Clinical Neurophysiology 123 (2012) 2422–2428

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Relationships between functional and structural corticospinal tract integrity and walking post stroke

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ARTICLE INFO

Article history:
Accepted 30 April 2012
Available online 19 June 2012

Keywords:
Stroke
Locomotion
Motor recovery
TMS
DTI

HIGHLIGHTS

- We investigated the relationship between walking impairment after stroke and integrity of the corticospinal tract (CST).
- We used transcranial magnetic stimulation and diffusion tensor imaging to assess CST integrity.
- We demonstrate that patients with more ipsilateral connectivity between the unlesioned M1 and the affected leg had more structural damage to their CST.

ABSTRACT

Objective: Studies on upper limb recovery following stroke have highlighted the importance of the structural and functional integrity of the corticospinal tract (CST) in determining clinical outcomes. However, such relationships have not been fully explored for the lower limb. We aimed to test whether variation in walking impairment was associated with variation in the structural or functional integrity of the CST.
Methods: Transcranial magnetic stimulation was used to stimulate each motor cortex while EMG recordings were taken from the vastus lateralis (VL) bilaterally; these EMG measures were used to calculate both ipsilateral and contralateral recruitment curves for each lower limb. The slope of these recruitment curves was used to examine the strength of functional connectivity from the motor cortex in each hemisphere to the lower limbs in chronic stroke patients and to calculate a ratio between ipsilateral and contralateral outputs referred to as the functional connectivity ratio (FCR). The structural integrity of the CST was assessed using diffusion tensor MRI to measure the asymmetry in fractional anisotropy (FA) of the internal capsule. Lower limb impairment and walking speed were also measured.
Results: The FCR for the paretic leg correlated with walking impairment, such that greater relative ipsilateral connectivity was associated with slower walking speeds. Asymmetrical FA values, reflecting reduced structural integrity of the lesioned CST, were associated with greater walking impairment. FCR and FA asymmetry were strongly positively correlated with each other.
Conclusions: Patients with relatively greater ipsilateral connectivity between the contralesional motor cortex and the paretic lower limb were more behaviorally impaired and had more structural damage to their ipsilesional hemisphere CST.
Significance: Measures of structural and functional damage may be useful in the selection of therapeutic strategies, allowing for more tailored and potentially more beneficial treatments.

1. Introduction

Stroke rehabilitation therapies may be more effective if they are tailored to an individual patient's surviving anatomical and physiological substrates. However, development of such strategies first requires identification of functional and structural measures that

Abbreviations: CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; FCR, functional connectivity ratio; M1, primary motor cortex; TMS, transcranial magnetic stimulation; VL, vastus lateralis.

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1388-2457
http://dx.doi.org/10.1016/j.clinph.2012.04.026

are associated with clinical status and that could in future be tested as predictors of outcomes.

Studies of upper-limb hemiparesis suggest that recovery depends in part on the degree of corticospinal tract (CST) damage (Binkofski et al., 1996; Shelton and Reding, 2001; Stinear et al., 2007). In addition, recovery is related to cortical excitability in the contralesional hemisphere, whereby higher levels of excitability and greater ipsilateral activity during paretic hand movement are associated with a poorer outcome (Caramia et al., 2000; Ward et al., 2003, 2006). While a considerable amount of data is available regarding upper limb motor recovery, there are fewer studies of structural and functional correlates of recovery of the lower limb.

Fundamental differences in the neural control of unilateral hand movements and more automated, bilateral movements of the lower limb such as walking, disqualify conclusions from upper limb studies being directly applied to the lower limb (Luft et al., 2002). In particular, the relationship between the degree of damage to the corticospinal tract and walking impairment remains unclear (Ahn et al., 2006; Dawes et al., 2008). There is some evidence of increased activity in the ipsilateral (contralesional) motor cortex during paretic lower limb movements in more severely impaired patients (Enzinger et al., 2009, 2008; Jang et al., 2005; Luft et al., 2005) but the functional and clinical significance of such activity is unclear.

We used transcranial magnetic stimulation (TMS) to directly assess functional connectivity from the motor cortex of each hemisphere to both lower limbs in chronic stroke patients with persistent paresis of their lower limb. We used diffusion tensor imaging (DTI) to assess the structural integrity of the CST in each hemisphere. We hypothesized that patients with a higher degree of structural damage to the CST in the lesioned hemisphere would have greater relative functional connectivity from the contralesional motor cortex to the ipsilateral paretic limb and greater walking impairment.

2. Methods

Nine individuals with persistent hemiparesis due to chronic stroke ($\geqslant$6 months) were recruited (see Table 1). All patients provided written informed consent in accordance with local ethical approval and the 2008 Declaration of Helsinki. Patients were screened for contradictions to MRI and TMS and any other cause for their reduced motor function. Patients participated in one clinical/neurophysiology data collection session and one Magnetic Resonance Imaging (MRI) session where DTI and structural imaging was acquired.

2.1. Clinical and neurophysiological testing

Each participant's overall impairment was assessed using the lower-limb section of the Fugl-Meyer (FM) scale (Fugl-Meyer et al., 1975), with higher scores reflecting greater function (maximum 34). Walking impairment measures were derived using a 10 m timed walk (Supplementary information, methods).

TMS was used to stimulate each motor cortex while EMG recordings were taken from the vastus lateralis (VL) bilaterally; these EMG responses were used to calculate both ipsilateral and contralateral recruitment curves for each lower limb (Supplementary information, methods). TMS motor evoked potentials (MEPs) were elicited every 5 s. The slope of each curve was obtained by fitting a line to each subject's data. All fits had $r > 0.85$. To quantify the balance between ipsilateral and contralateral connectivity, a functional connectivity ratio was calculated for each leg separately:

$$\textit{Functional Connectivity Ratio (FCR)} = \frac{\textit{Slope of Ipsilateral Recruitment Curve}}{\textit{Slope of Contralateral Recruitment Curve}}$$

Because of the close proximity of the two lower limb motor cortices and the low spatial resolution of TMS, it is assumed that all responses were a mix of ipsilateral and contralateral inputs to motor neurons but that inputs from the stimulated hemisphere would predominate each measurement, as we have shown previously (Madhavan et al., 2010) FCR values of >1.0 were therefore interpreted as reflecting predominantly ipsilateral connectivity between motor cortex and lower limb motor neurons and FCR values of <1.0 were interpreted as reflecting predominantly contralateral connectivity (Madhavan et al., 2010).

Table 1
Clinical Details.

Subject	Age/sex	Time post stroke (years)	Stroke hemisphere	Lesion location	Mobility aid	FM	Walking speed (m/min)	FA asymmetry	Affected limb FCR	Lesion volume (mm^3)	Lesion overlap (mm^3)
1	60/M	4.5	L	Frontal lobe	None	34	89.75	0.08	1.11	148,248	320
2	56/M	4.7	L	Intracerebral hemorrhage	AFO	25	40.95	0.1	1.42	2016	0
3	64/M	1.8	R	Subcortical infarct	Stick	26	45.11	0.04	1.21	608	392
4	74/F	1.8	L	MCA territory	AFO/tripod	15	4.75	0.12	1.96	3752	176
5	77/F	2.8	L	MCA territory	AFO	15	9.68	0.24	1.55	2432	112
6	65/M	1.3	R	MCA territory	None	29	35	0.17	2.05	2392	376
7	73/M	2.7	R	MCA/PCA territory	AFO/stick	15	5.4	0.43	2.63	355,960	440
8	79/M	2.0	L	Caudate	None	34	76.9	0	0.27	727	232
9	70/M	1.0	R	Frontal lobe	AFO/stick	20	42.9	0.13	1.62	6496	0
10	66/M	4.6	R	Occipital temporo-parietal	Cane	29	25.6	0.06	1.13	45,736	6220
11	56/M	11.3	L	Putamen	None	32	57.1	0.03	0.94	108,630	1308
12	57/F	4.0	R	Parietal lobe	Tripod	12	11.3	0.25	2.5	26,162	235
13	72/M	4.9	R	Preceneous cortex	AFO	25	49	0.12	0.55	22,204	0

AFO – Ankle Foot Orthosis.