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DOI:
10.1093/braincomms/fcae011

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Chih-Wei Tang[a,b], Catharina Zich[c,d], Andrew J. Quinn[c,e,f], Mark W. Woolrich[c,e], Shih-Pin Hsu[a], Chi-Hung Juan[g], I-Hui Lee[a,h], Charlotte J. Stagg[c,d]

[a]Institute of Brain Science, Brain Research Center, National Yang Ming Chiao Tung University, No.155, Sec. 2, Linong St., Beitou Dist., Taipei City 112, Taiwan

[b]Department of Neurology, Far Eastern Memorial Hospital, No.21, Sec. 2, Nanya S. Rd., Banqiao Dist., New Taipei City 220, Taiwan

[c]Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, UK

[d]MRC Brain Network Dynamics Unit, University of Oxford, Oxford, OX1 3TH, UK

[e]Oxford Centre for Human Brain Activity, Wellcome Centre for Integrative Neuroimaging, Department of Psychiatry, University of Oxford, Oxford OX3 7JX, UK

[f]Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham, UK.

[g]Institute of Cognitive Neuroscience, National Central University, No.300, Zhongda Rd., Zhongli Dist., Taoyuan City 320, Taiwan

[h]Division of Cerebrovascular Diseases, Neurological Institute, Taipei Veterans General Hospital, No.201, Sec. 2, Shipai Rd., Beitou Dist., Taipei City 112, Taiwan

Correspondence to Charlotte J. Stagg, Oxford OX3 9DU, UK, charlotte.stagg@ndcn.ox.ac.uk

Correspondence may also be sent to I-Hui Lee, No. 201, Sec. 2, Shipai Rd., Beitou Dist., Taipei City 112, Taiwan, ihlee@vghtpe.gov.tw

Short title: resting-state network in stroke recovery

Abstract

Motor recovery is still limited for people with stroke especially those with greater functional impairments. In order to improve outcome, we need to understand more about the mechanisms underpinning recovery. Task-unbiased, blood-flow independent post-stroke neural activity can be acquired from resting brain electrophysiological recordings, and offers substantial promise to investigate physiological mechanisms, but behaviourally-relevant features of resting-state sensorimotor network dynamics have not yet been identified. Thirty-seven people with subcortical ischemic stroke and unilateral hand paresis of any degree were longitudinally evaluated at 3 weeks (early subacute) and 12 weeks (late subacute) after stroke. Resting-state magnetoencephalography and clinical scores of motor function were recorded and compared with matched controls. Magnetoencephalography data were decomposed using a data-driven Hidden Markov Model into 10 time-varying resting-state networks. People with stroke showed statistically significantly improved Action Research Arm Test and Fugl-Meyer upper extremity scores between 3 weeks and 12 weeks after stroke (both $p<0.001$). Hidden Markov Model analysis revealed a primarily alpha-band ipsilesional resting-state sensorimotor network which had a significantly increased life-time (the average time elapsed between entering and exiting the network) and fractional occupancy (the occupied percentage among all networks) at 3 weeks after stroke when compared to controls. The life-time of the ipsilesional resting-state sensorimotor network positively correlated with concurrent motor scores in people with stroke who had not fully recovered. Specifically, this relationship was observed only in ipsilesional rather in contralesional sensorimotor network, default mode network or visual network. The ipsilesional sensorimotor network metrics were not significantly different from controls at 12 weeks after stroke. The increased recruitment of alpha-band ipsilesional resting-state sensorimotor network at subacute stroke served as functionally correlated biomarkers exclusively in people with stroke with not fully recovered hand paresis, plausibly reflecting functional motor recovery processes.

Key words: stroke, motor recovery, magnetoencephalography, Hidden Markov Model

Introduction

Motor recovery after stroke is still suboptimal for most people, and particularly for those with moderate to severe hand paresis.[1-3] Insights into the mechanisms underlying recovery could significantly advance the development of potential therapeutic options. While upper limb recovery can be predicted by initial motor impairment using the proportional recovery model in patients with less severe hand paresis, ~~it~~ this method often fails for severely impaired patients.[4] Studying changes in neural activity is therefore important in order to understand the mechanisms of motor recovery, and to then harness these to improve outcome. However, most task-based studies excluded people with stroke with poor hand motor function as they are unable to perform the motor tasks adequately. Resting-state biomarkers are unbiased by motor task performance and have the potential to disclose the post-stroke motor recovery processes independent of motor impairment. The motor evoked potential (MEP) induced by transcranial magnetic stimulation at rest can provide supplementary information in predicting motor outcome,[5] but it's reliability is still debated. [6] Resting-state functional MRI (rs-fMRI) studies have demonstrated decreased functional connectivity of the sensorimotor network early after stroke, which then increased with recovery of motor function.[7] However, fMRI is dependent on the Blood Oxygen Level Dependent (BOLD) signal, which may be unreliable post-stroke due to impaired vasoreactivity.[8]

Resting neural activity can be easily acquired using magneto- or electro-encephalography (MEG/EEG), which can give an insight into temporal, spectral and spatial features of neural activity, such as spectral power or connectivity, which may underly recovery. [9-13] Previous studies have shown increased power in low-frequency activity in the perilesional region early after stroke compared to controls, [11] which decreases during recovery. [10] Alpha coherence has also been noted to increase in perilesional regions after stroke, and the degree of coherence predicts motor outcome after controlling for age, stroke onset- time and lesion size in

voxel-wised coherence study. [12] However, these previous studies have investigated changes in neural activity within pre-defined frequency bands of interest, and have not investigated temporally-varying neural activity features, which are increasingly understood to be functionally relevant. [9-12]

Hidden Markov Models (HMM) enable the decomposition of electrophysiological data into discrete functional states with millisecond precision.[14-16] The HMM estimates brain states in a data-driven manner without pre-specification or constraining the timescale of dynamics and can be applied to resting[17,18] or task[17,19] data. The dynamic features of each brain state, such as interval-time (i.e., time between two state visits) or life-time (i.e., time of a state visit), can be quantified. HMM has been successfully used in a number of applications, including the study of memory replay[20] and in neurological diseases, including dementia and multiple sclerosis, [18,21,22] where the different metrics are able to give more specific insights into aspects of function. For example, the ability to switch between brain states, inversely reflected by the how long the brain spends in a given state at a time (the "life-time"), has been suggested to be important in flexible cognitive control, where rapid shifting may reflect faster behavioural responses.[14,23] The amount of time the brain spends in a given state (the "fractional occupancy" or FO) is closer to the classic spectral "power" of a standard, temporally invariate, analysis.[23] We therefore predict that people with stroke will have a low-frequency (delta – alpha) ipsilesional sensorimotor network, which will exhibit longer life-times and greater fractional occupancy than age matched control participants.

Here, we conducted a longitudinal MEG study in a cohort of people with stroke with first-time subcortical infarction in the middle cerebral artery (MCA) territory at week 3 (early subacute stage) and 12 (late subacute stage)[24] after stroke with different degree of hand paresis to

test a number of hypotheses: (1) Subacute stroke is characterised by specific temporal features of ipsilesional resting-state sensorimotor network, including longer-life times and greater fractional occupancy. (2) The resting-state sensorimotor network changes correlate with stroke severity and functional outcome; (3) Sensorimotor networks estimated from resting state data and applied to motor task data yield clinically-relevant information.

Methods

MEG recordings of people with stroke–and age- and sex-matched controls were collected from the MEG database established at Taipei Veterans General Hospital, Taiwan from 2009-2018. Inclusion criteria were: age 20-80, right-handed as determined by Edinburgh Handedness Inventory [25] and for people with stroke: first-ever, unilateral, subcortical ischemic stroke in the MCA territory, with hand weakness of any degree, 2-4 weeks after stroke. Exclusion criteria were concomitant major neurological diseases or severe medical diseases. The study was approved by the ethics committee of the Taipei Veterans General Hospital (2013-06-036B, 2014-01-006C, 2015-03-003C), with written informed consent obtained from each participant. The study adhered to the Declaration of Helsinki, except for preregistration. As there were no similar studies on which to base power calculations, all eligible people with stroke who consented within the recruitment period were included.

People with stroke attended at two timepoints: at 3 weeks post-stroke (range 2-4 weeks) as baseline, and at 12 weeks post-stroke (range 11-13 weeks). At each session, MEG data (see below) were recorded, and the FM-UE score[26] and the Action Research Arm Test (ARAT) score[27] were conducted by a clinical therapist blinded to the study design. The identical MEG protocol was performed once in controls. In addition, MRI data were acquired once (see below).

MEG Acquisition

MEG data were recorded in a magnetically shielded room using a whole-head array 306-channel Neuromag Vectorview™ MEG system (Elekta, Helsinki, Finland) with a 500 Hz

sampling rate. Head position indicator (HPI) coils were placed at four locations on the head to record head position relative to the MEG sensors. Head landmarks (pre-auricular points and nasion) and 30-40 points on the scalp, face and nose were digitized using a Polhemus Isotrak II system. Electrooculography channels over the right upper and left lower orbital regions and electrocardiography channels over both arms were recorded (500Hz) to detect blink, ocular and cardiac artefacts.

Resting-state MEG was acquired for 5 minutes, with the subject seated, eyes open and body relaxed. The motor task paradigm was a simple motor task [see[28] for details]. Briefly, subjects performed a self-paced unilateral index finger lifting task every 7 seconds for paretic (left in controls) hand then non-paretic (right in controls) hand consecutively. A total of 100 trials were collected for each hand, with a short break after the first 50 trials (total duration approximately 20 minutes). The movement onset of finger lifting was detected by an optical detection pad.

MRI Acquisition and Analysis

All subjects underwent 3-Tesla MRI scan (Discovery MR750, General Electric Company). This included high resolution 3-dimensional T1-weighted structural images (repetition time, TR=12.2 ms; echo time, TE=5.2 ms; flip angle=12°; voxel size=1x1x1 mm; field of view, FoV=256x256 mm) and diffusion weighted imaging (TR= 4060 ms, TE=64ms, thickness=5mm, b=1000 s mm^{-2}). Lesion volumes were manually delineated from the diffusion weighted images by an experienced vascular neurologist then plotted to standard space using MRIcron®. To produce group lesion maps, heatmaps of ischemic stroke lesions were generated for right and left-hemispheric strokes separately.

MEG Analysis

The resting-state MEG raw data were initially processed by spatiotemporal signal-space separation (TSSS) correction implemented in MaxFilter version 2.2.10 (Elekta Neromag, Elekta,

Stockholm, Sweden) to reduce external noise. Further MEG analysis was performed using the OHBA Software Library (OSL: https://ohba-analysis.github.io/osl-docs/) version 2.2.0.

Pre-processing steps were applied prior to HMM analysis, as detailed by Quinn et al. and briefly outlined here. First, the structural MRI and the MEG data were co-registered using RHINO (Registration of Head shapes Including Nose in OSL). Continuous MEG data were then down-sampled to 250 Hz to reduce computational demands. Independent component analysis (ICA) was used to estimate 64 independent components using temporal FastICA. Independent components representing stereotypical artifacts such as eye blinks, eye movements, and electrical heartbeat activity were manually identified and regressed out of the data. Cleaned data were then band-pass filtered (1-40 Hz) and projected onto an 8 mm grid in source space using a Linearly Constrained Minimum Variance (LCMV) vector beamformer. [29] A weighted (non-binary) parcellation with 39 cortical regions was applied and parcel-wise time courses were estimated following the methods of Colclough et al [30]. Symmetric orthogonalisation was applied to each dataset prior to concatenation to remove spatial leakage. Resting state data were analysed as continuous data (300 seconds). For the motor task, data were epoched from -3 seconds to 3 seconds relative to the movement onset.

We inferred the Time Delay Embedded HMM (TDE-HMM) for all 39 cortical regions, which allows for identification of states with distinct multi-region spectra and/or phase locking networks. The resting-state data from people with stroke and matched controls were temporally concatenated over subjects prior to HMM. Then, source-reconstructed time-courses for each parcel were time delay embedded using 15 lags corresponding to time indexes between −7 and 7, hence specifying a 30 ms lag in both directions at the sampling rate of 250 Hz. As 10 HMM states yield one lesion-side specific sensorimotor network, we opt for 10 HMM states in this study.

We then extracted temporal metrics that summarise the dynamics of each HMM state, including life-time, interval-time and fractional occupancy. Life-time (or dwell-time) of each state

is defined as the average time elapsed between entering and exiting a state. Interval length is defined as the time elapsed between visits to a state. Fractional occupancy is defined as the proportion of time spent in each state.[23]

Lastly, to assess whether the results inferred from HMM states during resting state are generalisable to a motor context, we used the HMM state descriptions estimated from the resting-state to investigate dynamics during motor activation. This approach allows to investigate the same properties of the data, rather than global changes and has been used previously to examine effects of transfer or generalisability. [18,31] The temporal metrics (life-time, interval-time and fractional occupancy) of these resting brain states during paretic [or left in controls] hand movement and non-paretic [or right in controls] were then quantified.

Statistical Analysis

All analyses on HMM parameters and behavioural data were performed using the SPSS software (version 25, Chicago, IL, USA). Demographic characteristics between the stroke and the control group were examined using chi-square tests for categorical data and Mann-Whiney U tests for continuous data. Multivariate analysis of variance (ANOVA)s were performed to compare the HMM parameters (life-time, interval-time, fractional occupancy) between control and stroke groups. To evaluate the changes in HMM parameters over time one-way repeated measures ANOVAs were performed. Significant effects in the ANOVAs were followed by *post-hoc* Mann-Whitney U test (independent data) or Wilcoxon Signed Rank Test (dependent data) with Bonferroni correction where appropriate. The relationship between motor scores and HMM parameters was examined using Spearman's rank correlation.

Results

Demographics

A total of 37 (25 male) people with stroke (18 right hemispheric strokes) and 22 age- and sex-matched controls were enrolled (Table 1). People with stroke had a median age of 60 years

(range 50-66), were a median of 22 days (17-25) after stroke onset, with a median NIHSS of 4 (2-7); an ARAT of 32 (6-52) and a FM-UE of 50 (23-62) at enrolment. All people with stroke had standard clinical care, which consists of 60 - 120 minutes of therapy at least 3 days per week for up to 6 months after stroke. People with stroke showed statistically significant improvements in both ARAT and FM-UE scores between 3 weeks and 12 weeks after stroke ($Z=4.8$ and 5.2 respectively, both $p < 0.001$). 14/29 people with stroke showed clinically significant improvements (12 points for the dominant and 17 points for non-dominant side[32]) in ARAT score and 14/29 people with stroke showed clinically significant improvements (>12.4 points[33]) in FM-UE. Two patients showed a clinically significant improvement in the ARAT but not FM-UE and two in the FM-UE but not the ARAT. No significant difference in motor scores were noted between people with stroke with right or left hemispheric strokes (all $p > 0.5$). The group lesion map (Fig. 1) showed a homogenous grouping, with infarctions in the corona radiata and basal ganglia within the middle cerebral artery territory without cortical involvement. All thirty-seven people with stroke had resting MEG recordings in week 3, with sixteen people with stroke having also resting MEG recordings at week 12. Participants declined the second scan for a variety of reasons, including transfer to other hospitals or to home. For stroke people with or without 12 week follow-up, the HMM metrics at post-stroke week 3 showed no group difference (see supplementary table 1).

HMM identified resting-state sensorimotor networks

First, to determine whether we could identify a sensorimotor network in our resting MEG data, all resting state data (i.e., two timepoints for the people with stroke and one timepoint for the controls) were submitted to a time-delay embedded HMM. Ten resting-state networks were decomposed with corresponding spectral profiles (Fig. 2A), spatial profiles (Fig. 2C-D) and temporal metrics (Fig. 2B), which replicated the pattern showed by Vidaurre et al. before.[34] We identified a resting-state sensorimotor network (SMN), with a frequency peak (10Hz) in the α-

(μ-) frequency range (state 3). The spatial distribution of this α- SMN is compatible with that seen in a previous resting-state fMRI study.[35] This initial proof-of-principle analysis demonstrated that sensorimotor networks could be identified in our data.

Our cohort contained people with both left and right hemisphere strokes. We reasoned that ipsilesional and contralesional hemispheres might be expected to show distinct changes post-stroke[12,36,37]. Therefore, we next applied two separate time-delay embedded HMM analysis for people with stroke with right (n=18; Fig. 3) and left (n=19; Fig. 4) MCA infarctions, both concatenated with control data (n=22). For both groups it was possible to identify an ipsilesional sensorimotor network (iSMN) and a contralesional sensorimotor (cSMN), in the α-frequency range, which had characteristic spectral and spatial features (Fig. 3A-C, 4A-C).

To test for specificity of any results involving the SMNs we defined two control states, i.e., two robust RSNs that did not include motor areas. We found a clear visual network (VN) in the α-frequency range (10Hz) (Fig. 2-4) comprising primary and associated visual cortices. Further, we identified a default mode network (DMN) in the θ frequency range (3-5Hz) (Fig. 2-4), which also shared common spatial distribution as seen in resting-state fMRI[35] and was characterised by the longest life-time and interval-time among all HMM states.

Post stroke life-time and fractional occupancy of ipsilesional resting-state sensorimotor networks are increased compared to controls and contralateral resting-state networks

Having identified robust sensorimotor networks, we next wished to investigate whether they changed after stroke. To this end we extracted HMM metrics (life-time, interval-time and fractional occupancy) from the iSMN and cSMN separately for each subject and timepoint. We then pooled together the data from right (n=18) and left (n=19) hemispheric people with stroke.

We ran three 2x2 mixed design ANOVAs, one for each temporal metric (life-time, interval-time, fractional occupancy), with a between-subject factor of group (controls, people with stroke at 3 week post-stroke) and a within-subject factor of regions (iSMN, cSMN). We found a significant main effect for group in life-time ($F(1,79)=16.27$, $p<0.001$, $\eta_p^2=0.171$), but not for fractional occupancy or interval-time (p's>0.5, see supplementary table 2 for full ANOVA statistics), indicating longer state visits in people with stroke. Further, we found differences between iSMN and cSMN (life-time: $F(1,79)=3.76$, $p=0.056$, $\eta_p^2=0.045$, longer life-times for iSMN; fractional occupancy: $F(1,79)=6.55$, $p=0.012$, $\eta_p^2=0.077$, higher fractional occupancy for iSMN; interval-time: $F(1,79)=6.47$, $p=0.013$, $\eta_p^2=0.076$, longer interval-time for cSMN). Moreover, there were significant region x group interactions in life-time ($F(1,79)=16.4$, $p<0.001$, $\eta_p^2=0.172$), fractional occupancy ($F(1,79)=20.77$, $p<0.001$, $\eta_p^2=0.208$) and interval-time ($F(1,79)=13.1$, $p<0.001$, $\eta_p^2=0.142$). Interactions were followed up using non-parametric Mann-Whitney U tests (corrected $\alpha=0.025$). Life-time and fractional occupancy were significantly greater people with stroke–than controls in iSMN ($U=342$, $p<0.001$, $r=0.497$; $U=449$, $p<0.001$, $r=0.385$, respectively), but comparable in cSMN ($U=771$, $p=0.684$, $r=0.045$; $U=655$, $p=0.131$, $r=0.168$, respectively). The interval-time showed no group difference in either iSMN ($U=628$, $p=0.078$, $r=0.196$) or cSMN ($U=1030$, $p=0.041$, $r=0.228$). For completeness, the results for the same analysis at 12 weeks post stroke is reported in the supplementary material which showed the life-time was still significantly greater in people with stroke than controls in iSMN ($U=210$, $p=0.018$, $r=0.31$), but not in cSMN ($U=326$, $p=0.66$, $r=0.06$).

The same analysis applied in the control states (DMN, VN) showed no significant main effects of group or region x group interactions (all p's > 0.1) in either of three HMM metrics. However, significant main effects of region between DMN and VN were noted in all temporal metrics (all p's <0.001, see supplementary table 2 for full statistics), indicating longer life-time, longer interval-time, and lower fractional occupancy in DMN, compared to VN. Having

established the importance of the ipsilateral sensorimotor network we next evaluated its temporal properties in more detail.

Life-times of ipsilesionsal sensorimotor network depend on lesion side

To determine whether the post-stroke change of life-time and fractional occupancy observed in iSMN were dependent on the side of the lesion, we ran Mann-Whitney U Tests. The life-time and fractional occupancy of iSMN was significantly greater in people with stroke-with either right MCA infarction [U=345, p<0.001, r=0.63; U=320, p<0.001, r=0.52, respectively] (Fig. 3D) or left MCA infarction [U=105, p=0.007, r=0.42; U=288, p=0.039, r=0.32, respectively] than controls (Fig. 4D). We further explored if there were differences between right and left MCA infarctions in life-time and fractional occupancy. The Mann-Whitney U Tests showed that the life-time was even more increased in left than right MCA infarction (U=73, p=0.003, r=0.49), but the fractional occupancy showed no side difference (U=221, p=0.129, r=0.25).

Ipsilesional sensorimotor network life-time and fractional occupancy trend towards normalising during stroke recovery

We next went on to investigate how the resting-state networks change during stroke recovery. To this end, we performed Wilcoxon Signed Rank Test for temporal metrics (life-time, interval-time, fractional occupancy) separately. The life-time and fractional occupancy of iSMN significantly decreased at post-stroke week 12 when compared to week 3 (Z=2.07, p=0.038, r=0.52; Z=2.23, p=0.026, r=0.56, respectively), with no difference in interval-time (Z=1.34, p=0.18, r=0.34).

Ipsilesional sensorimotor network life-time and fractional occupancy correlate with function in people with stroke-with not fully recovered hand paresis

Given the specific finding that the life-time and fractional occupancy of iSMN was changed early post-stroke, we next investigated whether life-time of iSMN relates to clinical recovery. Clinical recovery was assessed by two behavioural measures: the FM-UE and the ARAT. As we

hypothesised that people with stroke-with very good recovery might be at ceiling on our scores, we divided our cohort of people with stroke into two groups: those with an initially nearly fully recovered hand paresis, defined as ARAT score of >55 or FM-UE score of >64 at stroke week 3 (n=12, open circles) and those with not fully recovered hand paresis, defined as ARAT score <56 and FM-UE score <65 (n=25, closed circles) in Fig. 5.

In people with stroke-with initially not fully recovered hand paresis, life-time and fractional occupancy of iSMN at week 3 were positively correlated with ARAT at week 3 (life-time: r=0.49, p=0.013, Fig. 5A; fractional occupancy: r=0.43, p=0.030, supplementary figure 1A) and FM-UE at week 3 (life-time: r=0.57, p=0.003, Fig. 5B; fractional occupancy: r=0.44, p=0.029, supplementary figure 1B). Further correlation analysis was used to determine if early resting-state network related to final motor outcome, as a biomarker of stroke recovery. Week 3 iSMN life-time and fractional occupancy were significantly positively correlated with week 12 ARAT in people with stroke-with initially not fully recovered hand paresis (life-time: r=0.51, p=0.019 Fig. 5C; fractional occupancy: r=0.46, p=0.036, supplementary figure 1C), but not with FM-UE (life-time: r=0.34, p=0.127, Fig. 5D; fractional occupancy: r=0.40, p=0.071, supplementary figure 1D). We then wished to know whether week 3 iSMN life-time and fractional occupancy could independently predict behavioural recovery. We performed a partial correlation analysis between iSMN life-time and fractional occupancy at week 3 and ARAT at week 12, controlling for ARAT at week 3 and demonstrated that the relationship was no longer significant (life-time: r=0.42, p=0.063; fractional occupancy: r=0.38, p=0.096).

HMM resting-state ipsilesional sensorimotor networks in motor task

Finally, while the strength of this study is that these metrics can be obtained at rest, making them clinically-feasible, we wanted to determine the face validity of our metrics, by investigating how these resting-state networks interacted during motor task-as showed in supplementary results.

Discussion

This study characterized temporal features of post-stroke sensorimotor networks from resting-state brain activity. Robust resting-state networks with specific spatial, frequency and temporal features were extracted from whole brain inference of HMM. The life-time and fractional occupancy of the resting-state ipsilesional sensorimotor network was significantly increased at the subacute time period after stroke and correlated with motor functions specifically in people with stroke-with moderate to severe hand paresis.

Functionally correlated resting-state ipsilesional sensorimotor network at subacute stroke

The resting-state sensorimotor network constructed from fMRI, EEG or MEG shares the same spatial distribution across the different modalities[38,39]. In this study, the sensorimotor network arising from our HMM analysis (Fig. 2) could further be decomposed into ipsilesional and contralesional sensorimotor networks in people with stroke–(Fig. 3-4), the two networks showed differential changes during recovery. Both the life-time and fractional occupancy of the ipsilesional resting-state sensorimotor network were increased at 3 weeks after stroke as compared to controls. The increased recruitment of the ipsilesional sensorimotor network was positively correlated with motor scores in people with subacute stroke-with not fully recovered hand paresis, and gradually decreased during stroke recovery. This pattern of changes would support the hypothesis that the increased recruitment of the ipsilesional sensorimotor network in subacute stroke may reflect mechanisms of recovery after stroke. The finding of increased ipsilesional sensorimotor network recruitment post-stroke which then reduces with recovery is in line with previous task fMRI [37,40] and task MEG [28] studies, which have showed greater activity in these networks during movement of the paretic hand early after stroke, which gradually decreases during subsequent recovery.

The life-time and fractional occupancy of ipsilesional sensorimotor network at week 3 after stroke was also correlated with the motor outcome at week 12 after stroke, suggesting that dynamics within the ipsilesional sensorimotor network are relevant not only to current behaviour, but relate to subsequent improvements. Although the correlation was no longer significant when controlling motor scores at week 3 after stroke, this does not rule out the hypothesis that the ipsilesional sensorimotor network dynamics are a marker of pro-plastic processes: if they indeed are mechanistically involved in functional recovery then they would be expected to be tightly correlated with motor performance, as seen here. However, this hypothesis remains to be tested.

Several studies have demonstrated that early motor scores can independently predict motor outcome except in those people with severe limbs paresis.[4,5,41] The outliers in the proportional recovery model usually have FM-UE between 2-6[4], which is far more severe than our cohort. In this study, the life-time of resting-state iSMN correlated better in those with initially marked hand paresis (Fig. 5C) and could serve as a biomarker for those outliers in the proportional recovery model. People with stroke–with more severe hand paresis should be enrolled in further study to verify this finding.

Changes in network metrics were specific to the ipsilesional sensorimotor network

In addition to the ipsilesional and contralesional sensorimotor networks, the most prominent and robust resting-state networks from our data were default mode network and visual network. However, only the ipsilesional sensorimotor network showed significant post-stroke changes and behaviour correlations in this study. The consistency of DMN and VN metrics between people with stroke and controls demonstrate the specificity of our findings in this population of people with motor deficits post-stroke, and suggest that these changes were not driven by global differences between the group such as medications or drowsiness. However, DMN or VN may have post-stroke changes in different stroke cohort with homogenous dysfunction related to DMN or VN. [17]

Alterations in sensorimotor network dynamics may reflect disinhibition in subacute stroke

Previous resting-state TMS studies have demonstrated decreased ipsilesional MEP amplitude [5,42], but also decreased intracortical and interhemispheric inhibition [43] during the subacute recovery phase after stroke. Resting state fMRI studies have shown decreased functional connectivity within the sensorimotor network, particularly between the hemispheres.[44] Taken together, these findings highlight the disruption of functional networks, particularly a dissociation of the ipsilesional and contralesional motor cortices, accompanied with disinhibition phenomenon in the critical recovery period.[45] The increased recruitment of iSMN observed here was particularly prominent early rather than later after stroke, especially in people with greater hand paresis. The relative decrease in the ability of the brain to switch between states and to remain locked in one state could plausibly be a reflection of a disinhibited cortex, where increased cortical activity leads to an amplification and perseverance of ongoing activity. It is possible, therefore, that the increased ipsilesional SMN observed here reflects local disinhibition, potentially a reflection of cortical neuroplastic phenomena. The finding that the changes in iSMN lifetime are greater in people with dominant rather than non-dominant hemisphere strokes would fit with this hypothesis, as the dominant hemisphere receives relatively less interhemispheric inhibition from the non-dominant hemisphere than vice-versa. These results therefore add weight to the hypothesis that disinhibition leads to a dysregulation of sensorimotor connectivity, particularly reflected in decreased inter-hemispheric connections and increased local connectivity.

HMM Dynamics during motor task

Neural activity acquired during task has given us rich information about recovery post-stroke. However, it is often difficult to acquire in the subacute phase and relies on people with stroke having sufficient function and cognitive ability to perform a task. In this study,

therefore, we wanted to investigate whether resting data might be similarly informative. The HMM brain states decomposed from resting-state data were also applied in motor task data. We disclosed similar trend but less significant changes in ipsilesional sensorimotor network after stroke. Importantly, the life-time of resting-state ipsilesional sensorimotor network applied during task also correlated with motor scores, but only during paretic hand movement rather than non-paretic hand movement. These results suggest that the increased recruitment of sensorimotor network at rest may also be linked to paretic hand movement. However, further delicate state-shift studies are required to determine the relationship between resting-state sensorimotor network (α-range) and task-state sensorimotor network (β-range).

Considerations and further applications

The people with stroke in this study mostly had mild or moderate hand paresis, with only few with FM-UE less than 11.[46] This relatively well-recovered group may lead us to underestimate the correlation power of the life-time or fractional occupancy. In addition, the assumptions in the HMM may limit the interpretation of results in a number of ways. Firstly, a known limitation of HMM inference is the a priori selection of the number of HMM states. Here we inferred 10 HMM states as 10 HMM states yielded one ipsilesional and one contralateral sensorimotor network. Previous studies have validated the robustness of results using a range of HMM states and found that varying the number of states (within a reasonable range, i.e., 3-14) did not change the results.[23] Secondly, HMM assumes that the states are mutually exclusive and only a single state is active at a single time-point, which excludes the possibility that multiple networks may be active at the same time, which may be an over-simplification. New methods being developed should overcome this limitation, and are likely to be important in future studies. [47] Finally, our cohort only included people with subcortical strokes. It is not clear how these findings would translate to people with cortical lesions, although given that the HMM approach is data-driven and does not

rely on ROIs or assumptions about anatomy, it is likely that similar changes in dynamics would be observed.

Conclusions

We have demonstrated changes in the dynamics and connectivity of the ipsilesional sensorimotor network early after stroke at rest. The increased life-time and fractional occupancy of resting state x§ipsilesional sensorimotor network positively correlated with motor functions in people with stroke–with moderate hand paresis, suggesting that network dynamics may have a functional relevance. Our findings are in line with those from other modalities, suggesting that local disinhibition and inter-hemispheric dysconnectivity are prominent after stroke, and relate to motor function. That we can identify these markers in resting electrophysiological data overcomes many of the issues associated with task performance, and changes in neurovascular coupling in people with stroke, and therefore offers substantial promise to study recovery after stroke.

Acknowledgements

We thank the staff in the Clinical Research Core Laboratory and the Stroke Registry of the Taipei Veterans General Hospital for providing experimental facilities and registry data, respectively.

Data Availability

We will consider requests to access the raw data in a trusted research environment as part of a collaboration. Please contact Dr Lee with all requests.

Funding

This work was supported by the Taiwan Ministry of Science and Technology (MOST, 106-2314-B-075-019-MY3, 107-2634-F-008-003, 108-2634-F-008-003, 109-2314-B-418-008), the Taipei Veterans General Hospital (V106C-023, V107C-064, V108C-052), the Far Eastern Memorial Hospital (FEMH-2014-C-018, FEMH-2015-C-025, FEMH-2021-003), the Taiwan Ministry of Education (Academic Strategic Alliance Project between Taiwan and Oxford

University), and the National Yang Ming Chiao Tung University (Brain Research Center, from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Taiwan Ministry of Education). CJS holds a Senior Research Fellowship, funded by the Wellcome Trust (224430/Z/21/Z).

Competing interests

The authors report no competing interests.

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Figure legends

Figure 1

Stroke lesion map

Heatmap of infarct lesions in people with stroke with right (n=18) and left (n=19) hemisphere infarction overlaid on a standardized template (MRIcron®). All locations were subcortical regions in the middle cerebral artery territory, mostly involving the corona radiata and basal ganglia. R= right; L= left; IH = ipsilesional hemisphere.

Figure 2

HMM-derived MEG resting-state networks

Resting-state MEG signals concatenated from all participants including controls (n=22) and people with stroke (n=37 at week 3, n=16 at week 12) characterised by 10 HMM states. **(A)** Spectral profiles, **(B)** temporal metrics, and **(C-D)** spatial profiles. The major resting-state networks include a sensorimotor network (SMN, state 3), temporo-parietal network (TPN, state 7), visual network (VN, state 1) and default mode network (DMN, state 6). Their spatial activation profiles resemble those of resting-state fMRI networks.[35]

Figure 3

MEG resting-state sensorimotor networks from people with right hemispheric strokes

The major resting-state networks from people with stroke with right MCA infarction (n=18 at week 3, n=8 at week 12) and controls (n=22), with corresponding **(A)** spectral profiles, **(B)** spatial profiles, **(C)** spatial coherence and **(D)** temporal metrics. Shown are the ipsilesional sensorimotor network (iSMN), contralesional SMN (cSMN), default mode network (DMN) and visual network (VN). Full 2x2 mixed design ANOVAs were run for each temporal metric (life-time, interval-time, fractional occupancy) separately, with a between-subject factor of group (controls,

either 3 or 12 week post-stroke) and a within-subject factor of regions (iSMN, cSMN). For full statistical results see supplementary table 2. Bonferroni-corrected post-hoc tests demonstrated signficantly increased life-time and fractional occupancy in iSMN at 3 week post-stroke when compared to controls (Life-time: U=345, p<0.001, r=0.63; Fractional Occupancy: U=320, p<0.001, r=0.52). IH= ipsilesional hemisphere; R=right; L=left. * p<0.05, ** p<0.01.

Figure 4.

MEG resting-state sensorimotor networks from people with left hemispheric strokes

The major resting-state networks from people with stroke with left MCA infarction (n=19 at week 3, n=8 at week 12) and controls (n=22), with corresponding **(A)** spectral profiles, **(B)** spatial profiles, **(C)** spatial coherence and **(D)** temporal metrics. Shown are the ipsilesional sensorimotor network (iSMN), contralesional SMN (cSMN), default mode network (DMN) and visual network (VN). Full 2x2 mixed design ANOVAs were run for each temporal metric (life-time, interval-time, fractional occupancy) separately, with a between-subject factor of group (controls, either 3 or 12 week post-stroke) and a within-subject factor of regions (iSMN, cSMN). For full statistical results see supplementary table 2. Bonferroni-corrected post-hoc tests demonstrated signficantly increased life-time and fractional occupancy in iSMN Signficantly increased life-time and fractional occupancy were noted in iSMN at 3 week post-stroke when compared to controls (Life time: U=105, p=0.007, r=0.42; Fractional Occupancy: U=288, p=0.039, r=0.32). IH= ipsilesional hemisphere; R=right; L=left. * p<0.05, ** p<0.01.

Figure 5

Correlation between functional scores and ipsielsional resting-state sensorimotor networks

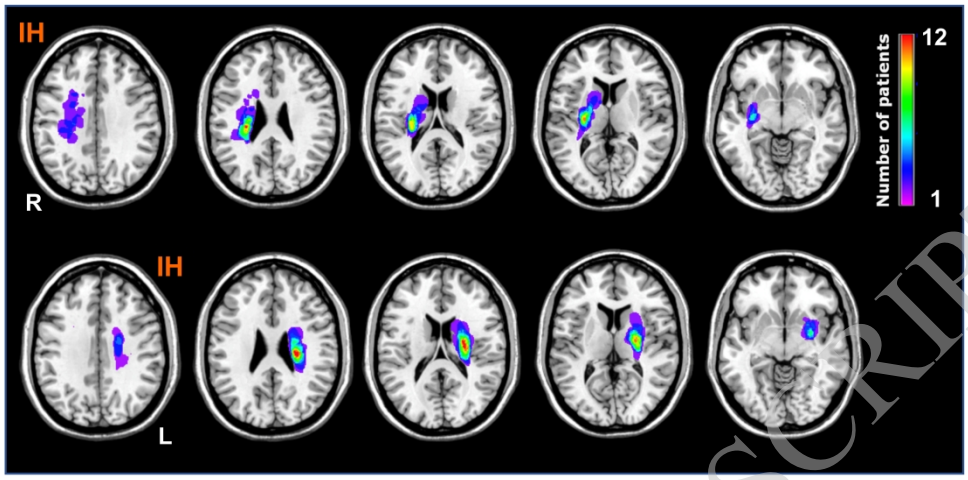
The mean life-time of ipsilesional sensorimotor network (iSMN) at week 3 after stroke in people with stroke showed a signficantly positive correlation with concurrent **(A)** action research arm test (ARAT) score and **(B)** Fugl-Meyer upper extremity (FM-UE) score, in those with initial moderate to severe hand paresis (n=25, dark circle ●) as defined by ARAT score <56 and FM-UE score <65 at stroke week 3. Such functional correlations were not seen in stroke survivoss with initial nearly fully recovered hand paresis (n=12, white circle ○), defined by ARAT score of 56-57 or FM-UE score of 65-66 at stroke week 3. **(C)** The life-time of iSMN at stroke week 3 also positively correlated with ARAT at stroke week 12 in those with initial moderate to severe hand paresis (n=21, dark circle ●), but not **(D)** FM-UE at stroke week 12. The fractional occupancy of iSMN showed similar results as the liftime (see supplementary figure 1).

Figure 6

The resting-state networks during motor task

The decomposed HMM resting-state networks applied in participants during **(A)** paretic [or left in controls] hand movement task, and **(B)** non-paretic [or right in controls] hand movement task disclosed similar but less significant changes than in the resting-state data of life-time and fractional occupancy in ipsilesional sensorimotor network (iSMN). Full 2x2 mixed design ANOVAs were run for each temporal metric (life-time, interval-time, fractional occupancy) separately, with a between-subject factor of group (controls, either 3 or 12 week post-stroke) and a within-subject factor of regions (iSMN, cSMN). For full statistical results see supplementary information. There were no significant post-hoc differences between the two groups in any HMM metric during movement of the paretic hand (A). Bonferroni-corrected post-hoc tests demonstrated that during movement of the non-paretic hand there was a significantly higher

Fractional Occupancy in iSMN in people with stroke at 3 weeks compared with controls (U=586, p=0.015, r=0.32; B). The life-time of iSMN during paretic hand movement showed significant functional correlations, which were not seen during movement of the non-paretic hand. cSMN= contralesinal sensorimotor network; DMN= default mode network; VN= visual network; ARAT= action research arm test; FM-UE= Fugl-Meyer upper extremity. * $p<0.05$, ** $p<0.01$.



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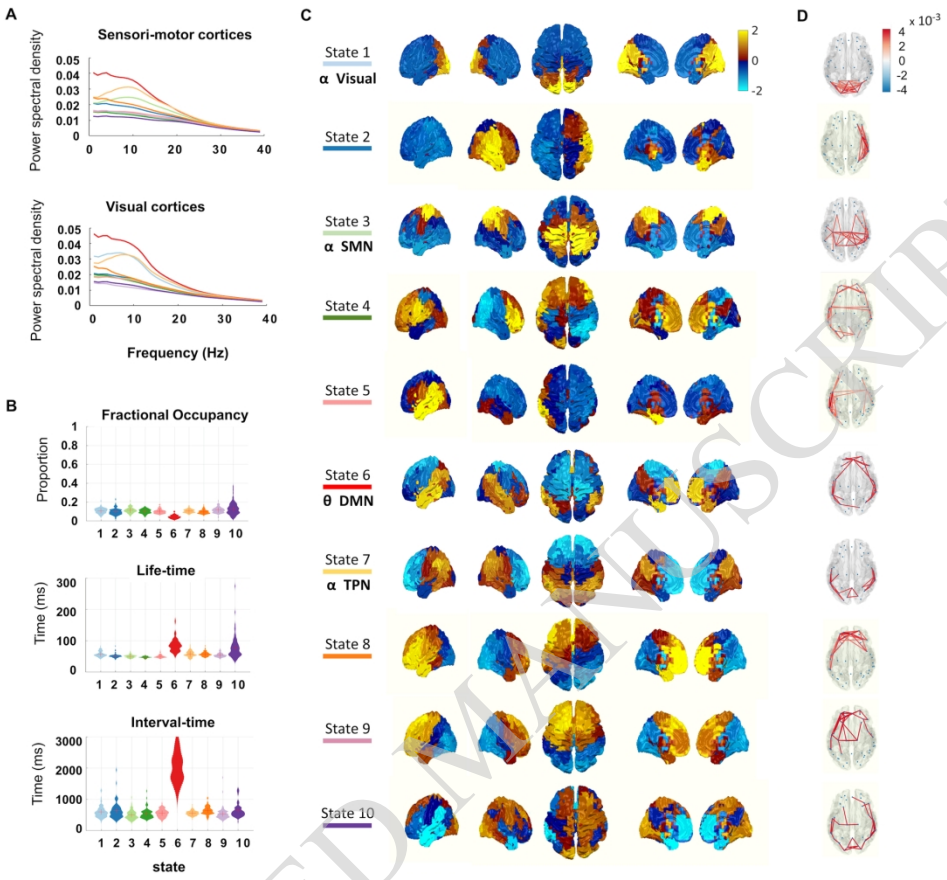

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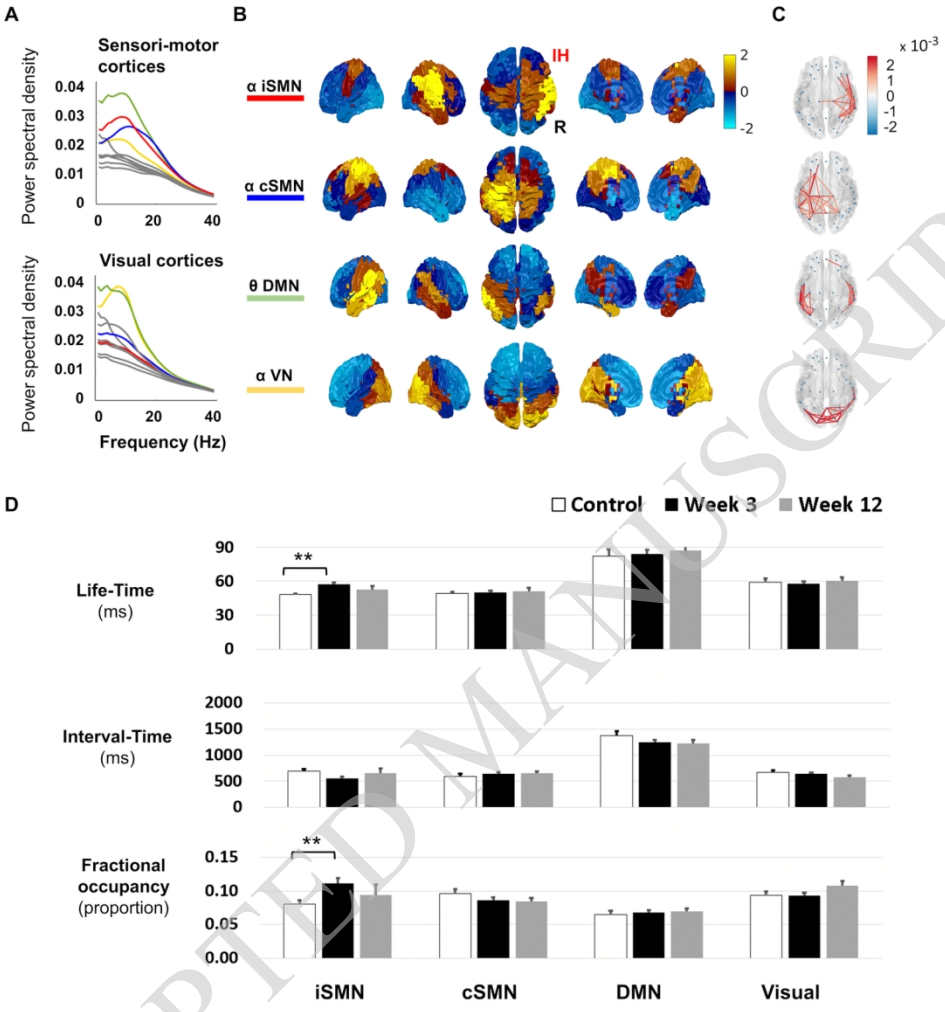

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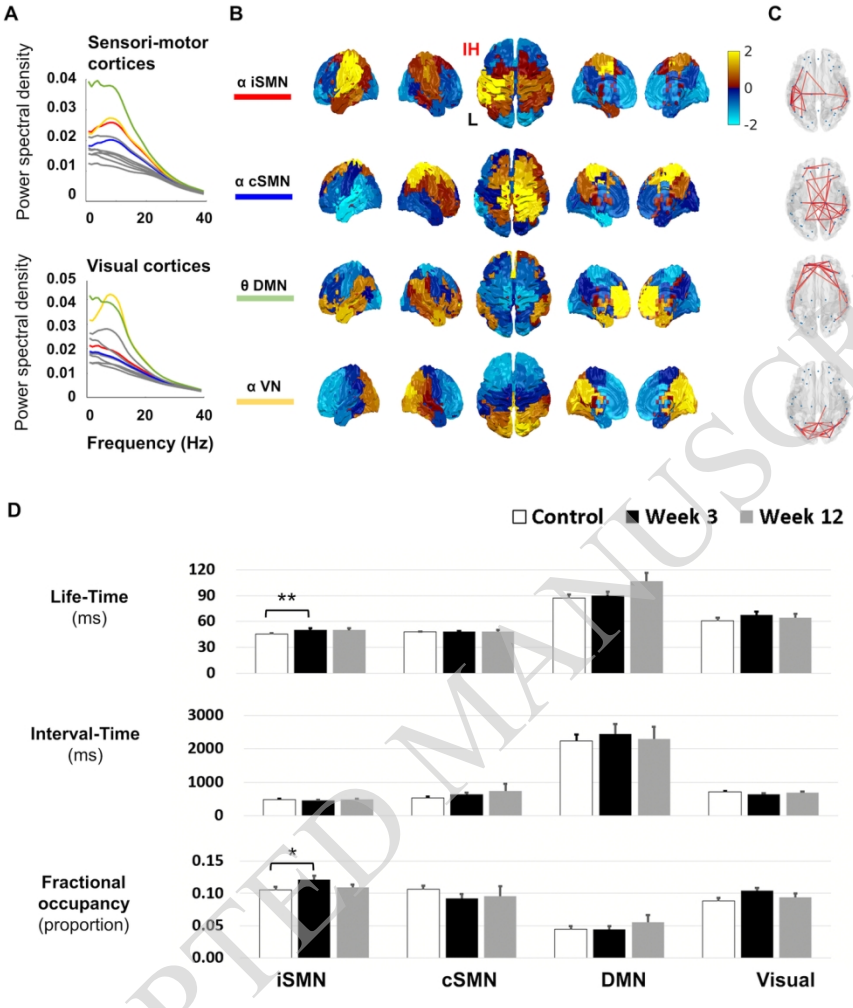

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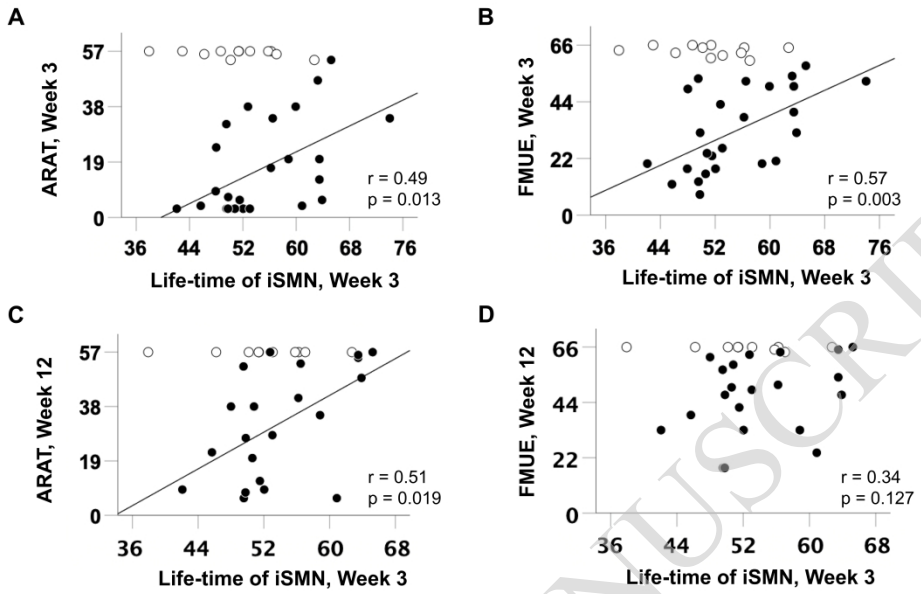

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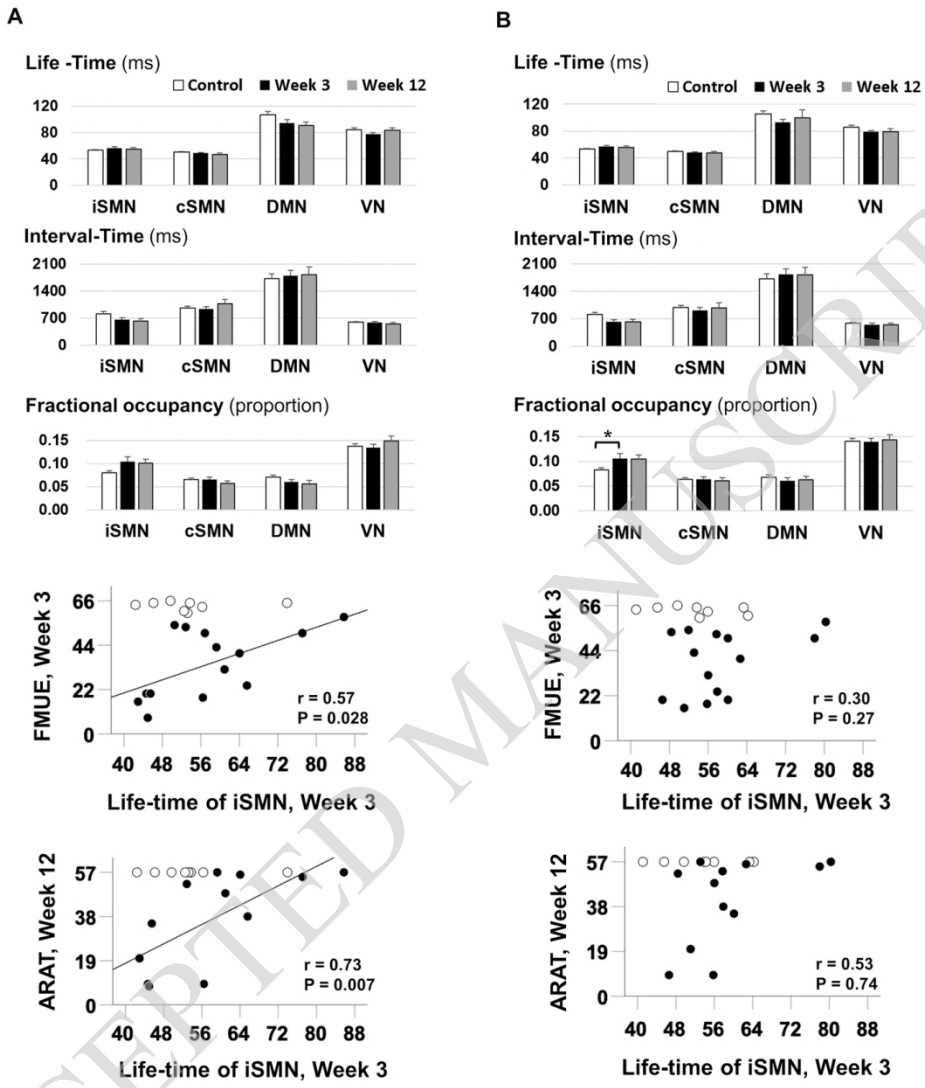

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129x150mm (300 x 300 DPI)

Table 1 Participant Characteristics

Participant	Age (years)	Sex	Affected hand	Time post stroke (days)	Day 0	Week 2~4			Week 12	
					NIHSS	mRS	ARAT	FM-UE	ARAT	FM-UE
1	49	M	R	26	8	3	3	18	9	33
2*	50	M	R	24	5	3	17	38	41	51
3*	41	F	R	28	5	3	3	20	9	33
4	57	M	L	17	3	2	38	50	-	-
5*	75	F	L	20	5	3	20	20	35	33
6	59	M	R	14	2	2	57	66	-	-
7	61	M	R	25	1	1	57	66	57	66
8*	68	F	L	20	1	1	54	58	57	66
9*	55	F	L	24	6	3	13	50	55	65
10	52	M	L	14	3	3	34	52	53	64
11*	56	M	R	16	1	2	54	65	57	66
12	75	M	L	27	12	4	4	21	-	-
13	74	F	L	23	7	4	6	23	-	-
14*	61	M	R	28	4	3	3	16	20	50
15	34	M	R	21	4	1	57	65	57	66
16*	64	M	L	15	8	4	3	13	6	18
17	73	M	L	24	2	4	47	54	-	-
18	41	M	R	27	11	4	9	18	-	-
19	46	M	R	20	3	1	57	66	-	-
20	67	M	R	28	3	4	56	63	57	66
21	68	F	L	14	2	4	57	62	57	66
22	41	F	R	25	15	5	24	49	38	62
23*	50	M	L	17	7	4	7	32	27	47
24	31	M	L	23	2	4	57	63	57	65
25*	63	M	R	24	7	4	4	12	22	39
26	66	M	L	20	7	4	3	24	38	59
27*	60	M	L	17	6	4	3	26	28	49
28	75	F	L	15	8	4	38	43	57	63
29	70	M	R	19	3	4	6	32	48	47
30	44	F	R	23	3	4	56	60	57	64
31	56	F	R	18	1	3	57	64	57	66
32*	63	M	R	28	2	3	32	53	52	57
33*	62	F	L	26	5	3	57	61	57	66
34*	59	M	R	20	3	4	3	8	8	18
35*	61	M	R	28	12	4	20	40	56	54
36	51	F	L	10	2	3	34	52	-	-
37*	60	M	L	22	2	3	54	65	57	66
People with stroke (n=37)	60 (50-66)	25 M /12 F	18 L/19 R	22 (17-25)	4 (2-7)	3 (3-4)	32 (6-52)	50 (23-62)	52 (25-57)	59 (45-66)
Control (n=22)	61 (52-62)	12 M /10 F	-	-	-	-	-	-	-	-

Demographics for people with stroke. * Subjects with two (3 weeks and 12 weeks post-stroke) resting-state magnetoencephalography evaluations; M = male; F = female; R = right; L = left; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; ARAT = action research arm test; FM-UE = Fugl-Meyer upper extremity score. Data are presented as the median with interquartile range.

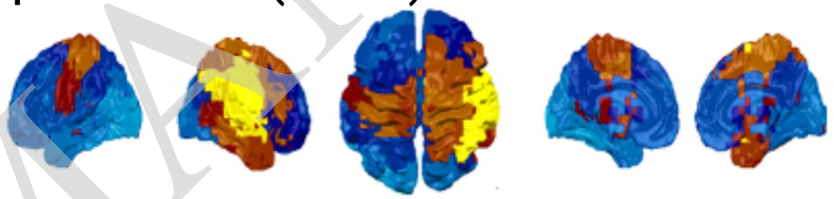
37 people with stroke scanned at 3 weeks and 12 weeks post-stroke

Magnetoencephalography (MEG) resting scan

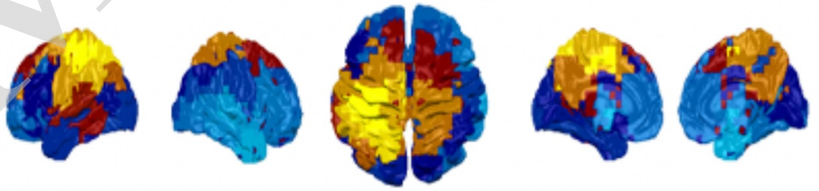
22 controls

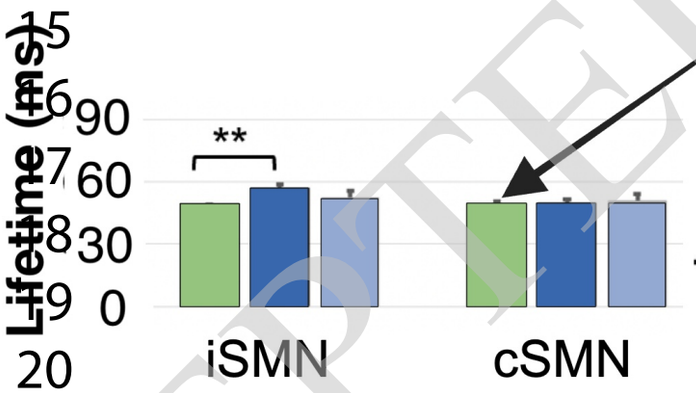
Analysis reveals separate unilateral sensorimotor networks (SMN)

Ipsilesional (iSMN)

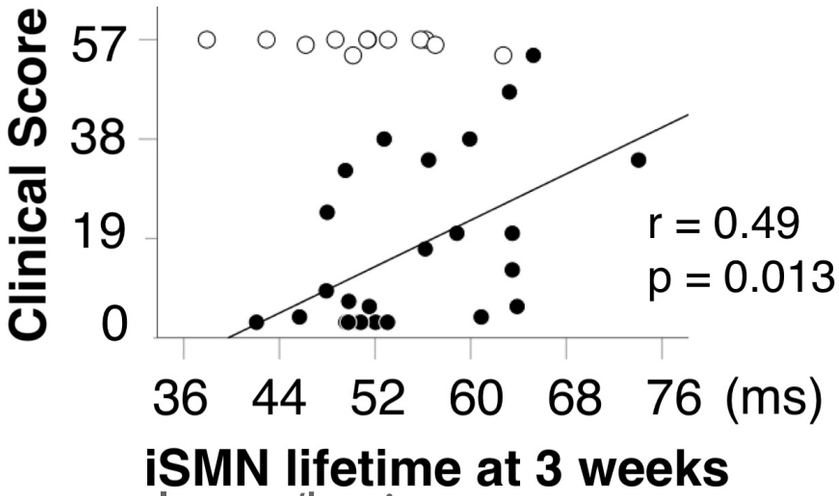


Contralesional (cSMN)





Longer lifetimes in iSMN early after stroke at 3 weeks



Longer lifetimes in iSMN early after stroke correlates with better function