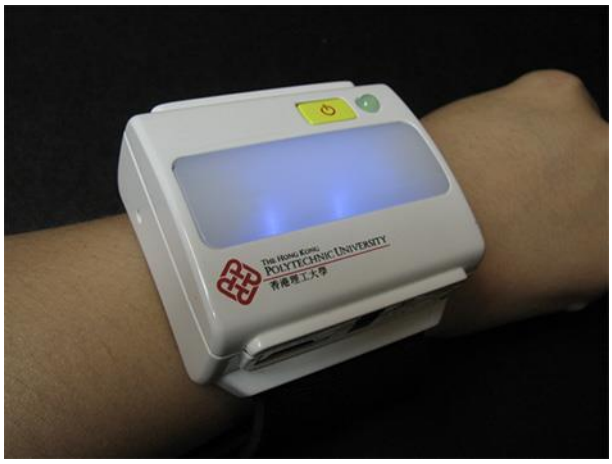

Fig. 2

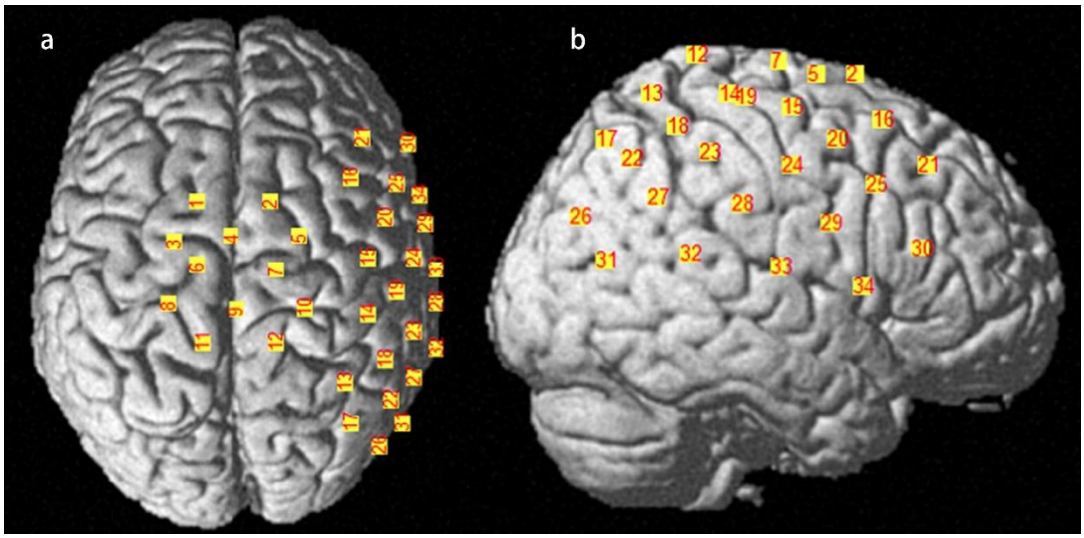

Fig. 3

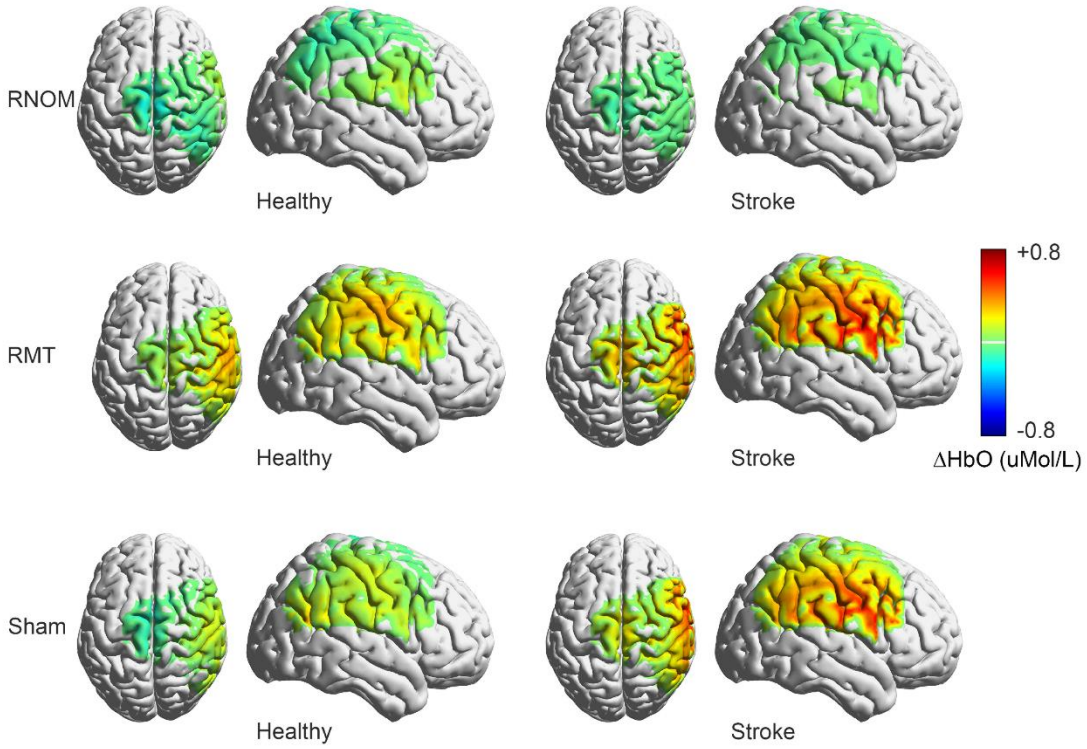
RNOM
Healthy
Stroke
RMT
Healthy
Stroke
+0.8
-0.8
ΔHbO (uMol/L)
Sham
Healthy
Stroke

Fig. 4

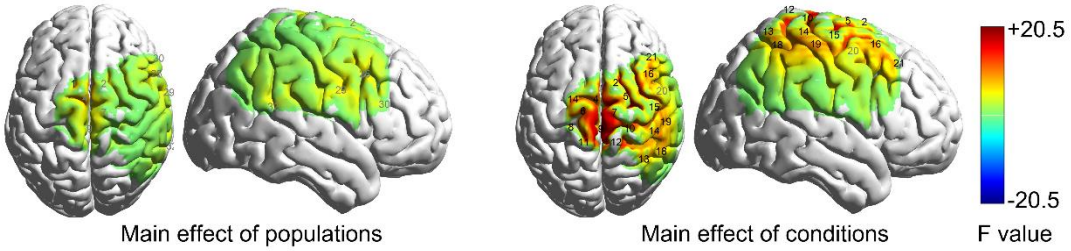
+20.5
-20.5
Main effect of populations
Main effect of conditions
F value

Fig. 5