OXFORD UNIVERSITY PRESS | Brain

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Journal:	*Brain*
Manuscript ID	Draft
Manuscript Type:	Letter to the Editor
Date Submitted by the Author:	n/a
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Subject category:	

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Letter to the Editor: Further evidence for a non-cortical origin of mirror movements after stroke

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1467 words

Ejaz et al (Ejaz *et al.*, 2018) are to be commended for showing no evidence for a cortical origin of post-stroke mirror movements (MMs). Using functional MRI (fMRI) during affected-finger presses in recovering adult-onset stroke patients, they found no consistent relationship between contralesional sensorimotor cortex (cSM1) activation and quantitative indices of MMs; specifically, MMs were not linked to the presence of cSM1 overactivation, arguing against the 'transcallosal' mechanism classically believed to cause MMs (Di Pino *et al.*, 2014). We wish to report findings, previously published in abstract form (Calautti, 2008), fthat urther support the idea that MMs are not cortically mediated. We also present data that confirm that MMs can involve the affected hand when patients move their unaffected hand, also argueing in favor of a disrupted, bilaterally-organized system.

In the present prospective study, MMs were quantified by means of tri-axial accelerometry (TAA) permitting simultaneous recording of the moving and contralateral homologous index fingers during auditory-cued 1.25Hz, non-forceful index-thumb (IT) tapping (Calautti *et al.*, 2006). fMRI was obtained during the same motor paradigm.

Twenty-five patients (mean age 63yrs; 5 women; 19 subcortical strokes; mean time since stroke onset: 6 months, range 17d-46m), partially recovered from left (n= 13) or right (n= 12) hemiparesis, were prospectively recruited according to the following criteria: i) first-ever ischemic stroke; ii) acute-onset hand motor deficit (MRC ≤3/5) lasting ≥1 week; iii) right-handedness; iv) age >40yrs; and v) ability to perform the above-described motor task. Exclusion criteria were: i) cognitive impairment impeding full cooperation; ii) previous stroke, including lacunar infarction or significant white matter small vessel disease (Fazekas score >2) on brain MRI; iii) proprioceptive deficit on clinical examination; iv) current medication potentially interfering with motor function, such as psychotropic agents; and v) normal cerebrovascular response on breatholding trancranial Doppler. All patients

received standard rehabilitation only. The Cambridgeshire Regional Ethics Committee approved the protocol, and all patients gave written informed consent. All patients underwent clinical scoring, TAA recording and fMRI on the same day. TAA was acquired in all 25 pts, and fMRI was available in 20 patients.

To quantify neurological deficit, we used the European Stroke Scale (ESS), which is heavily weighted towards motor deficit, including the distal upper limb and hand (Hantson *et al.*, 1994). In addition, the maximum number of IT taps in 15s (IT-Max) for the affected hand (Calautti *et al.*, 2006, Calautti *et al.*, 2007) was obtained; the instruction was to tap as fast as possible whilst keeping the rate as regular as possible.

TAA was also obtained in 28 healthy subjects (mean age 42yrs; range 18-79), including 13 subjects, age-matched to the stroke sample, who also underwent fMRI.

Light tri-axial accelerometers were placed on both index fingers and patients were instructed to perform the tapping task for 60s, first with the affected and then with the unaffected hand (right and left hand in controls). The reader is referred to (Calautti *et al.*, 2006) for a general description of the technique and preliminary steps of TAA data processing. To detect mirror movements, which reflect excessive coherence between movements of the two fingers, we computed the cross-correlation coefficient (CCC) between the accelerometric time-series from the two fingers (**Figure 1**), band-pass filtered so as to retain only frequencies close to the administered audiotones, i.e., 1.25Hz, and removing harmonics of that frequency. For each patient, both the CCC for the unaffected hand when moving the affected hand (CCC_{AH}), and the counterpart CCC when moving the unaffected hand (CCC_{UH}), were computed. The method was validated in a healthy subject performing pseudo (i.e., voluntary) MMs at different time lengths and amplitudes, in phase, out-of-phase and randomly, during the same motor task as above, for either hand. These tests revealed that the computed correlation was most robust when using filtered data, showing good sensitivity to the duration of MMs and ability to detect even brief and/or small-amplitude MMs. Note that this method is designed to detect MMs based on phase coherence, but is insensitive to their amplitude. In addition to MMs, we used TAA to derive the tapping regularity index (RI) for the affected-hand index finger (Calautti *et al.*, 2006, Calautti *et al.*, 2010).

To permit a meaningful comparison between the TAA measurements and brain activations, the fMRI paradigm involved exactly the same task. Briefly, block-design fMRI was obtained under two conditions, each replicated 4 times in pseudo-random and balanced order: *1)* Task, i.e., auditory-

cued IT taps at 1.25 Hz of the affected hand; and *2)* Rest, with auditory tones on (Calautti *et al.*, 2007). The fMRI datasets were processed using standard voxel-based statistical mapping procedures and software (https://www.fil.ion.ucl.ac.uk/spm/). Task minus Rest contrast images, i.e., 'activation' maps, were computed for each subject, and maps from right-lesioned hemispheres were flipped to the left side, to be referred to as "ipsilesional", as opposed to "contralesional". In addition, M1 (and S1) regions-of-interest (ROIs) for the affected and unaffected hemisphere were also applied, as detailed elsewhere (Calautti *et al.*, 2007), and an index of total ROI activation (Σt-M1) was computed for the ipsi- and contra-lesional M1, and from these a weighted Laterality Index (wLI-M1) (Calautti *et al.*, 2007).

In controls, the CCC for the right and left hands was 0.065 ± 0.07 and 0.075 ± 0.086, respectively (no significant difference; paired t-test), with no significant effect of age. In patients, the CCC_{AH} (0.145 ± 0.173) was significantly ($p<0.05$; two-sample t test) higher than the CCC from either hand of controls (**Figure 2**). The affected-hand IT-Max was significantly reduced compared to both unaffected-hand and age-matched controls ($p<0.001$). There was no significant correlation between the CCC_{AH} and the ESS, time since stroke onset, IT-max or RI.

There was no significant difference in fMRI activation maps between controls and patients, and no significant positive or negative correlation between the CCC_{AH} and the fMRI activation maps in either hemispheres, including in sensitivity analyses using liberal cut-offs. Adjusting for time or IT-max did not change the results. Likewise, there was no significant correlation between the CCC_{AH} and the ROI-based analysis-derived variables.

The CCC_{UH} was moderately and non-significantly smaller than the CCC_{AH} (0.114 ± 0.09; $p=0.31$, paired t-test), and was significantly larger than the CCC of either hand of controls (**Figure 2**). There was not even a trend for a correlation between the CCC_{AH} and the CCC_{UH} ($r = -0.059$, $p=0.78$), and no significant correlation between the CCC_{UH} and any of the clinical variables.

TAA revealed significantly higher mirroring than in control subjects, which was expected for stroke patients recovering from hemiparesis. No significant correlation was found between the CCC_{AH} and the heavily motor-weighted ESS, nor with indices of hand dexterity (i.e., IT-Max and RI). The lack of correlation with time since stroke differs from Ejaz et al, who used a longitudinal, as opposed to our study's cross-sectional design. That the CCC_{AH} and fMRI activation maps acquired while patients carried out the same task did not correlate agrees with Ejaz et al (Ejaz *et al.*, 2018), and also with Gerloff et al (Gerloff *et al.*, 2006) who reported significant contralesional M1 overactivation in stroke patients without significant MMs, as determined by EMG coherence. Earlier literature reviews had

already underlined the frequent dissociation between clinically overt MMs and cSM1 overactivations (Calautti *et al.*, 2003).

In their article, Ejaz et al (Ejaz *et al.*, 2018) interpret the lack of cSM1 overactivation despite MMs, and the observed pattern of MMs with individuated finger presses, as consistent with a brainstem involvement in post-stroke MMs, more specifically the rubrospinal and/or reticulospinal pathways. The lack of correlation between indices of MMs and fMRI maps at the level of the brainstem in our study does not contradict this hypothesis as it could merely reflect the poor sensitivity of fMRI to brainstem activation. MMs could also reflect disrupted neuronal networks at the spinal cord level *per se*. In either case, our findings showing no correlation with fMRI would support the idea that they may reflect a stroke-triggered upregulation of a physiological system. Indeed, MMs occur in normal childhood and disappear in the first decade of life, but can persist in up to 84% of normal adults with effortful and/or complex tasks (Nelles *et al.*, 1998). Accordingly, and consistent with Ejaz et al (Ejaz *et al.*, 2018) and others (Nelles *et al.*, 1998) using a force-based paradigm, here TAA using a non-force, non-complex paradigm detected the presence of physiological MMs in our adult controls, independently of age.

Also confirming previous reports using force-based paradigms (Nelles *et al.*, 1998, Ejaz *et al.*, 2018), we found that 'inverse' MMs involved the affected hand when moving the unaffected hand, though were less prominent than the classical MMs. Inverse MMs have received little attention so far. The lack of correlation between the CCC_{AH} and the CCC_{UH} indicates a degree of independence between the two MM subtypes, possibly suggesting a separate final pathway within a bilaterally-organized system.

Acknowledgements: we thank Benedict Schoenle and Diana J. Day for help with this study.

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Figure 1: Example of a tri-accelerometric time-series for the affected hand auditory-cued non-effortful index-thumb taps at 1.25Hz (in blue), and for the concurrently-recorded unaffected index finger (in red), showing clear in-phase movements (i.e., coherence) of the unaffected hand. The trace shown in this illustration is 50 seconds long (x axis). The cross-correlation coefficient (CCC_{AH}) in this patient was 0.299. Note that the movement-related amplitude (y axis) is in arbitrary units as it depends on various experimental factors such as index finger position in space, which was left free for optimal patient comfort as amplitude was not considered for the derivation of movement coherence (see text).

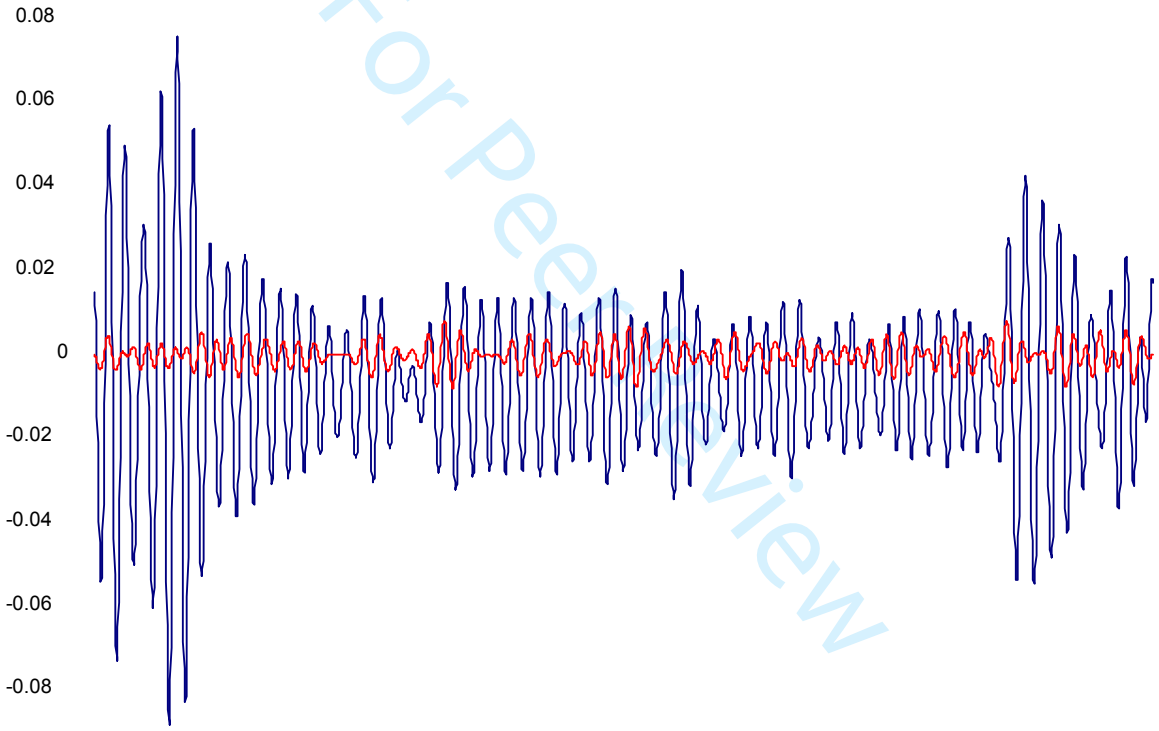

Figure 2: Mean (± 1SD) CCC_{AH} and CCC_{UH} of patients (N=25), and the CCC for the right and left hands of healthy controls (n= 28) (CCC_{RH} and CCC_{LH} respectively). Both the CCC_{AH} and CCC_{UH} of patients were significantly bigger than the CCC of either hand of controls, but not significantly different from each other (see text for details).