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ORIGINAL ARTICLE

Individual recovery profiles of manual dexterity, and relation to corticospinal lesion load and excitability after stroke —a longitudinal pilot study

Julia Birchenall[a,1], Maxime Térémetz[a,b,1], Pauline Roca[a], Jean-Charles Lamy[c], Catherine Oppenheim[a], Marc A. Maier[b,d], Jean-Louis Mas[a], Catherine Lamy[a], Jean-Claude Baron[a,2], Påvel G. Lindberg[a,b,2,*]

[a] *Centre de psychiatrie et neurosciences, Inserm U894, hôpital Sainte-Anne, université Paris Descartes, 75014 Paris, France*
[b] *FR3636 CNRS, université Paris Descartes, Sorbonne Paris Cité, 75006 Paris, France*
[c] *Inserm U 1127, CNRS UMR 7225, Sorbonne universités, UPMC université Paris 06 UMR S 1127, institut du cerveau et de la Moelle épinière, ICM, centre de neuro-imagerie de recherche (CENIR), 75013 Paris, France*
[d] *Université Paris Diderot, Sorbonne Paris Cité, 75013 Paris, France*

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Summary
Objectives. — In this longitudinal pilot study, we investigated how manual dexterity recovery was related to corticospinal tract (CST) injury and excitability, in six patients undergoing conventional rehabilitation.
Methods. — Key components of manual dexterity, namely finger force control, finger tapping rate and independence of finger movements, were quantified. Structural MRI was obtained to calculate CST lesion load. CST excitability was assessed by measuring rest motor threshold (RMT) and the amplitude of motor evoked potentials (MEPs) using transcranial magnetic stimulation (TMS). Measurements were obtained at two weeks, three and six months post-stroke.

* Corresponding author. Centre de psychiatrie et neurosciences, Inserm U894, 102—108, rue de la Santé, 75014 Paris, France.
E-mail address: pavel.lindberg@inserm.fr (P.G. Lindberg).
[1] Equal contribution.
[2] Authors share senior authorship.

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Results. — At six months post-stroke, complete recovery of hand gross motor impairment (i.e., maximal Fugl-Meyer score for hand) had occurred in three patients and four patients had recovered ability to accurately control finger force. However, tapping rate and independence of finger movements remained impaired in all six patients at six months. Recovery in hand gross motor impairment and finger force control occurred in patients with smaller CST lesion load and almost complete recovery of CST excitability, although RMT or MEP size remained slightly altered in the stroke-affected hemisphere compared to the unaffected hemisphere. The two patients with poorest recovery showed persistent absence of MEPs and greatest structural injury to CST.
Discussion. — The findings support good motor recovery being overall correlated with smaller CST lesion, and with almost complete recovery of CST excitability. However, impairment of manual dexterity persisted despite recovery in gross hand movements and grasping abilities, suggesting involvement of additional brain structures for fine manual tasks.

Introduction

Stroke is a main cause of physical disability in adults, with up to 85% of survivors experiencing upper limb paresis [42,52]. About 50% of stroke patients show impaired hand function in the chronic phase [47,71]. Importantly, in addition to reduced gross arm and hand movement control, persistence of impaired manual dexterity has specific impact on activities of daily living and may decrease quality of life [67]. Manual dexterity can be defined as the ability to perform accurate and rapid hand and finger movements and modulation of finger forces, in a coordinated manner. The corticospinal tract (CST) is highly specialized in humans, allowing for a high degree of manual dexterity compared to other species [35,53]. A high degree of manual dexterity is crucial for grasping and manipulation of objects, manual sensory exploration and gesticulation [40]. Accurate measurement of manual dexterity is therefore important for assessing post-stroke motor impairment and recovery. However, given its complexity, manual dexterity cannot be described with a single performance variable. The most commonly used assessments, e.g., the Fugl-Meyer Upper Extremity motor assessment (FM-UE) or the Action Research Arm Test (ARAT), allow for a good overall assessment of arm motor function, mass finger flexion-extension and simple grasping tasks, but fail to measure other components important for tasks requiring independence of finger movements, such as buttoning a shirt or typing [31,40,51,79,87].

To quantify the main components of manual dexterity, we have developed a device, the Finger Force Manipulandum (FFM), consisting of sensitive force sensors coupled with dedicated visuomotor tasks, for the quantitative assessment of multiple key components of dexterity, and showed that the method was feasible in moderately affected chronic stroke patients and that it could quantify impairment in finger force control, timing, motor sequencing and independence of finger movements [87].

Despite its functional impact, few longitudinal studies have assessed the evolution of post-stroke deficits in manual dexterity, particularly of independent finger movements. One recent study reported parallel post-stroke recovery of finger strength and individuation up to a 60% strength level [93]. Finger strength recovery beyond 60% was not associated with recovery in finger individuation and these findings suggest that two separate systems are responsible for post-stroke recovery of strength and individuation [93].

Conversely, recovery of global upper limb and hand motor impairment (i.e., strength, gross arm and hand function, simple grasp movements) has been more extensively studied and shown to take place during the first two to three months after stroke onset [48,49,66,72]. One major feature is that the amount of upper limb motor recovery (measured with FM-UE) is proportional to what the patients could potentially regain. At the group level, patients improve about 70% of their potential [total FM-UE minus initial FM-UE score], at least among patients with mild to moderate initial motor impairment [13,72,85,91]. Importantly, this proportional recovery seems to depend on the functional integrity of the CST as assessed by the presence of MEPs on early post-stroke transcranial magnetic stimulation (TMS). Thus, patients with measurable MEPs at two weeks post-stroke follow this 70% 'rule', whereas patients without MEPs and more severe motor impairment (FM-UE $\leq$ 10) do not [13,22]. These studies add evidence to earlier investigations showing that absence of MEPs early after stroke is related to poor recovery of upper limb motor impairment after stroke [61,84]. Degree of CST injury, measured as lesion-CST overlap using structural MRI, has also been shown to correlate closely with recovery of upper limb motor impairment (FM-UE) after stroke [26,94]. In addition, diffusion tensor imaging (DTI) studies show that structural integrity of the CST, both a few days after stroke [8] and in the chronic phase, correlate closely to degree of upper limb motor recovery [11,32,56,57]. These studies highlight the importance of CST integrity for recovery of upper limb strength and gross motor impairment of the hand. However, most of the above studies used the FM-UE or the ARAT to evaluate upper limb motor impairment [11,13,22,26,48,57,72,85]. How post-stroke structural and functional integrity of the CST relates to recovery of manual dexterity components has not been investigated so far.

In this prospective longitudinal pilot study, we aimed to obtain preliminary data on i) the recovery of dexterity over time and ii) to qualitatively describe the relationships between measures of major dexterity components and structural and functional integrity of the CST, in patients with moderate-severe initial hand motor deficit. Our emphasis in this pilot study is on recovery of key components of dexterity including independent finger movements, but

Table 1 Main clinical and demographic data.

Patient	Vascular risk factors				Medication	Aff side	Lesion localization	IV t-PA	NIHSS 2W (0—42)	Delay initial inclusion (days)	Dom. hand/ Lat. index
	HT	Db	Dys	Sm							
#1	Y	Y	N	N	Metformin, glibenclamide, atorvastatin, aspirin, perindopril, fluoxetine esomeprazole	R	Frontal, precentral gyrus and left centrum semiovale	N	0	11	R/MD
#2	Y	N	N	N	Aspirin, amlodipine, rosuvastatin, fluoxetine	R	Left pons	Y	7	6	R/67
#3	Y	Y	N	Y	Dabigatran, ramipril, atorvastatin, metformin, insulin, tramadol	R	Left internal capsule and lenticular nucleus	Y	8	12	R/100
#4	Y	N	Y	N	Bisoprolol, amlodipine, perindopril, dabigatran	L	Right insula, precentral, parietal cortex, internal capsule, centrum semiovale	Y	5	14	R/100
#5	Y	N	N	N	Clopidogrel, atorvastatin, perindopril, indapamide, amlodipine, bisoprolol	L	Right putamen, internal capsule, centrum semiovale	N	0	5	Ambi/-11
#6	Y	N	N	N	Enoxaparin, aspirin, lansoprazole, perindopril, amlodipine, hydroxyzine, fluoxetine, indapamide	R	Left, internal capsule, centrum semiovale	N	10	11	R/MD

F: female; M: male; HT: hypertension; Db: diabetes; Dys: dyslipidemia; Sm: smoking; Y: yes; N: no; Aff side: affected body side; L: left; R: right; IV t-PA: intravenous tissue plasminogen activator; Lat Index: laterality index [68]; NIHSS: National Institute of Health Stroke Scale; MD: missing data.

also on capacity to control forces and timing of finger movements, as assessed with the FFM. Recovery in dexterity components was compared to global motor recovery assessed with a comprehensive battery of conventional upper limb tests. Structural MRI was used to calculate weighted CST lesion load and TMS to probe CST functional integrity.

Methods

Participants and study design

The data was collected as part of a prospective study on the effects of fluoxetine on recovery of hand function after stroke that was terminated secondary to poor patient recruitment (ClinicalTrials.gov, NCT02063425). Initial inclusion occurred within 2 weeks post-stroke (i.e. 5 to 15 days' post-stroke, Table 1). Manual dexterity and TMS assessments were performed at two weeks (W2), at 3 (M3) and 6 months (M6) post-stroke. Ethical approval was obtained from the Regional ethical review board (île-de-France, Paris, France; CPP N° : 2013-001313-32), and written informed consent was required of all participants in accordance with the Declaration of Helsinki.

Inclusion criteria: (i) first-ever ischemic stroke (MRI-verified) with or without M1 involvement; (ii) initial FM-UE score < 45/66 with moderate-severe hand motor impairment

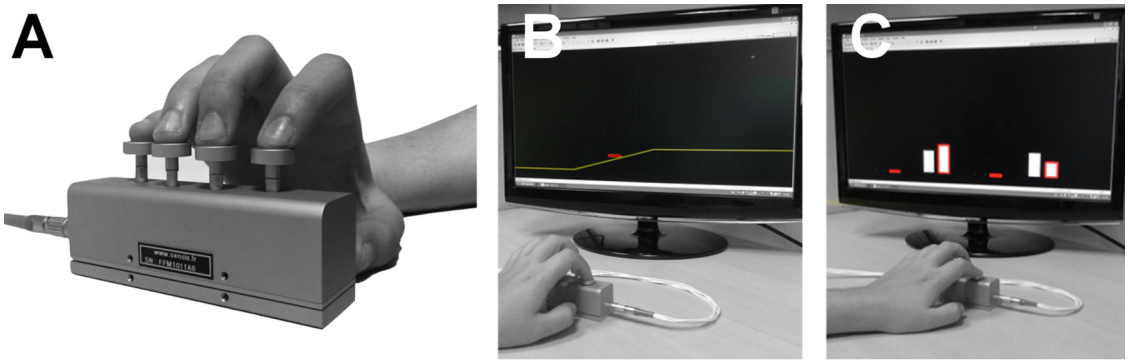

Figure 1 A. The Finger Force Manipulandum (FFM). Index, middle, ring and little finger each apply forces on separate spring-loaded pistons. B. Set-up with FFM and screen providing visuo-motor feedback during the force-tracking task. The yellow line represents the target force and the cursor (red, here close to the ramp) represents the instantaneous force exerted by the index finger. The subject has to match the vertical cursor position with the target force. C. Visuo-motor feedback provided in multi-finger tapping task. This example shows one trial with a two-finger target tap (index and ring finger targets shown in white bars) and corresponding two-finger user tap (bars with red border).

(FM-UE hand score < 10/14) [29]; (iii) age 18—80 years; (iv) able to provide written informed consent. The exclusion criteria were as follows: (i) presence of severe global neurologic deficit according to National Institute of Health Score Scale (NIHSS) score > 20/42 [10] or other impairments that could prevent informed consent or that could interfere with the study's behavioral measurements (e.g., aphasia, neglect, apraxia or impaired comprehension); (ii) planned carotid revascularization; (iii) presence of another severe condition making follow-up difficult; (iv) pregnancy or breast feeding; and (v) contraindications to TMS (in agreement with the international recommendations of good practice of TMS; [77]).

Diffusion tensor imaging (DTI) was obtained in 18 healthy subjects (10 males, aged 31.7 ± 8.2 years) to allow construction of CST template (see below). Written informed consent was obtained and this study part had also received ethical approval (CPP Cochin, île de France III).

Clinical measurement of upper limb function and dexterity

The FM-UE was used as a measure of gross upper limb and hand motor impairment [29,31,79]. The hand subsection of this assessment (FM-UE hand) informs on mass finger flexion-extension and ability to perform simple grasp movements. Improvement was classified as clinically significant if an increase in the total FM-UE was > 5 points [69]. The maximal index-thumb tapping speed, also reflecting degree of motor impairment, was assessed by counting the number of index-thumb taps in a period of 15 seconds [15]. The Moberg pick-up (MPUT) test was used as a functional assessment of precision grip function in the paretic and non-paretic hand: the time taken to pick-up and place 12 objects into the box was recorded (time > 18 s is considered abnormal) [2]. We assessed strength deficits by recording the maximal grip force (in Kg) in each hand with a hydraulic Jamar dynamometer (http://www.kinetec-byvivadia.com).

Quantification of manual dexterity using the Finger Force Manipulandum

Finger movements were measured with the FFM (www.sensix.fr), as previously described [87] (Fig. 1A). Individual forces of the index, middle, ring and little finger were sampled to a CED1401 (10 kHz sampling rate/digit) under Spike2v6 (Cambridge Electronic Design, www.ced.co.uk). Custom-written CED scripts provided real-time visual display of digit forces, target instructions or target forces. The four force signals were down-sampled to 100 Hz and analysis was performed off-line using Matlab (v7.5, The MathWorks, Inc., Natick, MA, USA).

We used two visuo-motor and one auditory-motor tasks to quantify specific components of manual dexterity:

- finger force-tracking task. This task assesses the ability to precisely generate and modulate fingertip forces in response to visual feedback. The subject varies the force applied on the piston with the index finger, which is shown as a vertically moving cursor on a computer screen. The subject is instructed to follow the target force trajectory as closely as possible with the cursor. The target force (a line) passed from right to left over the screen. Each trial consisted of a ramp-, a hold- (stable force) and a release-phase (instantaneous return to the resting force level), followed by a resting-phase. Trials were repeated 24 times (four blocks of six trials, two blocks with a 1N target force, two with a 2N target force). The 1N and 2N force levels correspond to a typical force range employed in daily object manipulation. Patients performed the task separately with the index and middle finger of the paretic hand;

  This task permitted quantitative assessment of (i) accuracy of force control (FC) and (ii) ability to quickly release force (RD = release duration) for each of the 24 trials. Good accuracy of force control is indicated by low tracking error, calculated as the root-mean-square error (RMSE) between the applied force and the target force during the ramp-and-hold trajectory (Fig. 1B). The RD was computed as the time taken to reduce the force from 75% to

25% of the target force and baseline force was calculated as mean force during rest periods between trials. Both tracking error and release duration have been shown to be affected post-stroke [54,87].

- single-finger tapping task. This task assesses the ability to perform repetitive finger tapping at frequencies indicated by auditory cues (1, 2 and 3 Hz). The subject was instructed to perform taps with index, middle, ring and little finger fingers separately. A target bar on the screen indicated which finger to tap with. Subjects were required to tap in time with auditory cues (beep sound). Subjects were instructed to match tapping rate as accurately as possible with the cued rate. After an initial tapping period (15 taps with auditory cues) the subject was instructed to maintain the tapping rate with the same finger for a similar period, without auditory cues;

  For the analysis of this tapping task, first finger taps were identified as forces exceeding a threshold (> 0.5 N). The timing (response delay) and amplitude of each tap were recorded. We then calculated the average tapping rate for each rate (1, 2, or 3 Hz) across taps performed with and without auditory cues. Subsequently, we determined the slope of the tapping rate for each finger across the 1 Hz, 2 Hz and 3 Hz conditions. The slope of the tapping rate indicated the ability to adapt the tapping rate to the target frequency of the cue. A slope = 1 indicates correct tapping rate, a slope < 1 slower execution (tapping rate, TR).
- multi-finger tapping task. This task assesses the ability to perform independent finger movements in one-finger and two-finger tap configurations. Independent finger movements are characterized by isolated movement execution (selection) in one finger while inhibiting movements in neighboring fingers not involved in the trial. Subjects were instructed to reproduce different finger tap configurations following the visual cue (Fig. 1C). Total trial duration was 2 s and visual force feedback was provided for 1s to assist correct selection of lead-finger. Subjects were instructed to prioritize correct finger selection and not to pay attention to level of force of taps. The configurations varied trial-by-trial (pseudo-randomized) and consisted of one-finger taps (separate tap of index, middle, ring or little finger) and two-finger taps (simultaneous index-middle, index-ring, index-little, middle-ring, middle-little or ring-little finger taps).

  The analysis of multi-finger tapping consisted of identifying finger taps (> 0.5N) and then categorizing taps as correct or incorrect in response to the displayed finger configuration, i.e., identical to or different from the required target taps during the 2 s trial duration. The selectivity index was based on the rate of correct target finger taps. Incorrect taps (not matching target taps displayed) in each finger were categorized as missing taps (omission taps), or as unwanted extra-finger-taps (UEFTs, one or several). Number of UEFTs from one-finger trials (not two-finger configurations) was analyzed in this study, and was used to indicate the degree of independence of finger movements (IFM).

Transcranial magnetic stimulation

Surface electromyography (EMG) recordings from the left and right first dorsal interosseus (FDI) muscles were obtained using Ag-AgCl electrodes using a belly-tendon montage. The EMG signal was amplified and band-pass filtered between 30 Hz and 1 kHz (Grass P511 amplifiers), and sampled at 2 kHz using CED Micro 1401 and signal software (version 6, Cambridge Electronic Design). TMS was applied separately to the ipsilesional and contralesional motor cortex using a figure-of-eight coil (7-cm diameter) connected to a Magstim 200 (Magstim, Whitland, UK). The coil was placed tangentially to the scalp and rotated 45 degrees away from the midline to induce current flow perpendicular to the central sulcus. We started searching for the ''hot-spot'', the area producing the largest amplitude MEP, at ~ 50% of the maximum stimulator output (MSO). If no MEP was found we increased MSO in steps of 10, to 100% MSO. Ten stimuli were applied at each level before increasing MSO. Stimuli were delivered with time intervals of 5 to 7 seconds. If no MEPs were found at rest the subject was asked to activate FDI to aid localization of hotspot. The coil position eliciting MEPs of the largest amplitude in the FDI muscle (the 'hot-spot') was marked. For the rest of the TMS experiment we ensured optimal 3D orientation of the coil with respect to the head using a neuronavigation system (Visor system, ANT Neuro, Enschede, Netherland). The resting motor threshold (MT) of the FDI muscle was defined as the lowest stimulus intensity that evoked MEPs of 50 μV amplitude in at least 5 of 10 trials [78]. A MEP was considered present when at least one MEP of ≥50 μV was recorded. A new hot-spot was identified at each session using the hot-spot location from the first neuronavigated TMS session, as the starting point for the hot-spot search.

Recruitment curves, showing how the MEP amplitude is affected by TMS intensity, describe the input-output properties of the corticospinal system [46]. Recruitment curves were obtained by calculating the mean amplitude of 5 MEP responses to stimulation at each 5% interval from 80 to 140% MT, in ascending order [12]. For each block of stimulus intensities, stimuli were delivered at varying time intervals of 5 to 7 seconds with the patient fully relaxed. Peak-to-peak MEP amplitudes (μV) were measured using off-line script (Signal software, Cambridge Electronic Design, www.ced.co.uk). The mean MEP amplitude for each stimulation interval was used to calculate the recruitment curves. The recruitment curve fits a sigmoid function [21]: $MEP(S) = MEP_{max}/1 + \exp[(S50-S)/m]$, where MEP_{max} represents the maximal MEP amplitude; S is the stimulator output intensity, S50 is S required to obtain 50% of MEP_{max}; m is the slope of the curve. MEP_{max} was obtained at high stimulation intensities and is considered to result from excitation of all target motor neurons [46]. The slope (m) of the recruitment curve is likely related to the strength of corticospinal projections [17]. These TMS parameters have been shown to have good reliability in stroke patients [58]. Recruitment curves were obtained from both the ipsilesional and the contralesional hemisphere (recorded in the contralateral hand only).

Magnetic resonance imaging (MRI)

Patients underwent a clinically routine 1.5T MRI scan 12—48 hrs post-stroke (GE Healthcare Medical System, Milwaukee, WI, USA) including (i) T1-weighted scans acquired with a sagittal gradient echo pulse sequence with the following parameters: FOV, 25.6 cm; matrix, 256×256, slice thickness, 5 mm, gap 0.5 mm; and (ii) a diffusion weighted imaging (DWI) sequence, consisting of a T2-weighted baseline image ($b = 0\,s/mm^2$) and the DWI ($b = 1000\,s/mm^2$), acquired with a single-shot echo planar spin-echo sequence with the following parameters: FOV, $24 \times 24\,cm^2$; matrix, 128×128; slice thickness, 6 mm, no gap; number of slices, 24; TE/TR, 81/6675 ms; 2 excitations; 53 s.

Construction of CST template. MRI in healthy subjects

In order to construct the CST canonical template a group of 18 healthy subjects (10 males, age 31.7 ± 8.2 years) underwent a 3T MRI (GE Healthcare Medical System, Milwaukee, WI, USA). DTI derived templates from younger healthy controls has been previously used for investigation of stroke-related CST damage [75]. Sequences included a three-dimensional T1-weighted inversion recovery fast spoiled gradient recalled MR sequence and a single-shot echo-planar spin-echo diffusion MR sequence. 3D T1-weighted inversion recovery MR acquisition parameters were as follows: FOV, $25 \times 25\,cm^2$; matrix, 256×256; slice thickness, 1.2 mm; number of slices, 140, TE/TI/TR, 4.3/400/11.2 ms. Diffusion MR scan parameters were as follows: FOV, $25.6 \times 20\,cm^2$; matrix, 128×128; slice thickness 3 mm; number of slices 40; TE/TR 100/5600 ms; one T2-weighted baseline image ($b = 0\,s/mm^2$); diffusion weighted images (DWI) 74 directions with b-value of $3000\,s/mm^2$.

Pre-processing, ROIs, and CST tractography

The DWI data from healthy controls were analyzed using the FMRIB Software Library (FSL 5.06, www.fmrib.ox.ac.uk/fsl). After being corrected for eddy current effects in FSL, diffusion data were re-sampled to 2-mm isotropic voxels using the Diffusion Imaging in Python module (http://nipy.org/dipy/; [30]). Skull stripping and estimation and fitting of diffusion parameters modelling two fibers per voxel were done using FMRIB's Diffusion Toolbox of FSL with bet2 [39] and bedpostX [6], respectively.

For each healthy control, the transformation from native DWI space into MNI space was computed with FSL by a two-stage registration using high-resolution T1-weighted image. First, a native diffusion to structural space transformation generated by an intra subject rigid body registration between skull stripped T2-weighted image and T1-weighted image using FLIRT [38], and second, a non-linear transformation between native structural and MNI space computed using FNIRT (template used: non-linear group average MNI 152 T1-weighted template, 2-mm resolution). In addition, the transformation from MNI space into native DWI space (inverse of the precedent transformation) was computed.

For tractography a set of regions of interest (ROIs) were defined in MNI standard space based on brain atlases available in FSL. Inclusion ROIs included: right and left precentral gyri ($z = 55$) using Harvard-Oxford cortical structural atlas; right and left posterior limb of internal capsule ($z = 5$); right and left superior cerebellar peduncles ($z = -24$) using the Jülich DTI-based white-matter atlas [63]; and pons ROI ($z = -28$) covered anteromedial pons in accordance with the anatomical location of the CST, similar to previous studies [94]. Exclusion ROIs included: middle sagittal brain stem and middle sagittal corpus callosum using the Harvard-Oxford subcortical structural atlas [20,27]. For each subject, ROIs were transformed into native DWI space using the previously defined non-linear transformation and manually corrected in MRIcro [76], using fractional anisotropy and T1-weighted images in order to best match each subject specific anatomy.

For each healthy control subject, probabilistic tractography of the CST was performed in each hemisphere using Probtrackx2 [6] with pons ROI as seed region (5000 streamlines initiated from each seed voxel) and posterior limb of internal capsule and precentral gyrus ROIs as waypoints. An exclusion mask including the middle sagittal corpus callosum and brain stem, middle cerebellar peduncle, superior cerebellar peduncle and contralateral precentral gyrus ROIs was applied to exclude cerebellar and interhemispheric fiber tracts. Resulting CST tracts were then normalized into MNI space using the transformation between native DWI and MNI space described earlier. A threshold of 5% of the path distribution estimates was applied to each CST tract to remove improbable pathways [70]. For each hemisphere, CST tracts of all healthy controls were then binarized and summed up to create the CST template.

Lesion mapping and weighted corticospinal tract lesion load computing

Lesion maps were manually drawn on DWI in MRIcro [76] by a researcher blinded to all clinical data except the side of the stroke. Lesion location was verified on T1 and FLAIR images whenever possible and questionable location was verified by a neurologist with experience in stroke imaging (JCB). For each patient, the lesion map was normalized using the computed transformation between native DWI and MNI standard space. The transformation between native DWI and MNI space was generated by a linear affine registration (12 degrees of freedom) between T2-weighted baseline image and T2-weighted SPM 12 brain template with 2-mm isotropic voxels (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; www.fil.ion.ucl.ac.uk/spm/software/spm12/). Before the registration, skull stripping of T2-weighted baseline image was done using FSL (bet2 tool) and SPM12 brain template was masked by the dilated MNI T1-weighted brain mask of FSL. Visual inspection of well-known anatomical landmarks (e.g., commissures, corpus callosum, central sulcus, lateral ventricles and outer borders of the brain) was done for each subject in order to detect potential normalization problems.

The weighted CST lesion load (wCST-LL) was calculated [26,94] by computing the overlap between a patient's lesion and the CST template. This method evaluates CST integrity and corrects for the narrowing of the CST when descending from the motor cortex to the pons: for each slice the CST-lesion overlap was weighted by the ratio of the maximum cross-sectional area of the CST over the cross-sectional area of that specific slice. We validated our procedure by comparing wCST-LL values derived by our method to those from a previously published study using the same population

Table 2 Clinical measures of upper limb impairment and assessment of manual dexterity.

Patient	Visit	NIHSS (0—42)	FM-UE (0—66)	FM-UE hand (0—14)	MaxF (kg)		MPUT (s)		Thumb-index tapping (#taps)[b]		FFM tasks performed
					Unaff	Aff	Unaff	Aff	Unaff	Aff	
#1	W2	0	26	6	20	14	13	[a]6 obj	47	0	FFT, SFT, MFT
	M3	0	64	14	24	16	15	16	55	34	FFT, SFT, MFT
	M6	0	58	14	24	19	12	13	55	38	FFT, SFT, MFT
#2	W2	7	0	0	40	0	16	—	48	0	
	M3	2	60	14	38	16	15	24	48	40	FFT, SFT; MFT
	M6	2	62	14	39	17	17	26	48	42	FFT, SFT, MFT
#3	W2	8	0	0	19	1	30	—	55	0	
	M3	5	19	5	21	2	18	—	55	0	
	M6	5	13	4	25	14	14	19	55	17	FFT
#4	W2	5	0	0	12	2	19	[a]1 obj	37	21	
	M3	1	54	14	15	3	16	22	37	33	FFT
	M6	1	40	9	17	4	16	36	37	28	FFT
#5	W2	0	50	4	30	6	14	[a]2 obj	50	11	FFT, SFT
	M3	0	54	13	30	16	12	20	50	38	FFT, SFT, MFT
	M6	0	56	14	33	23	15	18	50	34	FFT, SFT, MFT
#6	W2	10	0	0	31	0	21	—	60	0	
	M3	8	0	0	35	0	23	—	60	0	
	M6	8	0	0	38	0	16	—	60	0	

NIHSS: National Institute Health Stroke Scale; FM-UE: Fugl-Meyer Upper-Extremity Assessment; FM-UE hand: Fugl-Meyer Upper-Extremity hand assessment; W2: 2 weeks post-stroke; M3: 3 months post-stroke; M6: 6 months post-stroke; Unaff: unaffected side; Aff: affected side; obj: number of objects displaced in 60 s; FFT: Finger Force Tracking; SFT: Single Finger Tapping; MFT: Multi Finger Tapping. Note that FFM tasks were not performed by all subjects at each points (details provided in Results).

[a] Could not move all 12 objects within 60 s.

[b] Normal range in healthy controls of comparable age: right hand mean 51 ± 5, left hand 45 ± 5 [15].

of 52 stroke patients but a different CST template derived from age-matched healthy controls [41]. Our wCST-LL values correlated closely with those found by these authors ($R^2 = 0.94$, $P < 0.001$), although the slope of the linear regression diverged from identity (slope = 0.775, offset = 0.011; Pearson correlation), most likely reflecting the different CST canonical template used.

Statistical analysis

In this pilot report using a small sample, we performed a qualitative analysis of individual changes in clinical measures, in quantitative measures of manual dexterity components, and presence and size of MEPs over time. In order to compare performance in FFM tasks to healthy controls of similar age we used previously published Z-scores (control group's mean + 2SD; 11). Values exceeding a Z-score of 2 were considered indicative of abnormal performance.

Results

Clinical data

All patients were recruited from the Sainte-Anne hospital Stroke Unit, and received conventional acute care. Patients #2, #3, #4, and #6 were admitted to hospital-based inpatient neurorehabilitation after acute care, while patients #1 and #5 underwent outpatient physiotherapy sessions after hospital discharge. Two patients were females and the age of the patients ranged from 50—79 years (mean ± SD = 66 ± 10 years). Depression was monitored with the Montgomery

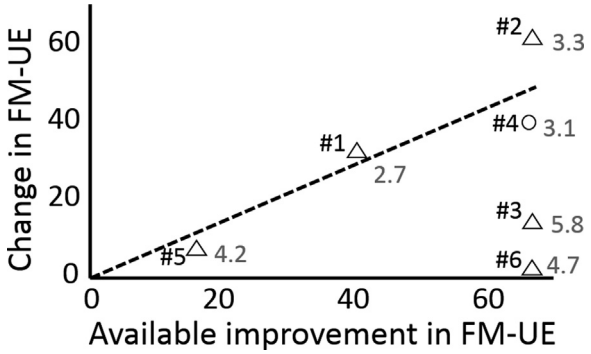

Figure 2 FM-UE recovery (change from W2 to M6) in relation to available improvement in FM-UE (66-FM-UE scores at W2) in patients with early MEPs (circles) and patients without early MEPs (triangles). Each patient's weighted CST lesion load value (cc) is indicated in gray. Patients #1, #2, #4 and #5 achieved expected ~ 70% of total possible FM-UE recovery (dotted line). However, patients #3 and #6 without early MEPs and with highest CST lesion load did not show such 'proportional recovery'.

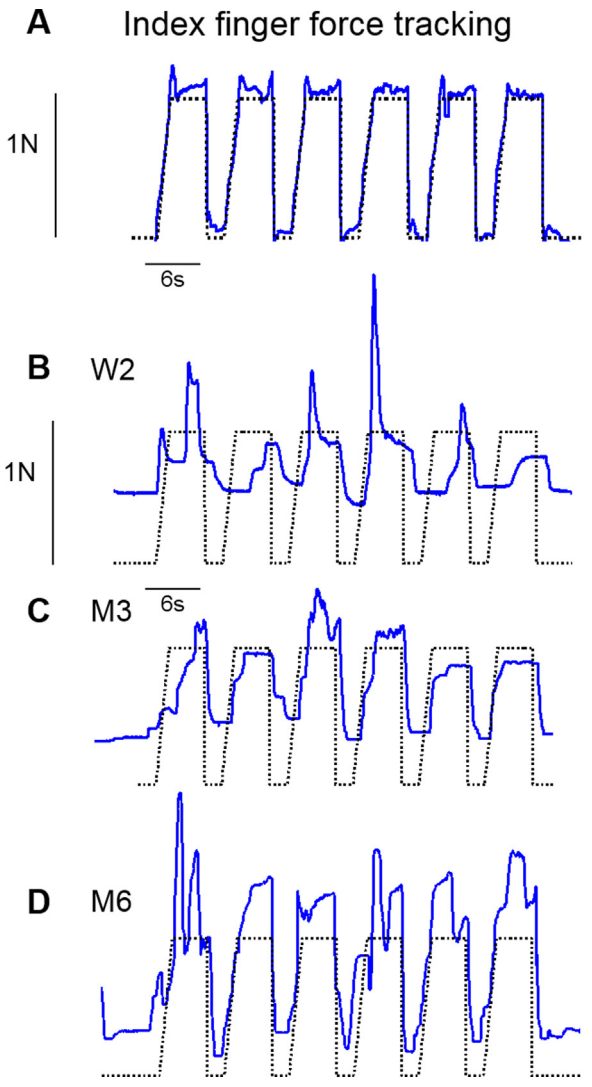

Figure 3 Index finger force tracking performance (blue) across six ramp-and-hold 1N trials (dotted line = target force) in a 60-year-old healthy control subject from previous study (11) (A) and in patient #1 (B—D, at time points W2, M3 and M6, respectively). Over time, tracking accuracy improved (particularly during the ramp phase), as did the ability to release force to baseline between trials (B—D).

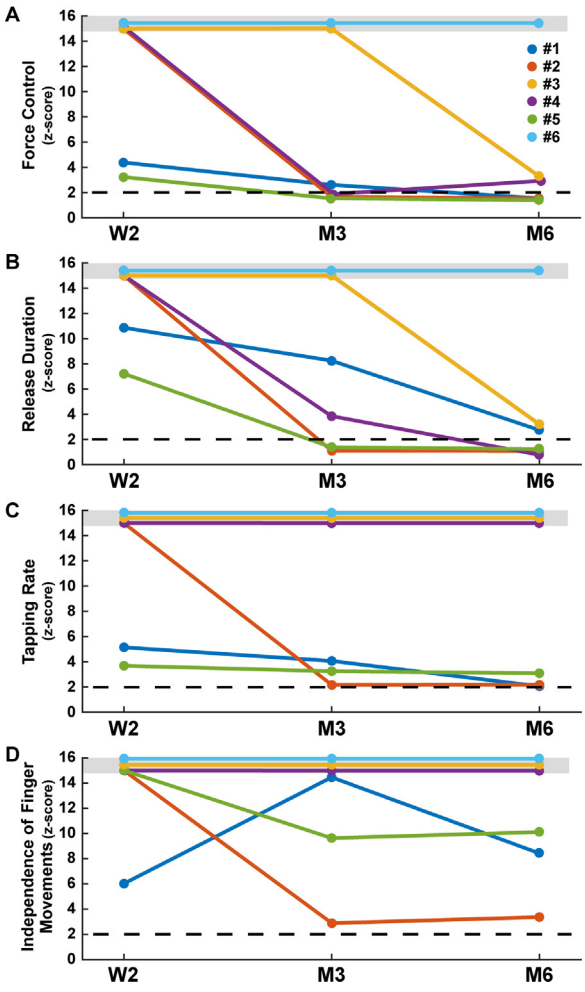

Figure 4 Individual manual dexterity recovery profiles in stroke patients. A. Longitudinal force control performance in patients with all patients showing improvement (reduced tracking error over time) except patient #6. Tracking error is shown in relation to performance previously found in healthy controls of comparable age (Z-scores; 11). Values in grey shaded zone depict abnormal performance (Z score > 2). Patients #1, #2 and #5 achieved normal tracking error at M6. Values in grey-shaded zone (Z-score ≥ 15) indicate patients unable to perform the FFM task. B. All patients also improved in time taken to release force (release duration) and patients #2, #4, and #5 showed values within normal range (Z-score < 2) at M6. C. Capacity to adapt tapping rate across 1, 2 and 3 Hz. Again values are shown as Z-score of performance in healthy controls. Although values improved over time (most dramatic in patient #2) all patients remained in abnormal range (Z-score > 2) at M6. D. Independent finger movements (measured in terms of unwanted extra finger taps) showed some recovery in patients #2 and #5 (from W2 to M3) and in patient #1 (between M3 and M6). However, performance remained markedly abnormal in all patients at M6 indicating poor ability to isolate selective finger movements in stroke patients.

Asberg Depression Scale [62]. Clinical and demographic details are shown in Table 1.

In the sub-acute phase (W2, mean = 10 days), all six patients had, as per protocol, moderate-severe arm and hand motor impairment, as indicated by low maximal grip force and FM-UE hand scores (Table 2). Manipulation of small objects in the MPUT was severely impaired ($n = 3$ patients) or impossible ($n = 3$, Table 2). Four patients were unable to perform index-thumb tapping, and two were able but performance was severely impaired (patient #4 and #5, Table 2).

All patients, except #6, showed clinically significant upper limb recovery over the six-month period (i.e., FM-UE improvement from W2 to M6 > 5; Fig. 2). The most pronounced recovery occurred in the early phase (W2to M3) with five patients improving their FM-UE hand scores and four improving their grip strength. In the later phase (M3 to M6) only patient #5 improved in FM-UE hand score and patient #1 and #5 improved in strength (Table 2). The occasional slight decline seen in some scores from M3 to M6 is a frequent observation following discharge to home. No patient developed depression at any time-point

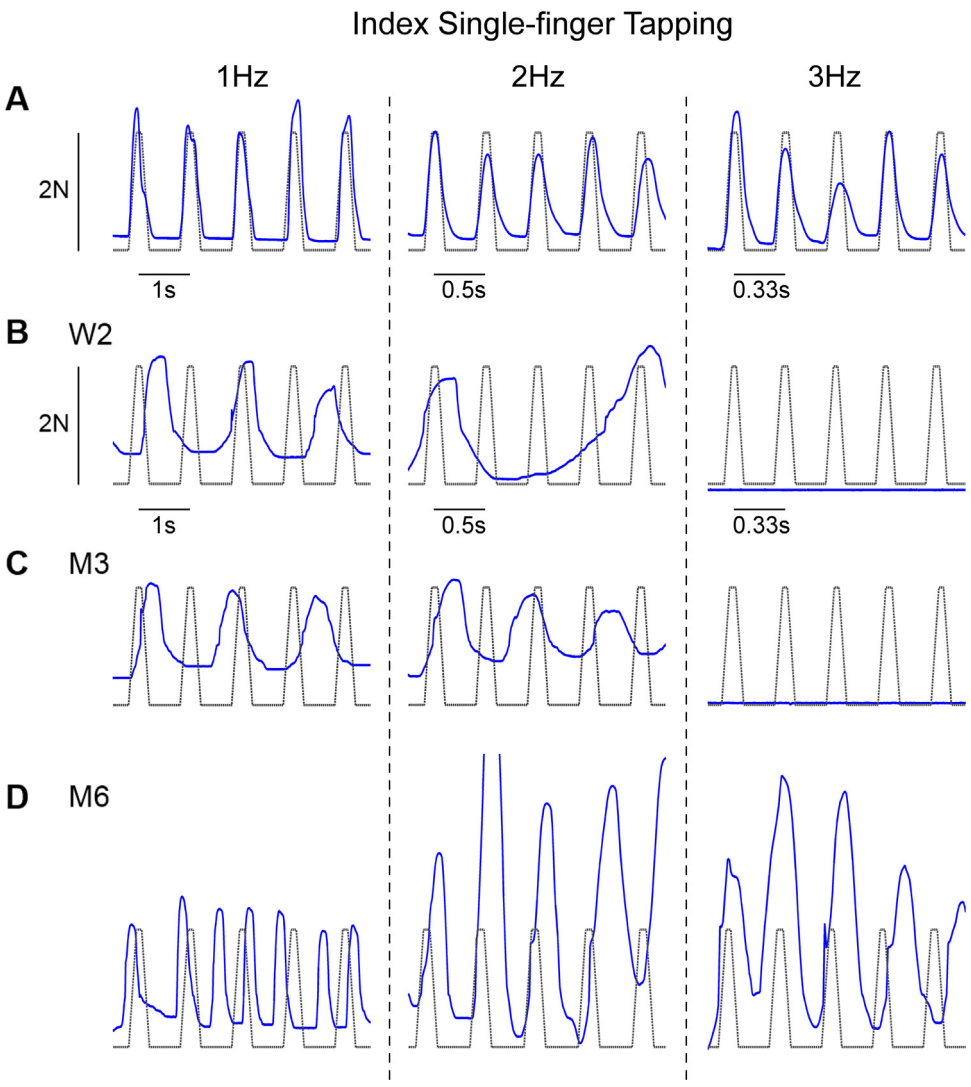

Figure 5 Index single finger tapping performance (blue) at three rates with auditory cue at 1, 2 and 3 Hz (from left to right; beeps indicated by up-strokes of the black line). Subjects were instructed to tap in time with the beep. A. Performance in a 60-year-old healthy control subject showing good ability to perform taps at different rates. B—D. Performance at two weeks (W2), three months (M3), and six months (M6) in patient #1. At M6, ability to tap at 1 Hz recovered clearly, though partially increased rate but still poor timing. However, performance remained impaired at 2 and 3 Hz with slowed high-force tapping.

(Montgomery Asberg Depression Scale < 16/60). As illustrated in Fig. 1, Patients #1, #2, #4 and #5 achieved expected ~ 70% of total possible FM-UE recovery (dotted line), but patients #3 and #6 (without early MEPs in affected hand on ipsilesional TMS and with highest CST lesion load, see below) did not show such 'proportional recovery' [49].

Finger Force Manipulandum tasks

Due to moderate-severe upper limb impairment, some patients were unable to perform some or all FFM tasks at one or several time points. By M6, five patients were able to perform the force-tracking task and three of these patients also performed the single and multi-finger tapping tasks (Table 2).

Force tracking

Fig. 3 illustrates the performance (single-trial raw data) of a control subject and of patient #1 at W2, M3 and M6. Fig. 4A shows the longitudinal evolution of tracking performance. At W2, four patients were unable to perform the task with the index or middle finger. In the two patients who achieved the task, tracking error exceeded normal range, i.e., Z score > 2 (Fig. 4A). At M6, patients #1, #2 and #5 showed error within normal range (Z score < 2). Of the five patients that recovered in this task, four showed more improvement in the early phase (between W2 and M3) compared to late phase (M3 to M6) (Fig. 4A). Release duration, indicating time taken to release finger force, also improved in five patients (patients #1—#5) and at M6 patients #2, #4, and #5 had release duration within normal range (Fig. 4B).

Single finger tapping

Fig. 5 illustrates performance across three rates (1, 2 and 3 Hz) in a control subject and in patient #1. Only three of six patients were able to perform the single finger tapping tasks

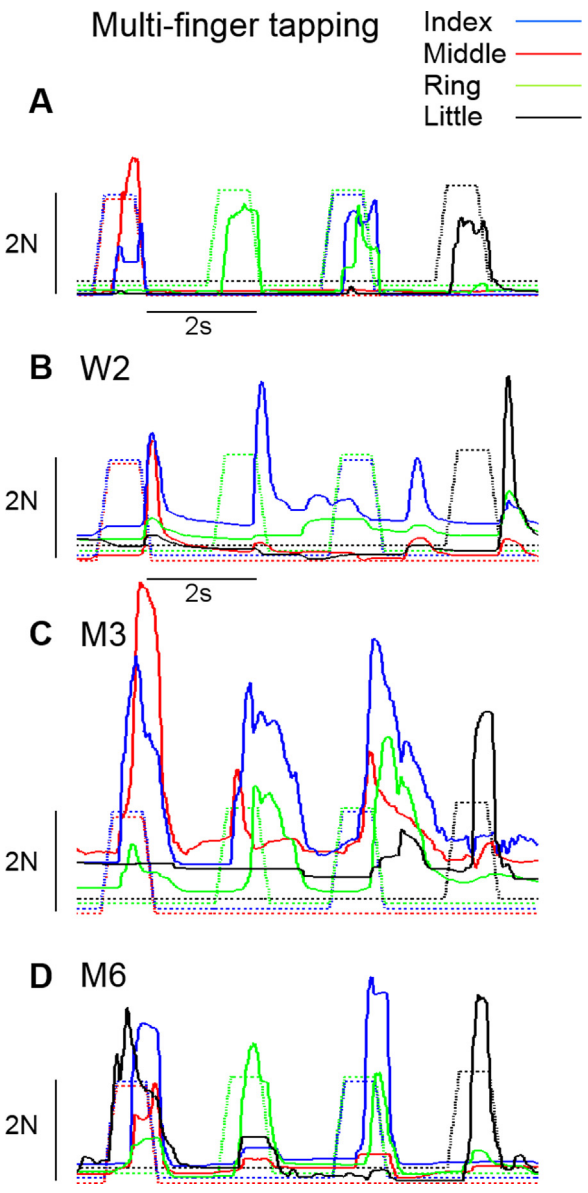

Figure 6 Multi-finger tapping performance in a 60-year-old healthy control subject (A) and in patient #1 (B—D, at W2, M3 and M6). These four trials represent, from left to right, a two-finger tap (dotted lines, index finger-blue together with the middle finger-red), a single finger tap (ring finger-green), a two-finger tap (index finger-blue together with the ring finger-green), and finally a single finger tap (little finger-black). The control subject (A) clearly tapped simultaneously with the two correctly selected fingers in the two-finger trials, and activated the correct finger during single finger trials. In all four trials, activation of non-target fingers was minimal. In patient #1 (B—D) the performance of single finger taps improved over time. For example, in trial two requiring a single finger tap of the ring finger (green): at W2 the patient tapped with the wrong finger (index, blue); at M3 (C) she tapped with the correct ring finger (green dotted), but also with the index (blue) and middle finger (red). At M6 (D), she tapped more distinctly and correctly with the ring finger (green; unwanted extra finger taps were clearly reduced). Qualitative improvement over time was less evident for the two-finger trials.

across all three-time points. Although the slope of the tapping rate improved, all the values at M6 were still affected (e.g., Fig. 5D). Again, recovery was more marked in the early phase (between W2 and M3) in two of the three patients (Fig. 4C). Qualitatively, task performance mirrored thumb-index finger tapping speed, with faster tapping in the three patients who could perform the single finger-tapping task (Table 2).

Multi-finger tapping

Fig. 6 shows four successive trials in a control subject and in patient #1. This illustrates that selective activation of certain digits, and simultaneous inhibition of others, leading to IFM, was hampered. In patient #1, the selectivity index (correct target finger tap) improved from 0.44 at W2 to 0.96 at M3. Patient #2 and #5 showed good selectivity on first performance of task at M3 (> 0.96). The number of errors (UEFTs) decreased in patients #2 and #5 and increased in patient #1 (Fig. 4D). However, performance was still impossible or impaired (Z-score >2) in all patients at M6 (Figs. 4D and 7C). Again, recovery was more pronounced in the early phase in both patients who showed improvements in this task.

CST lesion and MEPs

The CST was affected in all six patients (Fig 7A). Maximal overlap of the lesion with the CST occurred usually at the internal capsule (patient #3—#6) or at the brain stem (patient #2). The wCST_LL ranged from 2.7 to 5.8 cc.

Functional integrity of the CST was dramatically affected at W2, with absence of MEPs in affected hand on ipsilesional TMS in all patients except one (patient #4; Fig. 7B). However, MEPs were detectable in three patients at M3, and in four at M6. In the three patients in whom the MEP presence had recovered at M3 and M6, the motor threshold decreased and the maximal MEP amplitude increased over time (Table 3). However, MEPs tended to be polyphasic (e.g. patient #4 at M6, #2 at M3, Fig. 7B) and were smaller than those evoked from the contralesional hemisphere (Table 3). Patient #3 and #6, with greatest CST damage, failed to show any recovery of CST excitability, with absence of MEPs up to M6. Patients #1, #2, and #4, who had low structural injury to CST (< 4 cc), also showed earliest recovery in CST excitability with MEPs present at M3 (Fig. 7).

Qualitative relations between corticospinal tract injury and recovery

Two patterns of recovery were apparent in this study. Good recovery in strength, gross upper limb and hand movements, simple gripping and finger force control occurred in all four patients with low CST lesion (wCST_LL $\leq$ 4.2 cc, patients #1, #2, #4, and #5; Fig. 7A), who also showed recovery of CST excitability (see Trend, Table 3). Poor or no recovery of these clinical measures occurred in the two patients (#3 and #6) with wCST_LL > 4 cc, who also had no MEPs in the affected hand on ipsilesional TMS throughout the entire follow-up. Interestingly, the former group achieved expected ~ 70% of total possible FM-UE recovery, whereas the latter group did not show such 'proportional recovery' (Fig. 2).

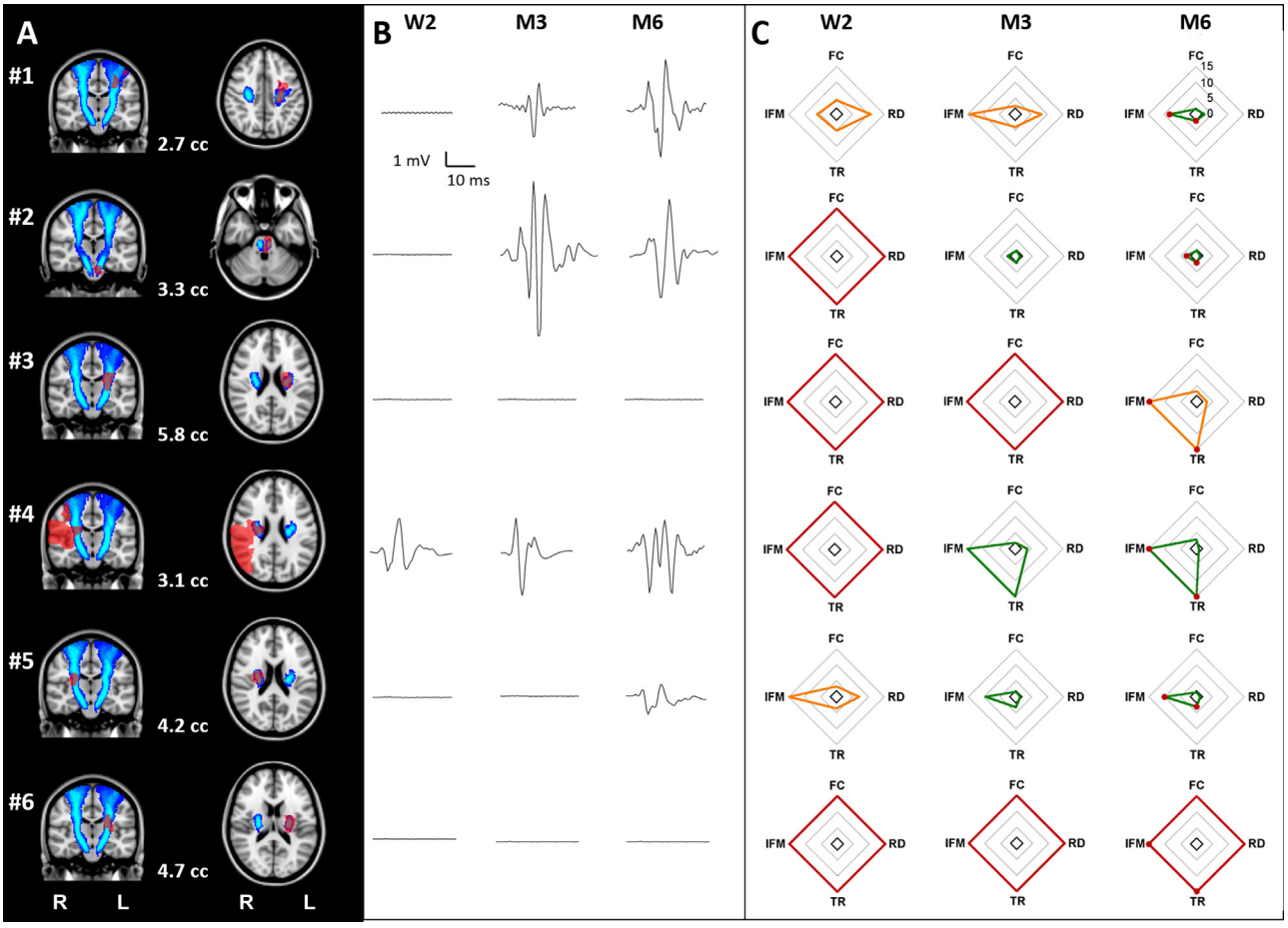

Figure 7 Corticospinal tract (CST) injury and recovery of dexterity. A. Illustration of the weighted CST lesion load (wCST-LL) measurement in each patient (#1—#6, from top to bottom) at W2 with corresponding wCST-LL volume (cc). Coronal and axial slices depict maximal overlap between lesion (red) and probabilistic canonical CST template (blue). B. Single maximal MEP examples in the affected hand shown at each time point for each patient. Note: flat line indicates absence of MEP at 100% stimulator output. C. Radar plots show longitudinal recovery profiles of dexterity components including measures from three FFM tasks: accuracy of force control (FC), ability to quickly release generated finger force (RD = release duration), slope of the tapping rate (TR), and measurement of unwanted extra finger taps indicating independence of finger movements (IFM). All values are given according to Z-scores from healthy controls ($n = 10$). Z-scores > 2 are considered indicative of pathological performance. A score of 15 was assigned when a patient was unable to perform a given task. Red profiles in radar plot indicate inability to perform any of the three FFM tasks. Yellow profiles indicate the ability to perform some tasks but with pathological performance. A green profile indicates normal performance level in at least one measure. Persistently abnormal values in TR and IFM at M6 are indicated by red dots.

Regardless of these overall upper limb recovery patterns, however, no patient recovered more complex dexterity components, particularly single-finger tapping rate and independence of finger movements (see red dots in Fig. 7C at M6). This was the case even in patients #1, #2 and #5, with highest MEP_{max} and who were able to perform the tasks at M6.

Discussion

Although involving only a small sample, this pilot study is the first to provide a longitudinal multi-component characterization of manual dexterity and its recovery in stroke patients. This recovery was qualitatively related to CST lesion load and to longitudinal TMS measures of CST excitability. Although the present findings will need to be replicated in a larger sample before definitive interpretation, descriptive results from the six stroke patients studied will be discussed below.

In agreement with earlier reports [26,94], the four patients with lowest CST damage recovered satisfactory global upper limb motor function (including gross hand movements and simple gripping function), reaching the expected degree of recovery according to the ''70% proportional recovery rule'' (Fig. 2) [85]. These patients showed this recovery despite absence of MEPs at W2, consistent with previous reports that absence of early MEPs post-stroke may not always be associated with poor recovery [13]. Increase in corticospinal excitability, indicated by presence of MEPs in the affected hand on ipsilesional TMS, by lower motor thresholds, and by increased MEP_{max} values over time, occurred in parallel with global motor recovery (in terms of

Table 3 TMS and its evoked contralateral responses: resting motor threshold and maximal MEP amplitude in patients over time, with overall trend shown with blue arrows.

	W2		M3		M6		Trend
Patient #	Unaffected side	Affected side	Unaff. side	Affected side	Unaff. side	Affected side	Affected side
1							
Motor threshold	65%	NO	66%	89%	42%	61%	↘
MEP_{max} (μV)	392	NO	441	303	987	904	↗
2							
Motor threshold	57%	NO	46%	73%	46%	61%	↘
MEP_{max} (μV)	841	NO	999	399	761	949	↗
3							
Motor threshold	41%	NO	50%	NO	46%	NO	→
MEP_{max} (μV)	NA	NO	264	NO	333	NO	→
4							
Motor threshold	53%	58%	50%	49%	58%	46%	↘
MEP_{max} (μV)	772	206	276	255	NA	382	↗
5							
Motor threshold	49%	NO	51%	NO	49%	87%	↘
MEP_{max} (μV)	789	NO	614	NO	529	512	↗
6							
Motor threshold	43%	NO	37%	NO	48%	NO	→
MEP_{max} (μV)	971	NO	611	NO	NA	NO	→

W2: 2 weeks' post-stroke; M3: 3 months post-stroke; M6: 6 months post-stroke; NO: no measurable MEPs; NA: data not available for recruitment curve measurement. Trend: up ↗, down ↘, stable →. Note: RMT and MEP_{max} were obtained at new hot-spot locations at each session. MEP_{max} was defined as maximal response from recruitment curves.

strength, FM-UE hand and finger force control). Conversely, the two patients with highest CST lesion load and absence of MEPs even by M6 showed less or no recovery, i.e., they would belong to the previously identified 'outliers' of the 70% rule, those with severe initial deficit, absent early MEPs and larger CST lesions [13]. Nevertheless, some recovery over time was also apparent despite absence of MEPs, suggesting recruitment of alternative motor pathways. However, the salient observation from this study is that recovery of key components of manual dexterity, such as finger tapping rate and independence of finger movements, was poor in all patients, regardless of global upper limb recovery.

Partially enhanced corticospinal excitability is not sufficient for recovery of manual dexterity

Adaptation of finger tapping rate (single finger tapping task) and ability to isolate single finger movements (multi finger tapping task) was incomplete (in patients #1, #2 and #5) or absent (in patients #3, #4 and #6) at six months, which contrasted with good recovery in gross motor hand movements overall. As Fig. 4 clearly illustrates, our patients showed considerable recovery in the finger force-tracking task at six months with accuracy of force modulation in the normal range (in patients #1, #2 and #5) and release duration in the normal range (in patients #2, #4, and #5). Patients #1 and #5 showed good recovery of maximal power-grip strength (force > 70% of unaffected side), achieved full FM-UE hand scores and performed MPUT in < 19 s suggesting normal precision grip performance. Despite this substantial functional recovery these two patients showed poor dexterous performance in single- and multi-finger tapping tasks (even when the dominant hand was affected, e.g., in patient #1). This therefore suggests that deficits in high-level finger control, requiring good manual dexterity, may persist in patients despite good recovery in gross hand movements and grasping abilities. Our findings suggested qualitative improvements in corticospinal excitability over time in four patients but excitability recovered only partially, with higher motor thresholds, lower maximal MEPs, and lower slopes in recruitment curves than those found on the unaffected side. MEPs were usually polyphasic, further suggesting altered CST conduction.

Some previous studies also showed that upper limb strength and gross motor function may more closely relate to CST integrity than does dexterity. A study reported slower recovery of dexterity (measured with Nine Hole Peg Test, NHPT) than more proximal strength and simple grasp movements (measured with ARAT) [86]. TMS measures of corticospinal excitability correlated more consistently with ARAT than with NHPT scores suggesting a closer relation between TMS measures and gross motor function [86]. Similarly, a TMS study in 23 chronic stroke patients showed that MEP amplitudes and motor thresholds correlated with hand strength but not with clinical measures of dexterity [88]. Our findings also agree with a recent study on recovery of finger strength and finger individuation after stroke in 54 hemiparetic stroke patients, which showed a similar initial time course of recovery in finger strength and individuation [93]. However, late improvements in strength did not correlate to recovery in individuation (after patients had recovered 60% of maximal strength). The authors interpreted the

divergence in strength and individuation recovery as a reflection of partially separable neural systems. Thus, independence of finger movements requires fractionation of multiple muscles (i.e., muscle specific timing and activity) thought to be provided by direct monosynaptic corticospinal connections [7], and functional MRI studies show that cortical control of finger force and individuated finger movements differs. Generation of small precision grip forces increases activation in sensorimotor circuits (ventral premotor cortex, prefrontal area 44, rostral cingulate motor area, and areas of the intraparietal cortex) compared to large forces [23]. And individuated finger movements correlate to finger-specific activity patterns in sensory-motor cortex [24,81]. Taken together with our findings, it seems likely that regaining corticospinal function [41,86] together with discrete motor cortex activation [24,81] and enhanced processing in sensorimotor circuits [23] is essential for a full recovery of manual dexterity after stroke, including independent finger movements. We cannot rule out a contribution of prefrontal cortical networks. Although patients did not have any clinical cognitive deficits, subtle impairments in executive functions (e.g., attention and working memory) could have contributed to poorer performance in high-level dexterity tasks [64].

Recruitment of alternative motor pathways

Only one patient had MEPs at two weeks post-stroke. Absence of MEPs in the early phase has been related to poor upper limb recovery after stroke [16,18,19,25,34,84]. A systematic review [36] reported that presence of a MEP early after stroke was a good predictor of upper limb strength recovery (measured according to MRC scale). However, we found that three patients without early MEPs did show substantial recovery of gross motor hand movements and simple grasping. Two patients also showed improved motor function between time points without MEPs re-appearing. This was the case for patient #3 who did not recover any MEPs (at any time point) but did show improvements from two weeks to six months in maximal grip force (7% to 56% of unaffected side), in FM-UE hand score (from 0 to 4 points) and even in MPUT (from unable to perform to 19s). Patient #5 did not recover MEPs by three months but improved in maximal grip strength (20% to 53% of unaffected side), in FM-UE hand score (from 4 to 13 points) and in MPUT (from 14 s to 12 s). Other CST projections (to other upper limb muscles than FDI) or alternative descending motor pathways are likely implicated in this recovery. A partial substitution for a non-functioning CST may occur by corticospinal projections descending from contra-lesional hemisphere [5], or enhanced use of reticulospinal or propriospinal tracts [4,89]. However, the recruitment of such alternative pathways does not lead to complete recovery of dexterity [89], which could explain why the above patients failed to recover some of the components of manual dexterity.

Clinical measures fail to detect deficits in manual dexterity

Four patients (#2, #3, #4, and #6) had FM-UE ≤ 10 at two weeks, considered to reflect severe impairment [22,91]. Even though all patients also had early moderate-severe impairment on the hand subsection of FM-UE (< 7/14), three (#1, #2, and #5) showed full recovery in this domain during follow-up. This likely reflects a ceiling effect of the FM-UE scale rather than a complete recovery of hand and finger motor function [31]. Indeed, these three patients (along with the other three) had persistent impairment in both adaptation of tapping rate and IFM. This illustrates the limited value of the FM-UE whenever studying manual dexterity after stroke. Likewise, other commonly used measures such as the Action Research Arm Test (ARAT) or the Wolf Motor Function Test also fail to quantify dexterity [79]. Maximal finger tapping rate and IFM capture other aspects that relate to hand function [14,15,87,93]. Although weakness has been shown to be the strongest predictor of hand function recovery [9,43,50], recovery of independent finger movements also correlates positively with hand function recovery [50,51].

Given its functional importance, reduced independence of finger movements may contribute to poor spontaneous hand use. Stroke patients have been reported not to properly use their affected hands even if capable [83], and improved upper limb function can occur without enhanced spontaneous hand use [73]. It is well established that stroke patients tend to under-use the affected hand, a phenomenon coined 'learned non-use' [92]. A deleterious consequence of non-use is that the affected hand receives less sensory input and patients likely have reduced attention to sensory stimuli to the affected hand (reflecting subclinical sensory extinction). Decreased attention to the hand could lead to reduced activity in cortical sensorimotor networks over time [55]. Future studies should investigate whether the degree of IFM impairment is related to spontaneous use of the hand outside the clinical setting.

The present findings suggest a need to develop rehabilitation approaches specifically targeting high level of control of finger movements. Intensive grip training in macaque monkeys recovering from experimentally induced motor cortex lesions, with up to thousands of daily repetitions over multiple weeks, fully restored precision grip [65], emphasizing the need for intense and targeted rehabilitation interventions. Preliminary findings in healthy elderly people suggest that training of independent finger movements can improve the ability to perform daily dexterous manipulation tasks [74]. Some studies also suggest enhanced efficacy of approaches targeting finger, rather than upper limb training in stroke patients [1,28,90].

Limitations

This was a pilot, proof-of-concept study performed in a small, although well-characterized sample, and the findings will need to be confirmed in larger samples and with group statistics. A larger sample would also allow study of whether recovery profiles relate to lesion size or age of stroke onset or differ between dominant and non-dominant sides or according to lesion side. Nonetheless, the approach adopted here allowed for a detailed description of individual profiles of recovery of manual dexterity components, highlighting differences that are often neglected in larger sample protocols. Another limitation was task feasibility:

this study showed that patients with moderate-severe motor impairments had considerable difficulty in performing some of the FFM tasks. The force-tracking task was the easiest to apply, and even patient #3 with large CST lesion and no MEPs could achieve it. A multi-component dexterity assessment, including single and multi-finger tapping tasks, would appear better suited in patients with mild-moderate impairments. Given that patients were included in an acute neurovascular unit, content or frequency of rehabilitation provided were not available. Three patients received fluoxetine (Table 1) which may have affected recovery of manual dexterity [59], or perhaps MEPs as well. Reliability of FFM measures in stroke have not been established yet, and caution is needed in interpreting changes of performance over time. However, learning likely did not contribute to change in manual dexterity components over time since (i) the changes across time points were larger than those observed within-session [78] and (ii) the sessions were not sufficient in number and too far apart in time for motor learning. Another limitation concerns TMS-induced MEPs post-stroke, which may vary to a large extent in about 25% of chronic stroke patients [45]. Recruitment curve measures have also been shown to vary greatly on repeated sessions and a larger number of stimulations (10 or more) at each MSO% intensity would have enhanced accuracy of our measures [80]. Nonetheless, good reliability has been reported for evaluation of presence of MEPs in subacute stroke suggesting reasonable robustness of our main results (Fig. 7) [37]. We collected MEPs in ascending, not random, order which may have affected results. Finally, we did not investigate how the lesion affected other descending motor pathways arising from premotor or parietal areas [82], or other pathways such as the reticulospinal [5,89] or propriospinal [14,44] pathways. We limited our search to M1, where the largest part ($\sim$ 50%) of the CST fibers originate [33]. M1 CST fibers have stronger connections to upper limb motoneurons than those arising from premotor areas [60]. Advances in DTI analysis techniques should allow extension of lesion load calculation to CST fibers arising from premotor and parietal cortices [3], i.e., areas of special interest for visuo-motor control.

Disclosure of interest

MT, MAM and PGL have patented the method for multidimensional measurement of manual dexterity (EP2659835A1, WO2016184935A3) but do not own the commercialization rights. The other authors report no financial interests and declare that they have no competing interest.

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