

1 **A study of parietal-motor connectivity by intraoperative dual cortical stimulation.**

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17

18 **Abstract** – the function of the primate’s posterior parietal cortex in sensorimotor transformations is well-
19 established, though in humans its complexity is still challenging. Well-established models indicate that the
20 posterior parietal cortex influences motor output indirectly, by means of connections to the premotor cortex,
21 which in turn is directly connected to the motor cortex. The possibility that the posterior parietal cortex could
22 be at the origin of direct afferents to M1 has been suggested in humans but has never been confirmed directly.
23 In the present work we assessed during intraoperative monitoring of the corticospinal tract in brain tumour
24 patients the existence of short-latency effects of parietal stimulation on corticospinal excitability to the upper
25 limb. We identified several foci within the inferior parietal lobule that drove short-latency influences on cortical
26 motor output. Active foci were distributed along the postcentral gyrus and clustered around the anterior
27 intraparietal area and around the parietal operculum. For the first time in humans, the present data show
28 direct evidence in favour of a distributed system of connections from the posterior parietal cortex to the
29 ipsilateral primary motor cortex.

30

31 Introduction

32 The role of the posterior parietal cortex in active behaviour

33 The last 40 years have witnessed a radical change in our view of the parietal cortex (Mountcastle *et al.*, 1975).
34 The posterior parietal cortex, once labelled as “associative cortex” is now well-known for receiving multimodal
35 sensory information and integrating it into a praxic, behaviourally-committed representation of the world
36 around us. Solid evidence in the field of neuropsychology, neuroimaging and neurostimulation indicates that
37 the posterior parietal cortex is necessary for goal-directed behaviour. Symptoms frequently caused by lesions
38 of the parietal lobe include deficits in sensorimotor processes, such as optic ataxia (Andersen *et al.*, 2014) or
39 apraxia (Goldenberg, 2009). Direct stimulation of the human parietal cortex has been shown to produce
40 movements in all body segments (Penfield and Boldrey, 1937; Balestrini *et al.*, 2015). Current evidence
41 indicates in the human superior parietal lobule the machinery for sensorimotor transformation in spatially-
42 oriented movements (for reviews see Culham and Valyear, 2006, Filimon, 2010 and Gallivan and Culham, 2015)
43 controlling also some aspects of distal prehension movements (Monaco *et al.*, 2015; Cavina-Pratesi *et al.*,
44 2018). Visual features of objects, used to guide distal, object-directed movements are represented in humans
45 in the anterior intraparietal region (Culham *et al.*, 2003; Frey *et al.*, 2005; Begliomini *et al.*, 2007; Grol *et al.*,
46 2007; Stark and Zohary, 2008; Hinkley *et al.*, 2009; Verhagen *et al.*, 2012; Orban, 2016). The role of the inferior
47 parietal lobule in movement is less clear. Grasping-related activity in the anterior intraparietal region is found
48 along the descending part of the precentral sulcus, up to the parietal operculum with some specialization for
49 tool use of the more ventral areas (Orban, 2016). More ventrally, the parietal opercular region is also thought
50 to be a site of sensorimotor integration, mainly in the somatosensory modality (Eickhoff *et al.*, 2006b, a, 2010).
51 Summing up, imaging data in humans indicate an extended region ranging from the superior parietal lobule to
52 the parietal operculum involved in sensorimotor processes and specialized in distinct functional aspects.

53 Parietal-motor pathways.

54 How does the motor cortex use motor-relevant information from the posterior parietal cortex? The influence
55 of the parietal cortex on motor output is generally considered to be indirect. According to influential models,
56 based on monkey anatomy, the parietal cortex modulates corticospinal activity in an indirect way, through the
57 premotor cortex (Murata *et al.*, 1997; Wise *et al.*, 2002; Rizzolatti *et al.*, 2014; Kaas and Stepniewska, 2016).
58 However, even anatomical data in monkeys are controversial in this respect. The existence of direct,
59 monosynaptic connections from the posterior parietal cortex to the upper limb representation of the primary
60 motor cortex has been demonstrated by several independent works (Strick and Kim, 1978; Rozzi *et al.*, 2006;
61 Bruni *et al.*, 2018). Such data offer the anatomical bases for a possible direct pathway by which the posterior
62 parietal cortex might control directly corticospinal output. In addition to this, it has been recently shown that
63 the posterior parietal cortex of macaques has a direct access to spinal motor neurons by means of corticospinal
64 axons (Rathelot *et al.*, 2017). In humans, several recent lines of evidence have suggested that the posterior
65 parietal cortex might have a more direct influence on motor output. Non-invasive brain stimulation, i.e.
66 transcranial magnetic stimulation (TMS) suggests that the parietal cortex could give origin to direct cortico-
67 cortical connections to the primary motor cortex (M1) (Koch *et al.*, 2007, 2008b, 2010; Ziluk *et al.*, 2010;
68 Cattaneo and Barchiesi, 2011; Karabanov *et al.*, 2013; Maule *et al.*, 2015), involved in skilled upper limb
69 movements. Summing up, there is ample evidence in both nonhuman and human primates to support the
70 possibility that the parietal lobe could modulate corticospinal output also directly through M1, besides the
71 well-established indirect pathway through a relay in the premotor cortex (see Koch and Rothwell (2009) and
72 Vesia and Davare (2011) for a review of parieto-M1 interaction models). The active role of the posterior
73 parietal cortex in producing movements is being currently re-evaluated as a potential source of “pre-motor”
74 afferents to the premotor cortex, where pre-motor is used here in a functional sense rather than anatomical.
75 Imaging data provided indirect evidence of posterior parietal-motor anatomical and functional connectivity
76 (Guye *et al.*, 2003; Koch *et al.*, 2010; Yin *et al.*, 2012). However, direct evidence in favour of direct connections
77 between the parietal and the motor cortex in humans are lacking.

78 **Testing direct parieto-motor pathways intraoperatively**

79 We aim to fill this gap in current knowledge with the present work in which we tested cortico-cortical
80 connectivity by means of intra-operative direct cortical stimulation (DCS) with a dual-pulse paradigm similar to
81 that employed with dual-coil TMS (Koch and Rothwell, 2009). Supra-threshold test stimuli were delivered to
82 M1 and the resulting motor evoked potentials (MEPs) were systematically recorded from distal upper limb
83 muscles, and in some cases from facial and lower limb muscles. In some trials a conditioning stimulus was
84 delivered to different regions of the parietal cortex at variable inter-stimulus intervals (ISIs) ranging from 4ms
85 to 16 ms. In some other trials, only conditioning stimuli were delivered. The conditioning stimulus itself does
86 not activate the corticospinal motor pathways, as witnessed by the systematic absence of MEPs in such trials.
87 The modulation of motor output by conditioning stimuli is generally considered as evidence of cortico-cortical
88 functional connectivity between the target of conditioning stimuli and the motor cortex. It is important to note
89 that a necessary pre-requisite for the realization of dual-stimulation paradigms is that the corticospinal tract
90 must be activated trans-synaptically by the test stimuli, because direct axonal stimulation of corticospinal
91 axons produces MEPs that arise downstream of the putative site of interaction between the conditioning and
92 the test stimuli. In this respect, the information currently available indicates that direct cortical stimulation
93 (DCS) is effective also under general anaesthesia in exciting cortical output trans-synaptically, also at low
94 stimulation intensities (Katayama *et al.*, 1988; Hanajima *et al.*, 2002; Yamamoto *et al.*, 2004; Lefaucheur *et al.*,
95 2010). Invasive intra-operative monitoring (IONM) in neurosurgery therefore offers the unique opportunity to
96 assess cortico-cortical connectivity *in vivo*, with extraordinary spatial resolution and anatomical precision.
97 Indeed, the results of the present work indicated a diffuse field of parietal spots exerting short-latency
98 modulation of corticospinal output in the range of 6-15 ms of inter-stimulus intervals, distributed along the
99 post-central sulcus. Such active spots showed higher density in two large clusters in the anterior intraparietal
100 region and in the parietal operculum. We show that the anterior portion of the inferior parietal lobule and
101 intraparietal region can be functionally considered as a “pre-motor” region. The behavioural significance of
102 such connections is yet to be determined.

103 **Methods**

104 **Patients**

105 The study proposal is in accordance with ethical standards of the Declaration of Helsinki. All stimulations and
106 recordings were performed in the context of clinical intraoperative neurophysiological monitoring (IONM).
107 Patients scheduled for tumour removal in the vicinity of the parietal cortex were screened for enrolment. The
108 inclusion criteria were: (1) brain tumour necessitating intraoperative neurophysiological monitoring (2) over 18
109 years of age. Exclusion criteria were (1) extended cortico-subcortical damage to the parietal lobe (2) voluntary
110 decision of the patient not to be included in the cohort. Seventeen patients (age 39-79; 10M-7F; 17 right-
111 handed) were included in this study, recruited from the Verona University Hospital. Patient’s characteristics are
112 presented in Table 1.

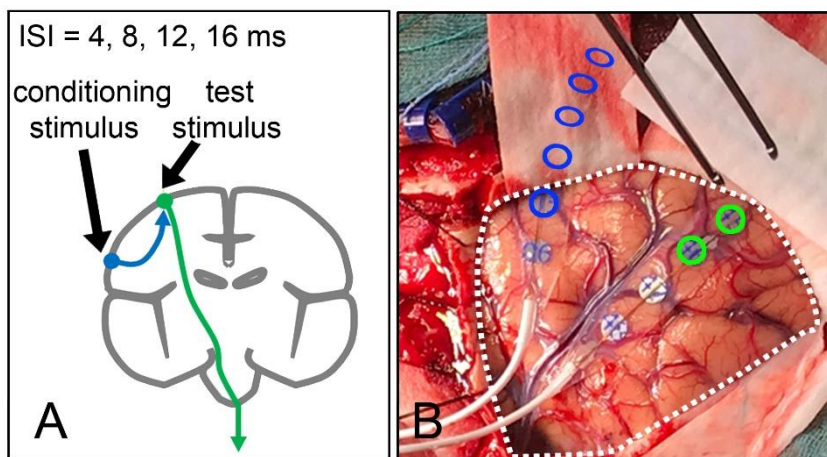
113 **Stereotaxic neuronavigation and electrode placement**

114 MRI scans of each patient’s brain were acquired before surgery on a 3T scanner with an eight-channel head coil
115 (Signa 3T, General Electric Healthcare, Milwaukee, USA). T1-weighted 3D MPRAGE images were acquired using
116 the following parameters (echo train length: 1, TE: 2.67ms, TR: 2.000, matrix size: 256 × 246, slice thickness:
117 1mm). T2-weighted, FLAIR images were also acquired (TR 6000ms, TE 150mss, TI 2000ms). The reconstruction
118 of the individual cortical surface was performed using Brainsuite (Brainsuite, UCLA Brain Mapping Center, San
119 Francisco, USA “Shattuck DW and Leahy RM (2002)”). For a clearer intraoperative visualization of sulcal
120 anatomy, a skull stripped T1 using a non-uniformity correction (Brainsuite, UCLA Brain Mapping Center, San
121 Francisco, USA “Shattuck DW and Leahy RM (2002)”) or a FLAIR images was added to the 3D visualization of the
122 Neuronavigation system (Stealth Station 7, Medtronic, Minneapolis, USA). Correspondence of 3D
123 reconstruction and individual patient’s sulcal anatomy was then performed using the Neuronavigation pointer.
124 Brain anatomy was systematically analysed prior to surgery so that main sulcal patterns of the postcentral and
125 parietal region could be readily identified during actual surgery. The stimulating strip was placed parallel to the

126 central sulcus, similarly to the montage used for studies of intra-operative motor evoked potentials, after
127 identification of the central sulcus by phase reversal (Romstöck *et al.*, 2002). Placement of the conditioning
128 electrode strip was roughly planned a priori but was systematically reprogrammed when in presence of
129 contingent surgical conditions preventing the placement of the strip in the desired position, such as presence
130 of large vessels or space requirements by the ongoing surgical procedures.

131 **Anaesthesia and conventional IONM**

132 The anaesthesia protocol applied was Total Intravenous Anaesthesia (TIVA). More precisely, a continuous
133 infusion of Propofol (100-150 µg/kg/min) and Fentanyl (1µg/kg/min) was used, avoiding bolus. Short acting
134 relaxants were administered for intubation purpose only and then avoided. Halogenated anaesthetic agents
135 were never used. Since all patients were candidates for IONM of the corticospinal tract, standard
136 neurophysiological monitoring and mapping was performed. This involved simultaneous acquisition of
137 continuous electroencephalography (EEG), electrocorticography (ECoG), recording of free-running
138 electromyographic (EMG) activity (ISIS-IOM, Inomed Medizintechnik GmbH, Emmendingen, Germany). Muscle
139 MEPs were initially elicited by Transcranial Electrical Stimulation (TES) via corkscrew-like electrodes (Ambu®
140 Neuroline Corkscrew, Ambu, Copenhagen, Denmark) from the scalp. Short trains of 5 square-wave stimuli of
141 0.5 ms duration, and interstimulus interval (ISI) of 4ms were applied at a repetition rate up to 2 Hz through
142 electrodes placed at C1 and C2 scalp sites, according to the 10/20 EEG system. Cortical and subcortical
143 stimulation were performed using a monopolar probe (45 mm, angled 30°, Inomed Medizintechnik GmbH,
144 Emmendingen, Germany) referenced to Fz. Stimulation parameters were as follows: a short train of five pulses,
145 pulse duration 0.5 milliseconds; interstimulus interval (ISI) 2 ms at 1 Hz repetition rate. Cortical stimulation was
146 anodal while subcortical stimulation was cathodal. Once the dura was opened, MEP monitoring was performed
147 using a 6-contacts strip electrode (diameter 2.5 mm, space 10 mm, contact strips: 0.7 mm thin, 10 mm width,
148 Inomed Medizintechnik GmbH, Emmendingen, Germany). EMG recordings were performed in a belly-tendon
149 montage, by means of subcutaneous needle monopolar electrodes (Ambu® Neuroline Subdermal, Ambu,
150 Copenhagen, Denmark). The *orbicularis oris*, the ABP, the *biceps*, the *abductor hallucis* and the *tibialis anterior*
151 muscles contralateral to the stimulated hemisphere were recorded.

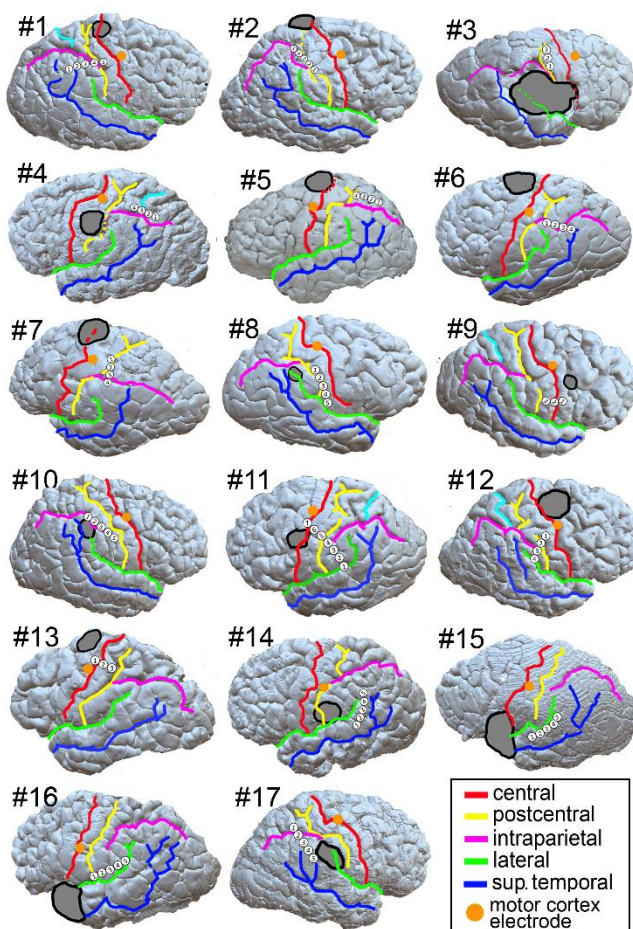


153 **Figure 1:** A- schematic representation of the dual strip protocol. Test stimuli are delivered to the motor cortex
154 and produce a measurable motor evoked potential via the corticospinal tract (green arrow). In some trials the
155 test stimulus is preceded by a conditioning stimulus, which alone cannot activate the corticospinal tract, applied
156 to the parietal cortex (blue arrow). The inter-stimulus interval (ISI) ranges between 4 and 16 ms. The finding of
157 MEPs to conditioning stimuli having a different amplitude or area than MEPs to test stimuli alone is considered
158 evidence for functional connectivity between the two stimulated regions. The short duration of the ISI, in the
159 range of milliseconds, indicates mono- or oligo-synaptic connections. B- Actual surgical scenario (patient #4).
160 The dashed white line represents the borders of the craniotomy. The two stimulation strips are shown. The test
161 stimulus dipole is indicated with the two green circles and is used to activate the corticospinal tract. The

162 conditioning strip is placed over the parietal lobe. The dipoles used for conditioning stimuli are indicated with
163 blue circles. Note that the electrode strip is inserted under the dura, therefore the electrode position extends
164 well beyond the craniotomy.

165 Dual strip stimulation

166 Direct electrical cortical stimulation was applied to the precentral gyrus (test stimuli) via a 6-contacts strip
167 electrode and to the parietal cortex by means of a 6-contacts or an 8-contacts strip electrode (Figure 1 shows a
168 schematic of the dual strip protocol and an example of surgical scenario). To optimize timing precision between
169 the conditioning and the test stimuli, the conditioning stimuli were always delivered in a short train of 2 stimuli
170 at 250 Hz and of 0.5 ms duration. Test stimuli were delivered with trains of the minimal duration required to
171 elicit a stable MEP in the ABP. This results in test stimulation with one single stimulus in 1 patient, with 2
172 stimuli in 12 patients and with 3 stimuli in 3 patients. Intensity of test stimulation was set to obtain a MEP from
173 the thenar muscle of around 500 μ V peak-peak amplitude. The ISI was considered as the interval between the
174 last stimulus of the conditioning train and the last pulse of the test train. The ISIs of 7, 13 and 18 ms were
175 systematically explored in separate blocks for each of the test-stimulus electrodes. Every block contained at
176 least 15 repetitions of the same dual stimulation. Dual-stimulation blocks were alternated with blocks with only
177 test-stimuli so that the unconditioned MEP amplitude was monitored throughout the recording session. The
178 timing of dual stimuli was managed entirely by the commercially available ISIS-IOM system (Inomed
179 Medizintechnik GmbH, Emmendingen, Germany) by means of the “facilitation” function, that allows
180 independent electrical stimulation through two separate output channels.



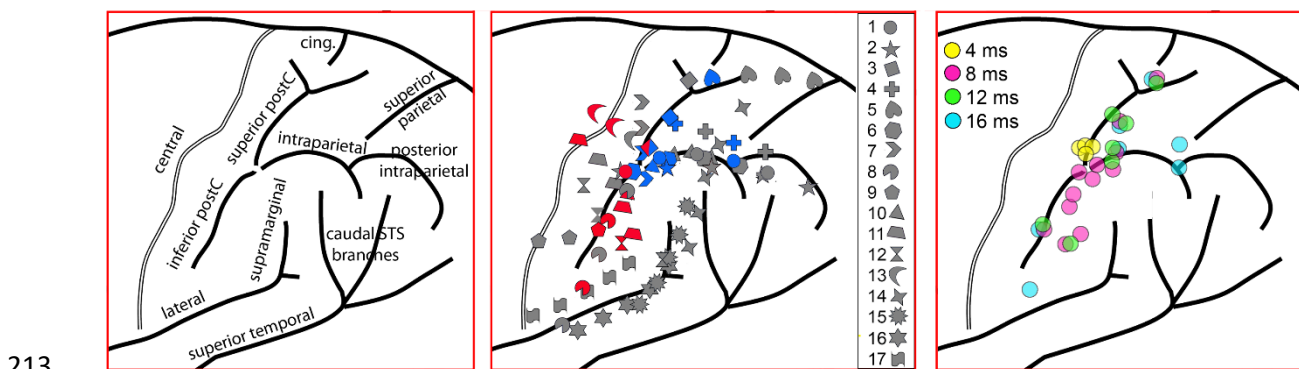
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182 **Figure 2:** rendering of the individual brains (only the stimulated hemisphere is shown. The projection of the
183 lesion on the surface is indicated with the grey shape. Main cortical sulci are indicated with a colour code as
184 indicated in the legend. The orange spot indicates the point of corticospinal stimulation (test stimulus). The

185 *white numbered circles indicate the position of the cathode of conditioning stimulation. (note that conditioning*
186 *stimuli have been delivered in bipolar modality).*

187 **Data analysis**

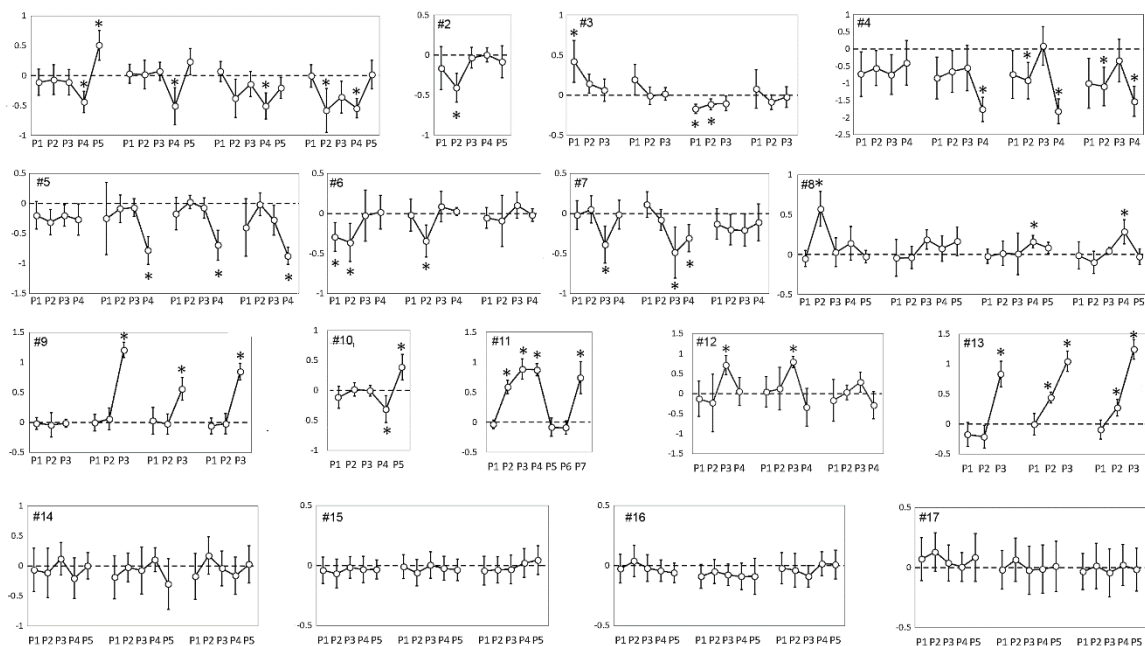
188 Pre-processing required the data to be exported in digital format and analysed with the MATLAB software. The
189 EMG traces were band-pass filtered (50-2000 Hz) and rectified. The duration of the MEP was determined
190 individually, and the corresponding area of the EMG recording was extracted. In this way each trial was
191 characterized by a single number, i.e. the MEP area. We then proceeded to normalizing conditioned MEPs to
192 test MEPs. However, MEPs to test stimuli alone are not stable throughout the surgical procedure because of
193 strip movements. To correct for such variability, we normalized blocks of conditioned MEPs only to a sliding
194 window of the blocks of test stimuli adjacent to each conditioned block. This was done by dividing the single
195 conditioned MEP areas by the median of the test MEP areas. The resulting normalized conditioned MEP areas
196 (normMEP) were used as main experimental variable. The main analysis was carried out in single patients,
197 comparing normalized conditioned MEP areas from test stimuli by means of independent-samples t-tests. This
198 test informs us whether, in single subjects, the trials in a given conditioned set are different from those in the
199 test set and the direction of the change (excitation or inhibition). Significance threshold was corrected to
200 account for the repeated comparisons. Analysis were performed therefore on single subjects, using a univariate
201 approach. The results of single t-tests were therefore corrected for multiple comparisons in each participant.
202 For example, patient #1 was tested on 20 cortical spots and therefore critical p-value was set to $p=0.05/20$ i.e.
203 $p=0.0025$. Qualitative assessment of the effects of conditioning stimuli at the population level was performed
204 by plotting on a standardized surface map of the parietal cortex the sites of conditioning stimulation of all
205 participants, indicating electrodes that had a significant effect on test stimuli in single participants. To this
206 purpose, we used the frameless stereotaxic neuronavigation system to pinpoint on individual brain anatomies
207 the real position of strip electrodes and the trajectory of strips that were not readily visible because in the
208 subdural space. The parietal region shows a considerable inter-individual variability, therefore, to remap
209 individual anatomies on the standardized space we made reference to the anatomical study of Zlatkina and
210 Petrides (2014), which resulted in slight warping of the strip positions. Figure 2 indicates individual brain
211 anatomies of the 16 patients together with the conditioning strip electrodes and Figure 3 Indicates the
212 population data in the standardized space.



214 **Figure 3:** standardized parietal anatomy showing the location of each participant's conditioning electrodes in
215 the parietal cortex. The anatomical template is based on (Zlatkina and Petrides, 2014; Zlatkina et al., 2016). The
216 **left panel** shows the label of the main sulci. The **middle panel** indicates the positions of conditioning stimuli
217 (cathodes) in each patient. The legend links symbols to each patient's numbers. Grey-filled symbols indicate
218 spots with no significant effect. Blue-filled symbols indicate spots with significant inhibitory conditioning effects.
219 Red-filled symbols indicate spots with significant excitatory conditioning effects. Spots in which both excitatory
220 and inhibitory effects were observed at different ISIs are indicated with both red and blue filling. The **right panel**
221 shows only conditioning spots with significant effects (active spots), pooled across patients and grouped
222 according to the ISI at which an effect was observed.

223 Results

224 In all participants it was possible to stimulate at least one conditioning spot, with a variable number of 3-6.
225 Figure 2 shows each patient's anatomy together with lesion location and electrode placement. For the sake of
226 clarity, participants have been numbered according to the presence of excitatory effect, inhibitory effects or no
227 effect. We observed in most subjects a significant modulation of MEPs by conditioning stimuli in one specific
228 electrode, at specific timings. The individual results are reported in Figures 3 and 4 and in Table 2. We observed
229 both inhibitory and excitatory effects of conditioning stimuli at different ISIs. The systematic between-subject
230 variations inherent in the mapping technique were reflected in the variability of the ISIs at which conditioning
231 stimuli exerted a significant effect on corticospinal excitability which ranged from 4ms to 16 ms. 6 participants
232 showed only inhibitory effects, 3 showed mixed effects, 4 showed facilitatory effects and 4 did not show any
233 effect of conditioning stimuli on corticospinal excitability.



234
235 **Figure 4.** Comprehensive data from all patients. The plots indicate the mean value of the log-transformed ratios
236 between conditioned and unconditioned MEPs. Negative values indicate that the mean conditioned MEP is
237 smaller than the mean test MEP (inhibitory effects). Positive values indicate that mean conditioned MEPs are
238 larger than mean test MEPs (excitatory effects). All log-ratios have been tested by single-sample t-tests against
239 a null hypothesis of mean value = 0. Significance threshold was Bonferroni corrected. Asterisks indicate
240 significant comparisons. Error bars indicate 95% confidence intervals of the mean).

241 Anatomical localization and chronometry of conditioning stimulus effects

242 Each patient was stimulated with conditioning stimuli in 2-5 pairs of stimulating electrodes (Figure 2 indicates
243 the cathode of the bipolar stimulation montages). Active spots were localized all along a region of the PPC
244 immediately posterior to the post-central sulcus (Figure 3 – middle panel). In addition, in the few participants in
245 which the conditioning stimulus strip reached the central sulcus, we observed a small cluster of active spots
246 corresponding to the hand motor cortex. We did not observe significant effects from stimulation of the post-
247 central gyrus at the ISIs adopted here. The polarity of the effect was spatially organized. We observed
248 inhibitory effects of conditioning stimuli applied to the superior parietal lobule and the anterior intraparietal
249 region. We found excitatory effects from conditioning stimuli applied to the inferior parietal lobule. Most
250 patients showed only facilitatory or inhibitory effects in all stimulation dipoles. In two patients (#1 and #10) we
251 observed a change in polarity of the effect from inhibitory to facilitatory moving the stimulating electrode

252 ventrally and rostrally. All spots showed the same polarity of effect, whenever present, at all ISIs, with the sole
253 exception of a single spot in a single patient (#3), localized in the intraparietal region, that showed facilitatory
254 effects at the 4ms ISI and inhibitory effects at the 12 ms ISI. Figure 3 – right panel, shows the anatomical
255 localization of effective conditioning stimuli, grouped by ISI. The spots with effects at 4 ms were all clustered in
256 proximity of the hand motor area, while effective spots at higher ISIs increased gradually their distance from
257 hand-M1.

258 **Discussion**

259 **Three distinct regions in the parietal cortex exert specific short-latency effects on upper-limb corticospinal** 260 **excitability.**

261 In the present work we demonstrate for the first time the existence of direct parietal-motor functional
262 connections in humans by means of direct cortical stimulation. The presence of short-latency modulations of
263 conditioning stimuli implies that the two regions are functionally connected. (Koch and Rothwell, 2009). We
264 identified several cortical spots in the posterior parietal cortex that exert a short-latency effect on the
265 excitability of the corticospinal pathway to the upper limb. Combining spatial distribution and polarity
266 (excitatory or inhibitory) of the conditioning effects, we identified three distinct regions: a ventral region,
267 corresponding to the part of the supramarginal gyrus immediately posterior to the inferior postcentral sulcus,
268 extending ventrally to the parietal opercular region, a dorsal inhibitory region comprising the junction between
269 the intraparietal sulcus and the precentral sulcus and the portion of the superior parietal lobule adjacent to the
270 postcentral sulcus. A third region was indicated by a small cluster of 2 electrodes along the intraparietal sulcus,
271 around its middle portion. However, we should consider that the spatial sampling procedure employed here
272 suffers from a main limitation, that is, conditioning stimuli have been delivered on the crown of the sulci,
273 because the surgical procedures do not imply the opening of the arachnoid and widening of the sulci. As such,
274 our map of the parietal cortex is patchy and strongly biased towards the crown of the gyri.

275 **Widespread representation of upper limb movements in the posterior parietal cortex.**

276 In our study we focussed on the motor representation of the distal upper limb. A striking result is that the
277 posterior parietal cortex seems to contain a widespread representation of the upper limb. Having tested only
278 one effector, we cannot draw any conclusions on somatotopy, but our partial results argue against a possible
279 somatotopic arrangement of motor representations in the PPC, in opposition of what we could have expected
280 in the premotor region where rough somatotopy is suggested by several studies (Cunningham *et al.*, 2013).
281 Conversely, the posterior parietal cortex, albeit embedded with consistent motor representations, has not
282 been shown to be organized effector-wise in humans. Action representations in the PPC of humans seem to
283 show an upper limb preference and a spatial organization that reflects the type of action rather than the
284 effector used, except for eye movements that are supported by a specialized network (Grefkes and Fink, 2005).
285 Most authors seem to agree on a motor map of the rostral PPC organized in a medial-lateral system. Spatially-
286 oriented stimuli are coded in the SPL, object-directed movements in the mid-portion, corresponding to the
287 intraparietal sulcus and more complex hand actions such as symbolic movements and tool use are coded in the
288 IPL (Gallivan and Culham, 2015; Orban, 2016). Consequently, the finding of hand representations throughout
289 its medio-lateral extension is supported by current knowledge on the physiology of motor properties of the
290 human PPC.

291 **A direct parieto-motor pathway in humans.**

292 Neuroimaging studies in humans however, are not able to specify the actual neural pathways by which the PPC
293 can modulate movement. The novelty of the present study is providing compelling evidence that one possible
294 neural substrate of the PPC influence on action is fast, probably direct, parieto-motor connectivity. The
295 temporal characteristics of the parieto-motor interactions are illustrated in Figure 3C. We show a general
296 pattern of active spots modulating the output of hand-M1 at ISIs that are roughly proportional to the distance
297 between the active spot and M1, compatibly with axonal conduction of action potentials. Active spots that
298 exert modulation at 4 ms ISIs are all clustered nearby the hand-M1. Active spots that are effective at longer ISIs

299 are located progressively further away from the hand-M1. The two spots in the mid-intraparietal cluster both
300 appeared at 16 ms. This pattern indicates that effective ISIs scale positively with linear distance to hand-M1.
301 There are two main inferences to be made from this finding: First, that the effect on conditioning stimuli on the
302 PPC is not likely to be due to current spread to M1, because current spread is *quasi*-instantaneous, and the
303 latency of its effect would not increase with distance. Second, the increasing latency of the conditioning effects
304 with increasing distance from M1 argues against the possibility that the site of interaction between parietal
305 output and the corticospinal pathway is subcortical or spinal because in that case we would expect similar
306 latencies of conditioning effects. On the contrary, the pattern of co-variation of distance to hand-M1 with
307 effective ISI is strongly in favour of cortico-cortical connections between PPC and hand-M1 mediating the
308 conditioning effect.

309 **Effects of anaesthesia**

310 All our patients have been tested under the TIVA protocol. The main effect of propofol is a strong enhancement
311 of GABAergic inputs (Franks, 2008). In terms of brain connectivity, Propofol dampens extensive cortico-cortical
312 connections, according to TMS-EEG studies (Sarasso et al., 2015). The strength of oligosynaptic pathways is
313 affected but generally not to the level of a conduction block, as witnessed by the validity of somatosensory
314 evoked potentials and motor evoked potentials, which are mediated by multi-synaptic neural chains. The TIVA
315 protocol is titrable, and it was systematically kept at low levels of neural suppression (see methods). Therefore,
316 the anaesthesiologic setting employed here is appropriate to test mono- or oligo-synaptic connections, though
317 we cannot make any inference on how these connections would work in the awake state. Summing up, the
318 implications of testing cortico-cortical connectivity under anaesthesia are that: A) significant effects can be
319 considered as genuine expression of oligo-synaptic connections, B) non-significant stimulations could underlie
320 either no connections or multi-synaptic connections which are dampened by anaesthesia and C) we cannot
321 make any inference on how the highlighted connections would function in the awake state and even more so
322 during active tasks.

323 **Relation to connectivity data obtained with non-invasive brain stimulation**

324 Ipsilateral PPC-M1 connections have been tested non-invasively by dual-coil TMS in awake subjects in a series
325 of studies (Koch *et al.*, 2007, 2008b, a, 2010; Koch and Rothwell, 2009; Ziluk *et al.*, 2010; Cattaneo and
326 Barchiesi, 2011; Vesia and Davare, 2011; Karabanov *et al.*, 2012, 2013; Vesia *et al.*, 2013, 2017; Chao *et al.*,
327 2015; Maule *et al.*, 2015). The present results cannot be compared to these studies in alert subjects in terms of
328 polarity (inhibition or excitation) nor of task-dependency of the response because of the anaesthesia, but they
329 can be compared in terms of cortical site in the PPC and timing of conditioning stimuli that exert a significant
330 effect onto M1. Our data are compatible with the findings of Karabanov *et al.* (2013) showing two foci along
331 the intraparietal sulcus, the two clusters of active spots along the intraparietal sulcus in the present findings
332 (Figure 3B). The cluster of spots active at 4 ms ISI (Figure 3C) shows striking similarities with the findings of
333 Vesia *et al.* (2013). The most ventral spots along the postcentral sulcus are in the same location as the
334 opercular region that was stimulated in Maule *et al.* (2015). The posterior intraparietal spot stimulated in Koch
335 *et al.* (2007, 2008b) is similar or slightly posterior to the posterior cluster of active spots observed here.
336 Summing up, the current systematic mapping of the PPC is consistent with most of the previous data testing
337 single cortical spots with non-invasive brain stimulation.

338 **Summary**

339 We show conclusive evidence that in humans direct parieto-motor pathways exist. We investigated motor
340 output to the distal upper limb and found a widespread representation of the hand with seemingly no specific
341 spatial distribution that could parallel the somatotopy of the adjacent somatosensory cortex. Such absence of
342 topographic distribution is well supported by previous data in non-human and human primates that indicate a
343 spatial organization of motor features in the PPC reflecting action types rather than effectors. We did find a
344 specific spatial clustering of motor spots in the PPC according to the polarity of the effect on corticospinal
345 output and to spatial location. A ventral cluster showed excitatory effects, while a dorsal cluster showed
346 inhibitory effects. A third cluster was identified due to its localization, in the mid-portion of the intraparietal

347 sulcus. The clinical neurosurgeon's attention toward motor function of the parietal lobe is increasingly
348 recognized (Rossi *et al.*, 2018). The present data are potentially exploitable as an IONM procedure for the
349 monitoring of complex motor functions, though further investigations are required.

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- 472

Patient #, age, dexterity, sex.	Symptoms at presentation	Anatomical location of the lesion	Characterization of the neoplastic lesion
#1 - 60 y-o right-handed female	Apraxia, gait disturbances, dysesthesia and weakness on the right side	Right post-central, inhomogeneous lesion	Glioma IV (WHO 2016, IDH-WT, MGMT+)
#2 - 71 y-o, right-handed male	Gait ataxia, dysarthria	Right frontal homogenous lesion	Meningioma I (WHO 2016, A)
#3 - 62 y-o right-handed female	Left facial palsy of central type	right post-Rolandic inhomogeneous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT+)
#4 - 71 y-o, right-handed male	dysesthesia and weakness of the right arm and face; mild language deficits	left anterior intraparietal inhomogeneous lesion	Metastatic melanoma (VBRaf+)
#5 - 62 y-o right-handed female	Leg weakness	Left pre-Rolandic inhomogeneous lesion	Metastatic lung adenocarcinoma (PDL-2 +)
#6 - 62 y-o right handed female	Headache	Left frontal parasagittal homogenous lesion	Meningioma I (WHO 2016, A)
#7 - 74 y-o, right-handed male	Right leg weakness	Left frontal parasagittal homogenous lesion	Meningioma II (WHO 2016, A)
#8 - 75 y-o right-handed female	Generalized seizures	Right parieto-temporal inhomogeneous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT-)
#9 - 60 y-o right-handed female	Mood change	Right pre-Rolandic inhomogeneous lesion	Metastatic lung adenocarcinoma (PDL-1 +)
#10 - 67 y-o, right-handed male	Dizziness, gait ataxia	Right parieto-temporal inhomogeneous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT+)
#11 - 77 y-o, right-handed male	Focal seizures, dizziness, left homonymous hemianopia	Right parieto-temporal inhomogeneous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT+)
#12 - 79 y-o right handed male	Dizziness	Right Rolandic homogenous lesion	Meningioma I (WHO 2016, A-B)
#13 - 74 y-o, right-handed male	Enhancing lesion on follow up (redo)	Left superior frontal inhomogeneous lesion	Glioma IV (WHO 2016, IDH-1, MGMT+)
#14 - 32 y-o, right-handed male	Focal seizures	Right superior temporal homogenous lesion	Ganglioglioma I (WHO 2016, A-B)
#15 - 37 y-o, right-handed male	Focal seizures, mild language deficits (Redo)	Left temporal inhomogenous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT-)
#16 - 49 y-o right-handed female	Generalized seizures (Redo)	Left temporo-polar inhomogeneous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT+)
#17 - 52 y-o, right-handed male	Right side weakness, mild language deficits	Left temporo-polar inhomogeneous lesion	Glioma IV (WHO 2016, IDH- WT, MGMT+)

473 **Table 1: Demographic information on the group of patients**

474

475

patient	ISI:	conditioning stimulus cathode				
		P1	P2	P3	P4	P5
#1	4ms	-0.113 (sd: 0.22) t(19)=-1.17 p=0.2582	-0.069 (sd: 0.25) t(19)=-0.63 p=0.5378	-0.112 (sd: 0.21) t(19)=-1.18 p=0.2544	-0.441 (sd: 0.18) t(19)=-5.62 p<0.00001	0.508 (sd: 0.25) t(19)=4.59 p=0.0002
	8ms	0.03 (sd: 0.16) t(19)=0.42 p=0.6856	0.016 (sd: 0.24) t(19)=0.15 p=0.8814	0.071 (sd: 0.15) t(19)=1.08 p=0.2949	-0.513 (sd: 0.31) t(19)=-3.69 p=0.0016	0.232 (sd: 0.22) t(19)=2.36 p=0.0288
	12ms	0.068 (sd: 0.17) t(19)=0.92 p=0.3688	-0.38 (sd: 0.32) t(19)=-2.66 p=0.0156	-0.143 (sd: 0.21) t(19)=-1.54 p=0.1407	-0.511 (sd: 0.22) t(19)=-5.16 p=0.0001	-0.209 (sd: 0.18) t(19)=-2.53 p=0.0201
	16ms	-0.005 (sd: 0.19) t(19)=-0.06 p=0.9584	-0.585 (sd: 0.37) t(19)=-3.51 p=0.0023	-0.362 (sd: 0.27) t(19)=-2.98 p=0.0077	-0.549 (sd: 0.16) t(19)=-7.81 p<0.00001	0.016 (sd: 0.24) t(19)=0.15 p=0.8814
#2	8ms	-0.164 (sd: 0.27) t(14)=-1.39 p=0.19	-0.408 (sd: 0.18) t(14)=-5.02 p=0.0002	-0.035 (sd: 0.13) t(14)=-0.6 p=0.57	0.002 (sd: 0.09) t(14)=0.05 p=0.96	-0.084 (sd: 0.2) t(14)=-0.93 p=0.37
#3	4ms	0.421 (sd: 0.26) t(14)=3.59 p=0.003	0.142 (sd: 0.12) t(14)=2.68 p=0.018	0.062 (sd: 0.14) t(14)=0.96 p=0.35		
	8ms	0.193 (sd: 0.19) t(14)=2.32 p=0.03	-0.01 (sd: 0.11) t(14)=-0.2 p=0.84	0.015 (sd: 0.08) t(14)=0.44 p=0.66		
	12ms	-0.172 (sd: 0.06) t(14)=-6.26 p<0.00001	-0.115 (sd: 0.07) t(14)=-3.77 p=0.002	-0.104 (sd: 0.09) t(14)=-2.57 p=0.02		
	16ms	0.077 (sd: 0.24) t(14)=0.72 p=0.48	-0.087 (sd: 0.09) t(14)=-2.13 p=0.05	-0.023 (sd: 0.13) t(14)=-0.41 p=0.69		
#4	4ms	-0.732 (sd: 0.56) t(14)=-2.53 p=0.02	-0.56 (sd: 0.44) t(14)=-2.45 p=0.028	-0.747 (sd: 0.5) t(14)=-2.88 p=0.01	-0.407 (sd: 0.56) t(14)=-1.41 p=0.18	
	8ms	-0.85 (sd: 0.53) t(14)=-3.12 p=0.008	-0.653 (sd: 0.53) t(14)=-2.38 p=0.032	-0.556 (sd: 0.57) t(14)=-1.9 p=0.078	-1.762 (sd: 0.3) t(14)=-11.33 p<0.00001	
	12ms	-0.744 (sd: 0.6) t(14)=-2.4 p=0.03	-0.92 (sd: 0.46) t(14)=-3.88 p=0.002	0.09 (sd: 0.49) t(14)=0.36 p=0.73	-1.821 (sd: 0.31) t(14)=-11.27 p<0.00001	
	16ms	-1.001 (sd: 0.63) t(14)=-3.09 p=0.008	-1.093 (sd: 0.49) t(14)=-4.36 p=0.0007	-0.334 (sd: 0.54) t(14)=-1.21 p=0.25	-1.529 (sd: 0.38) t(14)=-7.81 p<0.00001	
#5	4ms	-0.201 (sd: 0.23) t(19)=-1.92 p=0.069	-0.313 (sd: 0.21) t(19)=-3.29 p=0.0038	-0.2 (sd: 0.18) t(19)=-2.43 p=0.02	-0.269 (sd: 0.26) t(19)=-2.34 p=0.03	

	8ms	-0.251 (sd: 0.6) t(19)=-0.93 p=0.36	-0.087 (sd: 0.23) t(19)=-0.83 p=0.41	-0.07 (sd: 0.15) t(19)=-1.02 p=0.32	-0.783 (sd: 0.23) t(19)=-7.75 p<0.00001	
	12ms	-0.173 (sd: 0.27) t(19)=-1.43 p=0.16	0.023 (sd: 0.11) t(19)=0.47 p=0.65	-0.076 (sd: 0.17) t(19)=-1.01 p=0.33	-0.696 (sd: 0.25) t(19)=-6.23 p<0.00001	
	16ms	-0.403 (sd: 0.48) t(19)=-1.88 p=0.07	-0.018 (sd: 0.19) t(19)=-0.21 p=0.83	-0.276 (sd: 0.25) t(19)=-2.51 p=0.022	-0.874 (sd: 0.14) t(19)=-13.62 p<0.00001	
#6	8ms	-0.291 (sd: 0.18) t(12)=-3.59 p=0.004	-0.362 (sd: 0.24) t(12)=-3.36 p=0.006	-0.027 (sd: 0.32) t(12)=-0.19 p=0.86	0.016 (sd: 0.21) t(12)=0.17 p=0.87	
	12ms	-0.018 (sd: 0.2) t(12)=-0.2 p=0.84	-0.343 (sd: 0.2) t(12)=-3.79 p=0.0026	0.086 (sd: 0.19) t(12)=1.02 p=0.33	0.026 (sd: 0.05) t(12)=1.13 p=0.29	
	16ms	-0.054 (sd: 0.13) t(12)=-0.93 p=0.37	-0.093 (sd: 0.32) t(12)=-0.65 p=0.53	0.104 (sd: 0.16) t(12)=1.48 p=0.17	-0.019 (sd: 0.08) t(12)=-0.52 p=0.61	
#7	4ms	-0.02 (sd: 0.18) t(15)=-0.25 p=0.80	0.049 (sd: 0.17) t(15)=0.65 p=0.52	-0.388 (sd: 0.23) t(15)=-3.71 p=0.002	-0.015 (sd: 0.18) t(15)=-0.19 p=0.85	
	8ms	0.113 (sd: 0.16) t(15)=1.55 p=0.14	-0.081 (sd: 0.13) t(15)=-1.36 p=0.20	-0.488 (sd: 0.32) t(15)=-3.42 p=0.004	-0.309 (sd: 0.17) t(15)=-4.1 p=0.0009	
	16ms	-0.132 (sd: 0.19) t(15)=-1.55 p=0.14	-0.203 (sd: 0.19) t(15)=-2.44 p=0.03	-0.209 (sd: 0.2) t(15)=-2.39 p=0.030	-0.111 (sd: 0.23) t(15)=-1.1 p=0.29	
#8	4ms	-0.051 (sd: 0.1) t(14)=-1.16 p=0.27	0.573 (sd: 0.22) t(14)=5.72 p=0.0001	0.027 (sd: 0.18) t(14)=0.34 p=0.74	0.141 (sd: 0.21) t(14)=1.47 p=0.16	-0.027 (sd: 0.08) t(14)=-0.74 p=0.48
	8ms	-0.043 (sd: 0.23) t(14)=-0.43 p=0.67	-0.039 (sd: 0.14) t(14)=-0.65 p=0.53	0.188 (sd: 0.12) t(14)=3.37 p=0.004	0.076 (sd: 0.16) t(14)=1.05 p=0.31	0.165 (sd: 0.18) t(14)=2.05 p=0.06
	12ms	-0.022 (sd: 0.09) t(14)=-0.54 p=0.60	0.016 (sd: 0.15) t(14)=0.23 p=0.82	0.007 (sd: 0.26) t(14)=0.06 p=0.95	0.16 (sd: 0.08) t(14)=4.49 p=0.0005	0.084 (sd: 0.07) t(14)=2.54 p=0.02
	16ms	-0.012 (sd: 0.17) t(14)=-0.15 p=0.88	-0.099 (sd: 0.14) t(14)=-1.6 p=0.13	0.046 (sd: 0.04) t(14)=2.93 p=0.012	0.285 (sd: 0.15) t(14)=4.21 p=0.0009	-0.026 (sd: 0.1) t(14)=-0.57 p=0.58
#9	4ms	-0.018 (sd: 0.1) t(22)=-0.39 p=0.70	-0.042 (sd: 0.2) t(22)=-0.46 p=0.65	-0.014 (sd: 0.07) t(22)=-0.47 p=0.65		
	8ms	-0.006 (sd: 0.14) t(22)=-0.09 p=0.93	0.059 (sd: 0.18) t(22)=0.72 p=0.48	1.208 (sd: 0.13) t(22)=20.46 p<0.00001		
	12ms	0.026 (sd: 0.22) t(22)=0.26 p=0.7932	-0.026 (sd: 0.17) t(22)=-0.34 p=0.73	0.558 (sd: 0.19) t(22)=6.62 p<0.00001		

	16ms	-0.057 (sd: 0.13) t(22)=-0.95 p=0.35	-0.023 (sd: 0.17) t(22)=-0.3 p=0.77	0.845 (sd: 0.14) t(22)=13.17 p<0.00001		
#10	8ms	-0.116 (sd: 0.18) t(13)=-1.46 p=0.1676	0.016 (sd: 0.11) t(13)=0.33 p=0.7491	-0.007 (sd: 0.09) t(13)=-0.17 p=0.8681	-0.312 (sd: 0.22) t(13)=-3.17 p=0.0075	0.387 (sd: 0.21) t(13)=4.12 p=0.0012
#11	8ms	0.885 (sd: 0.17) t(13)=11.58 p<0.00001	0.871 (sd: 0.1) t(13)=19.65 p<0.00001	-0.085 (sd: 0.15) t(13)=-1.3 p=0.22	-0.091 (sd: 0.11) t(13)=-1.87 p=0.084	0.74 (sd: 0.27) t(13)=6.09 p<0.00001
#12	8ms	-0.131 (sd: 0.44) t(15)=-0.67 p=0.51	-0.231 (sd: 0.72) t(15)=-0.72 p=0.49	0.715 (sd: 0.24) t(15)=6.81 p<0.00001	0.058 (sd: 0.35) t(15)=0.37 p=0.71	
	12ms	0.041 (sd: 0.38) t(15)=0.24 p=0.81	0.122 (sd: 0.53) t(15)=0.52 p=0.61	0.791 (sd: 0.14) t(15)=12.91 p<0.00001	-0.343 (sd: 0.47) t(15)=-1.64 p=0.12	
	16ms	-0.167 (sd: 0.52) t(15)=-0.72 p=0.48	0.03 (sd: 0.18) t(15)=0.37 p=0.71	0.288 (sd: 0.25) t(15)=2.56 p=0.02	-0.288 (sd: 0.34) t(15)=-1.9 p=0.08	
#13	8ms	-0.174 (sd: 0.2) t(14)=-1.92 p=0.07	-0.211 (sd: 0.19) t(14)=-2.46 p=0.03	0.833 (sd: 0.21) t(14)=8.93 p<0.00001		
	12ms	-0.005 (sd: 0.18) t(14)=-0.06 p=0.95	0.441 (sd: 0.09) t(14)=10.64 p<0.00001	1.044 (sd: 0.17) t(14)=14.06 p<0.00001		
	16ms	-0.093 (sd: 0.16) t(14)=-1.29 p=0.22	0.274 (sd: 0.14) t(14)=4.54 p=0.0005	1.242 (sd: 0.16) t(14)=17.91 p<0.00001		
#14	8ms	-0.039 (sd: 0.11) t(13)=-0.81 p=0.43	-0.068 (sd: 0.12) t(13)=-1.29 p=0.22	-0.015 (sd: 0.09) t(13)=-0.37 p=0.72	-0.034 (sd: 0.11) t(13)=-0.7 p=0.49	-0.032 (sd: 0.08) t(13)=-0.91 p=0.38
	12ms	-0.009 (sd: 0.1) t(13)=-0.2 p=0.85	-0.061 (sd: 0.11) t(13)=-1.24 p=0.24	0.004 (sd: 0.11) t(13)=0.08 p=0.94	-0.023 (sd: 0.1) t(13)=-0.53 p=0.61	-0.035 (sd: 0.09) t(13)=-0.87 p=0.40
	16ms	-0.043 (sd: 0.12) t(-1)=-0.81 p=0.43	-0.036 (sd: 0.11) t(13)=-0.73 p=0.48	-0.032 (sd: 0.12) t(13)=-0.6 p=0.56	0.02 (sd: 0.12) t(13)=0.39 p=0.71	0.046 (sd: 0.12) t(13)=0.87 p=0.40
#15	8ms	-0.026 (sd: 0.12) t(13)=-0.48 p=0.64	0.037 (sd: 0.13) t(13)=0.63 p=0.54	-0.021 (sd: 0.11) t(13)=-0.43 p=0.67	-0.043 (sd: 0.09) t(13)=-1.12 p=0.28	-0.061 (sd: 0.08) t(13)=-1.74 p=0.11
	12ms	-0.091 (sd: 0.1) t(13)=-2.07 p=0.06	-0.049 (sd: 0.1) t(13)=-1.06 p=0.31	-0.077 (sd: 0.09) t(13)=-1.86 p=0.09	-0.091 (sd: 0.11) t(13)=-1.85 p=0.08	-0.089 (sd: 0.15) t(13)=-1.37 p=0.20
	16ms	-0.021 (sd: 0.13) t(-1)=-0.37 p=0.72	-0.038 (sd: 0.14) t(13)=-0.59 p=0.56	-0.09 (sd: 0.09) t(13)=-2.13 p=0.05	0.015 (sd: 0.1) t(13)=0.35 p=0.72	0.008 (sd: 0.12) t(13)=0.15 p=0.89
#16	8ms	0.071 (sd: 0.18) t(17)=0.9 p=0.38	0.13 (sd: 0.16) t(17)=1.88 p=0.07	0.038 (sd: 0.15) t(17)=0.57 p=0.58	0.005 (sd: 0.12) t(17)=0.1 p=0.93	0.084 (sd: 0.2) t(17)=0.94 p=0.36

	12ms	-0.018 (sd: 0.16) t(17)=-0.26 p=0.80	0.065 (sd: 0.18) t(17)=0.82 p=0.42	-0.022 (sd: 0.2) t(17)=-0.25 p=0.80	-0.013 (sd: 0.2) t(17)=-0.15 p=0.88	0.01 (sd: 0.21) t(17)=0.11 p=0.91
	16ms	-0.034 (sd: 0.15) t(-1)=-0.51 p=0.61	0.013 (sd: 0.19) t(17)=0.15 p=0.88	-0.044 (sd: 0.2) t(17)=-0.49 p=0.63	0.021 (sd: 0.17) t(17)=0.28 p=0.78	-0.017 (sd: 0.18) t(17)=-0.22 p=0.83
#17	4ms	-0.066 (sd: 0.36) t(13)=-0.42 p=0.68	-0.116 (sd: 0.41) t(13)=-0.64 p=0.53	0.118 (sd: 0.27) t(13)=0.97 p=0.35	-0.205 (sd: 0.34) t(13)=-1.37 p=0.19	0.002 (sd: 0.22) t(13)=0.02 p=0.98
	8ms	-0.189 (sd: 0.36) t(13)=-1.18 p=0.26	-0.022 (sd: 0.24) t(13)=-0.2 p=0.85	-0.074 (sd: 0.39) t(13)=-0.43 p=0.67	0.106 (sd: 0.2) t(13)=1.18 p=0.26	-0.302 (sd: 0.42) t(13)=-1.61 p=0.13
	16ms	-0.173 (sd: 0.38) t(13)=-1.03 p=0.32	0.174 (sd: 0.31) t(13)=1.28 p=0.22	-0.04 (sd: 0.29) t(13)=-0.3 p=0.77	-0.163 (sd: 0.31) t(13)=-1.18 p=0.26	0.026 (sd: 0.31) t(13)=0.19 p=0.85

476 **Table 2: statistics on individual patients, for each conditioning electrode and each ISI.** The data reported
477 correspond to the log of the ratio between conditioned MEPs and test MEPs. The table reports the mean value
478 (standard deviation), and the t-statistics of the single-sample t-tests: t-value (degrees of freedom) and p-value.
479 Please note that the log-ratio has no dimensions because it is obtained by dividing two identical dimensions.
480 Note also that degrees of freedom are variable according to the number of single trials that were performed in
481 that particular condition. Conditions with p-values exceeding the Bonferroni-corrected significance threshold are
482 highlighted in bold. A corresponding graphical representation of the data is provided in Figure 4.