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State-dependent interhemispheric inhibition reveals individual differences in motor behavior in chronic stroke

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HIGHLIGHTS

- Stroke survivors demonstrate reduced interhemispheric inhibition (IHI) at rest and reduced IHI modulation with muscle contraction compared to neurotypical older adults.
- Stroke survivors with greater reduction of IHI with contraction had greater motor impairment and mirroring.
- Findings support the importance of characterizing state-dependent neural circuitry to understand post-stroke motor behavior.

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ABSTRACT

Objective: To investigate state-dependent interhemispheric inhibition (IHI) in chronic stroke survivors compared to neurotypical older adult controls, and test whether abnormal IHI modulation was associated with upper extremity motor behavior.
Methods: Dual-coil transcranial magnetic stimulation (TMS) measured IHI bi-directionally, between non-lesioned and lesioned motor cortex (M1) in two activity states: (1) at rest and (2) during contralateral isometric hand muscle contraction. IHI was tested by delivering a conditioning stimulus 8-msec or 50-msec prior to a test stimulus over contralateral M1. Paretic motor behavior was assessed by clinical measures of impairment, strength, and dexterity, and mirroring activity in the non-paretic hand.
Results: Stroke survivors demonstrated reduced IHI at rest, and less IHI modulation (active – rest) compared to controls. Individual differences in IHI modulation were related to motor behavior differences where greater IHI modulation was associated with greater motor impairment and more mirroring. In contrast, there were no relationships between IHI at rest and motor behavior.
Conclusions: Abnormal state-dependent interhemispheric circuit activity may be more sensitive to post-stroke motor deficits than when assessed in a single motor state.
Significance: Characterizing state-dependent changes in neural circuitry may enhance models of stroke recovery and inform rehabilitation interventions.

1. Introduction

Interactions between motor cortices are necessary to generate precise and accurate movements. In a typical nervous system, there is mutual suppression between hemispheres at rest which is released during volitional unilateral activity. According to the traditional "interhemispheric imbalance model", this balance becomes disrupted after stroke, such that there is reduced interhemispheric inhibition (IHI) from the lesioned motor cortex (l-M1) to the non-lesioned M1 (nl-M1). This disruption results in excessive IHI from the nl-M1 to the l-M1, which classically has been suggested to contribute to motor impairment (Murase et al., 2004; Takeuchi et al., 2012; Ward and Cohen, 2004). However, this mechanism is unable to account for complex recovery profiles observed across levels of impairment post-stroke (Di Pino et al., 2014; Di Pino and Di Lazzaro, 2020; Lotze et al., 2012;

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McCambridge et al., 2018). Further, "rebalancing" interventions to upregulate l-M1 or downregulate nl-M1 excitability (e.g., via neuromodulation, constraint-induced movement therapy) have yielded variable effects (Boddington and Reynolds, 2017; McCambridge et al., 2018), suggesting an incomplete understanding of the dynamics of IHI in the healthy brain, its role in motor dysfunction, and factors that influence IHI post-stroke.

IHI post-stroke is typically assessed in a single motor state (e.g., at rest or during activity) using transcranial magnetic stimulation (TMS) (Bertolucci et al., 2018; Boddington and Reynolds, 2017). When a single TMS pulse is delivered over M1 during ipsilateral tonic contraction, a transient suppression of muscle activity, termed the ipsilateral silent period (iSP), is observed and used to quantify IHI (Wassermann et al., 1991). Greater iSP duration during paretic contraction, reflective of greater inhibition from nl-M1 to l-M1, has been linked to post-stroke motor impairment (Bolognini et al., 2011; Harris-Love et al., 2011). An alternative, less common TMS method to evaluate IHI that may have more functional relevance to paretic motor function uses a paired-pulse TMS method, with a pulse delivered over each M1 at a specific inter-pulse interval (Ferbert et al., 1992). In this dual coil approach, a conditioning TMS pulse is delivered 8–50 msec prior to a test TMS pulse that modulates the evoked muscle response (i.e., the motor evoked potential, MEP). Unlike iSP, the dual-coil method can probe IHI at rest, during motor preparatory activity, and/or during voluntary muscle contraction (Bertolucci et al., 2018).

In healthy individuals, IHI decreases during contralateral voluntary contraction compared to IHI at rest (Chen et al., 2003; Turco et al., 2019), suggesting that state-dependent IHI modulation may be a relevant probe of voluntary motor control, which may be more informative than IHI assessed in a single state to understand cortical interactions relating to paretic motor function. Indeed, a seminal study by Murase and colleagues demonstrated that individuals with less motor impairment had more IHI flexibility across motor states, indicated by reduced IHI from nl-M1 to l-M1 during a premovement period compared to rest, similar to observations in neurotypical adults. In contrast, those individuals who were unable to modulate IHI during the premovement period demonstrated greater chronic post-stroke motor impairment (Murase et al., 2004). Whether abnormal IHI modulation in the context of motor preparation extends to a sustained active motor state, such as tonic unilateral contraction, is unclear. Moreover, the notion that greater IHI onto l-M1 is associated with greater motor impairment post-stroke remains controversial. A recent meta-analysis of 112 studies using TMS-based measures of post-stroke neurophysiology concluded there is not a clear imbalance of IHI between hemispheres in either acute or chronic phases after stroke (McDonnell and Stinear, 2017). Further, some studies have found opposite or no relationships between IHI from nl-M1 to l-M1 and motor impairment (Mang et al., 2015; Takeuchi et al., 2010; Xu et al., 2019).

One issue with probing IHI during unilateral contraction is the possibility of unintended mirror activity in the nonparetic limb, which is known to increase in more impaired stroke survivors (Kim et al., 2003; Nelles et al., 1998). Functional magnetic resonance imaging (fMRI) findings suggest that mirror movements may arise due to bilateral cortical activation and/or hyperexcitability of nl-M1 in the acute and sub-acute stages (Calautti and Baron, 2003; Willer et al., 1993). However, bilateral activation has also been observed in patients without mirror activity (Cramer et al., 1997). Further, it was shown that while mirroring activity reduced as hand function improved longitudinally, there was no evidence for cortical hyper-excitability in either hemisphere, suggesting a potential subcortical origin of mirroring (Ejaz et al., 2018). TMS may elucidate mechanisms of mirroring activity post-stroke (Chieffo et al., 2013) but has rarely been simultaneously quantified during IHI assessments (Takeuchi et al., 2010). If normal communication between hemispheres prevents unintentional mirroring activity, abnormal IHI post-stroke may relate to the presence of mirroring activity and greater motor impairment.

Here, we used dual-coil TMS to investigate state-dependent modulation of IHI circuitry in chronic stroke and characterized its associations with paretic upper limb motor behavior. We hypothesized that stroke survivors would have reduced l-M1 IHI modulation (difference between IHI across motor states) compared to controls, and that the magnitude of IHI modulation would be related to mirroring activity and upper limb motor impairment.

2. Methods

2.1. Participants

Eighteen chronic stroke survivors (11 female, 63.4 ± 11.4 years [mean ± standard deviation]) and fifteen right-handed neurotypical older adult controls (6 female, 69.1 ± 5.9 years) participated in a single experimental session. Participants with stroke had a single ischemic subcortical or cortical stroke confirmed by magnetic resonance imaging (MRI) with a range of paretic limb impairment (Upper Extremity Fugl-Meyer assessment (UEFMA) score range: 15–66/66) and weakness (Shoulder Abduction/Finger Extension (SAFE) score range: 2–9/10) (Fig. 1). Controls were included if they had no neurologic conditions or musculoskeletal conditions affecting the upper limbs. Participants were excluded if they had significant cognitive impairment (Montreal Cognitive Assessment < 20) or contraindications to TMS. The experimental protocol was approved by the Emory University Institutional Review board, and all participants gave written informed consent before entering the study.

2.2. Measures of upper extremity motor behavior

Upper extremity clinical motor assessments included the Upper Extremity Portion of the Fugl-Meyer Assessment (UEFMA) and shoulder abduction/finger extension (SAFE) manual muscle strength. SAFE scores (max 10) were obtained by summing the Medical Research Council (MRC) grades (max 5), obtained separately for shoulder abduction and finger extension. We also assessed grip strength using a handheld dynamometer and manual dexterity with the Nine-Hole Peg Test (NHPT). For the NHPT, participants placed and removed nine pegs, one at a time, as quickly as possible. Since four participants could not complete the NHPT, the time to complete the NHPT was converted to a rate, or the number of pegs transferred per second.

2.3. TMS procedures

Participants were seated semi-recumbent in an armchair. Single monophasic TMS pulses (Magstim 200^2, MagStim, Wales, UK) were delivered using a 70 mm hand-held figure-of-eight coil over the l-M1 (nondominant (nd)-M1 in controls) and a 50 mm branding iron coil over the nl-M1 (dominant (d)-M1 in controls). Each coil was held tangentially to the scalp, oriented 45 degrees posterolateral from the mid-sagittal plane to induce a posterior-anterior (PA) current in M1. For each hemisphere, the location of first dorsal interosseous (FDI) hotspot, defined as the coil position that elicited the largest and most consistent response in the contralateral FDI muscle, was determined. Real-time stereotactic neuronavigation (BrainSight, Rogue Research) was used for consistent coil positioning throughout the session. The resting motor threshold (RMT) (% of maximum stimulator output) was determined bilaterally using

Stroke ID	Gender	Age (Years)	Chronicity (Months)	Paretic Side	Lesion Location	UEFMA (Max 66)	SAFE (Max 10)	Grip Strength (kgs)	NHPT (Pegs/Sec)	l-M1 RMT (%)	nl-M1 RMT (%)
●	F	40	16	R	MCA	–	3	6.8	0	67	60
●	F	58	6	L	–	15	2	NaN	0	MEP –	51
●	F	56	10	R	IC	28	3	4	0	70	55
●	F	63	48	R	IC	35	4	3.33	0.13	60	58
●	M	84	83	L	MCA	35	4	10.33	0.02	45	60
●	M	45	33	L	Pontine	36	6	2.33	0.11	*MEP –	71
●	M	57	64	R	Parietal, IC, BG	43	9	17.33	0.05	38	56
●	M	55	80	L	MCA	44	9	13.67	0	45	44
●	F	66	24	L	Striatum, IC, Caudate	45	5	NaN	0.15	51	53
●	F	68	13	R	IC, Putamen	50	8	16	0.21	63	53
●	M	74	31	R	Pons	51	6	17.33	0.25	46	48
●	F	81	84	R	Parietal Cortex	57	7	15	0.25	35	55
●	F	68	89	L	ACA	58	7	24	0.28	45	61
●	F	73	9	R	Striatum, IC, Thalamus	61	9	19	0.24	39	34
●	F	66	199	R	IC	61	9	21	0.28	50	46
●	M	68	10	R	IC, BG	65	8	31.67	0.26	46	55
●	F	53	6	R	Striatum, IC	66	8	17.33	0.27	55	71
●	M	67	180	R	BG	66	9	51.67	0.31	46	59
	11 F	63.4 ± 11.4	55 ± 57.5	12 R	–	48.0 ± 14.8	6.4 ± 2.4	16.9 ± 12.2	0.16 ± 0.12	50.1 ± 10.3	55.0 ± 8.8

Fig. 1. Each participant is color-coded for identification in figures. IC: internal capsule; BG: basal ganglia; ACA: anterior cerebral artery; MCA: middle cerebral artery. UEFMA: Upper Extremity Fugl-Meyer Assessment; SAFE: Shoulder Abduction/Finger Extension; NHPT: Nine-Hole Peg Test; RMT: resting motor threshold; l-M1: lesioned motor cortex; nl-M1: non-lesioned motor cortex; MEP –: motor evoked potential negative; *MEP –: MEP absent at rest, but present during paretic contraction. Data reported as mean ± standard deviation.

the ML-PEST method (maximum likelihood model of parameter estimation by sequential testing) (Awiszus, 2003).

Surface electromyography (EMG) was recorded from the FDI, abductor pollicis brevis (APB), and extensor carpi radialis (ECR) muscles bilaterally. Two disposable conductive adhesive hydrogel electrodes were attached over each muscle and a ground electrode was placed over the dorsum of each hand. EMG data were sampled using a 16-channel EMG system (BrainAmp ExG amplifier, Brain Products GmbH) at a rate of 5,000 Hz, and band-pass filtered at 10–1,000 Hz.

2.4. Interhemispheric inhibition protocol

IHI was examined by delivering a suprathreshold conditioning stimulus (CS) prior to a suprathreshold test stimulus (TS) over the contralateral M1 (Ferbert et al., 1992). CS and TS were delivered at 120% RMT. IHI was tested with both a short interval, biased to $GABA_A$ (type A gamma-aminobutyric acid) circuitry (Chen et al., 2003; Irlbacher et al., 2007), and a long interval, reflective of $GABA_B$ circuitry similar to iSP, (Avanzino et al., 2007; Chen et al., 2003) to better understand the mechanisms underlying IHI modulation and its relation to upper limb behavior. To assess short IHI, the CS was delivered 8 msec prior to the TS and for long IHI, the CS was delivered 50 msec prior to the TS (Fig. 2A). IHI was assessed bi-directionally, and in two motor states: (1) rest and (2) active. For the rest state, both hands were resting comfortably on a compliant surface and participants were asked to maintain a relaxed state in both hands (Fig. 2B). Resting state was confirmed online by the experimenter monitoring EMG signals in bilateral FDI, APB, and ECR muscles. For the active state, IHI was assessed during sustained isometric contraction of the *contralateral* FDI muscle at 50% of maximum voluntary contraction (Fig. 2C). Online visual feedback was provided to the participants to maintain a consistent level of muscle activity. If the level of contraction was not able to be maintained, rest breaks were provided to ensure consistent levels of muscle activity during active TMS assessments.

For each motor state, hemisphere, and ISI, a block of 20 trials was performed with an inter-trial interval of 4–6 seconds. In each block, 10 single TS pulses were delivered in isolation, and 10 CS-TS pulses were delivered, with the order of conditioned and unconditioned sets randomized across participants. The state, hemisphere, and ISI blocks were randomized within and across participants. Participants were given a ~1 minute break between each set of 10 pulses involving sustained muscle activity to minimize potential fatigue effects.

In two stroke participants, MEPs could not be elicited from l-M1 at rest. Since IHI can be obtained using a wide range of subthreshold and suprathreshold CS intensities (Chen et al., 2003), IHI in nl-M1 was evaluated using a CS intensity of 100% MSO.

2.5. Data analysis

For each trial, peak-to-peak amplitudes of the MEP were extracted. Rest and active IHI were computed as the percentage of the mean conditioned MEP (CS + TS) relative to the mean unconditioned MEP amplitude (TS alone). IHI was quantified separately for each hemisphere, state, and ISI. Larger IHI values represented less inhibition. We also quantified corticospinal excitability (CSE) by calculating the mean of the unconditioned MEP amplitude for each hemisphere and state. TS CSE indicates the mean MEP amplitude from the TS alone. CS CSE indicates the mean MEP amplitude elicited by the conditioning stimulus over the hemisphere contralateral to the test hemisphere.

To investigate how IHI is modulated across states, we calculated the difference in IHI between rest and active states (ΔIHI = IHI Active – IHI Rest). Therefore, ΔIHI = 0 indicated no modulation of inhibition, ΔIHI > 0 indicated less inhibition, and ΔIHI < 0 indicated greater inhibition. The same approach was applied for CSE. ΔTS CSE represents modulation of CSE contralateral to the contracted hand while ΔCS CSE represents modulation of CSE ipsilateral to the contracted hand.

Mirroring activity was quantified in the nonparetic hand from the background EMG activity in FDI during paretic contraction. We normalized the FDI activity when the nonparetic FDI muscle was instructed to be relaxed (i.e., IHI during paretic contraction), relative to when the nonparetic FDI muscle was voluntary acti-

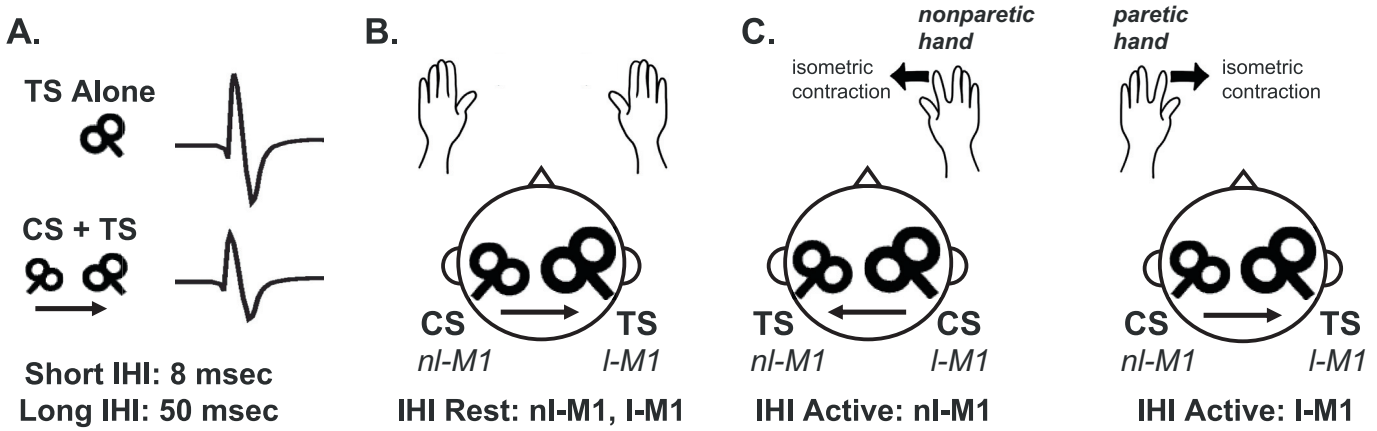

Fig. 2. Illustration of interhemispheric inhibition (IHI) procedures. A. A contralateral conditioning (CS) stimulus delivered prior to a test stimulus (TS) over motor cortex (M1) inhibits the motor evoked potential (MEP) amplitude compared to TS alone. B. IHI Rest: IHI assessed with both hands relaxed. C. IHI Active: IHI assessed during sustained isometric contraction of the contralateral first dorsal interosseous (FDI) muscle.

vated (i.e., IHI during nonparetic contraction). Larger values represented greater mirroring activity.

2.6. Statistical analysis

Group differences in demographics, RMT difference, and motor behavior (NHPT, mirroring activity) were assessed with independent sample t-tests. We used RMT difference instead of RMT for each hemisphere since different TMS coils were used. For instance, the RMT of nl-M1 appears higher than that of l-M1 (Fig. 1), opposite of what is typically observed (McDonnell and Stinear, 2017), but this is not unexpected since the smaller diameter coil was used to elicit responses in nl-M1. Therefore, we computed the RMT difference between hemispheres (l-M1 – nl-M1 in stroke, nd-M1 – d-M1 in controls).

Linear mixed effects models were performed using the lmerTest package in R (Kuznetsova et al., 2017) to assess the contributions of Group, Hemisphere, and State on IHI using the following general model structure:

$$IHI = \beta_0 + \beta_1 \cdot Group + \beta_2 \cdot Hemisphere + \beta_3 \cdot State + \beta_4 \cdot Group \cdot Hemisphere + \beta_5 \cdot Group \cdot State + \varepsilon \quad (1)$$

Group, Hemisphere, and State are dichotomous variables, with reference levels of Stroke (vs. Control), l-M1/nd-M1 (vs. nl-M1/d-M1), and Rest (vs. Active), respectively. ε represents the random effect of participant. Hemispheres were matched across groups consistent with previous literature (l-M1 with nd/M1 and nl-M1 with d-M1) (Mang et al., 2015; Palmer et al., 2019). Since we used dummy coding, significant regression coefficients are in relation to the intercept β_0 which represents l-M1 IHI in stroke at rest. Therefore, the regression coefficient β_1 indicates differences in IHI between controls (nd-M1) and stroke (l-M1) at rest, β_2 indicates differences between hemispheres within stroke at rest, and β_3 indicates differences between rest and active within stroke. β_4 indicates an interaction between Group and Hemisphere on IHI at rest. β_5 indicates an interaction between Group and State on IHI targeting l-M1/nd-M1. Separate models were performed for short IHI and long IHI.

The null hypothesis of a linear mixed effects model corresponds to a regression coefficient of zero. To test whether IHI at rest was different between hemispheres for stroke versus controls, we evaluated $\beta_4 = 0$. To test whether state had different effects on IHI for stroke (l-M1) versus controls (nd-M1), we evaluated $\beta_5 = 0$. Degrees of freedom were approximated using the Satterthwaite method.

Since several motor behavior variables (UEFMA, NHPT, SAFE, grip strength) were correlated with one another, we performed principal component analysis (using ppca.m in MATLAB) to reduce the number of variables and account for correlations between related variables. The first principal component accounted for 83.3% of the total variance of the regression variables and is referred to as *motor impairment score*. We then performed Pearson correlations among three main variables: IHI, motor impairment score, and mirroring activity.

The ISI (short versus long IHI) used for correlation analyses was determined post-hoc, based on the metric that showed the strongest Group × State interaction in the linear mixed effects models. Separate correlations were performed for IHI Rest and ΔIHI, correcting for multiple comparisons using the false discovery rate (FDR) p-values (p_{corr}).

As an exploratory analysis, we investigated whether state-dependent differences in IHI were a function of cortical excitability of the conditioning (i.e., MEPs elicited by the conditioning stimulus over nl-M1, CS CSE) and/or the target hemisphere, (i.e., MEPs elicited by the test stimulus over l-M1, TS CSE). We first tested if CSE was influenced by stroke and activity using a linear mixed effects model with fixed factors Group, State, and Hemisphere and the following general model structure:

$$CSE = \beta_0 + \beta_1 \cdot Group + \beta_2 \cdot Hemisphere + \beta_3 \cdot State + \beta_4 \cdot Group \cdot Hemisphere + \beta_5 \cdot Group \cdot State + \beta_6 \cdot Group \cdot State \cdot Hemisphere + \varepsilon \quad (2)$$

As in equation (1), we used dummy coding such that significant regression coefficients are in relation to the intercept β_0 which represents l-M1 CSE in stroke at rest. If the 3-way interaction was significant, we then examined separate models for each Hemisphere.

We then explored whether CSE modulation predicted IHI modulation in stroke compared to controls with multiple regression using the following formula:

$$\Delta IHI = \beta_0 + \beta_1 \cdot Group + \beta_2 \cdot \Delta TS + \beta_3 \cdot \Delta CS + \beta_4 \cdot \Delta TS \cdot Group + \beta_5 \cdot \Delta CS \cdot Group + \varepsilon \quad (3)$$

where ΔTS indicates TS CSE modulation (Active – Rest) for MEPs elicited over the target M1 (l-M1 in stroke, nd-M1 in control), and ΔCS indicates CS CSE modulation for MEPs elicited over the nontarget M1 ipsilateral to contraction (nl-M1 in stroke, d-M1 in control).

For all behavioral and TMS outcome measures, values greater than three standard deviations from the mean were classified as extreme outliers and removed from analysis (only applicable to one control participant's mirroring EMG data).

3. Results

3.1. Demographics and baseline neurophysiology

Two stroke participants were MEP- at rest. One participant had no volitional paretic FDI contraction and was excluded from all neurophysiological analyses. The other participant had volitional paretic FDI contraction and quantifiable MEPs in the active state (dark green color in each figure) and therefore were included in analyses where appropriate (e.g., linear mixed effects models that account for presence of missing data from l-M1 at rest).

The RMT difference between hemispheres was similar in stroke and controls ($F_{1,29}$ = 0.90, p = 0.35, η^2 = 0.030). Stroke and controls were similar in age (p = 0.32) and gender distribution (p = 0.27). As expected, NHPT was slower in stroke (0.16 ± 0.12 pegs/second) compared to controls (0.38 ± 0.06 pegs/second) (p < 0.0001). Mirroring activity in the nonparetic hand (30.1 ± 30.7%) was larger compared to that in the dominant hand for controls (8.61 ± 9.45 %) (p = 0.014).

3.2. IHI at rest for short and long IHI

The linear mixed effects model for short and long IHI are shown in Table 1. Since we used dummy coding, significant predictor variables are in relation to the intercept which represents l-M1 IHI in stroke at rest. For short IHI in stroke, there was greater IHI targeting nl-M1 compared to l-M1 at rest [Hemisphere: β(CI) = −13.22 (−23.90 – −2.54), $t_{91.64}$ = −2.46, p = 0.016]. Between groups, there was greater IHI targeting nd-M1 in controls compared to l-M1 at rest [Group: β(CI) = −32.67 (−48.52 – −16.82), $t_{88.58}$ = −4.10, p < 0.001]. The significant Hemisphere × Group interaction reflects no difference in IHI between groups for nl-M1/d-M1 IHI, but a decrease in IHI for l-M1 in stroke compared to nd-M1 in controls at rest [β(CI) = 20.86 (5.33 – 36.39), $t_{91.42}$ = 2.67, p = 0.009] (Fig. 3-A-i.). A similar pattern was observed for the linear mixed effects model for long IHI (Table 1, Fig. 3A-ii). There was greater long IHI targeting nl-M1 compared to l-M1 at rest [Hemisphere: β(CI) = −16.29 (−30.58 – −2.01), $t_{91.93}$ = −2.27, p = 0.026] and greater long IHI targeting nd-M1 in controls relative to l-M1 at rest [Group: β(CI) = −29.84 (−48.74 – −10.93), $t_{109.43}$ = −3.13, p = 0.002].

3.3. Motor state effects on IHI

State-dependent effects for short IHI targeting l-M1 in stroke versus nd-M1 in controls are shown in Fig. 4A and Table 1. There was no significant difference in l-M1 IHI between rest and active states in stroke [State: β(CI) = 9.17 (−1.51 – 19.85), $t_{91.64}$ = 1.70, p = 0.092] (Fig. 4A-i). In contrast, controls demonstrated a reduction in nd-M1 IHI between rest and active states [Group × State: β(CI) = 26.61 (11.08 – 42.14), $t_{91.42}$ = 3.40, p = 0.001] (Fig. 4A). State-dependent differences between groups were also observed for long IHI (Fig. 4B, Table 1). There was a decrease in l-M1 IHI from rest to active states in stroke [State: β(CI) = 14.46 (0.17 – 28.74), $t_{91.93}$ = 2.01, p = 0.047] (Fig. 4B-i). However, IHI modulation across states was larger in controls compared to stroke [Group × State: β(CI) = 23.95 (3.17 – 44.72), $t_{91.62}$ = 2.29, p = 0.024] (Fig. 4B). Overall, the direction and magnitude of IHI modulation was highly variable across stroke participants, with the largest state-dependent group differences pertaining to short IHI targeting the l-M1 (Fig. 4A).

3.4. Associations of IHI with upper limb motor impairment and mirroring activity

We observed no significant correlations between l-M1 short IHI at rest and the motor impairment score or mirroring activity (Fig. 5A and B, top row). In contrast, a larger decrease in l-M1 IHI (i.e., more release of inhibition) with activity was associated with more motor impairment (r = −0.55, pcorr = 0.046) and greater mirroring activity (r = 0.55, p_{corr} = 0.046) (Fig. 5C and D, bottom row). Those with more motor impairment also showed greater mirroring activity (Fig. 5E; r = −0.80, p_{corr} = 0.0006).

3.5. Exploring neurophysiological mechanisms of state-dependent IHI

At rest, CSE in stroke was not significantly different across the two hemispheres [Hemisphere: β(CI) = 104.37 (−1108.94 – 1317.68), $t_{89.33}$ = 0.17, p = 0.87], nor was it different between stroke and control for the target M1 (l-M1 vs nd-M1) [Group: β(CI) = 739.86 (−259.63 – 1739.35), $t_{106.12}$ = 1.47, p = 0.15]. There was no interaction between Group and Hemisphere, indicating similar CSE at rest across hemispheres and between groups [Group × Hemisphere: [β(CI) = −802.04 (−2054.46 – 450.38), $t_{89.31}$ = −1.27, p = 0.21]. There was a significant 3-way interaction between Hemisphere, State, and Group [β(CI) = −2312.74 (−4076.65 – −548.84), $t_{89.10}$ = −2.61, p = 0.011], which appear to be driven by a Group × State interaction for the target M1 (l-M1,

Table 1
Multilevel effects model table results for Short and Long IHI.

	Short IHI				Long IHI			
Predictors	*β (95% CI)*	Statistic	p	df	*β (95% CI)*	Statistic	p	df
Fixed Effects								
Intercept	87.16 (76.20 – 98.11)	15.80	**<0.001**	89.93	85.67 (72.58 – 98.76)	12.97	**<0.001**	110
Hemisphere	−13.22 (−23.90 – −2.54)	−2.46	**0.016**	91.64	−16.29 (−30.58 – −2.01)	−2.27	**0.026**	91.93
Group	−32.67 (−48.52 – −16.82)	−4.10	**<0.001**	88.58	−29.84 (−48.74 – −10.93)	−3.13	**0.002**	109.4
State	9.17 (−1.51 – 19.85)	1.70	0.092	91.64	14.46 (0.17 – 28.74)	2.01	**0.047**	91.93
Group:Hemi-sphere	20.86 (5.33 – 36.39)	2.67	**0.009**	91.42	17.61 (−3.17 – 38.39)	1.68	0.096	91.62
Group:State	26.61 (11.08 – 42.14)	3.40	**0.001**	91.42	23.95 (3.17 – 44.72)	2.29	**0.024**	91.62
Random Effects								
σ2	483.20				865.49			
τ00 sub_ID	135.67				61.03			
N sub_ID	32				32			
Observations	127				127			

Dummy coding was used for predictor variables, with reference levels of lesioned motor cortex (l-M1), stroke, and rest. The intercept represents the estimated interhemispheric inhibition (IHI) for l-M1 in stroke at rest. For single predictor variables, negative beta coefficients indicate an increase in estimated IHI relative to the intercept while positive beta coefficients indicate a decrease in estimated IHI relative to the intercept. p-values were estimated using Satterthwaite method.

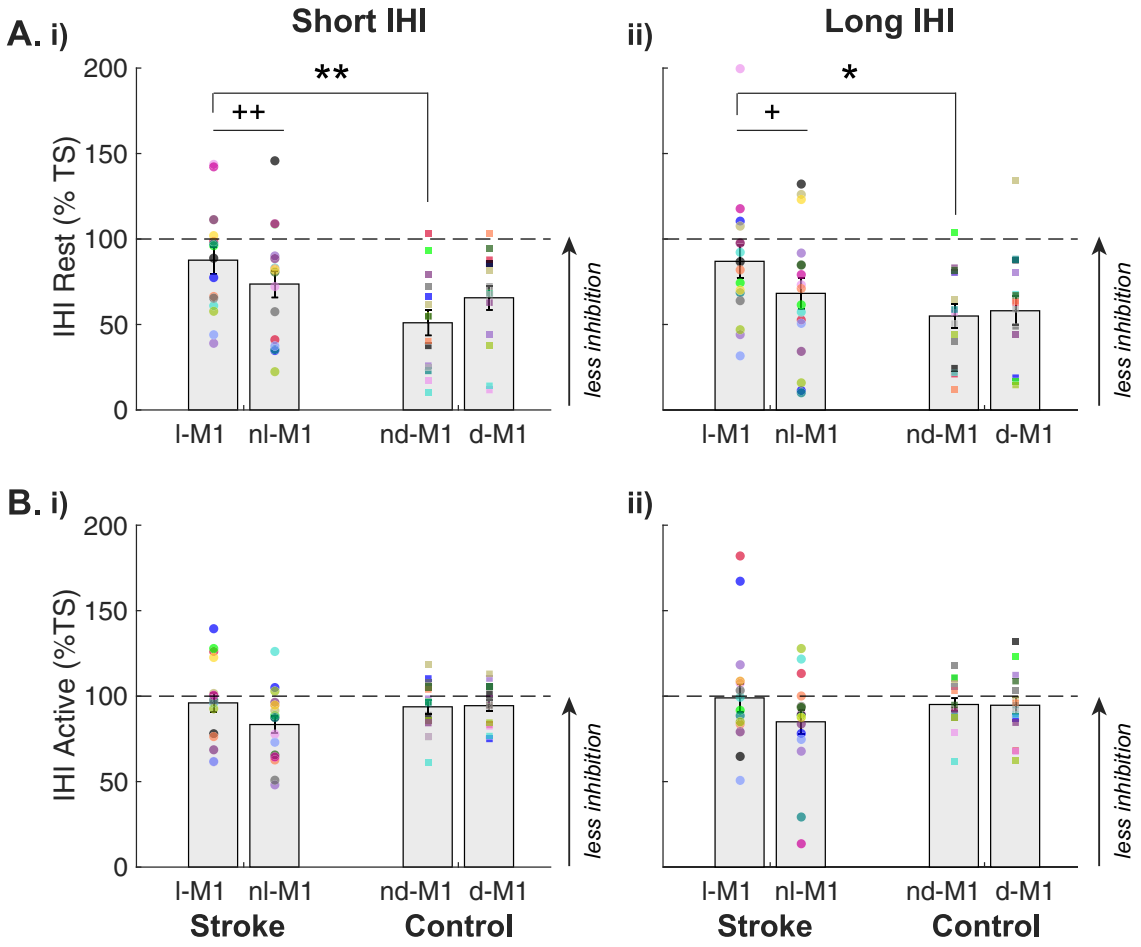

Fig. 3. Short and long interhemispheric inhibition (IHI) in stroke and controls in the Rest (A) and Active (B) States. IHI expressed as a percentage of the unconditioned motor evoked potential (MEP) amplitude. Larger values denote less inhibition. Predictor variables of Hemisphere and Group from the linear mixed model (Table 1) are in relation to the reference variable lesioned motor cortex (l-M1) in stroke. Both short (i.) and long IHI (ii.) at rest (A, top row) was greater in nonlesioned M1 (nl-M1) relative to l-M1 in stroke, and greater in nondominant M1 (nd-M1) relative to l-M1 in stroke. Error bars are standard error of the mean. β Hemisphere: ++ denotes p = 0.016, + denotes p = 0.026. β Group: ** denotes p < 0.001, * denotes p = 0.002.

nd-M1) (Fig. 6A) but no Group × State interaction for the conditioning M1 (nl-M1, d-M1) (Fig. 6B). This was confirmed with separate two-way mixed effects models for each hemisphere. For the target M1, muscle contraction (active state) resulted in an increase in CSE modulation in l-M1 in stroke [State: β(CI) = 1155. 80 (322.46 – 1989.14), $t_{29.87}$ = 2.83, p = 0.008]; however, the magnitude of modulation was smaller in stroke compared to controls [Group × State: β(CI) = 2256.13 (1052.62 – 3459.64), $t_{29.50}$ = 3.83, p = 0.001] (Fig. 6A). For the nontarget-M1, CSE in the nl-M1 (ipsilateral to FDI contraction) increased relative to rest [State: [β(CI) = 1253.38 (583.89 – 1922.87), $t_{30.00}$ = 3.82, p = 0.001]. However, the magnitude of CSE modulation was similar to that of controls [Group × State: β(CI) = −49.83 (−1027.68 – 928.03), $t_{30.00}$ = −0.10, p = 0.92] (Fig. 6B). These results indicate that stroke-related alterations in CSE are specific to state-dependent modulation in the l-M1.

The overall regression model for IHI modulation using CSE modulation as a predictor was significant ($F_{5,25}$ = 4.43, p = 0.005, R^2 = 0.47, Adj. R^2 = 0.36). In stroke, larger increases in l-M1 CSE (more positive ΔTS CSE) predicted larger increases in IHI (more negative ΔIHI) with activity (p = 0.009). This pattern was absent in controls, evidenced by a ΔTS × Group interaction (p = 0.031) (Fig. 7). Differences in ΔIHI were not predicted by ΔCS CSE (nl-M1) (p = 0.38) nor an interaction between ΔCS CSE and group (p = 0.20).

4. Discussion

The present study investigated state-dependent changes in intercortical interactions targeting the l-M1 and nl-M1 post-stroke and their association with upper limb motor behavior. Compared to older adult controls, stroke survivors demonstrated reduced l-M1 IHI at rest and reduced l-M1 IHI modulation with voluntary paretic contraction. This pattern was observed for both short and long IHI, suggesting a global downscaling of intercortical interactions post-stroke. While controls demonstrated a consistent release of inhibition with activity, IHI modulation was variable across stroke survivors. The novel finding is that release of inhibition with activity was related to lower motor function and greater mirroring activity in stroke.

The predominant framework for motor recovery and rehabilitation post-stroke has largely been based on the interhemispheric imbalance model (Boddington and Reynolds, 2017; Hummel and Cohen, 2006). Despite earlier literature that suggested greater nl-M1 activity, and hence greater inhibition onto l-M1, was associated with paretic motor impairment (Duque et al., 2005; Murase et al., 2004; Ward and Cohen, 2004), recent literature has found opposite or no relationship between IHI and motor impairment (Cunningham et al., 2015; Mang et al., 2015; Takeuchi et al., 2010; Xu et al., 2019). Our results counter the classical model given that there was reduced IHI targeting l-M1 relative to nl-M1. The

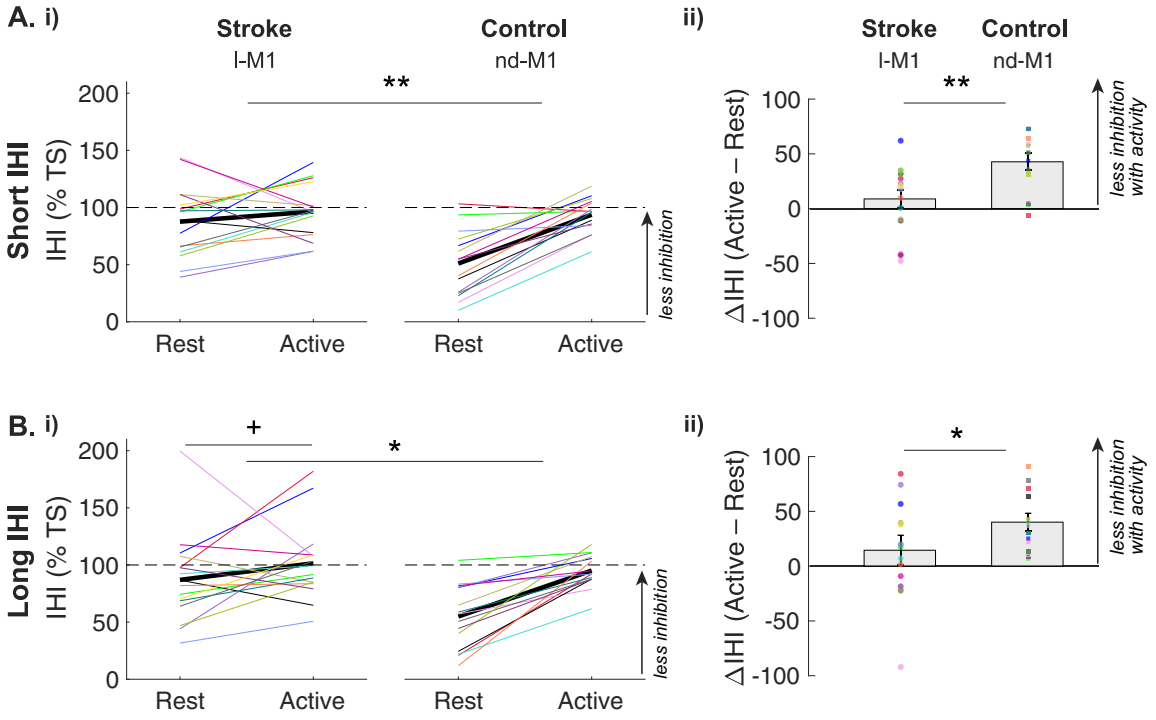

Fig. 4. Short (A) and long (B) interhemispheric inhibition (IHI) across motor states in stroke (lesioned M1 [l-M1]) and controls (nondominant M1 [nd-M1]). IHI is expressed as a percentage of the unconditioned motor evoked potential (MEP) amplitude. Predictor variables of Group, State, and Group × State from the linear mixed model (Table 1) are in relation to the reference variable l-M1 in stroke. A. (i) There was no difference in short IHI across motor states in stroke (β State: not significant). Modulation across motor states (ii), represented by less IHI with activity, was greater in controls relative to stroke (** denotes β Group × State: p = 0.001). B. (i) Long IHI in stroke was reduced with activity (+denotes β State: p = 0.047); However, IHI modulation across motor states (ii) was greater in controls relative to stroke (* denotes β Group × State: p = 0.024).

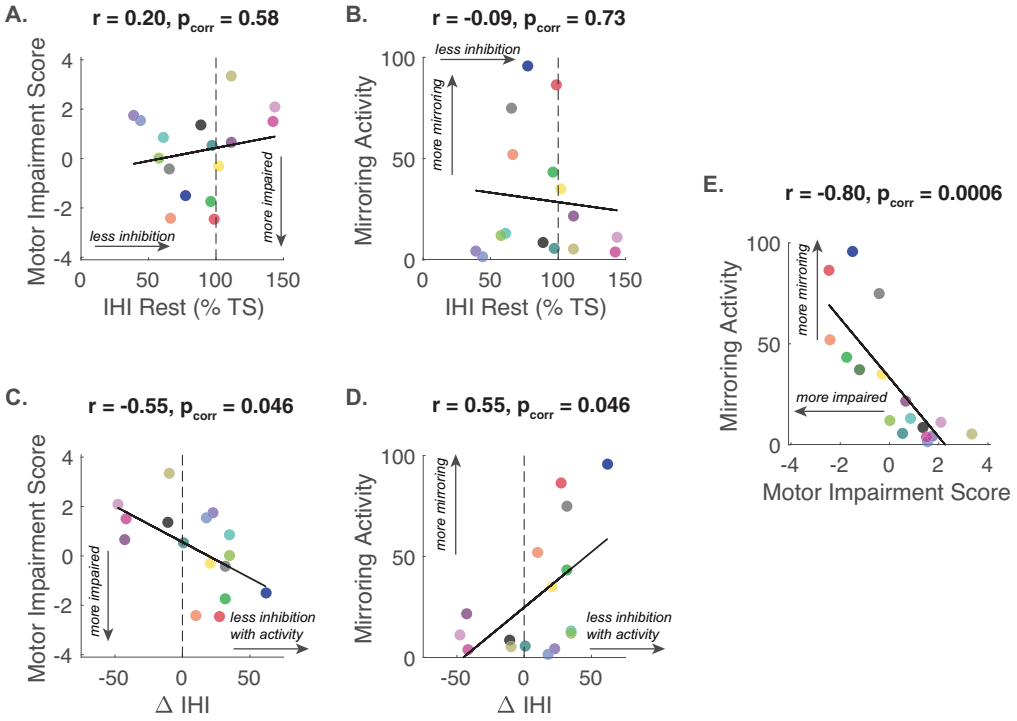

Fig. 5. Associations between lesioned motor cortex (l-M1) short interhemispheric inhibition (IHI), mirroring activity, and motor impairment. Motor Impairment Score was derived from the first principal component of Upper Extremity Fugl-Meyer Assessment (UEFMA), Shoulder Abduction/Finger Extension (SAFE), Nine-Hole Peg Test (NHPT), and grip strength. More negative scores equate to greater motor impairment. Top row: IHI Rest was not associated with motor impairment (A) or mirroring (B). Bottom row: Individuals who showed release of IHI with activity were more impaired (C) and showed greater mirroring (D). Those who were more impaired also showed greater mirroring (E). Corrected p-values are presented.

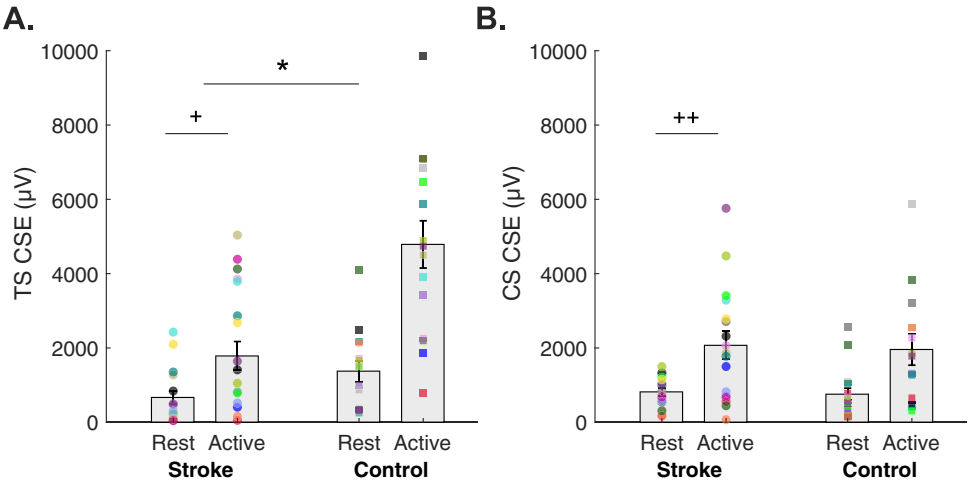

Fig. 6. Corticospinal excitability (CSE) from test stimuli (TS) over the target hemisphere (A) and conditioning stimuli (CS) over the nontarget hemisphere (B) across motor states in stroke and controls. Active indicates either paretic FDI contraction or nondominant FDI contraction. A. CSE in lesioned motor cortex (l-M1) increased in the active state (+denotes β State: p = 0.008); however, the magnitude of CSE modulation was less than that of controls (* denotes β Group × State: p = 0.001). B. CSE in nonlesioned M1 (nl-M1) increased in the active state (++ denotes β State: p = 0.001). A similar pattern was observed in controls, as there was no significant effects nor interactions involving Group.

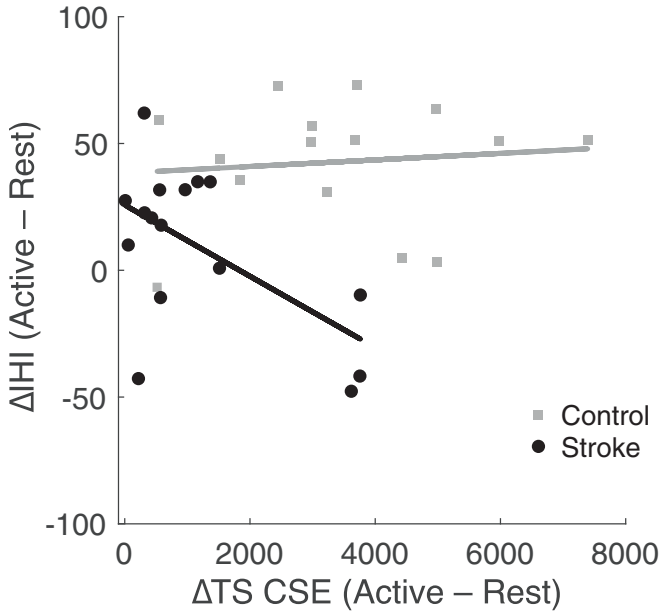

Fig. 7. Multiple regression for corticospinal excitability modulation (ΔTS CSE) and interhemispheric inhibition modulation (ΔIHI) across groups. CSE modulation in the target hemisphere (lesioned motor cortex) predicted IHI modulation in stroke but not controls.

lack of consistent evidence on whether there is a true "imbalance" of IHI post-stroke reflects the complex nature of cortical interactions underlying stroke recovery.

Reduced nl-M1 IHI at rest has been shown in the acute and subacute stage (Bütefisch et al., 2008), but typically normalizes in the chronic stage (Duque et al., 2005; Murase et al., 2004). Consistent with this notion, we found that nl-M1 IHI was similar to that of controls. In contrast, l-M1 IHI at rest was reduced relative to controls. Reduced l-M1 IHI at rest may reflect the reduced capacity to generate IHI, which is mediated by excitatory transcallosal projections onto intracortical inhibitory networks, which then inhibit corticospinal output neurons (Reis et al., 2008). In the current study, we did not measure other circuits, such as short-intracortical inhibition (SICI) that mediate IHI but speculate that reduced l-M1 IHI at rest may be a function of abnormal SICI or other local circuits in either hemisphere.

Stroke-related alterations in IHI during volitional contraction have primarily been inferred from the iSP. Though iSP is thought to share overlapping mechanisms with long IHI (Avanzino et al., 2007; Chen et al., 2003), the dual-coil TMS approach may offer additional insight into state-dependent changes in IHI interactions that may be more functionally relevant to motor behavior. Healthy adults demonstrate release of inhibition during motor preparation, while chronic stroke survivors demonstrate persistent inhibition (i.e., less modulation) with preparatory activity (Murase et al., 2004; Xu et al., 2019). Here, we extend these findings by demonstrating that stroke survivors also show less IHI modulation with tonic contraction. Contrasting with those previous reports, we found that chronic stroke survivors with greater release of IHI with activity had more impaired motor function. A positive association between greater inhibition to l-M1 during contraction and better motor function is similar to findings using the iSP method (Mang et al., 2015; Takeuchi et al., 2010). Together, greater inhibition to l-M1 may represent a compensatory mechanism IHI supporting post-stroke motor function.

The conflicting relationships between IHI and motor impairment despite using a similar methodology (dual-coil TMS) to quantify IHI from the nl-M1 to the l-M1 during contralateral movement are difficult to interpret. One possible explanation relates to different levels of motor impairment. Murase et al. (2004) studied eight participants with relatively mild impairment, with an average MRC of the finger of 4 (max 5) and ability to perform finger tapping. Similarly, Xu et al. studied 21 participants who at 6 months post-stroke had UEFMA scores ranging from 44–66 (mean of 64). Our study is novel in that we tested 18 participants of varied motor impairment with SAFE scores ranging from 2–9 (max 10) and UEFMA scores ranging from 18–66 (mean of 48). A second possibility is that mechanisms mediating IHI modulation during motor preparation and volitional tonic contraction may be distinct. Future research is needed to characterize IHI during both motor preparation and tonic contraction in the same cohort to better understand state-dependent IHI circuitry post-stroke.

To our knowledge, only one other study has investigated the effects of tonic contraction on short IHI in chronic stroke (Dimyan et al., 2014). In a small cohort, they also found a positive

relationship between IHI modulation and manual dexterity. At first glance, our findings of reduced IHI modulation post-stroke appear to be consistent with their observations. However, we assessed IHI from the resting M1 to the active M1 during contralateral contraction (contralateral to the target hemisphere) whereas the previous study assessed IHI in the opposite direction: IHI from the active to the resting M1 during ipsilateral contraction (ipsilateral to the target hemisphere). Taken together, stroke survivors appear to have reduced interhemispheric network flexibility across motor states at the group level, but have unique individual differences in their global and local inhibitory/excitatory circuitry that may lead to the reduced IHI modulation during volitional contraction that relate to motor impairment in specific ways.

Further support for altered state-dependent neurophysiology post-stroke is the finding that there was reduced CSE modulation in l-M1, but not nl-M1 in the stroke group, compared to the control group. The lack of hemisphere or group differences in CSE at rest highlights the importance of characterizing CSE during an active state. Our results indicate that nl-M1 CSE modulation was not different between groups, and increased IHI modulation was more related to a lack of l-M1 CSE modulation with activity. Importantly, CSE modulation only predicted IHI modulation when the target hemisphere was the lesioned side in the stroke group suggesting that the mechanisms of IHI modulation are likely different post-stroke and specific to the lesioned hemisphere. Together, these findings raise the question of whether altered state-dependent IHI in stroke is a true reflection of interhemispheric circuits or if it is driven by CSE in l-M1. It's also possible that IHI is influenced by other local intra-cortical circuits (e.g., intracortical inhibition). While the majority of studies in stroke have probed intracortical circuitry at rest (McDonnell and Stinear, 2017), Ding and colleagues demonstrated that atypical SICI was only observed during voluntary motor tasks performed with the paretic limb: reduced SICI within the lesioned hemisphere during voluntary activity, but not at rest, was associated with greater motor dysfunction (Ding et al., 2019). Future research is needed to characterize state-dependent SICI and other excitatory/inhibitory circuits (Avanzino et al., 2007; Cabibel et al., 2020; Reis et al., 2008) in conjunction with IHI assessments within the same stroke cohort to better understand complex cortical circuit interactions that may be altered after stroke.

Previous research in neurotypical adults suggests that short and long IHI may be mediated in part by different mechanisms, with long IHI being more similar to circuits probed by iSP, and also may be differentially modulated by age and tonic contraction of the contralateral limb (Chen, 2004; Chen et al., 2003; Talelli et al., 2008). To our knowledge, this is the first study reporting state-dependent modulation of long IHI in chronic stroke survivors. Extending reports of reduced short IHI modulation during movement preparation (Murase et al., 2004; Xu et al., 2019), we found that long IHI modulation during contraction was also reduced in stroke patients. The similar pattern of short and long IHI in stroke again supports a more generalized downscaling of cortical activity. Our results are consistent with a recent study in healthy young adults that showed that short and long IHI circuits are similarly modulated by tonic contraction (Turco et al., 2019). Therefore, short and long IHI may still be mediated by distinct circuits that show similar state-dependency, or are actually more similar physiological phenomenon than initially suggested.

Unintended mirror movements of the nonparetic limb during paretic voluntary contraction are common after stroke, and may be associated with the severity of motor impairment, but are rarely directly assessed together with IHI measures to examine relationships with interhemispheric interactions. Consistent with past literature (Kim et al., 2003; Nelles et al., 1998), we found patients who present with greater mirror activity in the nonparetic side during voluntary contraction of the paretic hand had greater motor impairment. Our current understanding of mirroring activity post-stroke is largely based on fMRI (Calautti and Baron, 2003; Ejaz et al., 2018; Kim et al., 2003; Willer et al., 1993). Mirroring may reflect bilateral recruitment of sensorimotor cortices, particularly in stroke survivors with severe motor impairment (Kim et al., 2003). However, bilateral activation has been observed in patients without mirroring activity (Cramer et al., 1997), suggesting that nl-M1 activation may be compensatory in some stroke survivors. A more recent longitudinal study found that while mirroring reduces as hand function improves it was not associated with cortical activation of either l-M1 or nl-M1 (Ejaz et al., 2018).

One challenge with understanding mirroring based on fMRI is that one cannot infer the contributions of specific excitatory or inhibitory networks, such as IHI circuits probed with TMS. In neurotypical adults, mirroring was associated with reduced short IHI during *ipsilateral* contraction (i.e., ipsilateral to the target M1) (Fling and Seidler, 2012; Hübers et al., 2008). Here we assessed IHI in the M1 contralateral to the contracting hand. If IHI is similarly reduced for ipsilateral and contralateral contraction, as suggested by Turco et al. (2019), then it may not be surprising that stroke survivors with reduced IHI show greater mirroring activity. However, since release of IHI with activity is the neurotypical pattern observed here and in previous literature (Murase et al., 2004; Xu et al., 2019), the present results are intriguing. Since CSE modulation in lesioned M1 was reduced and predicted IHI modulation in stroke but not controls, we speculate that the mechanisms of IHI are different between stroke and healthy adults. In healthy adults, reduced IHI with activity was associated with cortical map expansion (Turco et al., 2019). This may be the predominant mechanism of IHI observed in controls, which would result in inhibition of the contralateral hemisphere to suppress mirror movements. In stroke survivors, especially those who are more impaired, there may be less capacity to expand the cortical map in l-M1, evidenced by reduced modulation of CSE in lesioned M1; instead, reduced IHI with activity is likely mediated by other inter- or intracortical networks, potentially through circuits in the non-lesioned hemisphere. As the non-lesioned hemisphere may serve a compensatory role in more impaired stroke patients (Di Pino et al., 2014), the net result may be a reduced ability to suppress mirroring activity. In more mildly impaired individuals, other networks within the lesioned hemisphere may have the capacity to modulate with activity to prevent mirroring activity. Indeed, individuals with greater ability to modulate l-M1 CSE showed less IHI modulation with activity. Therefore, while IHI networks may be less flexible in mildly impaired stroke, network flexibility in other circuits in the lesioned hemisphere may inhibit mirroring activity. While we can only speculate on the mechanisms of mirror activity and IHI post-stroke, our findings are consistent with Takeuchi (2010) that demonstrated that mirroring was more common in those individuals with reduced inhibition from nl-M1 to l-M1 using the iSP method (Takeuchi et al., 2010). Together, reduced inhibition with activity may be a compensatory mechanism underlying mirror movements in those with poor motor function. Mirror movement may be an informative behavioral phenomenon that reflects differences in interhemispheric communication and motor impairment but a greater understanding of the underlying connection between mirroring, motor impairment and atypical neural network interactions will be required.

5. Conclusion

State-dependent interactions between hemispheres were reduced after stroke, and were related to individual differences in paretic motor impairment and nonparetic mirroring activity.

State-dependent interactions between hemispheres may also offer a neurophysiological mechanism of mirroring activity, a sign of abnormal motor control in more impaired stroke survivors. Greater release of inhibition with activity in more impaired stroke survivors suggests that IHI circuitry is complex and cannot be explained by the interhemispheric imbalance model. Further investigations of state-dependent neurophysiological measures post stroke may elucidate underlying mechanisms of functional plasticity during recovery and in response to rehabilitative interventions, which will contribute to the development of more effective interventions to enhance motor recovery post-stroke.

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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