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Ipsilateral corticospinal maps correspond to severe poststroke motor impairment

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Motor recovery in the chronic stage, i.e., more than 6 months after stroke is often limited. While there is increasing interest in the development of novel therapies for this patient cohort [1], only very few trials focus on severely impaired chronic stroke patients [2]. Refined therapies are therefore required for this patient population. Furthermore, reliable measures for studying the underlying physiological mechanisms and effectiveness of interventions are crucial. In this context, cortical motor maps appear to be promising, i.e., by assessing the cortical representation of the affected muscles as measured by motor evoked potentials (MEP) following transcranial magnetic stimulation (TMS) [3]. However, severely impaired patients with extended damage of the corticospinal tract often show no MEP when standard TMS procedures are applied [4]. Mapping the motor area with refined techniques may facilitate the identification of corticospinal reorganisation and detection of residual connections beyond the primary motor cortex even in severely impaired stroke patients [5]. It remains unclear, however, as to whether the hemisphere and size of the area investigated influence the detection of clinically relevant connections to paralysed muscles.

In this study, cortical motor maps were acquired on two separate days in eighteen severely impaired chronic stroke patients without active finger extension of the paretic hand (age: 62.28 ± 9.50 years, 5 female, 15 ischemic, time since stroke: 60.39 ± 56.57 months, FMUE: 12 ± 5.52). All patients gave written informed consent prior to participation in the study which was approved by the ethics committee of the university hospital of Tuebingen and conducted in accordance with the declaration of Helsinki. None of the patients reported contraindications to TMS. Biphasic TMS pulses (MagPro-R30 with MagOption, MagVenture Denmark) were delivered through a figure-of-eight coil (MCF-B70, MagVenture) at an orientation of 45° relative to the midsagittal plane. In the non-lesioned hemisphere, the motor hotspot was determined by applying standard procedures. For the lesioned hemisphere, the hotspot of the non-lesioned hemisphere was mirrored with respect to the midsagittal plane. Electromyographic (EMG) data was recorded over the paralysed extensor digitorum communis (EDC) muscle. On both days, a TMS map with a 5 × 5 grid centered around the motor hotspot was acquired. The distance between the stimulation points was 0.5cm on day one and 1cm on day two, resulting in a smaller (i.e., 2.5cmx2.5cm) and larger (i.e., 5cmx5cm) grid, respectively. Each grid-point was stimulated 5 times with an interstimulus interval of 5 ± 1.25s at 100% maximum stimulator output. The EMG data was cut into epochs of −100 to +100 ms surrounding the TMS artifact, visually inspected for the presence of motor evoked potentials (MEP) and rejected if artifacts or muscle pre-activation of more than 20μV within 50 ms prior to the TMS pulse was detected. Ipsi- and contralateral MEP of any amplitude were included for further analyses. The map area was determined by multiplying the number of active grid-points with the size of the grid-point. The impairment level was assessed with the Fugl-Meyer Assessment of the Upper Extremity (FMUE), excluding the parts related to reflexes and coordination/speed [1]. Furthermore, the FMUE was correlated with the motor map area in either hemisphere using the Pearson's correlation coefficient.

In the smaller maps, MEP could be identified in ten (55.56%) and eleven patients (61.11%) in the lesioned and non-lesioned hemisphere, respectively. Altogether, MEP could be detected in fourteen of the eighteen patients (77.78%) when considering both hemispheres. In the larger maps, MEP was identified in sixteen (88.89%) and twelve patients (67.67%) in the lesioned and non-lesioned hemisphere, respectively. MEP were therefore detected in seventeen of our eighteen patients (99.44%) when considering both hemispheres. Thus, detection of corticospinal connectivity improved when large maps were assessed. Notably, the areas with the strongest connections were missed or not fully captured by the smaller maps (Fig. 1). In the lesioned hemisphere, no correlation of the motor map area with motor impairment was found in either the larger ($r = .13$, $p = .60$) or smaller ($r = 0.041$, $p = .87$) grids. In the non-lesioned hemisphere, significant correlations of the motor map area with motor impairment were detected in the larger ($r = -.52$, $p = .026$), but not in the smaller ($r = -0.27$, $p = .28$) grids.

This study indicates that a higher impairment level after stroke was associated with an increased map area in the non-lesioned hemisphere, and that a larger grid size was necessary to detect this relationship. These findings may be relevant for the outcome prediction, monitoring and treatment of severely impaired stroke patients:

Specifically, current algorithms that predict the recovery potential after stroke often apply TMS to the lesioned hemisphere and motor hotspot only [4,6]. They may therefore overlook functionally relevant corticospinal connectivity. Thus, taking extended motor

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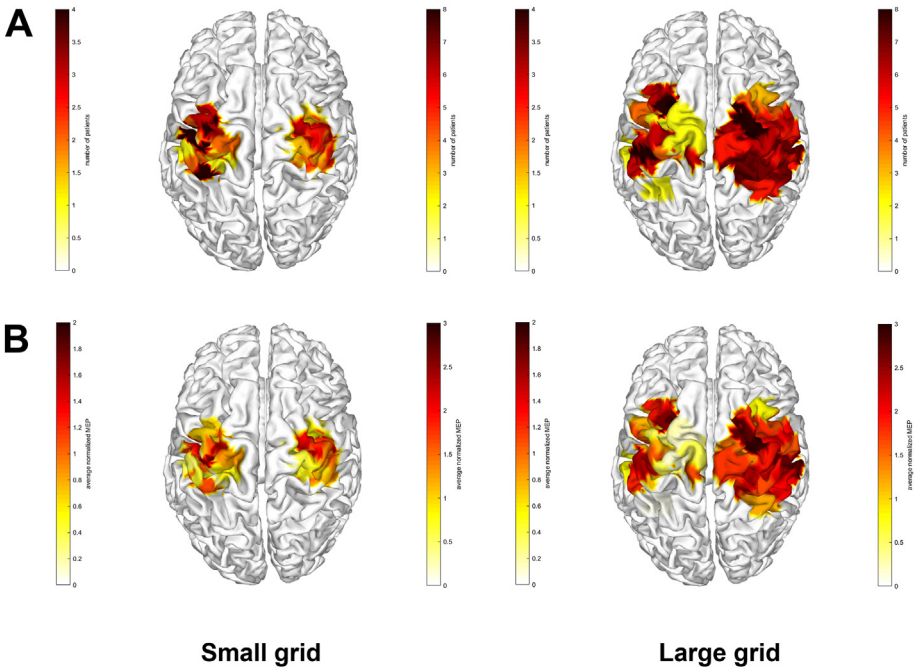

Fig. 1. A. Group data indicating the number of patients that showed a MEP at each grid-point is displayed for the small (left) and large (right) grid sizes, respectively.
B. Group data indicating the average normalised MEP score at each grid-point for the small (left) and large (right) grid sizes, respectively. Normalisation was performed per patient by taking the grid-point with the maximum mean MEP and assigning it a score of 10. All other grid-points of the same patient were categorised with scores from 0 to 10, in relation to the grid-point with the maximum MEP. Finally, the scores of all 18 patients were averaged per grid-point.

maps of both hemispheres into consideration might improve the accuracy of predictions.

Furthermore, previous work indicated that poststroke motor recovery may be associated with plastic changes in distributed areas [2,5,7,8]. While motor recovery is often associated with plasticity in the lesioned hemisphere [7], ipsilateral corticospinal pathways originating in the non-lesioned hemisphere may play a key role in promoting recovery in severely impaired patients [8]. The present findings suggest that motor maps beyond the primary motor cortex of both hemispheres should be considered to gain a better picture of the ongoing reorganisation.

Interestingly, the extent of corticospinal connectivity from the non-lesioned hemisphere to the paralysed muscle corresponded to the motor impairment level in our patient cohort. This suggests that acquiring bilateral cortical maps may be particularly relevant in patients with severe motor impairments. However, our cross-sectional study design could not reveal the functional role of extended motor maps in the non-lesioned hemisphere. They may reflect either detrimental (maladaptive) [9] or restorative (but not yet sufficient) [10] post-stroke reorganisation; a question requiring attention in future longitudinal studies.

In conclusion, assessing extended bilateral motor maps may provide further insight into the motor recovery of severely impaired stroke patients. The findings are, furthermore, consistent with the concept of compensatory plasticity in the non-lesioned hemisphere and may inform novel interventions that target alternate corticospinal pathways.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Ward NS, Brander F, Kelly K. Intensive upper limb neurorehabilitation in chronic stroke: outcomes from the Queen Square programme. J Neurol Neurosurg Psychiatry 2019;90:498–506. https://doi.org/10.1136/jnnp-2018-319954.
[2] Belardinelli P, Laer L, Ortiz E, Braun C, Gharabaghi A. Plasticity of premotor cortico-muscular coherence in severely impaired stroke patients with hand paralysis. NeuroImage Clin 2017;14:726–33. https://doi.org/10.1016/j.nicl.2017.03.005.
[3] Lüdemann-Podubecká J, Nowak DA. Mapping cortical hand motor representation using TMS: a method to assess brain plasticity and a surrogate marker for recovery of function after stroke? Neurosci Biobehav Rev 2016;69:239–51. https://doi.org/10.1016/j.neubiorev.2016.07.006.
[4] Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain 2012;135:2527–35. https://doi.org/10.1093/brain/aws146.
[5] Leão MT, Naros G, Gharabaghi A. Detecting poststroke cortical motor maps with biphasic single- and monophasic paired-pulse TMS. Brain Stimul 2020;13:1102–4. https://doi.org/10.1016/j.brs.2020.05.005.
[6] Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: a biomarker-based algorithm for predicting upper limb function after stroke. Ann Clin Transl Neurol 2017;4:811–20. https://doi.org/10.1002/acn3.488.
[7] Plow EB, Sankarasubramanian V, Cunningham DA, Potter-Baker K, Varnerin N, Cohen LG, et al. Models to tailor brain stimulation therapies in stroke. Neural Plast 2016;2016. https://doi.org/10.1155/2016/4071620.
[8] Bradnam LV, Stinear CM, Byblow WD. Ipsilateral motor pathways after stroke: implications for noninvasive brain stimulation. Front Hum Neurosci 2013;7:1–8. https://doi.org/10.3389/fnhum.2013.00184.

[9] Wilkins KB, Yao J, Owen M, Karbasforoushan H, Carmona C, Dewald JPA. Limited capacity for ipsilateral secondary motor areas to support hand function post-stroke. J Physiol 2020;598:2153–67. https://doi.org/10.1113/JP279377.
[10] Veldema J, Nowak DA, Gharabaghi A. Resting motor threshold in the course of hand motor recovery after stroke : a systematic review. J NeuroEng Rehabil 2021:1–28. https://doi.org/10.1186/s12984-021-00947-8.

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