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Further evidence for a non-cortical origin of mirror movements after stroke

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Manuscripts

Cinzia Calautti[1], P. Simon Jones[1], Marcello Naccarato[1], Nikhil Sharma[1], T. Adrian Carpenter[2], Elisabeth A. Warburton[1], Jean-Claude Baron[1,3]

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

1.   Stroke Research Group, Dept of Clinical Neurosciences, University of Cambridge, UK
2.   Wolfson Brain Imaging Centre, Dept of Clinical Neurosciences, University of Cambridge, UK
3.   Dept of Neurology, Sainte-Anne Hospital, Université Paris Descartes, INSERM U894, Paris, France

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 classic 'transcallosal' mechanism heretofore widely believed to cause MMs (Di Pino *et al.*, 2014). We wish to report findings, previously published in abstract form (Calautti, 2008), that further support the idea that MMs are not cortically mediated. We also present data that confirm that MMs can involve the affected (i.e., paretic) hand during movement of the unaffected (i.e., non-paretic) hand, also argueing in favor of disruption of a 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 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 hemiparesis including significant hand motor deficit (MRC score ≤ 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 breath-holding 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 index-thumb 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 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 our earlier article (Calautti *et al.*, 2006) for a general description of the technique and preliminary steps of TAA data processing. To detect MMs, which are characterized by frequency coherence of the intended and non-intended movements (Nelles *et al.*, 1998), 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, the TAA data were also used to derive the index-thumb tapping Regularity Index for the affected-side 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 index-thumb 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 to this whole-brain voxel-based analysis, 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 values a weighted Laterality Index (wLI-M1) was calculated (Calautti *et al.*, 2007).

The distribution of CCC values was significantly non-normal on Shapiro-Wilke test for all data subsets. In controls, the CCC values (mean ± SD) for the right and left hands were 0.065 ± 0.07 and 0.075 ± 0.086, respectively (no significant difference; Wilcoxon), with no significant effect of age. In patients, the CCC_{AH} (0.145 ± 0.173) was significantly higher than the CCC of controls (p=0.031 and 0.048 for the right and left hands, respectively; Mann-Whitney) (**Figure 2**). The affected-hand IT-Max was significantly reduced (p<0.001) compared to both unaffected-hand ITMax and age-matched controls. There was no significant correlation between CCC_{AH} and ESS score, time since stroke onset, IT-max or Regularity Index.

Analysis of the whole brain fMRI activation maps revealed no significant difference between controls and patients, and no significant positive or negative correlation with CCC_{AH} in either hemisphere, including in sensitivity analyses using liberal statistical cut-offs. Adjusting for time since stroke or IT-max did not change the results. Likewise, there was no significant correlation between CCC_{AH} and the ROI-based analysis-derived fMRI data.

The CCC_{UH} was moderately and non-significantly smaller than the CCC_{AH} (0.114 ± 0.09; p=0.43, Wilcoxon), and was significantly larger than the CCC of the right hand of controls, with a similar trend for the left hand (p=0.048 and 0.079, respectively; Mann-Whitney) (**Figure 2**). There was not even a trend for a correlation between the CCC_{AH} and the CCC_{UH} (p=0.93, Kendall), and no significant correlation between the CCC_{UH} and any of the clinical variables.

As expected for recovering stroke patients, our study revealed significantly higher mirroring in the non-paretic hand during paretic hand movement as compared to healthy controls. There was no significant

correlation between the coherence index and the ESS, which is heavily motor-weighted, nor with the IT-Max and the Regularity Index, which reflect hand dexterity. The lack of correlation with time since stroke differs from Ejaz et al (Ejaz *et al.*, 2018), who used a longitudinal design, as opposed to cross-sectional here. The lack of correlation between the coherence index and whole-brain fMRI activation maps acquired during the same task agrees with Ejaz et al (Ejaz *et al.*, 2018). It is also consistent with Gerloff et al (Gerloff *et al.*, 2006), who found significant contralesional M1 overactivation in a stroke sample that excluded per protocol patients in whom MMs were detected by EMG coherence. The frequent occurrence of discrepancies between MMs and cSM1 overactivations was underlined already in early literature reviews (Calautti and Baron, 2003).

Regarding the mechanisms underlying post-stroke MMs, Ejaz et al (Ejaz *et al.*, 2018) interpret their finding of a lack of cSM1 overactivation despite MMs, together with the pattern of MMs observed with individuated finger presses, as consistent with an involvement of the brainstem, more specifically the rubrospinal and/or reticulospinal pathways. The lack of correlation between TAA-derived measures of MMs and whole-brain fMRI maps at the level of the brainstem in our study does not contradict this hypothesis given the poor sensitivity of fMRI in this anatomical region. Admittedly, MMs might also reflect disrupted neuronal networks at the spinal cord level *per se*. Notwithstanding the exact pathway involved, both Ejaz et al's and our findings would be consistent with the idea that MMs may reflect a stroke-triggered upregulation of a still elusive physiological system. Indeed, MMs are present in normal childhood and although they disappear in the first decade of life, they can be found in up to 84% of normal adults with effortful and/or complex motor 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, MMs were detected here by means of TAA in adult healthy controls, independently of age and using a non-force, non-complex paradigm. Given that post-stroke MMs involve more than just the homologous fingers (Ejaz *et al.*, 2018), further studies assessing coherence in a more distributed fashion will likely further our understanding of MM mechanisms.

Consistent with previous reports that used force-based paradigms (Nelles *et al.*, 1998, Ejaz *et al.*, 2018), our study also showed the presence of 'inverse' MMs, i.e., involving the affected hand when moving the unaffected hand. Inverse MMs have received little attention so far. We found inverse MMs to be substantially larger than that in normal controls, but less prominent than conventional MMs. In both Nelles et al (Nelles *et al.*, 1998) and Ejaz et al (Ejaz *et al.*, 2018), the incidence of inverse MMs in the first few weeks after stroke was not different than in healthy controls, but the latter authors found that

inverse MMs subsequently significantly increased; this timing effect may explain the differences with our study. The complete lack of correlation between the CCC_{AH} and CCC_{UH} found in our study indicates a high degree of independence between these two MM subtypes, suggesting a separate final pathway within a bilaterally-organized system.
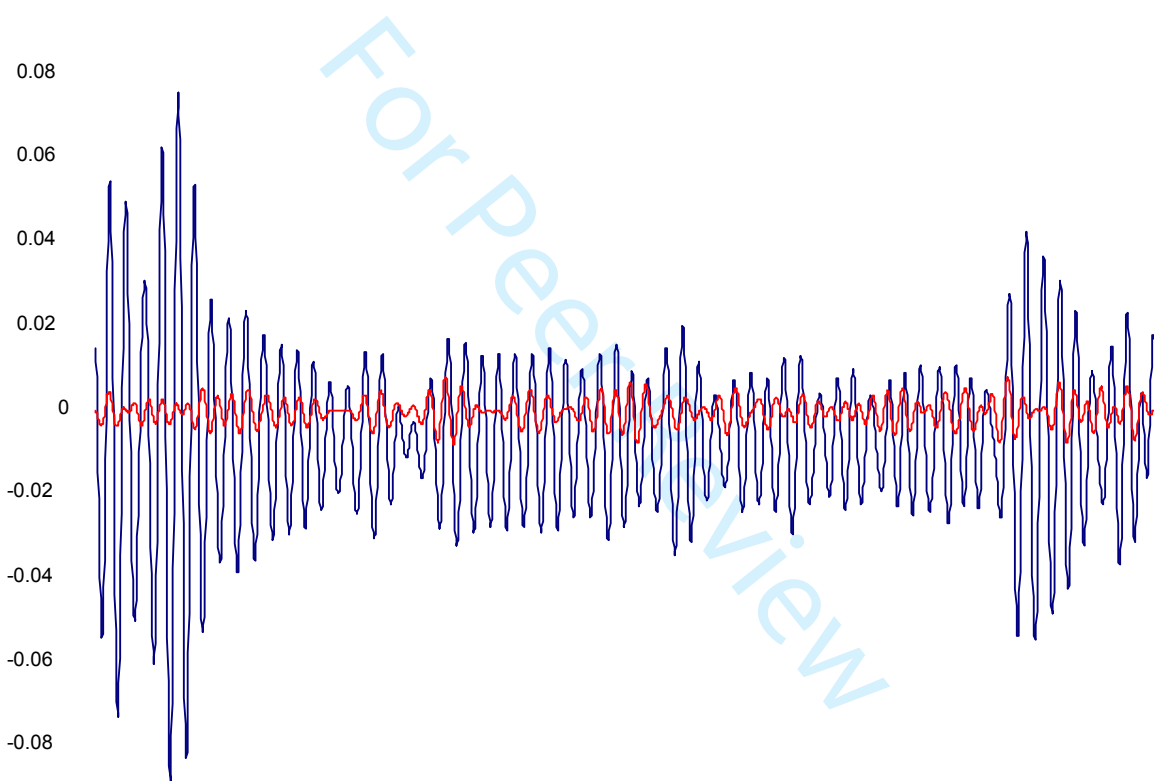
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Figure Legends

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 ($\pm$ 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). The CCC_{AH} was significantly larger than the CCC of either hand of controls. The CCC_{UH} was significantly larger than the CCC_{RH} and showed a simlilar trend with the CCC_{LH}, and was smaller than the CCC_{AH} but not significantly so (see text for details).

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