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The unsolved role of heightened connectivity from the unaffected hemisphere to paretic arm muscles in chronic stroke

Ulrike Hammerbeck [a,b,*], Damon Hoad [a], Richard Greenwood [a,c], John C. Rothwell [a]

[a] Institute of Neurology, University College London, WC1N 3BG, UK
[b] School of Nursing, Midwifery and Social Work, University of Manchester, M6 8HD, UK
[c] National Hospital of Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

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HIGHLIGHTS

- Corticospinal connections from the unaffected hemisphere are strengthened after stroke.
- Ipsilateral corticospinal connectivity is not correlated to functional ability.
- The functional role of increased ipsilateral connectivity after stroke remains unclear.

ABSTRACT

Objective: Ipsilateral connectivity from the non-stroke hemisphere to paretic arm muscles appears to play little role in functional recovery, which instead depends on contralateral connectivity from the stroke hemisphere. Yet the incidence of ipsilateral projections in stroke survivors is often reported to be higher than normal. We tested this directly using a sensitive measure of connectivity to proximal arm muscles.
Method: TMS of the stroke and non-stroke motor cortex evoked responses in pre-activated triceps and deltoid muscles of 17 stroke survivors attending reaching training. Connectivity was defined as a clear MEP or a short-latency silent period in ongoing EMG in $\geq$ 50% of stimulations. We measured reaching accuracy at baseline, improvement after training and upper limb Fugl-Meyer (F-M) score.
Results: Incidence of ipsilateral connections to triceps (47%) and deltoid (58%) was high, but unrelated to baseline reaching accuracy and F-M scores. Instead, these were related to contralateral connectivity from the stroke hemisphere. Absolute but not proportional improvement after training was greater in patients with ipsilateral responses.
Conclusions: Despite enhanced ipsilateral connectivity, arm function and learning was related most strongly to contralateral pathway integrity from the stroke hemisphere.
Significance: Further work is needed to decipher the role of ipsilateral connections.

1. Introduction

Recovery from motor stroke depends upon the presence of functional connections between the cortex and the spinal cord (Byblow et al., 2015; Ward et al., 2006; Netz et al., 1997; Lemon, 2008). However, the relative role and importance of connections from the lesioned hemisphere versus those from the non-lesioned hemisphere is still unclear (Buetefisch, 2015; Bradnam et al., 2013; Alawieh et al., 2017; Dodd et al., 2017). In rodent models a large body of evidence has shown that recovery following a cortico-subcortical lesion on one side is accompanied by intraspinal sprouting of connections from pathways originating from the non-lesioned hemisphere (Rouiller et al., 1991; Krakauer et al., 2012; Biernaskie et al., 2005). Yet in humans the situation is less clear. Imaging data show that during attempted movement of the paretic arm there may be over-activation of areas in the non-lesioned hemisphere (Ward et al., 2003; Buetefisch et al., 2005). But although virtual lesion experiments show that this activity contributes to functional recovery (Johansen-Berg et al., 2002), the anatomical pathways involved have not been established. One pathway could be via callosal connections from the

* Corresponding author at: Stroke and Vascular Centre, Faculty of Medical and Human Science, University of Manchester, Clinical Sciences Building, Room B300, Salford Royal NHS Foundation Trust, Stott Lane, Salford M6 8HD, UK.
E-mail address: ulrike.hammerbeck@manchester.ac.uk (U. Hammerbeck).

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contralesional to the lesioned hemisphere and thence to spinal cord (Hayward et al., 2017), or there could be direct pathways from the contralesional hemisphere to the ipsilateral spinal cord (Buetefisch, 2015). The latter could involve the ipsilateral component of the corticospinal tract, as in the rodent model (Brosamle and Schwab, 1997). However, this seems unlikely in humans as it represents less than 10% of the corticospinal output (Palmer et al., 1992; Palmer and Ashby, 1992) similar to what is seen in primates in which only 2% terminate directly on motoneurons (Rosenzweig et al., 2009; Lawrence and Kuypers, 1968; Lemon, 2008). In primates there is virtually no evidence for any monosynaptic ipsilateral connections (Soteropoulos and Baker, 2009). A more likely connection would be an indirect cortico-reticulospinal connection (Bradnam et al., 2013; Baker et al., 2015). Indeed unilateral lesions of the pyramidal tract in primates are accompanied by an increase in excitability of reticulospinal inputs to spinal motoneurones from the non-lesioned side of the brain (Zaaimi et al., 2012; Fregosi et al., 2018; Fregosi and Rouiller, 2017) whereas there is little change in excitability of the smaller number of ipsilateral corticospinal synapses from the non-lesioned hemisphere (Zaaimi et al., 2012).

Despite this evidence for upregulation of excitability in cortico-reticulospinal pathways from animal models, most data in humans strongly suggest that, in the arm (but perhaps not for trunk muscles (Fujiwara et al., 2001)), functional recovery depends on the integrity of remaining corticospinal connections from the lesioned hemisphere (Byblow et al., 2015, Ward et al., 2006). The small number of studies that have examined ipsilateral connections suggest that if anything they are associated with poor recovery (Turton et al., 1996; Misawa et al., 2008) and increased incidence of shoulder/arm synergies (McPherson et al., 2018; Schwerin et al., 2008). A recent report from Barker et al. in stroke survivors illustrates this quite well (Barker et al., 2012). They used TMS to elicit motor evoked potentials (MEPs) in contralateral and ipsilateral biceps and triceps brachii from both hemispheres. The latency of the ipsilateral responses was longer than contralateral responses consistent with them traversing an indirect, potentially cortico-reticulospinal pathway. Although the incidence of ipsilateral responses was higher after stroke than in healthy individuals, the excitability of the ipsilateral connection from the non-lesioned hemisphere was related neither to functional arm ability nor to the effectiveness of a 12 h training regimen to improve function. Baseline function as well as response to training was instead related to excitability of the contralateral connection from the lesioned hemisphere. The results appear to reinforce the conclusion that in the human proximal arm muscles, recovery is critically dependent on the integrity of the corticospinal pathway from the damaged hemisphere.

However, one feature seems at odds with this conclusion: although ipsilateral connectivity does not seem to be functionally relevant, the work by Barker et al., as well as others (Misawa et al., 2008; Turton et al., 1996) have shown that its excitability is upregulated compared to normal. Why this should be is unclear. The present study was designed to test whether a more liberal measure of ipsilateral connectivity, that classifies connections as present even when a TMS pulse produces a short latency suppression in ongoing EMG activity (in the absence of an MEP), would reveal a role of ipsilateral connections in recovery of function in 17 chronic stroke survivors given a consecutive 4-day arm reaching treatment program.

2. Methods

The study was approved by the Joint Ethics Committee of University College London and the National Hospital for Neurology and Neurosurgery (NHNN). Participants provided informed consent according to the Declaration of Helsinki.

2.1. Participants

Data were collected from 17 individuals of a group of 36 stroke survivors who participated in a larger study investigating learning mechanisms after stroke (Hammerbeck et al., 2017), Table 1. These 17 individuals were eligible and agreed to single pulse transcranial magnetic stimulation measurement. All patients met the following inclusion criteria: (1) Chronic stroke survivors ($\geq$1 year history) with (2) persistent upper limb weakness ($\leq$4 Medical Research Council (MRC) of either triceps or anterior deltoid muscles (3) Participants had to be able to perform the training task of $\geq$15 cm reach with the weight of the arm supported in a robotic manipulandum and (4) be reported to engage in therapy sessions. We excluded individuals with (1) history of previous stroke or other concomitant neurological or musculoskeletal disease, (2) cerebellar stroke, (3) proximal upper limb hypertonus $\geq$3 on Modified Ashworth scale (MAS), (4) severe sensory impairment ((light-touch <50% accuracy on 1 g Bailey© monofilament sensory testing on dorsum and palm of hand). (5) Shoulder pain $\geq$3/10 on self-rated continuous visual analogue scale, (6) uncorrected visual impairment, (7) hemi-spatial neglect established by the Star Cancellation Task and (8) cognitive and language impairment impeding co-operation in study protocol.

Clinical assessments, consisting of the Fugl-Meyer upper limb subset (/66), deltoid muscle strength using Medical Research Council rating (/5) and elbow flexor hypertonus (modified Ashworth scale) (Bohannon and Smith, 1987), were performed by a neurologist (DH).

Reaching accuracy was assessed in a robotic manipulandum which fully deweighted the affected upper limb during reaching movements (for details see: (Hammerbeck et al., 2017). Participants were asked to perform 20 cm forward reaching movements to a target projected on a computer screen, while vision of their upper limb was occluded. Movement was performed at 4 movement speeds calibrated to their ability. The reaching accuracy was re-assessed after 4 consecutive days of training, consisting of 420 reaching movements/day at either slow or fast movement speed. We here report all movements performed at the challenging, fast movement speed.

2.2. EMG recording

EMG activity was recorded with self-adhesive Ag/AgCl electrodes (Skintact®) using a muscle belly montage for the proximal muscles involved in reaching; triceps brachii (lateral head) and anterior deltoid, in accordance with SENIAM EMG recording recommendations (Hermens et al., 2000) (Kendall McCreary et al., 2010) (Loeb, 1986). EMG signals were amplified (1000x) and band-pass filtered (20 Hz to 1 kHz) with a D360 amplifier (Digitimer Limited Welwyn Garden City, UK). The signals were sampled at 5 kHz, digitised using a laboratory interface (Power 1401, Cambridge Electronics Design CED, Cambridge, UK) and stored on a laboratory computer for display and off-line data analysis with custom written SIGNAL software scripts.

2.3. TMS procedure

Single pulse TMS was delivered using a 70-mm figure-of-eight shaped TMS coil and a Magstim 200 magnetic stimulator (Magstim Company, Whitland, Dyfed, UK). The coil was placed over M1 tangentially over the scalp with the handle pointing postero-laterally at 45 degrees to the sagittal plane inducing a posterior-anterior current in the brain.

Individuals were instructed to perform a phasic reach forward with both arms against a weak elastic band before each stimulation. This procedure was used to elicit a phasic bimanual

Table 1
Clinical presentation of participants and their response to TMS.

Patient ID	Age	Affected UL	Months since onset	Fugl-Meyer Upper Limb/66	MAS	MRC strength	Lesion location	cMEP Triceps	iMEP Triceps	cMEP Ant Deltoid	iMEP Ant Deltoid
4	52	L	32	38	2	3	cortical	–	√	–	√
6	56	R	48	41	2	2	sub-cortical	–	√(s)	–	√(s)
10	49	L	15	32	2	1	cortical	–	–	–	–
11	54	L	12	51	2	3	cortical	–	√(s)	–	√
12	54	L	20	64	0	4	unknown	√	–	√	–
14	88	R	84	61	1	3	cortical	√	–	√	–
15	60	L	36	48	2	3	sub-cortical	√	–	√	√(s)
18	57	R	60	38	2	3	cortical	–	√(s)	√	√
19	47	L	72	55	2	4	sub-cortical	√	√	√	√
20	52	R	100	28	2	3	cortical	–	–	–	√
25	58	R	42	49	1	3	unknown	√	–	√	–
27	49	R	28	49	2	4	mixed	–	√	√(s)	√(s)
29	63	R	18	58	1+	4	unknown	√	–	√	–
30	74	L	15	63	0	3	cortical	√	√(s)	√	√(s)
31	65	L	82	32	1	2	unknown	–	√	–	√
32	71	R	17	62	0	4	cortical	√	–	√	–
33	49	L	52	39	2	1	sub-cortical	√	–	–	–
Mean	**58.7**	**R = 8**	**43.1**	**47.5**		**2.9**	**c = 8, s = 4,**	**9**	**8**	**10**	**10**
SD	**10.8**		**27.9**	**11.8**		**1.0**	**m = 1**	**both = 2**		**both = 5**	

Abbreviations: ID = identifier, UL = upper limb, MAS = modified Ashworth Scale, sub-cort = sub-cortical, s = suppression.

contraction as previous work has established that ipsilateral responses are only observed with contractions above 20% of maximum voluntary contraction (Ziemann et al., 1999; Bawa et al., 2004). Muscle activity was displayed on the computer desktop and the experimenter monitored these and only delivered stimulation, using a footswitch, when clear evidence of activity was observed.
ndividuals were encouraged to increase the muscle activity of the affected upper limb if poor activation was observed in EMG traces.

Both hemispheres were stimulated but only MEPs recorded in the affected weak upper limb muscles were analysed. The ipsilateral 'motor hotspot' for MEPs of the hemiplegic shoulder muscles was initially determined for the unaffected hemisphere. The motor area of proximal upper limb muscles was mapped by giving three stimulations at 70% maximum stimulator output (MSO) per site over a 3x3 1 cm grid marked on a cap, centred 3 cm lateral and 1 cm anterior of the vertex, over the proximal upper limb representation of the primary motor cortex (Wassermann et al., 1992). After mapping, MEPs were averaged offline per stimulation site and visually inspected for the greatest amplitude and consistent activation of either the affected triceps lateral head and/or anterior deltoid. The ipsilateral hotspot was determined as the location with the best responses, if any, of the affected ipsilateral upper limb muscles. If no responses were detected in the affected upper limb the site with the optimal contralateral responses was used.

A train of 20 stimulations was delivered to the hotspot at 70% MSO while performing reaching movements thereby measuring ipsilateral MEPs (iMEP) while stimulating the unaffected hemisphere. Although we acknowledge that the motor threshold is variable in individuals and can be much higher in the ipsilateral pathways all subjects were stimulated at 70% MSO to maintain comfort, reduce the amount of stimulations and optimise participant cooperation and retention.

The procedure was repeated for the affected hemisphere but the optimal stimulation site was now established for the muscles of the contralateral affected upper limb, if any. If no hotspot was evident stimulations were delivered at the centre of the grid, namely 3 cm lateral and 1 cm anterior of the vertex (Wassermann et al., 1992). Responses of the contralateral muscles were recorded when stimulating the affected hemisphere (cMEP). Stimulations were kept to a minimum and 94 stimulations were delivered (47 each hemisphere: 3 × 3 mapping = 27 and 20 stimulation).

2.4. TMS analysis

Triceps and deltoid muscle responses of the affected upper limb were investigated for both contralateral (T cMEP, D cMEP) (Fig. 1A) and ipsilateral activation (T iMEP and D iMEP) (Fig. 1B–E). The 20 trials when stimulating the affected hemisphere and when stimulating the unaffected hemisphere were overlaid for visualization (Schwerin et al., 2008) (Fig. 1A, B & D) and individual traces investigated for one of two features by a custom written Signal script (Fig. 1C & E). The individual traces were investigated to ensure a

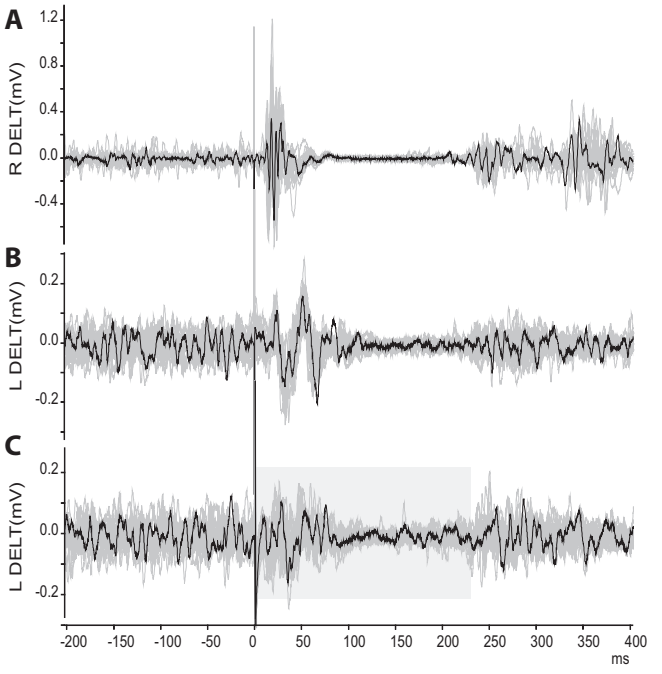

Fig. 1. Classification of MEPs (A) Overlay of 20 traces (grey) in pre-activated muscles demonstrating a clear contralateral MEP with a single example MEP indicated in black. (B) Overlay of 20 traces in pre-activated muscle in an example study participant, with a clear ipsilateral MEP indicated on a single trace. (C) Overlay of 20 traces in another participant, indicating a short latency silent period in the absence of a preceding MEP indicated by grey box.

consistent response because a single large MEP could dominate an average trace. Either a clear MEP (Fig. 1C), larger than 50 μV, that exceeded mean pre-activation by at least 1 standard deviation (Ziemann et al., 1999), or a consistent short latency suppression of ongoing EMG in the absence of a clear MEP (Fig. 1E), with a reduction of at least 1 standard deviation of pre-activation for more than 5 ms (Ziemann et al., 1999; Petersen et al., 2011). The feature (MEP or EMG suppression) had to be present in more than 50% of the 20 trials to be classed as a consistent response (Schwerin et al., 2008). We used the suppression of the EMG activity as a marker because it is more consistent and easier to identify than an MEP in pre-activated muscles at times. Short latency suppression of EMG is caused by activation of intracortical inhibitory circuits and therefore demonstrates motor cortex contribution to muscle activity in limb muscles (Luu et al., 2015; Petersen et al., 2011).

2.5. Statistical analysis

Statistical analysis is performed as repeated measures ANOVA between Muscle (2, triceps and anterior deltoid) * Path (2, iMEP and cMEP). Post hoc Student's t-test were performed when the ANOVA indicated significant differences in the data and Bonferroni corrections applied for tests involving multiple comparisons. One-way ANOVA investigating differences in Fugl Meyer scores and endpoint reaching error when grouped according to MEP presentation, i.e. no connectivity, only contralateral connectivity, only ipsilateral connection or evidence of both contra- and ipsilateral connections.

3. Results

3.1. Responses/connectivity

In our sample of stroke survivors (n = 17) we observed responses in paretic triceps and anterior deltoid muscles from both contralateral (ipsilesional) and ipsilateral (contralesional) hemispheres (Table 1). These responses were comprised predominantly of MEPs; however suppression of activity was also observed in both muscles (Fig. 1). It is interesting that suppression (in the absence of an MEP) was seen in about half of the ipsilateral responses but this was not evident in contralateral responses (except in subject 27). Occasionally we could not elicit either response, despite these participants being able to generate reaching movements to participate in the training protocol (Hammerbeck et al., 2017) but this phenomenon has been reported before in the upper as well as in the lower limb (Sivaramakrishnan and Madhavan, 2018; Barker et al., 2012).

In triceps, ipsilateral responses were seen in a total ('cIMEP and iMEP' as well as 'only iMEP') of 47%; in anterior deltoid the total was 58% (Table 2). Previous studies of healthy individuals have either failed to find iMEPs in triceps (Ziemann et al., 2008) or only elicited them in 9% of individuals (Barker et al., 2012); ipsilateral responses in deltoid have been reported in 40% of individuals (Strutton et al., 2004).

The latency of the MEPs observed in the affected upper limb differed from the latency of contralateral MEPs observed in the unaffected arm rmANOVA Path(3). This was evident both in the triceps ($F_{(2,32)} = 52.373$, $p \leq 0.001$) and the deltoid muscle ($F_{(2,32)} = 51.219 p \leq 0.001$), Fig. 2.

3.2. Relationship of different connectivity to Fugl-Meyer upper limb scores

We investigated the relationship between the F-M score and connectivity in contralateral and ipsilateral pathways by separating individuals into 4 groups depending on the connectivity observed (only contralateral, only ipsilateral, both and neither) (Fig. 3A & B). In both triceps and deltoid, one-way ANOVA showed that the FM scores differed significantly between groups (triceps: $F_{(3,13)} = 7.318$, $p = 0.004$; deltoid: $F_{(3,13)} = 6.159$, $p = 0.008$). Patients with either no connectivity or only ipsilateral connectivity to the two muscles had lower scores than patients with either contralateral connections or both contralateral and ipsilateral connections. Post hoc t-tests confirmed that individuals with contralateral connectivity had less impairment than those with only ipsilateral connectivity (triceps: $t_{(11)} = 2.538$, $p = 0.028$; deltoid: $t_{(8)} = 3.803$, $p = 0.005$). We investigated whether proximal movements were less reliant on crossed corticospinal connectivity by subdividing the Fugl Meyer upper limb score to only indicate the proximal impairment (/42) (Lee et al., 2015) (Fig. 3C&D). However, in both triceps and deltoid muscle an effect of group (Fig. 3C&D) (triceps: $F_{(3,13)} = 4.828$, $0 = 0.018$; deltoid: $F_{(3,13)} = 12.612$, $p<=0.001$) indicated that connectivity through contralateral connections was also important for proximal connections. This finding could be attributed to less impairment in individuals with contralateral connectivity to deltoid but this feature did not reach statistical significance for triceps (triceps: $t_{(11)} = 1.7784$, $p = 0.102$; deltoid: $t_{(8)} = 3.936$, $p = 0.004$).

3.3. Reaching and learning

Similar results were observed when we assessed how connectivity related to endpoint reaching error prior to training. One-way ANOVA showed that error differed between the four connection groups (triceps: $F_{(3,13)} = 5.787$, $p = 0.010$; deltoid: $F_{(3,13)} = 8.709$, $p = 0.002$) (Fig. 4A & B). Post hoc t-tests confirmed that endpoint accuracy was greater in individuals with only contralateral connectivity compared with those who only had ipsilateral connectivity (triceps: $t_{(11)} = -3.847$, $p = 0.003$ Fig. 4A; deltoid: $t_{(8)} = -4.240$, $p = 0.003$, Fig. 4B).

The relationship of connectivity to performance improvement in this task, quantified as the reduction in absolute error was not clear (Fig. 4C & D). In triceps no main effect of group was observed (one-way ANOVA: $F_{(3,13)} = 2.244$, $p = 0.132$). However a post-hoc exploratory comparison showed that individuals with only ipsilateral connectivity reduced their error more than those with contralateral connectivity ($t_{(15)} = -2.147$, $p = 0.049$). For the deltoid muscle, Fig. 4D, a main effect was evident in the ANOVA ($F_{(3,13)} = 3.592$, $p = 0.043$) which was also due to individuals with ipsilateral connections having a larger reduction in error after training ($t_{(15)} = -2.265$, $p = 0.039$).

Table 2
Summary of TMS responses. Number of participants presenting with only contralateral, only ipsilateral, both or neither pathway in triceps and anterior deltoid muscle.

	Only cMEP	cMEP and iMEP	Only iMEP	Neither
Triceps (n)	7 (0 s)	2 (1s iMEP)	6 (3s)	2
Triceps percentage	41%	12%	35%	12%
Anterior deltoid (n)	5 (0 s)	5 (1s cMEP& iMEP)	5 (3s)	2
Deltoid percentage	29%	29%	29%	12%

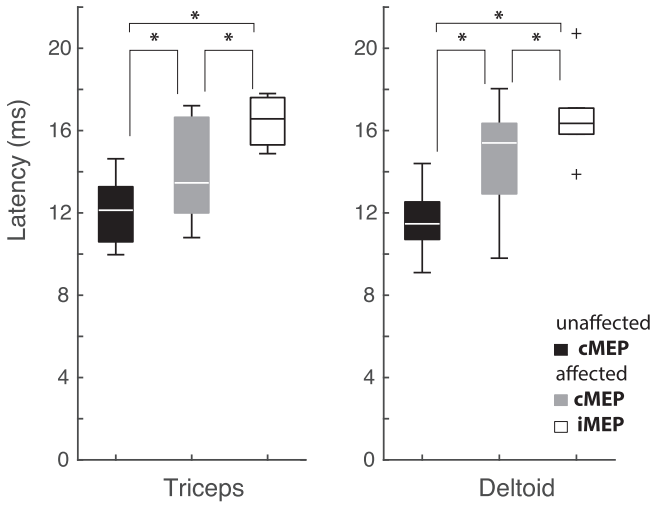

Fig. 2. MEP latency. Box and whisker plots of the MEP latency in the triceps and deltoid muscle. The latency of the unaffected cMEP is shown as well as the cMEP and iMEP latency for the affected pathway. The box indicates the median, 75% quartile and the whiskers the range.

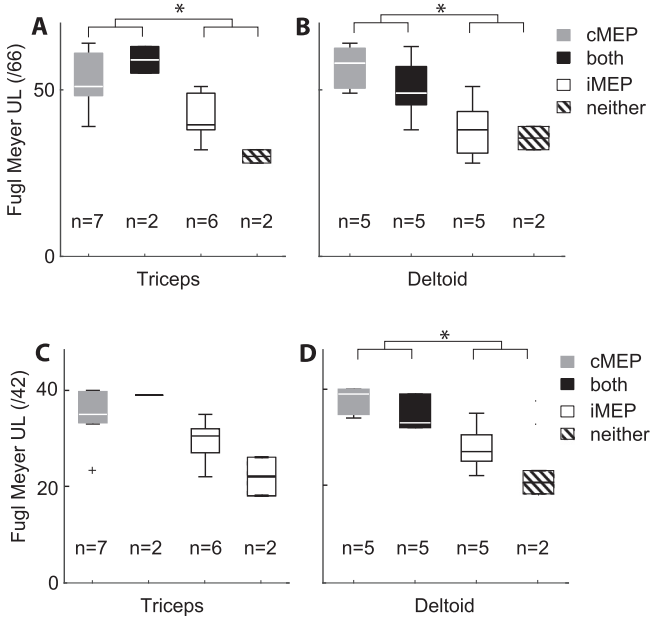

Fig. 3. Fugl-Meyer upper limb score for individuals with different connectivity classifications for (A) triceps and (B) deltoid muscle. The box indicates the median, 75% quartile and the whiskers the range. Fugl-Meyer scores of all proximal test (/42) for individuals with different connectivity classifications for (C) triceps and (D) deltoid muscle.

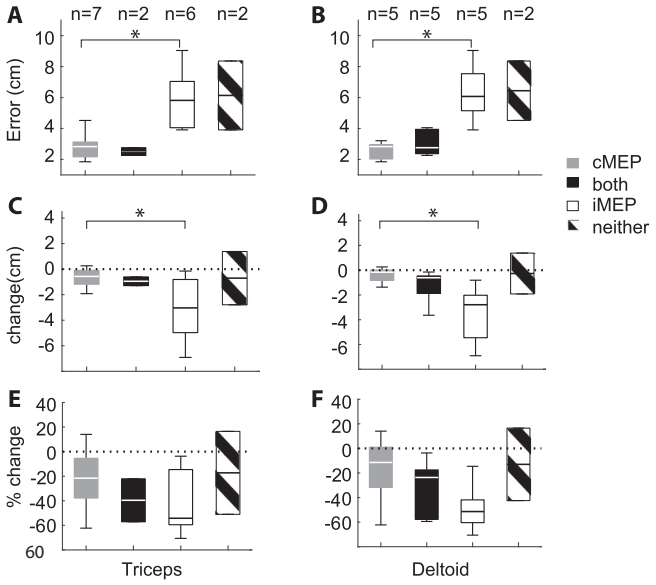

Fig. 4. (A) Size of reaching root mean square (rms) error for individuals with different connectivity classifications for triceps and (B) deltoid muscle. (C) & (D) Reduction in rms error after 4 days of training for triceps and deltoid muscle. (E) & (F) Percentage change of error for individuals with different connectivity classifications for triceps and deltoid muscle.

However, as the size of the error was much larger at baseline in the individuals without contralateral connectivity this finding could be due to a ceiling effect since the scope for improvement in the latter group was small. We investigated if the findings persisted if we investigated the percent change observed (Fig. 4E & F). There was no main effect for either of the muscles, nor was there evidence of a difference between contralateral and ipsilateral connectivity for either.

4. Discussion

In the present study, following methods used by Ziemann et al. (Ziemann et al., 1999), we identified an ipsilateral connection if stimulation evoked either a consistent short-latency excitatory motor evoked potential (MEP) or if the stimulus produced an appropriately timed suppression in EMG activity in ongoing EMG activity. The rationale is that in stroke patients we may fail to detect a clear MEP because of dispersion of conduction in damaged corticospinal fibers or because of subthreshold stimulation. The suppression of activity is less sensitive to dispersion of conduction and has a lower threshold (Barker et al., 2012; Strigaro et al., 2014). It is therefore a more sensitive indicator of weak ipsilateral innervation. The latency of these responses replicate previous findings that cMEPs in the weak upper limb are observed at a delay in comparison to the unaffected pathway and iMEPs are even later and more variable (Ziemann et al., 1999). Our findings re-enforce the theory that iMEPs are not conducted by direct ipsilateral corticospinal pathways but rather by indirect oligo-synaptic pathways that are probably relayed via brainstem pathways (Ziemann et al., 1999).

We observed iMEPs or suppression of activity in 47% and 58% (triceps and deltoid respectively) of stroke survivors tested. This compares with an incidence of 0–9% in triceps and 40% in deltoid observed in healthy individuals (Strutton et al., 2004; Ziemann et al., 1999). We conclude that, particularly in triceps, the excitability of ipsilateral pathway(s) from the contralesional hemisphere is enhanced after stroke. However, the presence of these ipsilateral connections is not indicative of less arm impairment. Instead, arm function is closely related to the integrity of contralateral projections. This therefore suggests that control of these proximal arm muscles after stroke is similar to that of distal muscles in which many reports have shown that functional recovery is tightly linked to the integrity of the crossed corticospinal tract (Alawieh et al., 2017; Byblow et al., 2015; Ward et al., 2006). It differs from what has been reported in axial muscles, in which the presence of ipsilateral responses after stroke is related to increased trunk control (Bradnam et al., 2011; Turton et al., 1996; Misawa et al., 2008; Tsao et al., 2008; Matthews et al., 2013).

Interestingly, individuals with ipsilateral connections in the present study made greater absolute gains in movement accuracy during the days of arm reaching training than individuals with

contralateral connections, but this may be related to the fact that their movements were less accurate at baseline. It is important to note that this does not deny a possible role of the contralesional hemisphere in recovery of function. For example, the contralesional hemisphere may assist recovery via callosal connections to remaining pathways in the affected hemisphere (Hayward et al., 2017). The question the results pose is the particular role, if any, of the enhanced excitability of ipsilateral connections in recovery of proximal arm function.

4.1. Functional relevance

In healthy individuals, both proximal arm muscles and axial muscles have greater ipsilateral connectivity than distal muscles, perhaps because of their greater involvement in bimanual and postural activity (Bawa et al., 2004; Marsden et al., 1999; Ziemann et al., 1999; Palmer and Ashby, 1992). Thus it is not unexpected that upregulation of excitability of ipsilateral projections to axial muscles after stroke appears to be associated with improved function. However it is surprising that this does not seem to be the case for the closely related projections to proximal arm muscles. One possibility is that the ipsilateral input to arm muscles is only functionally effective when these muscles participate in compensatory trunk movements commonly observed after stroke to enable task completion (Levin et al., 2009; 2016). Alternatively upregulation of ipsilateral projections to proximal arm muscles could be instrumental in the expression of another clinical presentation frequently observed after stroke, namely stereotypical movement synergies (Owen et al., 2017; McPherson et al., 2018). The increased ipsilateral activation previously reported in wrist flexors and biceps supports this theory (Zaaimi et al., 2012; Stinear and Byblow, 2004), and this is consistent with animal studies that show that reticulospinal tract axons terminate over several spinal segments, consistent with the multi-segmental activation of stereotypical synergy patterns (Schepens and Drew, 2006; Jankowska and Edgley, 2006). Recent studies report that synergistic movement patterns are more detrimental to function than spasticity or high muscle tone (McPherson et al., 2018). If this were the case we might even expect that the upregulated ipsilateral connections observed in our sample would be correlated with worse impairment, but this was not observed. This may partly be due to the muscles we investigated. Both triceps brachii as well as anterior deltoid are not muscles typically associated with the stereotypical upper limb flexion pattern (Dewald et al., 1995). Neck rotation can modulate the expression of iMEPs in healthy individuals and after stroke (Ziemann et al., 1999; Ellis et al., 2012) due to changes in motoneurone excitability. This is thought to be through the asymmetric tonic neck reflex (Ellis et al., 2012), a primitive reflex which re-emerges after stroke, where rotation of the head results in upper limb extension on that side and flexion synergy in the other arm. However it should be noted that in our study, individuals were instructed to look straight ahead and they performed a bilateral reaching task. Therefore the responses we report are not modulated by alterations in motoneurone excitability, elicited by neck rotation.

Although upregulation of this ipsilateral widespread connectivity may increase development of unwanted synergies, it may also provide a useful excitatory drive to spinal motorneurones that can add to remaining weak input from the lesioned hemisphere and reduce the threshold for excitation (Bradnam et al., 2013; Buetefisch, 2015; Ellis et al., 2012). In patients with moderate to severe stroke in whom remaining inputs from the lesioned hemisphere are minimal, it could be an essential partner in recovery, even if not directly implicated in fractionated muscle control (Buetefisch, 2015). In contrast, this extra input could interfere with recovery of movement in mildly affected stroke survivors by reducing the functional specificity of surviving connections (e.g. see (Bradnam et al., 2011)).

4.2. Pathways

The pathways that mediate the upregulated responses in the ipsilateral pathways are still not clear (Baker et al., 2015) but they are proposed to be dependent on cortico-reticulospinal connections (Bradnam et al., 2013). In macaque monkeys, increased excitability of reticulo-spinal tract input to motoneurons has been observed in forearm and hand muscles (Zaaimi et al., 2012; Baker et al., 2015; Zaaimi et al., 2018). In addition upregulation of reticulospinal projections to the C3/C4 propriospinal neurons has been proposed to play a role (Bradnam et al., 2013), and has been observed in humans (Stinear and Byblow, 2004). However whether this is seen after a lesion in animals has not been investigated to our knowledge.

4.3. Limitations

Although corticospinal responses are usually measured in terms of MEP amplitude, in the present study we used the presence or absence of responses ($\geq$10/20 stimulations) at a MSO of 70% as the primary measure of excitability. One reason for this is that proximal muscles require pre-activation to measure MEPs reliably (Bawa et al., 2004; Alagona et al., 2001; Barker et al., 2012) and in the presence of significant weakness; precise, consistent pre-activation is very difficult to achieve. Documenting the presence of a response in the context of some level of activity is a useful way to avoid this problem. It should however be noted, that the TMS threshold could be lower during stronger muscle contractions, but we are not aware of papers that have examined this question directly. If this is the case we may have missed responses in some individuals that were not activating their muscles strongly enough during TMS testing. We also used a predetermined MSO as in previous studies (Turton et al., 1996; Schwerin et al., 2008) which enabled us to select an intensity to maintain patient comfort and compliance. In more excitable pathways, stimulation at 70% MSO could lead to stimulation intensity of over 150% motor threshold with resultant response saturation (Devanne et al., 1997). When using the frequency of responses as the primary outcome a ceiling effect of overstimulating does not pose a problem (Barker et al., 2012; Schwerin et al., 2008). However, a floor effect is possible as it is likely that responses would have been observed in some of the subjects if we had stimulated at higher intensities. By accepting the presence of EMG suppression in the absence of an MEP as evidence of connectivity we hoped to minimize this problem, as low-intensity TMS, below motor threshold, has been found to produce this feature (Petersen et al., 2011). An uncertainty that remains in this patient sample, investigated in the chronic stage after stroke is whether ipsilateral connections were present prior to the stroke and if contralateral connections were damaged by the stroke. Future studies investigating longitudinal changes from the early period after stroke may be able to address this definitely.

5. Conclusion

In summary we found an increased incidence of ipsilateral input to proximal muscles after stroke. But this increased incidence was not associated with better arm reaching function. Why these ipsilateral pathways are upregulated is therefore intriguing and raises the question of whether it is a maladaptive response that encourages development of synergies or a compensatory one that can lower the threshold for activation from damaged pathways from the ipsilesional hemisphere.

Conflict of interest

The authors declare that they have no conflict of interest.

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