

1 **Simultaneous stereo-EEG and high-density scalp EEG recordings to study the**
2 **effects of intracerebral stimulation parameters**

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29
30 **Abstract**

31
32 *Background:* Cortico-cortical evoked potentials (CCEPs) recorded by stereo-
33 electroencephalography (SEEG) are a valuable clinical tool to investigate brain reactivity
34 and effective connectivity. However, these invasive recordings are spatially sparse since
35 they depend on clinical needs. This sparsity hampers systematic comparisons across-
36 subjects, the detection of the whole-brain spatiotemporal properties of CCEPs, as well as
37 their relationships with classic sensory evoked potentials.

38 *Objective:* To demonstrate that CCEPs recorded by high-density electroencephalography
39 (hd-EEG) are sensitive to changes in stimulation parameters and compensate for the
40 limitations typical of invasive recordings.

41 *Methods:* SEEG and hd-EEG activities were simultaneously recorded during SPES in
42 drug-resistant epileptic patients (N=36). Changes in stimulation parameters encompassed
43 physical (pulse intensity and width), geometrical (angle and position with respect to
44 white/grey matter) and topological (stimulated cortical area) properties. Differences were
45 assessed by measuring the overall responses and the amplitude of N1 and N2
46 components of the CCEPs, and by their spectral profiles.

47 *Results:* While invasive and non-invasive CCEPs were generally correlated, differences in
48 pulse duration, angle and stimulated cortical area were better captured by hd-EEG.
49 Further, hd-EEG responses to SPES reproduced basic features of responses to
50 transcranial magnetic stimulation and showed a much larger amplitude as compared to
51 typical sensory evoked potentials.

52 *Conclusions:* The present results show that macroscale hd-EEG recordings are exquisitely
53 sensitive to variations in SPES parameters, including local changes in physical and
54 geometrical stimulus properties, while providing valuable information about whole-brain
55 dynamics. Moreover, the common reference space across subjects represented by hd-
56 EEG may facilitate the construction of a perturbational atlas of effective connectivity.

57

58 **Highlights**

- 59 • CCEPs recorded with hd-EEG and SEEG are correlated.
- 60 • hd-EEG recording is highly sensitive to changes in stimulation parameters.
- 61 • hd-EEG responses show higher amplitude responses with respect to non-invasive
62 ones.
- 63 • Simultaneous recordings provide a fixed observation point across subjects.

64 **Key words**

65 Single pulse electrical stimulation, stereo-EEG, scalp hd-EEG, CCEP, stimulation
66 parameters

67

68 **Introduction**

69 Intracortical electrical stimulation is an invaluable tool for surgical planning [1–3] and
70 provides a direct assessment of brain evoked reactivity and effective connectivity in
71 humans [4–6]. Clinical protocols often combine Single Pulse Electrical Stimulation (SPES)
72 with stereotactic electroencephalography (SEEG) to evoke responses in areas explored
73 with intracerebral electrodes [7,8]. Conceived for localizing the origin and diffusion of the
74 epileptogenic activity [9–12] in patients with focal drug-resistant epilepsy, SPES typically
75 elicits consistent cortico-cortical evoked potentials (CCEPs) whose features reflect
76 physiological and pathological characteristics of the underlying neural tissue [7–9,13,14].

77 Thanks to their high functional specificity [15], signal fidelity [16], and high spatial
78 and temporal resolution [12–14], CCEPs can be used as an electrophysiological tool to
79 assess brain reactivity and effective connectivity complementing functional and structural
80 connectivity measures [4,13,17,18]. However, invasive recordings are necessarily sparse
81 since intracerebral electrodes are typically circumscribed to a limited set of brain regions
82 differing from one subject to another depending on clinical needs [8,9,12,14,19]. The
83 variability and sparsity of electrode placement clearly restricts a systematic comparison
84 across subjects, the detection of the stimulation effects at the whole-brain level, as well as
85 a direct comparison between CCEPs and other EEG potentials such as those evoked by
86 non-invasive sensory, electrical or magnetic stimulation.

87 In the present work, we overcame these limitations by simultaneously acquiring
88 high-density EEG recordings, which provide a fixed observation point to reliably compare
89 the responses evoked by SPES across subjects and to assess their whole-brain dynamics,
90 as well as their amplitude at the scalp level. Specifically, we analyzed the effects induced
91 by the systematic manipulation of different stimulation parameters on CCEPs recorded
92 from both SEEG and scalp EEG during wakefulness. We assessed CCEPs changes
93 associated to physical (pulse intensity and width), geometrical (angle and position with
94 respect to white/gray matter) and topological (stimulated cortical area) stimulation
95 properties and found that, when compared to SEEG, high-density scalp EEG detects
96 specific patterns that are more consistent across subjects. Notably, the differences in the
97 overall response when stimulating different topological areas were systematically captured
98 only by scalp recordings. We also observed a rostro-caudal gradient of the spectral
99 properties of CCEPs evoked by the stimulation of different cortical areas, confirming
100 previous results with Transcranial Magnetic Stimulation combined with EEG (TMS-EEG)
101 studies [20]. Further, comparing the absolute amplitude of clinical SPES-evoked EEG

102 responses to the typical amplitude of somatosensory, visual, auditory, or TMS-evoked
103 EEG potentials revealed that the former are the largest electrical responses that can be
104 elicited in the awake human brain.

105

106 **Materials and Methods**

107 *Participants*

108 A total of 36 patients (median age=33±8 years, 21 female, Table S1) from the "Claudio
109 Munari " Epilepsy Surgery Center of Milan in Italy were enrolled in the study. All subjects
110 had a history of drug-resistant, focal epilepsy, and were candidates for surgical
111 removal/ablation of the seizure onset zone (SOZ). 31 patients did not show any
112 anatomical malformation in the MRI, while the other 5 patients showed small anatomical
113 alterations (see Table S1). All patients had no neurological or neuropsychological deficits.
114 The investigated hemisphere/s and electrodes location was decided based on
115 electroclinical data and reported - for each subject - in Figure S1. All patients provided
116 their Informed Consent in accordance with the local Ethical Committee (ID 348-
117 24.06.2020, Milano AREA C Niguarda Hospital, Milan, Italy) and with the Declaration of
118 Helsinki.

119

120 *Electrodes placement and localization*

121 Electrodes placement was performed as reported in [8] while electrode localization and
122 anatomical labelling was performed as in [21]. Detailed descriptions can be found in
123 Supplementary Materials.

124

125 *Simultaneous SEEG and hd-EEG Recordings*

126 During the 1-3 weeks of hospitalization, SEEG activity was continuously recorded through
127 a 192-channel recording system (NIHON-KOHDEN NEUROFAX-1200) with a sampling
128 rate of 1000Hz. All acquisitions were referenced to two adjacent contacts located entirely
129 in white matter [22]. During their last day of hospitalization all subjects included in the
130 present study underwent simultaneous scalp non-invasive recordings by means of high-
131 density Electroencephalogram (hd-EEG - 256 channels, Geodesic Sensor Net, HydroCel
132 CleanLeads). Placement of the hd-EEG net on the head was performed by trained
133 neurosurgeons using sterile technique, following a precise step-by-step protocol: (1)
134 sterilization of the net, (2) removal of the protective bandage from the subject's head, (3)
135 skin disinfection with Betadine and Clorexan, (4) positioning of the hd-EEG net, and (5)

136 reduction of the impedances below 25-50 kOhm using conductive gel. An example of this
137 setup is shown in Figure 1. Hd-EEG was then recorded at 1000 Hz sampling rate using an
138 EGI NA-400 amplifier (Electrical Geodesics, Inc; Oregon, USA) referenced to Cz. SEEG
139 and hd-EEG recordings were aligned using a digital trigger signal generated by an external
140 trigger box (EMS s.r.l., Bologna, Italy). At the end of the simultaneous data acquisition, the
141 spatial locations of hd-EEG contacts and anatomical fiducials were digitized with a
142 SofTacticOptic system (EMS s.r.l., Bologna, Italy) and coregistered with a pre-implant 3D-
143 T1MRI. The net was then removed, and the skin was disinfected again.

144

145 *Single Pulse Electrical Stimulation*

146 During simultaneous hd-EEG and SEEG recordings, electrical single biphasic pulses
147 (positive-negative) were injected between pairs of adjacent intracranial contacts pertaining
148 to the same electrode with an inter-stimulus interval of at least one second across a wide
149 range of intensities and pulse widths (see next paragraph). Brain activity was continuously
150 recorded both from all other SEEG contacts as well as from the 256 scalp hd-EEG
151 contacts. A single stimulation session consisted of 30/40 consecutive trials. The number of
152 sessions varied between subjects (9 ± 4). All the sessions included in the present work
153 (N=379) were selected following these criteria: stimulations (i) were delivered through a
154 bipolar contact far from the SOZ (as indicated by electrical pathological activity and a
155 *posteriori* confirmed by post-surgical assessment); (ii) were delivered through a bipolar
156 contact that did not show spontaneous interictal epileptic activity (by visual inspection by
157 P.dO., J.L., I.S.); (iii) did not elicit muscle twitches, somatosensory, or cognitive
158 manifestations.

159

160 *Physical, geometrical, and topological stimulation parameters*

161 This work includes a dataset collected in the context of presurgical evaluation during which
162 SPES was delivered based on clinical assessment, thus employing different stimulation
163 parameters. Retrospectively, we decided to group these parameters into three categories,
164 namely *physical*, *geometrical* and *topological*.

165 *Physical stimulation parameters* included (i) stimulation intensity and (ii) pulse width.
166 Stimulation intensities ranged from 0.1mA to 5mA. Specifically, SPES was delivered at
167 0.1mA (N=3), 0.5mA (N=13), 1mA (N=23), 3mA (N= 63) and 5mA (N= 223). Given the low
168 number of sessions performed with intensities ≤ 1 mA we decided to group together all
169 these intensities (N=39). Pulse widths were instead 0.5ms (n=184) or 1ms (n=139).

170 *Geometrical stimulation parameters* refer (i) to the position of the stimulating bipolar
171 contact with respect to the interface between grey matter and white matter and (ii) to the
172 angle of insertion of the SEEG electrode with respect to the cortical surface. To derive
173 both parameters we used the 3D meshes of the grey and white matter obtained with
174 Freesurfer [25]. The distance to the grey/white matter boundary was computed as the
175 distance between the center of the stimulating bipolar contact and the closest point on the
176 white matter mesh (see Figure 1D and Figure 3A) using the *trimesh* library. The distances
177 of the bipolar contacts were then lumped into three categories: both contacts in grey
178 matter (*GG*), both contacts in white matter (*WW*) and one contact in grey matter and one
179 in white matter (*GW*). The angle with respect to the cortical surface was calculated using
180 the vector formed by the SEEG bipolar contact, and the normal vector of the closest
181 segment of the white matter mesh (see Figure 1D and Figure 3C). Also the angles were
182 lumped into two categories with respect to the cortical surface: *parallel* ($\delta < 45^\circ$; $\delta > 315^\circ$;
183 and $135^\circ < \delta < 225^\circ$) and *perpendicular* ($45^\circ < \delta < 135^\circ$ and $225^\circ < \delta < 315^\circ$).

184 *Topological stimulation parameters* included the following stimulated cortical areas:
185 Cingulate cortex (n=30), Frontal cortex (n=93), Insula (n=26), Occipital cortex (n=37),
186 Parietal cortex (n=113), Temporal cortex (n=80) using the Desikan-Killiany atlas for the
187 anatomical labelling.

188

189 *Data pre-processing*

190 The joint visual inspection of both SEEG and hd-EEG CCEPs allowed to retain 323/379
191 sessions (~85%), excluding 9 sessions that showed evoked epileptic spikes either at the
192 scalp or intracerebral EEG level (Figure S1, see also [12]), and 47 sessions characterized
193 by a number of retained trials lower than 25 due to overall bad data quality or the presence
194 of interictal activity.

195 For the retained SPES sessions SEEG data were processed as in [24] while hd-
196 EEG data were preprocessed as in [25]. Detailed procedures are reported in
197 Supplementary Material.

198

199 *Amplitude Analysis*

200 The effects of SPES parameters were assessed both at the SEEG and the hd-EEG level
201 by measuring standard features of CCEP waveforms (amplitude of N1 and N2) as well as
202 surrogate measures of the overall response (Figure 2). Specifically, at the SEEG level, the
203 latter was quantified as the number of contacts responding with a significant CCEP (above

204 6 STD of the baseline, Figure 2B) to SPES [26], while the amplitudes of N1 and N2 were
205 obtained at the single contact level [27,38] and then averaged across contacts.
206 Conversely, at the hd-EEG level, the overall response was obtained as the Global Mean
207 Field Power (GMFP, between 0ms and 500ms, shaded blue area in Figure 2B) and the
208 amplitude of N1 and N2 were detected as the maximum peak of the GMFP (black circles
209 in Figure 2B), respectively in the 0-50ms (dash and dot vertical line in Figure 2) and 50ms-
210 300ms time window. SNR was calculated in the same time windows.

211

212 *Spectral Analysis*

213 We performed an analysis similar to [20], in which we compared the spectral properties of
214 the CCEPs elicited by the stimulation of the occipital, parietal and frontal cortices.
215 Specifically, for each session, we conducted a time-frequency spectral analysis (Event
216 Related Spectral Perturbations, ERSP [29]) that was averaged across contacts within each
217 session. The resulting time-frequency power distribution was cumulated over time between
218 10ms and 150ms. Finally, due to the prominent presence of a non-specific response (*i.e.*,
219 the N1 - N2 complex), we characterized the spectral profile as the mean frequency -
220 instead of the maximum peak [20].

221

222 *Statistical Analyses*

223 Correlations between SEEG and hd-EEG measures were performed with non-parametric
224 Spearman's correlation analyses. Differences among multiple groups were assessed with
225 Kruskal-Wallis test (KW), followed by a post-hoc Wilcoxon Rank Sum test (WR, corrected
226 for multiple comparisons using the False Discovery Rate method-FDR). Statistical
227 interactions among stimulation parameters were performed with ANalysis Of VAriance
228 (ANOVA). All descriptive values are reported along the manuscript as the mean \pm standard
229 deviation. All statistical analyses were performed in R.

230 **Results and Discussion**

231 To the best of our knowledge, this is the first time that responses to intracortical SPES
232 were studied simultaneously with SEEG and scalp hd-EEG, as previous concurrent
233 recordings were only carried out for spontaneous activity while using low-density standard
234 10-20 systems [30–33].

235 Here, simultaneous scalp hd-EEG and intracranial SEEG recordings of CCEPs
236 were performed in 36 awake drug-resistant epileptic patients undergoing SPES for
237 presurgical evaluation (see Figure 1A-B-C). Overall, our dataset included 323 artefact-free
238 recording sessions encompassing different stimulation parameters, which were clustered
239 in three categories (see Figure 1D): *physical* (stimulation intensity and pulse width),
240 *geometrical* (position of the bipolar contact with respect to grey/white matter and angle of
241 the electrode with respect to the cortical surface), and *topological* (stimulated cortical
242 area).

243

244 *General features of CCEPs were consistent between SEEG and hd-EEG*

245 CCEPs were highly reproducible from trial to trial (Figure 1C) and characterized by a high
246 signal-to-noise ratio both in intracerebral ($\text{SNR} = 7.45 \pm 10.73$) and in hd-EEG ($\text{SNR} =$
247 6.96 ± 4.94) recordings (Figure 1D). We first quantified the overall strength of the response
248 to SPES by computing GMFP (cumulated between 0ms and 500ms) at the hd-EEG level,
249 and the percentage of significantly responding contacts at the SEEG level (Figure 2B).
250 Then, we evaluated the waveshape of CCEPs by measuring the average amplitude of N1
251 and N2 across all sessions (Figure 2B and Methods). Despite displaying different
252 waveshapes at the single contact level (see for example Figure 1E), hd-EEG and SEEG
253 showed on average a similar waveform characterized by a prominence of the typical
254 [27,34–36] N1 and N2 components ($\text{N1} = 9.5 \pm 5.04\mu\text{V}$; $\text{N2} = 11.36 \pm 9.86\mu\text{V}$ for hd-EEG
255 and $\text{N1} = 13.90 \pm 7.04$ z-value; $\text{N2} = 15.20 \pm 7.02$ z-value for SEEG; Figure 2A).
256 Importantly, we found significant positive correlations (GMFP and number of responding
257 contacts, $r=0.592$; N1 amplitude, $r=0.313$; N2 amplitude, $r=0.553$. All $p < 0.001$) between
258 the above-mentioned SEEG and hd-EEG measures (Figure 2C), suggesting that general
259 features of CCEPs could be captured at both levels.

260

261 *Physical stimulation parameters: the effects of pulse intensity and width*

262 The effects of varying stimulation intensity could be appreciated in the CCEPs when
263 measuring N1, N2 and overall strength of the response both at the SEEG and hd-EEG

264 level (Figure 3A). Statistical analysis performed with KW and post-hoc pairwise
265 comparisons using WR tests revealed that the differences among the three stimulation
266 intensities ($\leq 1\text{mA}$, 3mA and 5mA) could be fully captured by both SEEG and hd-EEG
267 (Figure 3B). Specifically, SEEG showed a significant difference in the percentage of
268 contacts responding to SPES ($H_{(2)}=25.70$, $p<0.001$), in the N1 amplitude ($H_{(2)}=25.39$,
269 $p<0.001$) and in N2 amplitude ($H_{(2)}=36.60$, $p<0.001$). Similarly, hd-EEG showed significant
270 differences in the GMFP ($H_{(2)}=10.05$, $p=0.006$), in N1 amplitude ($H_{(2)}=12.13$, $p=0.002$), as
271 well as in N2 ($H_{(2)}=11.95$, $p=0.002$). Post-hoc statistical analyses are reported in Table S2.

272 Conversely, differences in pulse width (0.5ms vs 1ms) were captured only by hd-
273 EEG but not by SEEG (Figure 3C). Specifically, at the hd-EEG level, WR test showed that
274 GMFP, amplitude of N1 and amplitude of N2 were significantly larger for 1ms than for
275 0.5ms pulse width ($W=14193$, $W=13916$, $W=12663$, respectively, all $p<0.001$; Figure 3D).
276 Of note, both physical stimulation parameters (intensity and width) were not biased by any
277 specific spatial distribution (see Figure S3A-B).

278 Overall, these results are in line with previous intracerebral studies which
279 demonstrated that the amplitude of N1 and N2 components and, more in general, the
280 amplitude of CCEPs depend on the amount of injected current [37–40]. However, while the
281 effect of stimulation intensity has been clearly described, the effects of pulse width are less
282 consistent across the literature [14,28,39,41]. Here, the larger hd-EEG responses elicited
283 by longer pulse width stimulations may suggest the involvement of a larger network,
284 implying broader polysynaptic activations [27] and recurrent activities [24,42]. In summary,
285 complementing intracerebral explorations with whole brain hd-EEG measures confirms
286 previous findings regarding stimulation intensity and suggests that the effects of pulse
287 width may not be fully captured by SEEG recording alone.

288

289 *Geometrical stimulation parameters: the effects of contact position with respect to the*
290 *cortex*

291 First, we assessed the SEEG and hd-EEG responses to SPES when stimulating at
292 different distances from grey-white matter interface (operationalized as GG/GW/WW;
293 Figure 4A). We observed that this geometrical stimulation parameter affected CCEPs both
294 at the SEEG and hd-EEG level, as assessed by KW statistical analyses. Specifically, this
295 was true for all measures at the hd-EEG level (for GMFP, $H_{(2)}=15.03$, $p<0.001$; for AMP N1,
296 $H_{(2)}=26.41$, $p<0.001$; for AMP N2 $H_{(2)}=11.95$, $p<0.01$). Instead, at the SEEG level only the
297 percentage of responding contacts and the amplitude of N2 showed a significant

298 difference ($H_{(2)}=12.66$, $p<0.01$; $H_{(2)}=17.47$, $p<0.001$; respectively), while the N1 amplitude
299 was not significantly affected ($H_{(2)}=5.12$, $p=0.077$). In particular, except for N1 in SEEG,
300 post-hoc comparisons showed that the stimulation of WW was more effective (*i.e.*, larger
301 CCEP response) with respect to the stimulation of GW, which in turn was more effective
302 than the stimulation of GG (Figure 4B and Table S3).

303 The second geometrical parameter we considered was the angle with respect to the
304 grey-white matter interface (operationalized as parallel/perpendicular, Figure 4C). In this
305 case (Figure 3C), perpendicular stimulations led to significantly larger responses only at
306 the hd-EEG level (for GMFP, $W=6361$ $p=0.045$; for AMP N1 $W=6483$ $p=0.038$; for AMP N2
307 $W=6551$ $p=0.044$). On the contrary, none of the SEEG measures showed significant
308 differences ($W=6588$ $p=0.125$, $W=5491$ $p=0.473$, and $W=5491$ $p=0.286$ for percentage of
309 responding contacts, AMP N1, and AMP N2, respectively). Of note, both geometrical
310 parameters (white matter distance and angle) were not biased by any specific spatial
311 distribution (Figure S3C-D).

312 Studies on intracerebral techniques that focused on the effect of geometrical
313 stimulation parameters have been performed to optimize Deep Brain Stimulation protocols.
314 According to these studies, small differences in electrode location [43–46], as well as
315 orientation [47] can generate considerable differences in the activated white matter
316 pathways. In line with these findings, the larger hd-EEG responses observed both with
317 WW and perpendicular stimulations could be ascribed to the more extensive involvement
318 of white-matter fiber bundles.

319

320 *Interactions between physical and geometrical stimulation parameters*

321 The above-mentioned stimulation parameters could in principle interact at different levels.
322 However, a model with the interaction of all the explored physical and geometrical
323 parameters would require a larger sample. For this reason, we tested the interactions
324 using pairwise bivariate ANOVAs. Overall, we observed significant interactions only at the
325 hd-EEG level in pulse width/angle, pulse width/distance from white matter,
326 intensity/distance from white matter (Figure S4). Specifically, the first two were found both
327 for GMFP and amplitude of N2 while the latter was found only for N1 amplitude. Although it
328 is conceivable that longer pulse widths and higher intensities might have stronger effects
329 when delivered closer or perpendicular to white matter fiber bundles [48-51] and that this
330 might reflect in more effective whole-brain level effects (*i.e.*, recorded with hd-EEG), future

331 studies including a larger sample size and a multivariate analysis would be needed to
332 reach an exhaustive interpretation of these interactions.

333

334 *Topological stimulation parameters: the effect of stimulating different areas*

335 Further, we evaluated whether the stimulation of different cortical areas was associated
336 with differences in CCEP amplitude. At the hd-EEG level, we systematically observed that
337 responses to the stimulation of the frontal cortex were larger than those obtained when
338 stimulating any other cortical area. Specifically, as shown in Figure 5C, KW test and
339 Wilcoxon Rank Sum post-hoc pairwise comparisons revealed a significant difference for all
340 the measures at the hd-EEG level (GMFP: $H_{(5)}=15.45$, $p=0.008$; AMP1 $H_{(5)}=20.32$, $p=0.001$;
341 AMP2 $H_{(5)}=19.85$, $p=0.001$). On the contrary, among all the considered S EEG measures,
342 only N1 showed a significant effect (percentage of responding contacts: $H_{(5)}=10.41$, $p=0.06$;
343 AMP1 $H_{(5)}=20.71$, $p=0.0009$; AMP2 $H_{(5)}=9.29$, $p=0.09$). Post-hoc statistical analyses are
344 reported in Table S4.

345 High-amplitude responses to SPES of the frontal cortex could be due to the
346 involvement of the circuits related to saliency [52,53], which are thought to be responsible
347 for the generation of high amplitude scalp EEG graphoelements such as the K-complex
348 [54] and the Vertex Wave [55]. Intriguingly, the latter is the largest graphoelement that can
349 be evoked by sensory stimulation in an awake brain and is on average 25 μ V, with a peak-
350 to-peak maximal amplitude of 35 μ V [52–55].

351

352 *Comparing invasive and non-invasive brain stimulation techniques*

353 In our dataset, CCEPs voltage at Cz were on average 43.42 μ V (average reference;
354 53.1 μ V when referenced to mastoid), reaching a peak-to-peak maximum of 172.16 μ V
355 (average reference; 214.43 μ V when referenced to mastoid), and thus much larger than
356 any sensory evoked potential recorded during wakefulness. This finding is particularly
357 interesting when considering CCEPs impact on the subjects' awareness: despite eliciting
358 massive and long-lasting activations of cortical circuits, none of our intracranial stimulation
359 resulted in any reportable perceptual event.

360 Interestingly, CCEPs' voltages at the scalp EEG level were also out of scale with respect
361 to the scalp EEG responses typically obtained when perturbing similar circuits with non-
362 invasive peripheral or direct stimulation in awake healthy subjects. Indeed, sensory (be it
363 auditory, somatosensory or visual) evoked potentials may range from a fraction of a
364 microvolt to few microvolts, while TMS evoked potentials (TEPs) may reach amplitudes of

365 about 20 μ V [56–59]. Importantly, our results showed that, similarly to TMS, SPES could
366 elicit large EEG components that persist for hundreds of milliseconds, thus corroborating
367 the idea that late components genuinely reflect the effects of direct cortical rather than
368 peripheral activation [60].

369 Furthermore, combining hd-EEG with SPES allowed to directly compare invasive
370 and non-invasive (TMS) stimulation methods in terms of spectral properties emerging at
371 the local and at whole brain level when perturbing the brain at different sites - as in TMS-
372 EEG investigations [20]. To this aim, we calculated time-frequency spectra (ERSP) of the
373 CCEPs collected with SEEG and hd-EEG when stimulating occipital, parietal or frontal
374 cortices (Figure 6A-B). Then, we cumulated the ERSPs over time (between 5ms and
375 150ms) to obtain a spectral profile for each session, whose grand average is depicted in
376 Figure 6C-D. This analysis showed that the CCEPs evoked by the stimulation of the
377 occipital, parietal and frontal cortices were characterized by a rostro-caudal gradient of
378 mean frequencies - *i.e.*, occipital<parietal<frontal (Figure 6C-D). These differences were
379 significant both at the hd-EEG and at the SEEG level as assessed by KW tests (hd-EEG:
380 $H_{(2)}=16.49$, $p=0.0002$; SEEG: $H_{(2)}=8.31$, $p=0.013$) and post-hoc one-tailed WR tests (Table
381 S5). These results obtained with intracortical SPES confirm previous non-invasive TMS-
382 EEG assessments [20,56] and reflect site specific spectral properties that are amplitude-
383 independent and can be observed both at the whole brain level (*i.e.*, with the scalp EEG)
384 as well as locally (SEEG).

385

386 *Limitations*

387 Our results were obtained from a population of epileptic patients whose clinical condition
388 and specific treatment [61] may affect both invasive and non-invasive recordings. To
389 minimize this confound, we did not include any SEEG contact located in the SOZ (as
390 verified by surgical resection) or exhibiting sustained pathological interictal activity.
391 Moreover, we excluded from the analyses all the CCEPs showing evoked epileptic activity
392 at the SEEG and/or at the hd-EEG level [9].

393 Clinical needs also constrained the exploration of physical stimulation parameters to
394 few pulse intensities and two pulse widths. Future studies encompassing multiple intensity
395 and pulse width steps, like Paulk and colleagues [63], will allow for a more systematic
396 comparison between invasive and non-invasive stimulation techniques.

397 Finally, the combination of SEEG and hd-EEG entails specific data acquisition
398 protocols to prevent infective risks. This implies a short duration of SPES procedures and

399 thus the acquisition of few trials from a limited number of sites per patient. To compensate
400 for these constraints, we verified that the number of acquired trials led to reliable
401 responses in terms of SNR - both at the SEEG and hd-EEG level - and we included a
402 relatively large number of stimulation sessions (N=323) and subjects (N=36). This sample
403 size allowed to perform univariate analyses and to assess interactions through bivariate
404 models (Figure S4). Larger datasets will ensure the possibility of performing multivariate
405 analyses considering all the explored variables. In this respect, the results shown in the
406 present manuscript represent a first step toward a more comprehensive description of the
407 scalp EEG responses to SPES and their relationship with intracerebral recordings.

408

409 *Conclusions*

410 The present results show that CCEPs recorded with hd-EEG are overall aligned with those
411 obtained with invasive SEEG recordings. Most important, they show that macroscale hd-
412 EEG recordings are exquisitely sensitive to variations in stimulation parameters, including
413 local changes in physical and geometrical stimulus properties, while overcoming the
414 limitations typical of sparse recordings.

415 In general, the possibility of studying and comparing across subjects the effects of multiple
416 local intracortical perturbations at the whole brain level opens interesting fields of
417 investigations. For example, it may complement current datasets on the structural [64] and
418 functional [65] connectomes with an effective connectome [28] whereby intracortical
419 interactions are systematically studied by a causal perspective in the common recording
420 space of scalp EEG and with a full assessment of spatio-temporal dynamics. Moreover,
421 hd-EEG recordings allow direct comparisons between the CCEPs and classic evoked
422 potentials elicited by non-invasive stimulation. For example, EEG responses to SPES
423 reproduced the rostro-caudal spectral gradient as previously shown by TMS-EEG
424 measurements and were found to be systematically larger than any sensory evoked
425 potential that can be elicited during wakefulness, including those associated with stimulus
426 perception. Along these lines, future studies should also explore, in terms of their whole-
427 brain spatio-temporal features, why some brain responses are associated with perceptual
428 events and others do not.

429 **Authors contributions**

430 Conceptualization: S.P., E.M., S.R. and A.P.; supervision: A.P. and M.M.; data collection:
431 S.P., S.R. A.P., F.Z., A.R., and I.S. data curation: E.M. and AP; data analyses: S.P., E.M.,
432 A.P., S.R., M.F., A.C.; clinical investigation: I.S., J.L., D.G., P.dO, statistical analysis: E.M.,
433 S.P., S.R. and A.P.; writing original draft: S.P., A.P., E.M., S.R, and S.S.; review and
434 editing: all authors.

435

436 **Declarations of interest**

437 None of the authors have conflicts of interest to disclose in relationship with the current
438 work.

439

440 **Funding**

441 This research has received funding from the European Union's Horizon 2020 Framework
442 Programme for Research and Innovation under the Specific Grant Agreement No. 720270
443 (Human Brain Project SGA1- to M.M.), No. 785907 (Human Brain Project SGA2 - to M.M.
444 and P.A.), and No. 945539 (Human Brain Project SGA3 - to M.M. and P.A.). The study has
445 also been partially funded by the grant "Sinergia" CRSII3_160803/1 of the Swiss National
446 Science Foundation (to M.M.) and the Tiny Blue Dot Foundation (to M.M.).

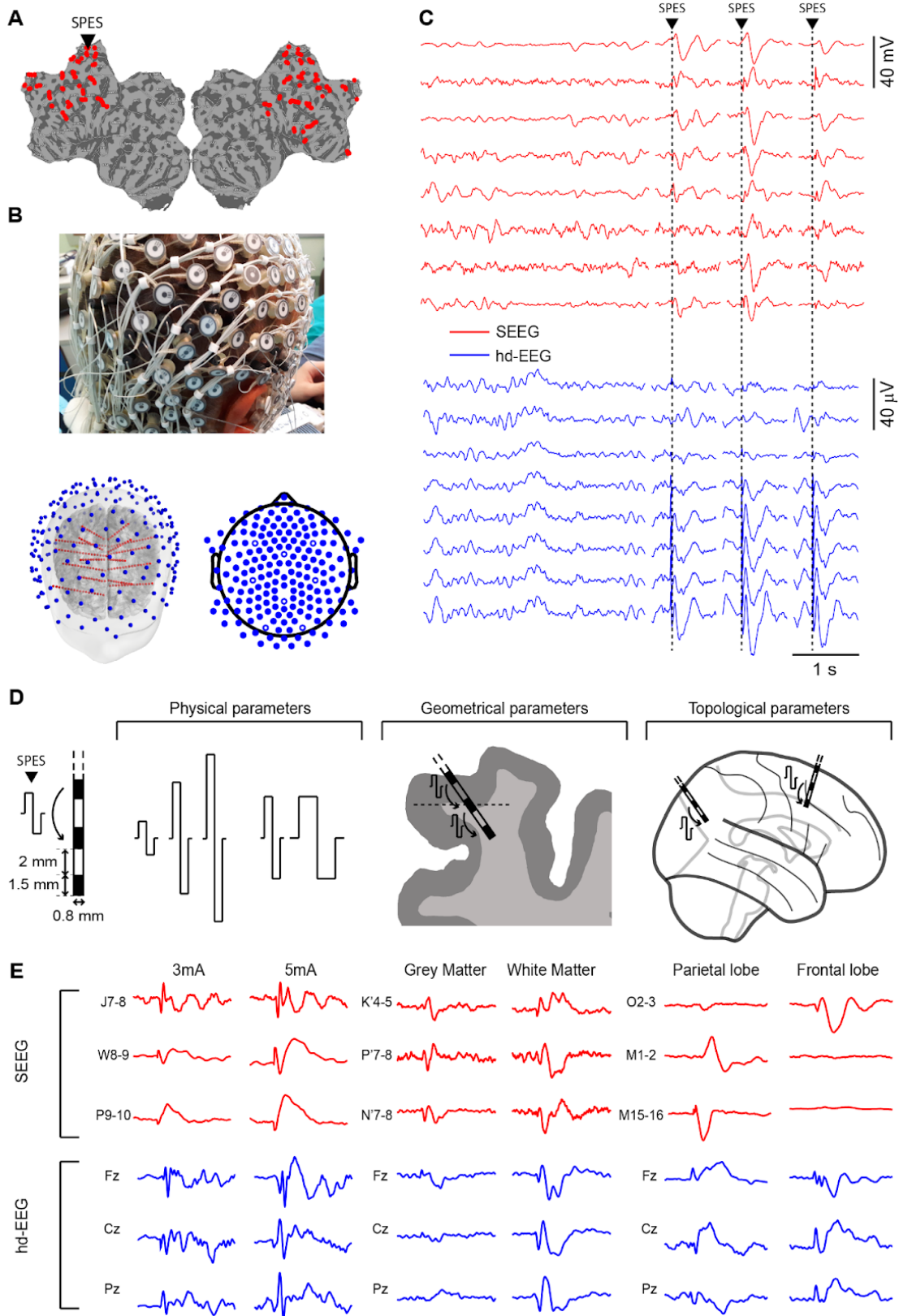
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448 **Acknowledgements**

449 We are grateful to Mario Rosanova, Susanna Bianchi, Jacopo Favaro, Michela Solbiati,
450 Aurora Sium, Alessandro Viganò, Renzo Comolatti, Giulia Furregoni and Martina Revay
451 for their comments and suggestions.

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Figures

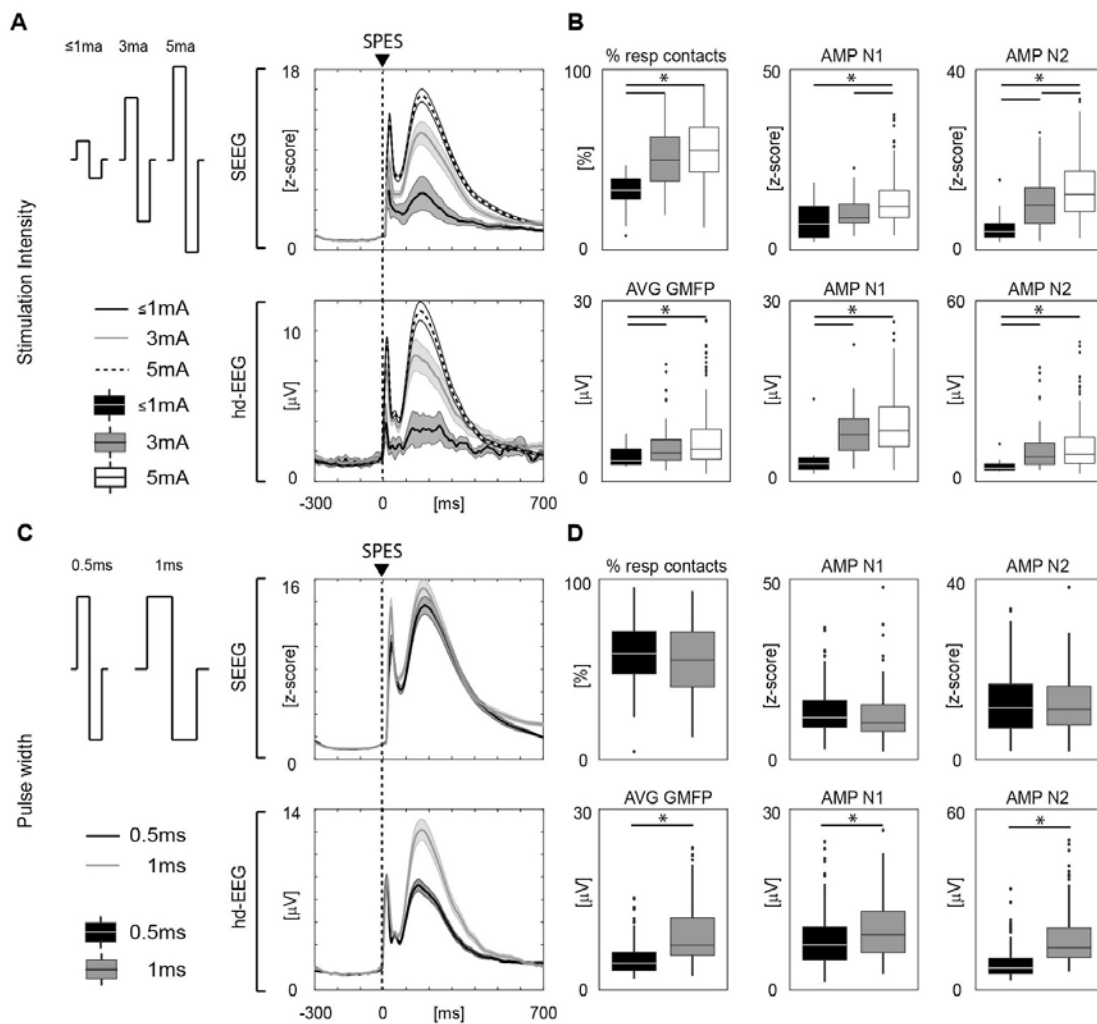


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456 **Figure 1. Experimental setup. Panel A.** Topographical representation, on a flatmap, of
457 the SEEG contacts in one representative subject. The black triangle indicates the contact
458 used for SPES (anterior cingulate). **Panel B.** Picture of simultaneous SEEG and hd-EEG
459 recordings, 3D reconstruction of the brain and SEEG implant of one representative patient
460 (same as A) and topographical representation of hd-EEG contacts. **Panel C.** Concurrent
461 raw intracerebral SEEG (red) and hd-EEG (blue) signals recorded respectively from eight
462 representative bipolar contacts and from eight scalp EEG contacts. The black triangle and
463 dashed vertical line indicate the time at which SPES was delivered. **Panel D.** Left, outline
464 of a multi-lead intracerebral electrode. Right, overview of stimulation parameters
465 categories: physical, geometrical and topological. **Panel E.** Examples of intracerebral
466 SEEG (red) and hd-EEG (blue) signals recorded from representative bipolar contacts
467 when delivering SPES with different physical (3mA vs 5mA), geometrical (white matter vs
468 grey matter) and topological (parietal vs frontal lobe) parameters.

487 comparing hd-EEG (on y-axes) and SEEG measures (on x-axes). From left to right, linear
488 regression between GMFP calculated at the hd-EEG level and the number of SEEG
489 contacts responding to SPES with a significant CCEP ($r=0.592$, $p<0.001$); linear
490 regression between the amplitude of N1 component calculated both at the hd-EEG and at
491 the SEEG level ($r=0.313$, $p<0.001$); linear regression between the amplitude of N2
492 component calculated both at the hd-EEG and at the SEEG level ($r=0.553$, $p<0.001$).

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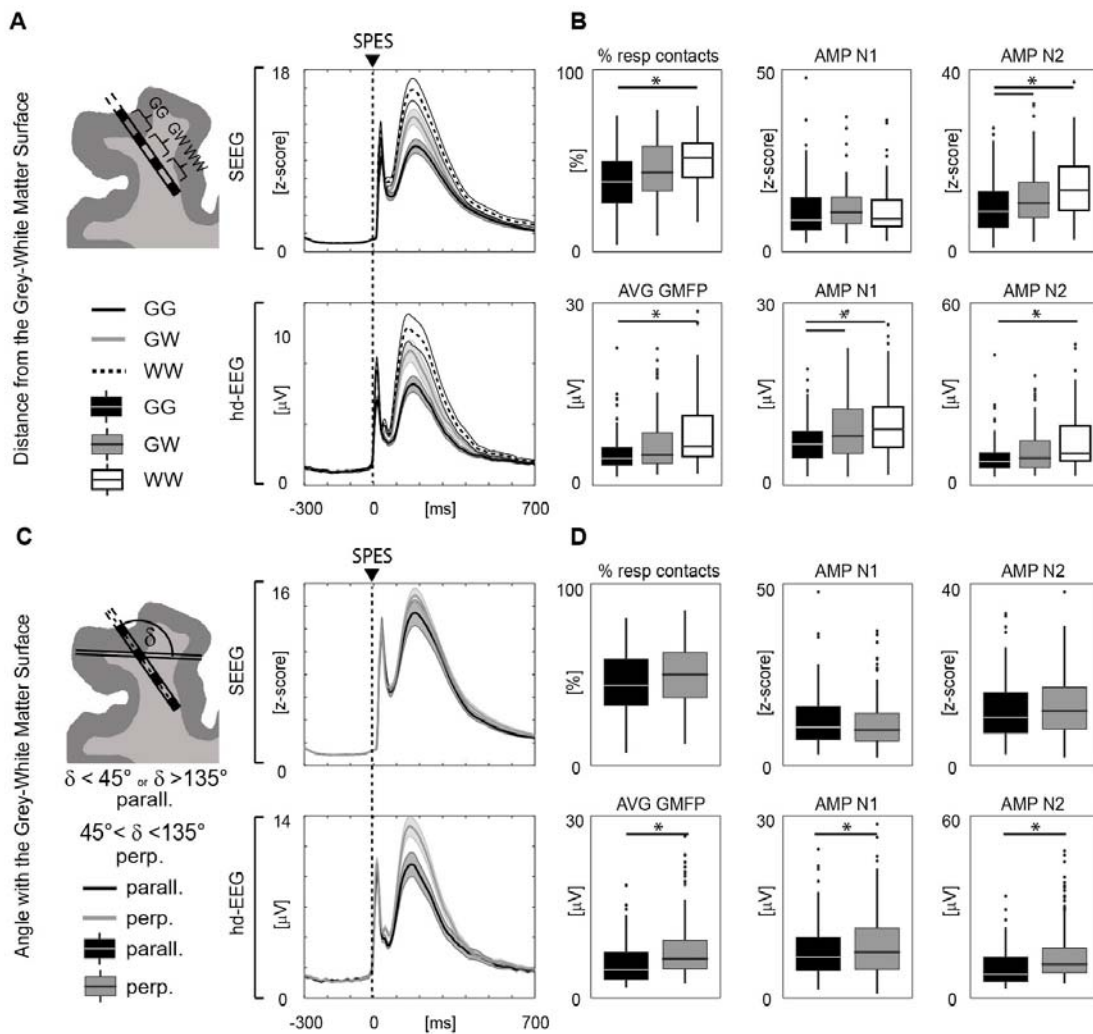
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Figure 3. hd-EEG and SEEG responses to SPES delivered at different physical stimulation parameters: intensities and pulse durations. Panel A. Left, outline of the different pulse intensities; right, grand average of data obtained from all the subjects and sessions. **Panel B.** *Upper line:* from left to right, percentage of responding contacts and N1 and N2 amplitudes for all sessions, recorded in SEEG. *Lower line:* from left to right, GMFP voltage and N1 and N2 amplitudes, for all sessions, recorded in hd-EEG. Asterisks indicate significant statistical differences (post-hoc, two-tailed WR, $p < 0.01$, FDR corrected). **Panel C.** Left, outline of the different pulse durations; right, grand average of data obtained from all the subjects and sessions. **Panel D.** *Upper line:* from left to right, percentage of responding contacts and N1 and N2 amplitudes for all sessions, recorded in SEEG. *Lower line:* from left to right, GMFP voltage and N1 and N2 amplitudes, for all sessions, recorded in hd-EEG. Asterisks indicate significant statistical differences (WR, $p < 0.01$, FDR corrected).



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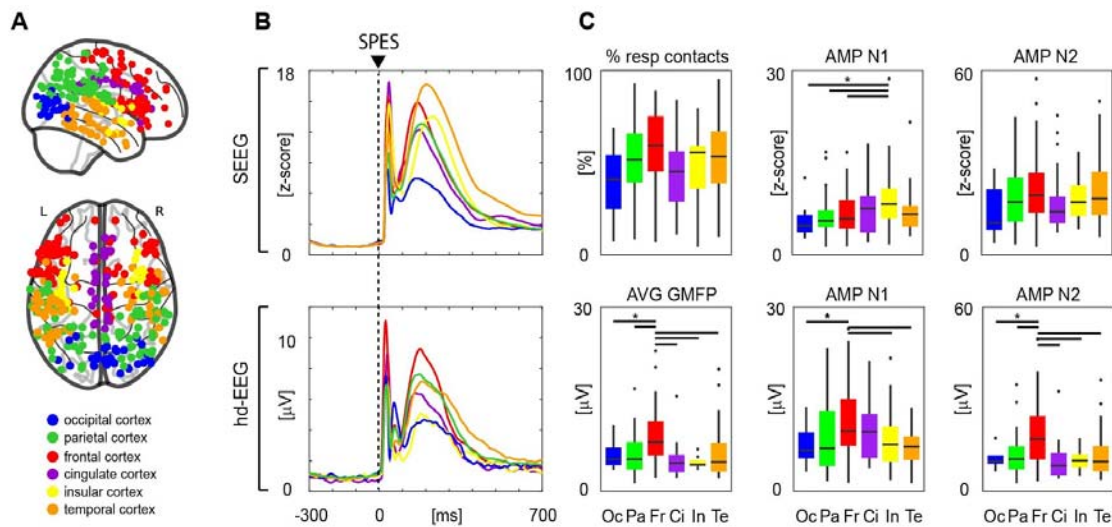
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Figure 4. Hd-EEG and SEEG responses to SPES delivered at different geometrical stimulation parameters. Panel A. Left, outline of the distance from the gray-white matter surface (G and W respectively); right, grand average of data obtained from all the subjects and sessions. **Panel B.** *Upper line:* from left to right, percentage of responding contacts and N1 and N2 amplitudes for all sessions, recorded in SEEG. *Lower line:* from left to right, GMFP voltage and N1 and N2 amplitudes, for all sessions, recorded in hd-EEG. Asterisks indicate significant statistical differences (post-hoc, two-tailed WR, $p < 0.01$, FDR corrected). **Panel C.** Left, outline of the angle with respect to the gray-white matter surface (parallel, perpendicular); right, grand average of data obtained from all the subjects and sessions. **Panel D.** *Upper line:* from left to right, percentage of responding contacts and N1 and N2 amplitudes for all sessions, recorded in SEEG. *Lower line:* from left to right, GMFP voltage and N1 and N2 amplitudes, for all sessions, recorded in hd-EEG. Asterisks indicate significant statistical differences (WR, $p < 0.01$, FDR corrected).



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Figure 5. Hd-EEG and SEEG responses to SPES delivered through contacts in

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different cortical cortices (topological parameters). Panel A. Topographical distribution

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of the stimulations performed through bipolar SEEG contacts located in different cortical

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areas (cingulate cortex, insula, frontal cortex, occipital cortex, parietal cortex, temporal

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cortex). Color coding is consistent across the figure. **Panel B.** Grand average across

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sessions and subjects of the GMFP obtained by SPES of all the six cortices reported in

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Panel A; dashed vertical line indicates SPES timing. Here and across the figure, top

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panels refer to SEEG recordings, while bottom panels refer to hd-EEG recordings. **Panels**

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C. From left to right, boxplots of Average GMFP, amplitude of N1 and amplitude of N2.

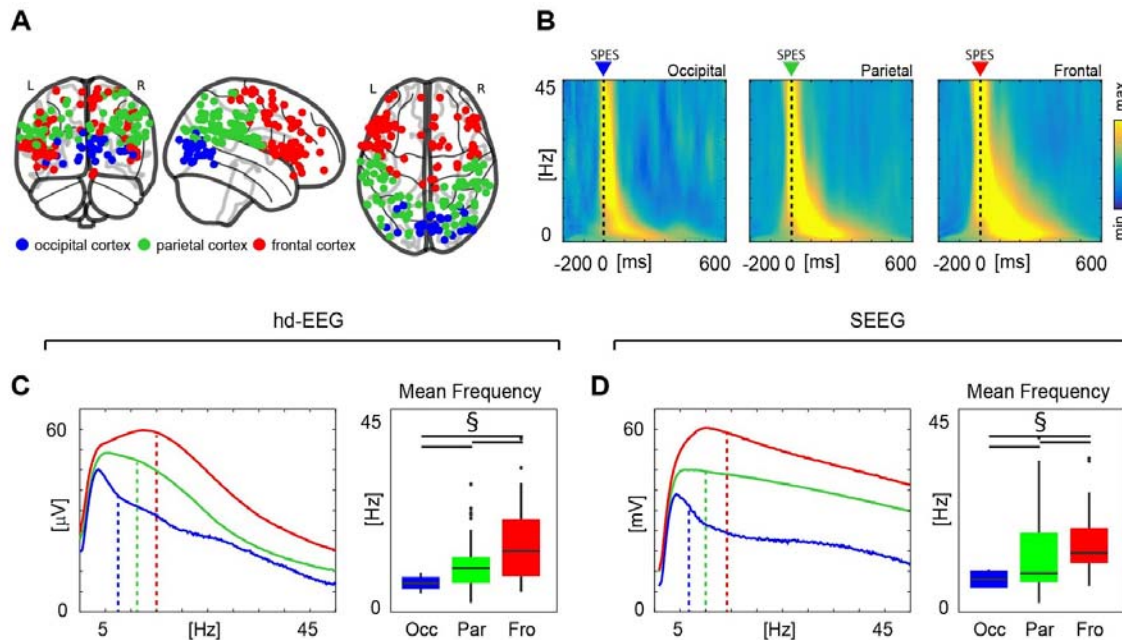
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Asterisks indicate significant statistical differences obtained with a post-hoc, two-tailed WR

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test ($p < 0.05$, FDR corrected).

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Figure 6. Reproducing TMS-EEG experiments: rostro-caudal gradient of cortical spectral features. **Panel A.** Topographical distribution of the stimulations performed through bipolar SEEG contacts located in different cortices (occipital cortex, parietal cortex, frontal cortex). Color coding is consistent across the figure. **Panel B.** The spectral properties (ERSP) emerged at the whole brain level after SPES in the three different sites (occipital, parietal, frontal), recorded with hd-EEG. **Panel C** concerns hd-EEG recordings. *Left.* Grand average across sessions and subjects of spectral profile, namely ERSPs cumulated over time (between 5ms and 150ms), obtained by SPES of occipital, parietal and frontal cortices; dashed vertical lines indicate mean frequencies. *Right.* Boxplot of the mean frequency for occipital, parietal, and frontal cortices. § indicates significant statistical differences ($p < 0.05$) obtained with one-tailed Wilcoxon test, under the assumption that the mean frequency of occipital, parietal and frontal cortex are characterized by a rostro-caudal gradient [22]. **Panel D.** Same as C but concerning SEEG recordings.

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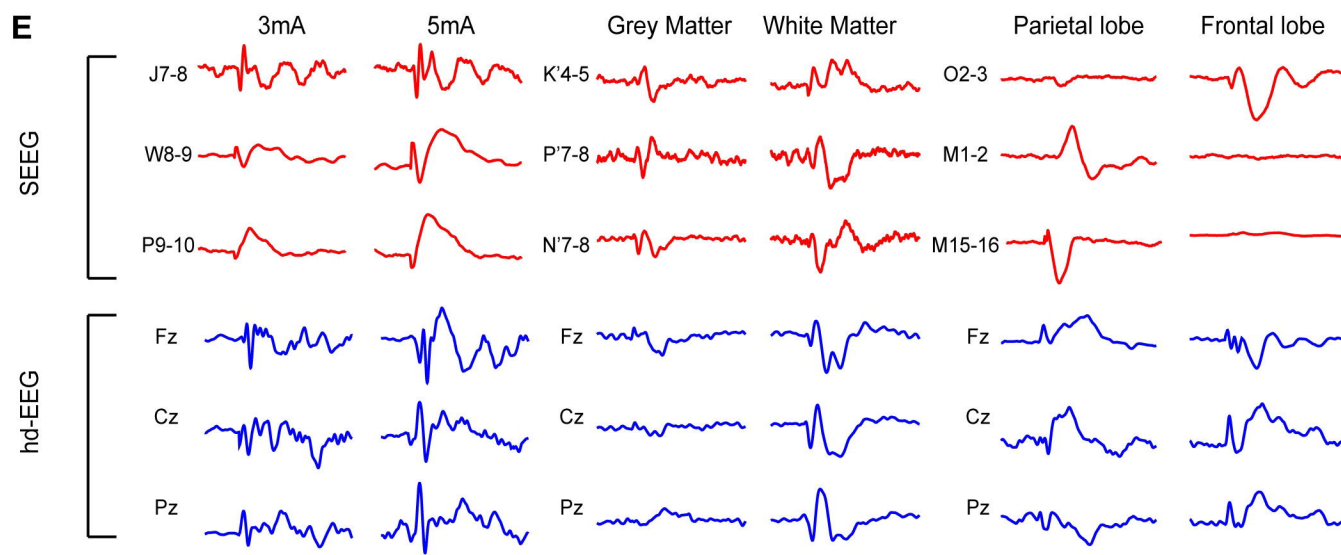
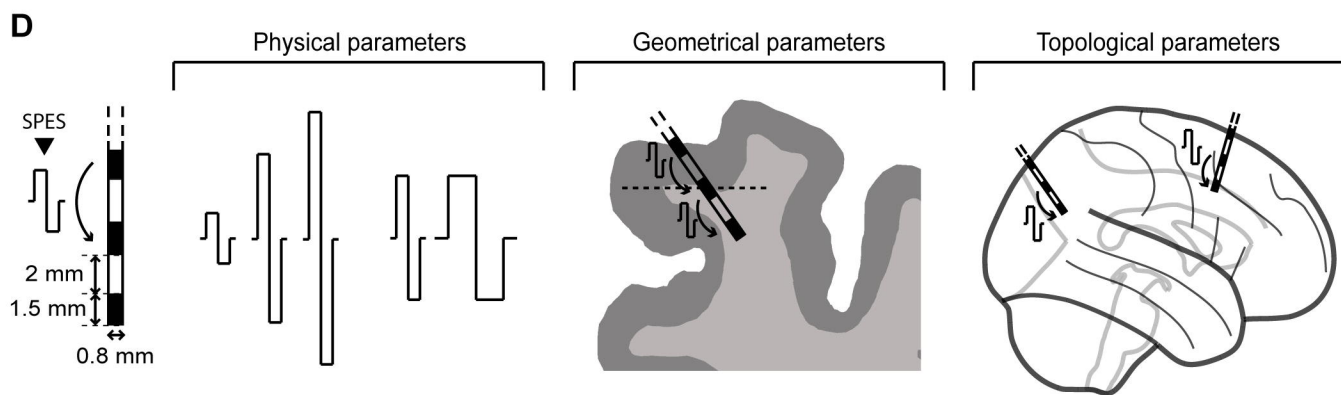
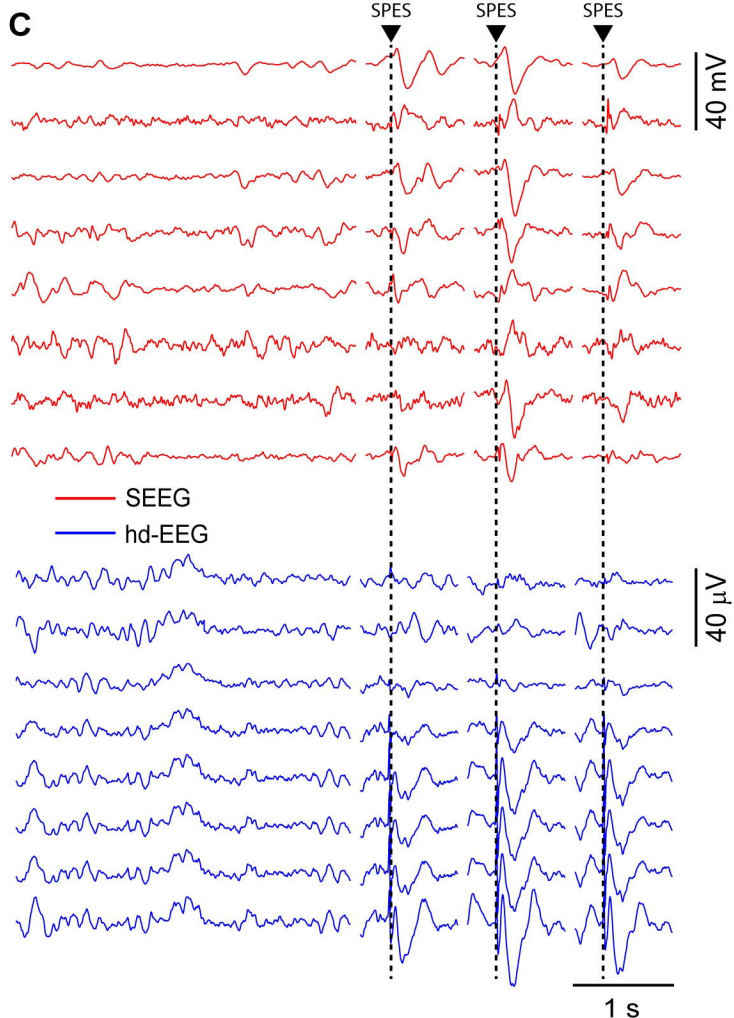
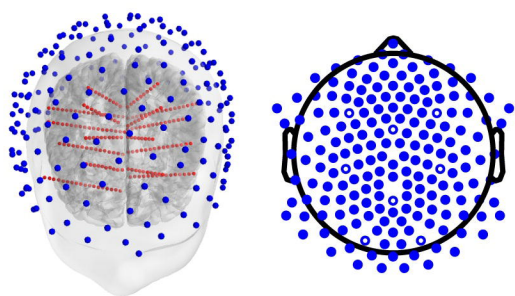
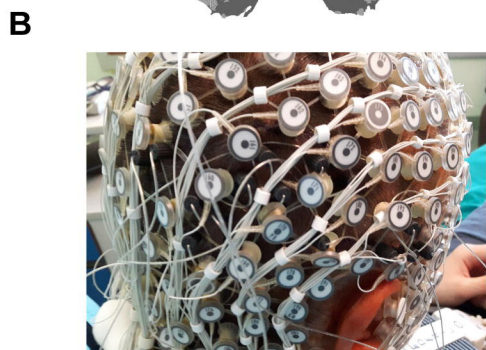
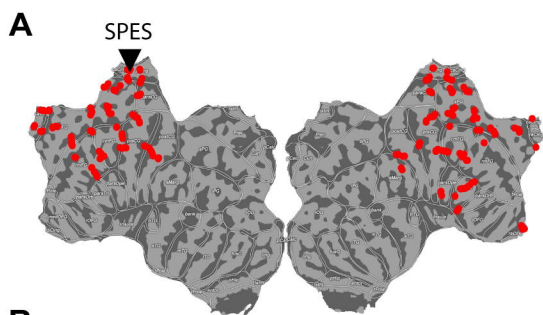
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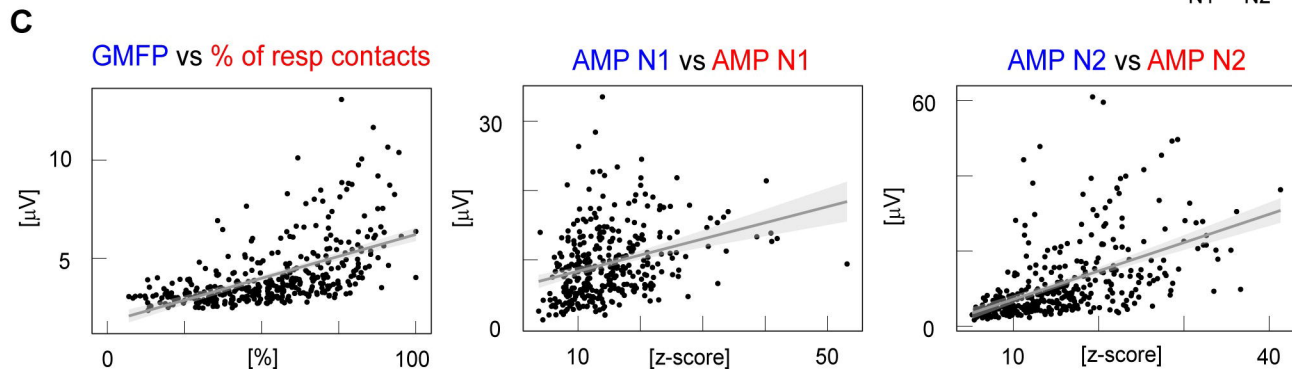
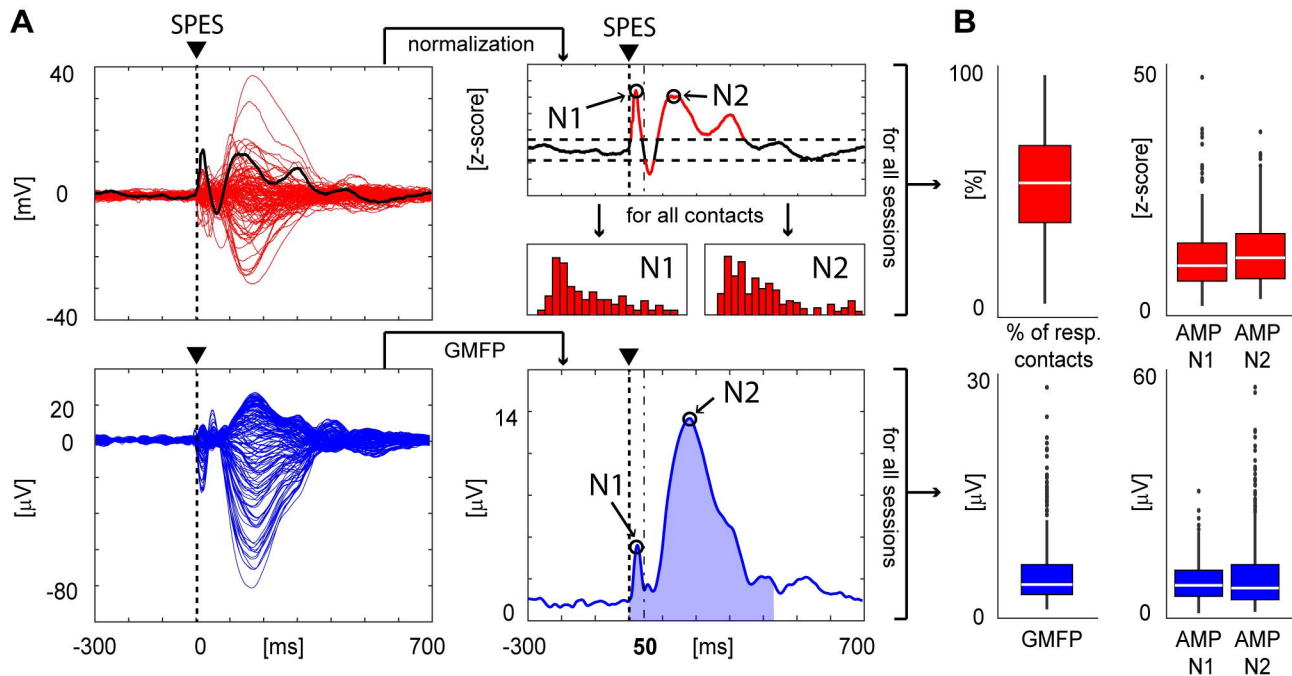
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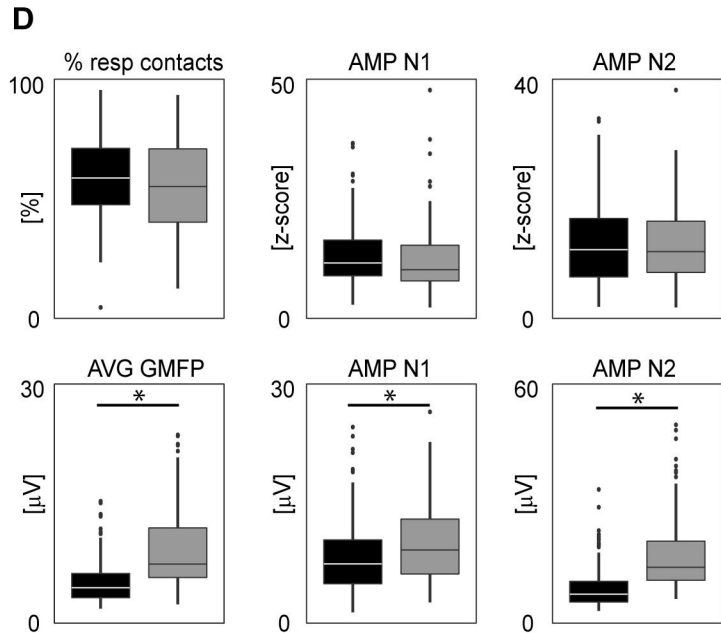
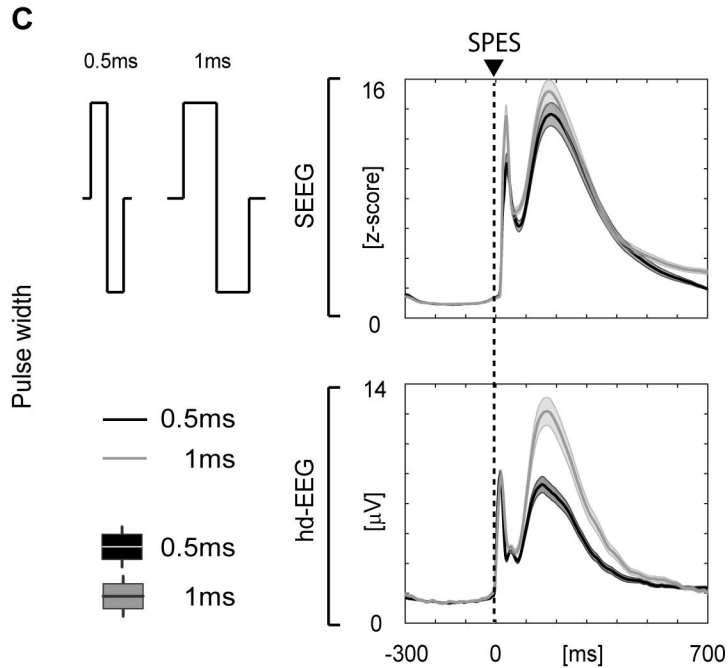
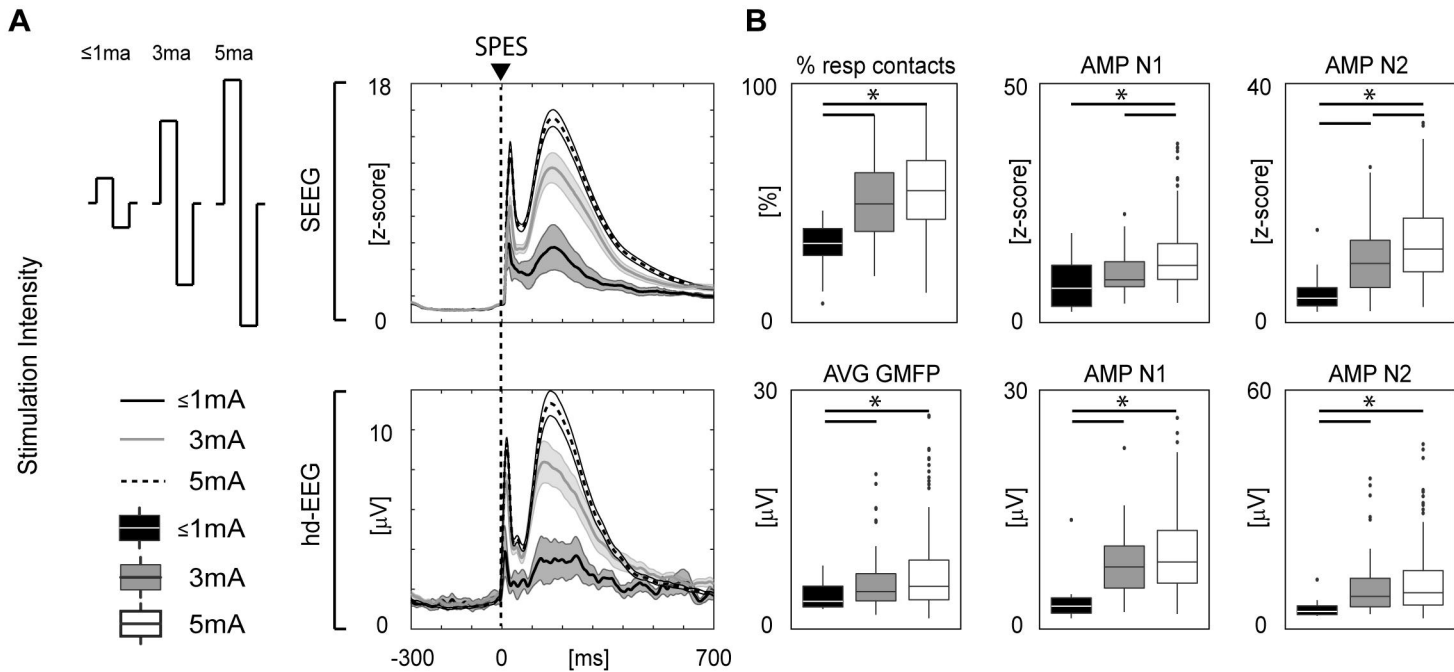
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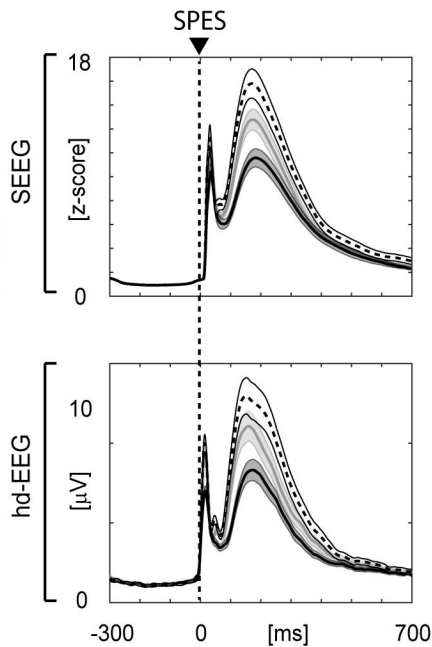
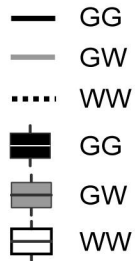
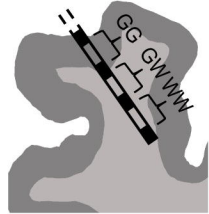
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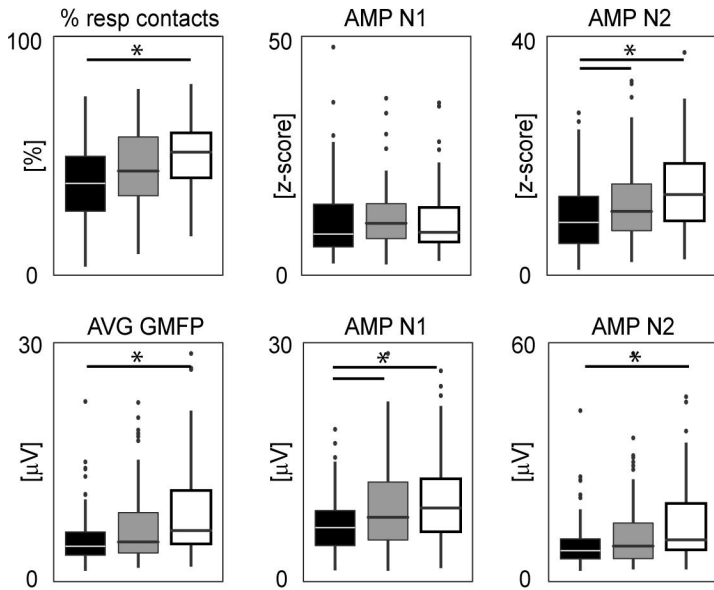




Distance from the Grey-White Matter Surface

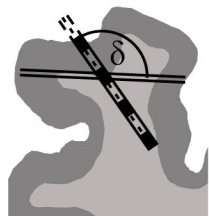


B



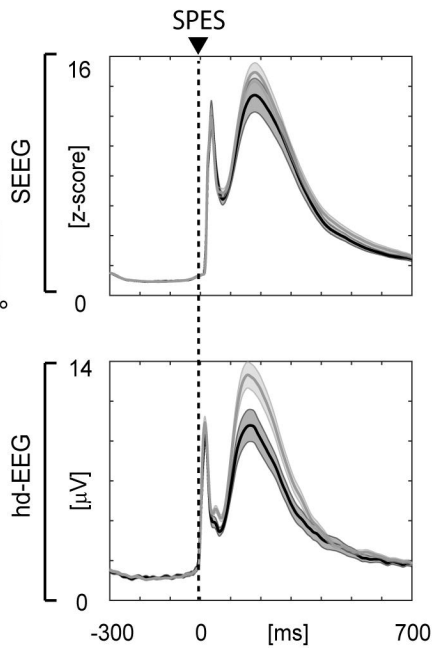
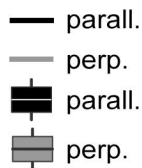
C

Angle with the Grey-White Matter Surface

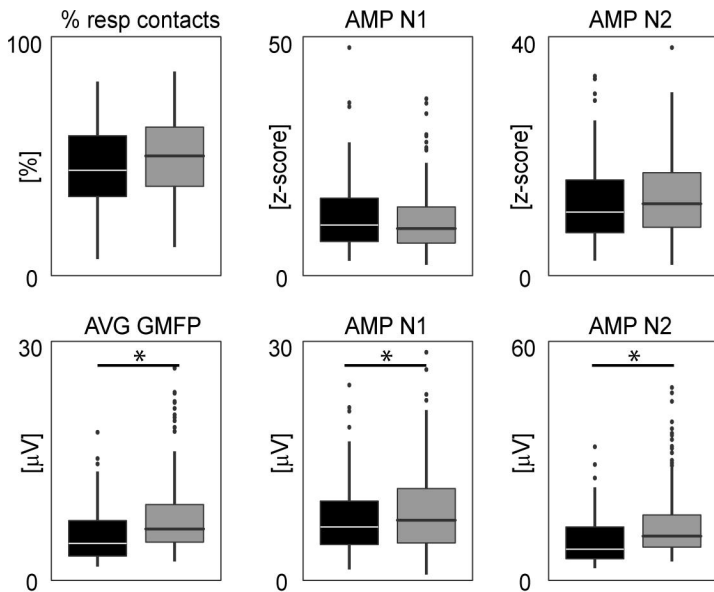


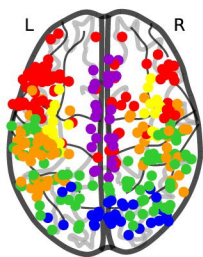
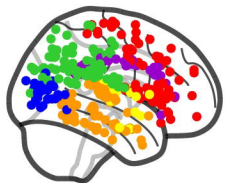
$\delta < 45^\circ$ or $\delta > 135^\circ$
parall.

$45^\circ < \delta < 135^\circ$
perp.

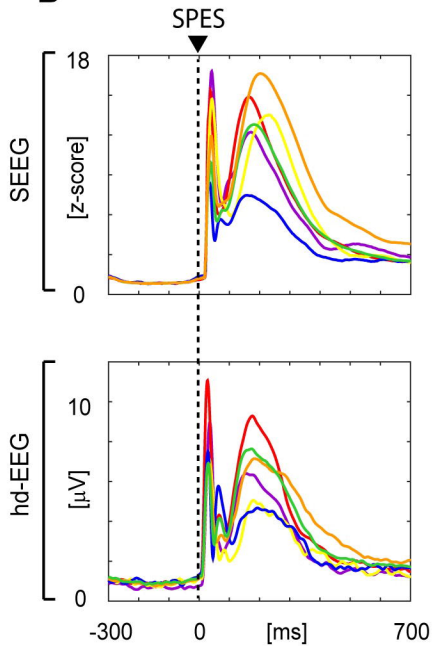
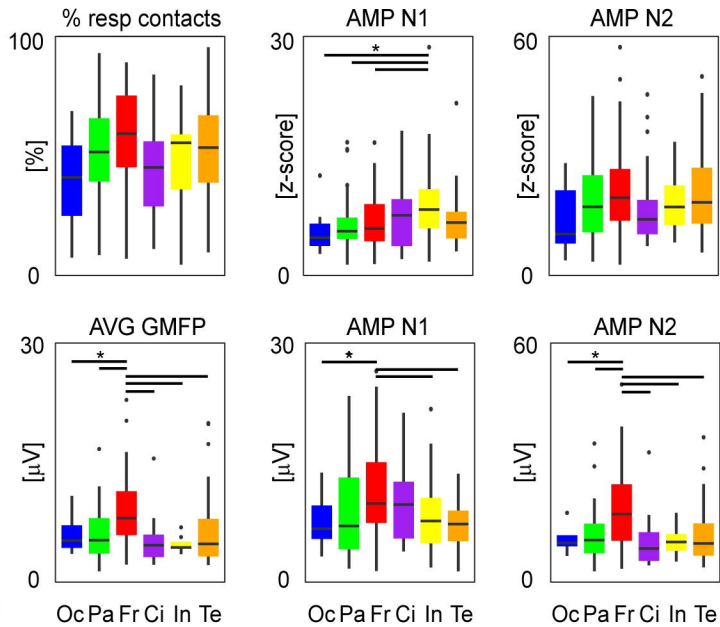


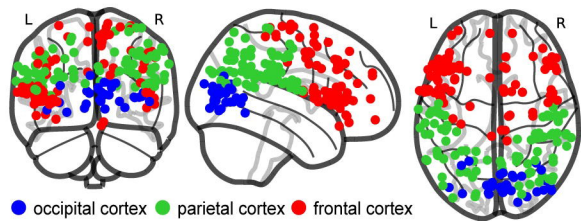
D



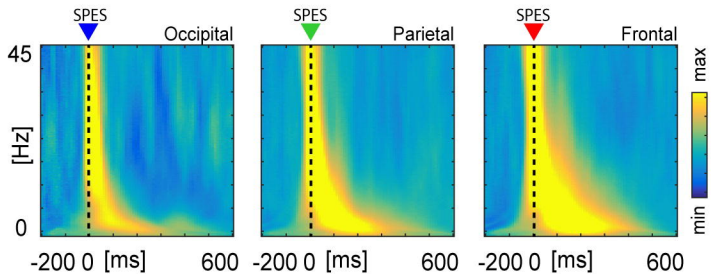
A

- occipital cortex
- parietal cortex
- frontal cortex
- cingulate cortex
- insular cortex
- temporal cortex

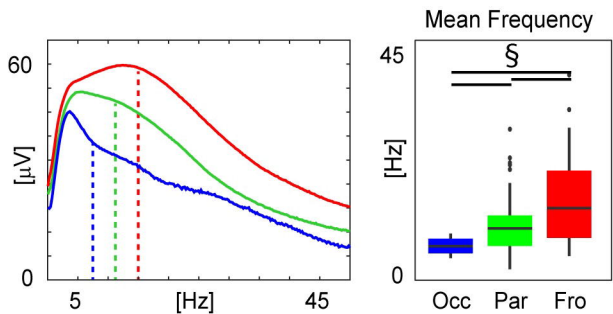
B**C**

A

hd-EEG

B

SEEG

C**D**