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**Research Articles: Behavioral/Cognitive**

**Dynamic reconfiguration of visuomotor-related functional connectivity networks**

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\*equal contribution

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2 **Dynamic reconfiguration of visuomotor-related**  
3 **functional connectivity networks**

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34 Abbreviations

35 MEG: magnetoencephalography

36 EEG: electroencephalography

37

38 Keywords

39 High-gamma activity; functional connectivity dynamics; MEG; SEEG; executive  
40 functions; dynamic reconfiguration

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42

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51 (grant ANR-11-INBS-0006).

52 **ABSTRACT**

53 Cognitive functions arise from the coordination of large-scale brain networks. Yet, the  
54 principles governing interareal functional connectivity dynamics (FCD) remain  
55 elusive. Here, we test the hypothesis that human executive functions arise from the  
56 dynamic interplay of multiple networks. To do so, we investigated FCD mediating a  
57 key executing function, known as arbitrary visuomotor mapping, using brain  
58 connectivity analyses of high-gamma activity recorded using  
59 magnetoencephalography and intracranial electroencephalography. Visuomotor  
60 mapping was found to arise from the dynamic interplay of three partly-overlapping  
61 cortico-cortical and cortico-subcortical FC networks. First, visual and parietal regions  
62 coordinated with sensorimotor and premotor areas. Second, the dorsal fronto-parietal  
63 circuit together with the sensorimotor and associative fronto-striatal networks took the  
64 lead. Finally, cortico-cortical interhemispheric coordination among bilateral  
65 sensorimotor regions coupled with the left fronto-parietal network and visual areas.  
66 We suggest that these networks reflect the processing of visual information, the  
67 emergence of visuomotor plans and the processing of somatosensory reafference or  
68 action's outcomes, respectively. We thus demonstrated that visuomotor integration  
69 resides in the dynamic reconfiguration of multiple cortico-cortical and cortico-  
70 subcortical FC networks. More generally, we showed that visuomotor-related FC is  
71 non-stationary, and displays switching dynamics and areal flexibility over time scales  
72 relevant for task performance. In addition, visuomotor-related FC is characterized by  
73 sparse connectivity with density less than 10%. To conclude, our results elucidate the  
74 relation between dynamic network reconfiguration and executive functions over short  
75 time scales, and provide a candidate entry point towards a better understanding of  
76 cognitive architectures.

77 **SIGNIFICANCE STATEMENT**

78       Executive functions are supported by the dynamic coordination of neural  
79 activity over large-scale networks. The properties of large-scale brain coordination  
80 processes, however, remain unclear. Using tools combining  
81 magnetoencephalography and intracranial electroencephalography with brain  
82 connectivity analyses, we provide evidence that visuomotor behaviors, a hallmark of  
83 executive functions, are mediated by the interplay of multiple and spatially  
84 overlapping sub-networks. These sub-networks span visuomotor-related areas,  
85 whose cortico-cortical and cortico-subcortical interactions rapidly evolve and  
86 reconfigure over time-scales relevant for behavior. Visuomotor-related Functional  
87 Connectivity Dynamics (FCD) is characterized by sparse connections, non-  
88 stationarity, switching dynamics and areal flexibility. We suggest that these properties  
89 represent key aspects of large-scale functional networks and cognitive architectures.

90 **INTRODUCTION**

91 The dynamic coordination of neural activity over large-scale networks is  
92 thought to support cognitive functions (Varela et al., 1999; von der Malsburg et al.,  
93 2010; Bressler and Menon, 2010). Growing evidence from fMRI has shown that  
94 spontaneous and task-related activity is composed of multiple and spatially  
95 overlapping sub-networks that dynamically evolve over tens of seconds to minutes  
96 (Hutchinson et al., 2013; Yeo et al., 2013; Allen et al., 2014; Calhoun et al., 2014;  
97 Cole et al., 2014; Zalski et al., 2014; Hansen et al., 2015). Indeed, dynamic  
98 network reconfiguration has been suggested to represent a fundamental  
99 neurophysiological process supporting executive function (Bassett et al., 2011; Braun  
100 et al., 2015).

101 A hallmark of executive function is the ability to rapidly associate arbitrary  
102 actions to visual inputs and internal goals. This ability, known as arbitrary visuomotor  
103 mapping, recruits a large-scale network comprising the sensorimotor and  
104 frontoparietal circuits, in addition to medial prefrontal areas and basal ganglia (Wise  
105 et al., 1996; Murray et al., 2000; Passingham et al., 2000; Wise and Murray, 2000;  
106 Hadj-Bouziane et al., 2003; Petrides, 2005). In the current study, the goal was to  
107 investigate whether visuomotor mapping results from the dynamic interplay of  
108 multiple sub-networks. More precisely, we tested the hypothesis that multiple sub-  
109 networks reconfigure in a dynamic fashion over time scales relevant for executive  
110 behaviors.

111 To do so, we exploited the high-gamma activity (ranging from approximately  
112 60 to 150Hz), which reflects population-level local neural activity (Ray et al., 2008;  
113 Ray and Maunsell, 2011). In humans, power modulations in the high-gamma range  
114 are commonly recorded using magnetoencephalography (MEG) and intracranial  
115 electroencephalography to map task-related brain regions (Brovelli et al., 2005;  
116 Crone et al., 2006; Vidal et al., 2006; Ball et al., 2008; Jerbi et al., 2009; Darvas et  
117 al., 2010; Lachaux et al., 2012; Cheyne and Ferrari, 2013; Ko et al., 2013).  
118 Additionally, high-gamma power modulations can be used to characterize functional  
119 connectivity (FC) among brain regions supporting executive functions (Brovelli et al.,  
120 2015).

121 Here, we predicted visuomotor mapping to reflect an initial activation of visual  
122 circuits mediating the processing of sensory input, followed by fronto-parietal and

123 motor networks for visuomotor integration and motor planning. We tested these  
124 hypotheses in a group of healthy participants during MEG recordings by combining  
125 FC analysis of atlas-based HGA with methods from network science and graph  
126 theory. In particular, we investigated the presence of multiple visuomotor-related  
127 spatiotemporal patterns through the analysis of functional connectivity dynamics  
128 (FCD). Intracranial assessment of HGA activations from MEG was also performed in  
129 three epileptic patients performing the same task during stereo-  
130 electroencephalographic (SEEG) recordings.



## 131 **MATERIALS & METHODS**

### 132 Experimental procedure and data acquisition

#### 133 Experimental conditions and behavioral tasks

134       Eleven healthy participants and three epileptic patients accepted to take part  
135 in our study. Healthy participants were right handed and the average age was  
136 approximately 23 years (the standard deviation was 3.8 years), 4 were females and 7  
137 males. All gave written informed consent according to established institutional  
138 guidelines and local ethics committee, and received monetary compensation (€ 50).  
139 Three patients (one right-handed female aged of 29, two right-handed males aged of  
140 29 and 43) undergoing presurgical evaluation of drug-resistant epilepsy (Epilepsy  
141 Unit, La Timone Hospital, Marseille, France) participated in this study. They all gave  
142 their informed consent prior to their participation. The SEEG study was approved by  
143 the Institutional Review Board of the French Institute of Health. Healthy participants  
144 and patients performed the same behavioral task. We asked participants to perform  
145 an associative visuomotor mapping task, where the relation between visual stimulus  
146 and motor response is arbitrary and deterministic (Wise and Murray, 2000; Brovelli et  
147 al., 2015). As shown in Figure 1A, the task required participants to perform a finger  
148 movement associated to a digit number: digit “1” instructed the execution of the  
149 thumb, “2” for the index finger, “3” for the middle finger and so on. Maximal reaction  
150 time was 1s. After a fixed delay of 1 second following the disappearance of the digit  
151 number, an outcome image was presented for 1 s and informed the subject whether  
152 the response was correct, incorrect, or too late (if the reaction time exceeded 1 s).  
153 Incorrect and late trials were excluded from the analysis, because they were either  
154 absent or very rare (i.e., maximum 2 late trials per session). The next trial started  
155 after a variable delay ranging from 2 to 3 s (randomly drawn from a uniform  
156 distribution) with the presentation of another visual stimulus. Each participant  
157 performed two sessions of 60 trials each (total of 120 trials). Each session included  
158 three digits randomly presented in blocks of three trials. The average reaction time  
159 was  $0.504s \pm 0.004s$  (mean  $\pm$  s.e.m.).

160

#### 161 Anatomical, functional and behavioral data acquisition in healthy participants

162       Anatomical MRI images were acquired for healthy participant using a 3-T  
163 whole-body imager equipped with a circular polarized head coil. High-resolution

164 structural T1-weighted anatomical image (inversion-recovery sequence,  $1 \times 0.75 \times 1.22$   
165 mm) parallel to the anterior commissure-posterior commissure plane, covering the  
166 whole brain, were acquired. Magnetoencephalographic (MEG) recordings were  
167 performed using a 248 magnetometers system (4D Neuroimaging magnes 3600).  
168 Visual stimuli were projected using a video projection and motor responses were  
169 acquired using a LUMItouch® optical response keypad with five keys. Presentation®  
170 software was used for stimulus delivery and experimental control during MEG  
171 acquisition. Reaction times were computed as the time difference between stimulus  
172 onset and motor response. Sampling rate was 2034.5 Hz. Location of the  
173 participant's head with respect to the MEG sensors was recorded both at the  
174 beginning and end of each session to potentially exclude sessions and/or participants  
175 with large head movements. For each session and participant, we computed the  
176 displacement between the beginning and end of a session. A supine position was  
177 chosen to minimize head movements. This cut-off was decided by considering the  
178 spatial distance between sources (5mm), as described in the following sections.  
179 None of the participants moved more than 3 mm during all sessions. Thus, all  
180 participants were considered for further analysis.

181

#### 182 Anatomical, functional and behavioral data acquisition in epileptic patients

183 The surgical treatment of drug-resistant epilepsy may require direct  
184 intracerebral recording of cortical activity IEEG in multiple brain areas in order to  
185 localize the epileptic tissue to be removed. Before SEEG all patients had high  
186 resolution MRI, performed with a 3T Siemens Magnetom scanner (Siemens AG,  
187 Erlangen, Germany) including a three-dimensional T1-weighted acquisition.  
188 Intracerebral multiple contacts electrodes (10 to 15 contacts, length: 2 mm, diameter:  
189 0.8 mm, 1.5 mm apart) were implanted using a stereotactic method (Talairach et al,  
190 1992). A post-operative computerized tomography (CT) scan without contrast was  
191 used to verify the absence of bleeding and the location of each recording lead.  
192 During this pre-surgical evaluation period, we asked patients to participate in our  
193 behavioral protocol at the Timone Hospital. They were seated in a Faraday cage and  
194 stimuli were presented on a display monitor at 70 cm to patient's eyes with an  
195 angular size of  $1.26^\circ$ . Presentation® software was used for stimulus delivery and  
196 experimental control during SEEG acquisition. Motor responses were acquired using  
197 a 5-button response pad. SEEG signals were acquired on referential montage with a

198 sampling frequency of 1000 Hz and an acquisition band-pass filter between 0.1 and  
199 200Hz.

200

## 201 Brain parcellation

202 In order to map brain activations and Functional Connectivity (FC) patterns to  
203 specific anatomical brain networks, single-subject brain parcellation can be created  
204 from macro-anatomical information, such as primary and secondary sulci, using  
205 either volume-based (Lancaster et al., 2000; Tzourio-Mazoyer et al., 2002) or  
206 surface-based (Fischl et al., 1999; Van Essen and Drury, 1997; Desikan et al., 2006)  
207 algorithms. Recent developments now allow single-subject cortical parcellation  
208 complying with a model of anatomo-functional gradients in the rostro-caudal and  
209 dorso-ventral directions (Auzias et al., 2013) optimized for functional mapping using  
210 HGA (Auzias et al., 2016). Such approach allows group-level analyses and  
211 comparison between individual patients and healthy participants in control group. To  
212 do so, we created a whole-brain parcellation including cortical (Figure 1B) and  
213 subcortical (Figure 1C) regions based on macro-anatomical information. The  
214 identification of the cortical regions requires several processing steps. After denoising  
215 using a non-local means approach (Coupé et al., 2008), T1-weighted MR-images  
216 were segmented using the FreeSurfer “recon-all” pipeline (<http://freesurfer.net>). Grey  
217 and white matter segmentations of each hemisphere were imported into the  
218 BrainVisa software and processed using the Morphologist pipeline procedure  
219 (<http://brainvisa.info>). White matter and pial surfaces were reconstructed and  
220 triangulated, and all sulci were detected and labelled automatically (Mangin et al.,  
221 2004; Perrot et al., 2011). A parameterization of each hemisphere white matter mesh  
222 was performed using the Cortical Surface toolbox ([http://www.meca-](http://www.meca-brain.org/software/)  
223 [brain.org/software/](http://www.meca-brain.org/software/)). It resulted in a 2D orthogonal system defined on the white  
224 matter mesh, constrained by a set of primary and secondary sulci (Auzias et al.,  
225 2013). This parameterization naturally leads to a complete parcellation of the cortical  
226 surface, the *MarsAtlas* model (Auzias et al., 2016).

227 *MarsAtlas* complies with the dorsoventral and rostrocaudal trends of cortical  
228 organization (Régis et al., 2005; Pandya and Yeterian, 1985) and provides a good  
229 level of both functional segregation and inter-subject matching for functional analysis  
230 using single-trial MEG high-gamma activity (Auzias et al., 2016). The resulting

231 cortical surface parcellation was then propagated to the volume-based grey matter  
232 segmentation, using a front propagation from the surface through the volumetric  
233 cortex segmentation (Cachia et al., 2003), hence producing a volume-based  
234 parcellation of the entire cortex. The parcels corresponding to the subcortical  
235 structures were extracted using Freesurfer (Fischl et al, 2002). The subcortical  
236 structures included in the brain parcellation were the caudate nucleus, putamen,  
237 nucleus accumbens, globus pallidus, thalamus, amygdala and hippocampus. The  
238 whole-brain parcellation therefore comprised 96 areas (41 cortical and 7 subcortical  
239 areas per hemisphere) (Figure 1). All these processing steps can be performed using  
240 the BrainVisa neuroimaging platform (<http://brainvisa.info/web/index.html>). *MarsAtlas*  
241 is included in the cortical surface toolbox.

242

## 243 Single-trial high-gamma activity (HGA) in *MarsAtlas*

### 244 Preprocessing and spectral analysis of MEG and SEEG signals

245 The preprocessing and spectral analyses steps for MEG and SEEG signals  
246 were identical. Concerning SEEG signals, electrode's contacts owning to the  
247 epileptogenic zone were excluded from the analysis. SEEG contacts outside the  
248 epileptogenic zone were chosen for analysis. In addition, epochs with signs of  
249 epileptic activity were removed. MEG and SEEG signals were first down-sampled to  
250 1 kHz, low-pass filtered to 250 Hz and then segmented into epochs aligned on finger  
251 movement (i.e., button press). Epoch segmentation was also performed on stimulus  
252 onset and the data from -0.5 and -0.1 s prior to stimulus presentation was taken as  
253 baseline activity for the calculation of the single-trial high-gamma activity (HGA).  
254 Artefact rejection was performed semi-automatically and by visual inspection. For  
255 each movement-aligned epoch and channel, the signal variance and z-value were  
256 computed over time and taken as relevant metrics for the identification of artefact  
257 epochs. All trials with a variance greater than  $1.5 \cdot 10^{-24}$  across channels were  
258 excluded from further search of artefacts. Metrics such as the z-score, absolute z-  
259 score, and range between the minimum and maximum values were also inspected to  
260 detect artefacts. Channels and trials displaying outliers were removed. Two MEG  
261 sensors were excluded from the analysis for all subjects.

262 Spectral density estimation was performed using multi-taper method based on  
263 discrete prolate spheroidal (slepian) sequences (Percival and Walden, 1993; Mitra

264 and Pesaran, 1999). To extract high-gamma activity from 60 to 120, MEG time series  
265 were multiplied by  $k$  orthogonal tapers ( $k = 8$ ) (0.15s in duration and 60Hz of  
266 frequency resolution, each stepped every 0.005s), centered at 90Hz and Fourier-  
267 transformed. Complex-valued estimates of spectral measures  $X_{sensor}^n(t, k)$ , including  
268 cross-spectral density matrices, were computed at the sensor level for each trial  $n$ ,  
269 time  $t$  and taper  $k$ .

270

#### 271 MEG source analysis and high-gamma activity

272 Source analysis requires a physical forward model or leadfield, which  
273 describes the electromagnetic relation between sources and MEG sensors. The  
274 leadfield combines the geometrical relation of sources (dipoles) and sensors with a  
275 model of the conductive medium (i.e., the headmodel). For each participant, we  
276 generated a headmodel using a single-shell model constructed from the  
277 segmentation of the cortical tissue obtained from individual MRI scans as described  
278 in section 3.2 (Nolte, 2003). Leadfields were not normalized. Sources were placed in  
279 the single-subject volumetric parcellation regions. For each region, we computed the  
280 number of sources  $nSP$  as the ratio of the volume and the volume of a sphere of  
281 radius equal to 3 mm. The k-means algorithm (Tou & Gonzalez, 1974) was then used  
282 to partition the 3D coordinates of the voxels within a given volumetric region into  $nS$   
283 clusters. The sources were placed at the center of each partition for each brain  
284 region. The headmodel, source locations and the information about MEG sensor  
285 position for both models were combined to derive single-participant leadfields. The  
286 orientation of cortical sources was set perpendicular to the cortical surface, whereas  
287 the orientation for subcortical sources was left unconstrained.

288 We used adaptive linear spatial filtering (Veen et al., 1997) to estimate the  
289 power at the source level. In particular, we employed the Dynamical Imaging of  
290 Coherent Sources (DICS) method, a beamforming algorithm for the tomographic  
291 mapping in the frequency domain (Gross et al., 2001), which is a well suited for the  
292 study of neural oscillatory responses based on single-trial source estimates of band-  
293 limited MEG signals (for a series of review see, Hansen et al., 2010). At each source  
294 location, DICS employs a spatial filter that passes activity from this location with unit  
295 gain while maximally suppressing any other activity. The spatial filters were  
296 computed on all trials for each time point and session, and then applied to single-trial  
297 MEG data. DICS allows the estimate of complex-value spectral measures at the

298 source level,  $X_{source}^n(t, k) = A(t)X_{sensor}^n(t, k)$ , where  $A(t)$  is the spatial filter that  
299 transforms the data from the sensor to source level and  $X_{sensor}^n(t, k)$  is the complex-  
300 valued estimates of spectral measures, including cross-spectral density matrices,  
301 computed at the sensor level for each trial  $n$ , time  $t$  and taper  $k$  (for a detailed  
302 description of a similar approach see (Hipp et al., 2011)). The single-trial high-gamma  
303 power at each source location was estimated by multiplying the complex spectral  
304 estimates with their complex conjugate, and averaged over tapers  $k$ ,  $P_{source}^n(t) =$   
305  $\langle X_{source}^n(t, k)X_{source}^n(t, k)^* \rangle_k$ , where angle brackets refer to the average across tapers  
306 and  $*$  to the complex conjugate. Single-trial power estimates aligned on movement  
307 and stimulus onset were log-transformed to make the data approximate Gaussian  
308 and low-pass filtered at 50Hz to reduce noise. Single-trial mean power and standard  
309 deviation in a time window from -0.5 and -0.1 s prior to stimulus onset was computed  
310 for each source and trial, and used to z-transform single-trial movement-locked  
311 power time courses. Similarly, single-trial stimulus-locked power time courses were  
312 log-transformed and z-scored with respect to baseline period, so to produce HGAs  
313 for the prestimulus period from -1.6 to -0.1 s with respect to stimulation for  
314 subsequent functional connectivity analysis. Finally, single-trial HGA for each brain  
315 region of *MarsAtlas* was computed as the mean z-transformed power values  
316 averaged across all sources within the same region.

317

318 SEEG localization and high-gamma activity

319 Electrodes were localized using the CTMR toolbox (Hermes et al., 2010).  
320 Briefly, post-implant CT scans were coregistered and re-sliced to the MRI coordinate  
321 scans of each subject using SPM12. A manual procedure was then carried out to  
322 mark the electrodes in the co-registered CT space using the CTMR toolbox. The  
323 coordinates of each electrode were transformed to MRI space (1mm resolution).  
324 Since we used bipolar derivations, we computed the coordinates of the mid-point  
325 between pairs of adjacent electrodes. A cube of 5mm in size was placed at these  
326 positions (i.e., at the position of the bipolar derivation) and each voxel of the cube  
327 (1mm resolution) was labeled according to *MarsAtlas*. The location of each bipolar  
328 derivation was then labelled according to the label associated to the largest number  
329 of voxels within the cube. Bipolar derivations labelled in the white matter were  
330 excluded from further analyses.

331 Similarly to MEG HGA estimation, single-trial power estimates in the high-  
332 gamma range (60-120Hz) aligned on movement and stimulus onset were log-  
333 transformed and low-pass filtered at 50Hz to reduce noise. Single-trial estimates of  
334 high-gamma power were z-transformed with respect to baseline period from -0.5 and  
335 -0.1 s prior to stimulus onset. Finally, single-trial HGA for each labelled brain region  
336 of *MarsAtlas* was defined as the mean z-transformed power values averaged across  
337 all electrodes within the same region.

338

### 339 Single-trial Functional Connectivity Dynamic (FCD) measures

340 Power modulations in the high-gamma range reflect the activity of local neural  
341 populations (Ray et al., 2008; Ray and Maunsell, 2011). Here, we assume that  
342 tracking statistical dependencies between HGA from different brain regions provides  
343 information about how local processing units coordinate at the large-scale level  
344 during cognitive tasks. The goal is not infer the mechanisms mediating inter-areal  
345 communication. This would require complementary approaches based on the study  
346 of role of neural oscillations and synchrony for inter-regional communication (e.g.,  
347 Buzsáki & Schomburg, 2015; Fries, 2015). Rather, the aim was to map task-related  
348 FCD onto anatomical circuits. Given the sparseness of brain regions sampled with  
349 SEEG, FCD was exclusively performed for whole-brain MEG data.

350 We used linear correlation analysis to study the functional connectivity (FC)  
351 between brain regions. To quantify the evolution of FC over time (i.e., FCD), we  
352 computed the Pearson's correlation coefficient between pairs of HGA signals over  
353 sliding windows of 500msec, stepped every 10 msec. The same procedure was  
354 performed across all pairs of brain regions and for each trial. This resulted in a 4-  
355 dimensional FCD matrix (i.e., regions x regions x time points x trials) representing the  
356 evolution of linear correlation across all pairs of brain areas from -0.7 to 0.7s around  
357 movement onset. The single-trial FCD matrix was also computed during the pre-  
358 stimulus period, from -0.8 to -0.1s prior to stimulus onset for baseline. Statistical  
359 analyses searched for significant modulations in movement-related FCD with respect  
360 to those in the prestimulus interval.

361

### 362 Statistical analysis

363 Linear Mixed Effect (LME) model

364 Statistical inference of single-trial HGAs was performed using a linear mixed-  
 365 effect (LME) model approach at the group level. We used a LME model, because  
 366 they are particularly suited for the analysis of data collected from multiple subjects (or  
 367 sessions) where it is important to take into account inter-individual variability. These  
 368 models formalize the relation between a response variable and independent  
 369 variables using both fixed and random effects. Fixed effects model the response  
 370 variable in terms of explanatory variables as non-random quantities. For example,  
 371 experimental conditions related to population mean may be considered as fixed  
 372 effects. Random effects are associated with individual experimental units drawn at  
 373 random from a population, which may correspond to different participants in the study  
 374 (or experimental sessions). In other words, whereas fixed effects are constant,  
 375 random effects are drawn from a prior known distribution. A LME model is generally  
 376 expressed in matrix formulation as,

$$377 \quad y = X\beta + Zb + e \quad (1)$$

378 where  $y$  is the  $n$ -by-1 response vector and  $n$  is the number of observations.  $X$  is an  $n$ -  
 379 by- $p$  fixed-effects design matrix and  $\beta$  is the fixed-effect vector of  $p$ -by-1, where  $p$  is  
 380 the number of fixed effects.  $Z$  is an  $n$ -by- $q$  random-effects design matrix and  $b$  is a  $q$ -  
 381 by-1 random-effects vector, where  $q$  is the number of random effects;  $e$  is the  $n$ -by-1  
 382 observation error. The random-effects vector,  $b$ , and the error vector,  $e$ , were  
 383 assumed to be drawn from independent normal distributions. Parameter estimation  
 384 was performed using maximum likelihood method, using the *fitlme.m* function in the  
 385 Statistical Toolbox of Matlab (The MathWorks, Inc.). In order to test for significant  
 386 modulations in single-trial HGA and FCD measures around movement onset with  
 387 respect to the baseline period, we used a random-intercept and random-slope LME  
 388 model, which is described by,

$$389 \quad y(t) = \beta_0(t) + \beta_1(t)x_j + b_{0j}(t) + b_{1j}(t)z_j + \epsilon_j(t) \quad (2)$$

390 where  $y(t) = [y_{bl}(1), y_{bl}(2), \dots, y_{bl}(np), y_{mv}(1, t), y_{mv}(2, t), \dots, y_{mv}(np, t)]$ .

391 For MEG data analysis,  $y_{bl}(j)$  was a vector containing the baseline neural  
 392 activity (i.e., the HGA from single brain regions or FCD values for single pairs of  
 393 regions) for all trials and sessions (i.e., data from both sessions were concatenated,  
 394 because they were acquired in uninterrupted succession) for subject  $j = 1, 2, \dots, np$ ,  
 395 where  $np$  is the number of participants, at time instant  $t$ . Note that  $t$  does not refer to  
 396 trials, but time within each trial.  $y_{mv}(j, t)$  was a vector including brain activity across



397 all trials for subject  $j$  at time  $t$  with respect to movement onset.

398 For SEEG data analysis, statistical inference was performed at the single-  
 399 participant level, due to the limited number of patients and limited sampling of  
 400 *MarsAtlas* regions. However, given that the SEEG experiments were composed of  
 401 two sessions acquired at different times (approximately 1 hours interval), we modeled  
 402 sessions as random effects.  $y_{bl}(j)$  was then a vector containing the baseline neural  
 403 activity (i.e., the HGA from single brain regions) for all trials for sessions  $j = 1,2$ , at  
 404 time instant  $t$ . As before,  $t$  did not refer to trials, but time within each trial.  $y_{mv}(j, t)$   
 405 was a vector including brain activity across all trials for session  $j$  at time  $t$  with respect  
 406 to movement onset.

407 The following statistical analysis was similar for both MEG and SEEG data.  
 408 The design matrices contain two columns. The first column is a vector of ones to  
 409 model the intercept, and thus it was eliminated from eq. 2. The second column  
 410 contains negative ones for baseline trials and ones for event-related trials, therefore  
 411 modelling the change with respect to baseline, or slope, and it is referred as  $x_j$  and  $z_j$   
 412 in eq. 2. Thus, the first and third terms in the right-hand-side of eq. 2 model the  
 413 intercepts, which correspond to the mean values between baseline and movement-  
 414 related activity. The second and fourth terms model the slopes, which are the  
 415 differences between baseline and movement-related activity. The  $\beta_1(t)$  values are  
 416 fixed across subjects, whereas the  $b_{1j}(t)$  values model the random variations across  
 417 subjects (for MEG) or sessions (for SEEG). In other words, the parameter  $\beta_1(t)$   
 418 models the change in neural activity (e.g., HGA or FCD for MEG data) with respect to  
 419 baseline at each time point  $t$  at the group level; the parameter  $b_{1j}(t)$  models the  
 420 change in neural activity with respect to baseline for each participant (or sessions)  $j$   
 421 and therefore explains the across-subjects (or across-session) variability for MEG  
 422 and SEEG data, respectively. The across-subject and across-session variability was  
 423 considered of no interest for the scope of the current analyses. We thus analyzed  
 424 fixed-effects. Given the structure of the fixed-effect design matrix, significant  
 425 differences in movement-related neural activity with respect to baseline can thus be  
 426 inferred by testing whether  $\beta_1$  coefficients are significantly greater than zero. More  
 427 formally, the significance of movement-related modulations was inferred using a t-test  
 428 by testing the null hypothesis  $H_0: \beta_1 \leq 0$ .

429 Statistical inference was performed for each time point  $t$  and each brain area

430 for the analysis of HGAs. To account for the multiple comparisons problem, we  
431 controlled the false discovery rate (FDR) (Benjamini and Yosef, 1995). For mean  
432 HGA statistical analyses, we corrected for the number of time points and brain  
433 regions; for FCD analyses, we corrected for the number of time points and for the  
434 number of pairs of brain regions. To further assess the validity of our results, we  
435 quantified the minimum number of consecutive significant time points required to  
436 reject a null hypothesis of absence of a cluster given a chance probability  $p_0 = 0.5$   
437 (two possible outcomes, significant or non-significant), and kept only those clusters  
438 whose duration exceeded a given significance level. Details of the calculation are  
439 given in the appendix of (Smith et al., 2004).

440 The statistical analyses of MEG HGA modulations resulted in a group-level  
441 FCD matrix containing time-evolving t- and p-values for each brain region in  
442 *MarsAtlas* (whole-brain analysis). For brain regions covered by the SEEG implants,  
443 the analysis of HGA modulations produced intracranial validation at the single-  
444 participant level. The analysis of FCD from MEG HGA produced t- and p-value time  
445 courses for all pairs of brain regions.

446

## 447 Graph theoretical analysis

### 448 Strength of Functional Link (SFL)

449 To gain insight into the topology of the task-related functional network arising  
450 from group-level MEG analyses, we performed graph theoretical analyses of the FCD  
451 matrix containing the p-values associated with the LME analysis. The weight or  
452 strength of the evidence of a functional link was defined as the minimum Bayes  
453 Factor (BF) associated with such p-values (Goodman, 1999b). The rationale behind  
454 the transformation of p-values to minimum Bayes Factors is an attempt to move  
455 towards statistical measures that can be better interpreted (Goodman, 1999a). The  
456 BF is a convenient measure of the strength of statistical evidence and it can be  
457 computed from p-values as  $BF_{up} < -1/(e p \ln(p))$ , if p-values satisfy the relation  $p <$   
458  $1/e$ , in which  $e \approx 2.72$ . This estimate provides an upper bound ( $BF_{up}$ ) on the BF, and it  
459 can be thought as providing an 'optimistic' limit of the BF for a given p-value  
460 (Goodman, 2001; Stephens and Balding, 2009). We log-transformed the BFs so to  
461 give a measure which quantifies the strength in the evidence of the presence of a  
462 functional link between two brain regions, Strength of the Functional Link  $SFL =$

463  $\log_{10} BF_{up}$ . The *SFL* matrix has the same dimensions of group-level FCD matrix (i.e.,  
464 regions x regions x time points). A value between 1 and 2 can be interpreted as  
465 providing strong to very strong evidence of a functional link (i.e., increase in  
466 correlation with respect to baseline), whereas a value higher than 2 is interpreted as  
467 decisive.

468

#### 469 Analysis of time-averaged and time-dependent SFL

470 A caveat of FC analysis is the dependence of functional links on the threshold  
471 chosen for statistical significance. Thus, to explore how graph theoretical measures  
472 vary according to significance levels, we multiplied the *SFL* matrix with different  
473 binary masks obtained from the FDR-correction of the FCD matrix over a wide range  
474 from highly significant values ( $p_{FDR-corrected} = q < 0.001$ ) to non-significant ( $q <$   
475  $0.99999$ ). Note that a FDR adjusted p-value is denoted as q-value. This produced  
476 several thresholded *SFL* matrices, each one associated with a given level of  
477 significance.

478 As a first analysis, we computed the mean *SFL* matrices over time, thus giving  
479 an adjacency matrix (regions x regions) representing the mean strength between  
480 brain regions at different significance levels. We computed the density *D* (the ratio  
481 between the number of functional links and the number of possible connections) as a  
482 function of the q-value. In addition, to identify the most important brain regions in  
483 average *SFL* graph, we computed the strength of each region (sum of functional links  
484 of a region) and two indicators of centrality, such as the eigenvector centrality *EC*,  
485 defined as the absolute value of the eigenvector associated with the largest  
486 eigenvalue of the adjacency matrix *W* and it measures the importance of a region,  
487 and the betweenness centrality *BC*, equal to the fraction of all shortest paths that pass  
488 through a given region, so it measures the number of times a region acts as a  
489 “bridge”. These measures were, however, computed only at  $q < 0.05$ . Finally, to  
490 evaluate the evolution of density of the thresholded FCD, we computed it for each  
491 time slice rather over the averaged FCD. Graph theoretical measures were computed  
492 using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010).

493

#### 494 Detection of functional sub-networks

495 A critical step in the analysis of brain networks is the detection of communities,  
496 which may correspond to functional subnetworks. Subnetworks, however, may

497 overlap spatially, such that a given brain region may belong to more than one group.  
498 Link communities, defined as groups of links rather than nodes, provide an  
499 appropriate framework for capturing the relationships between overlapping  
500 communities while revealing hierarchical organization (Ahn et al., 2010). To detect  
501 time-varying link communities, we used an approach based on the analysis of the  
502 correlation of edge weights over time, rather than nodes, similarly to previous works  
503 analyzing "cross-links" or "hyper-edges" (Bassett et al., 2014; Davison et al., 2015).

504 First, we computed the Pearson linear correlation between significant (at  $q <$   
505 0.05) pairs of *SFL* time courses. This produced an adjacency matrix (number of links  
506 in size) representing the temporal correlation between functional links. Secondly, we  
507 searched for the optimal subdivision of such graph into groups of links. To do so, we  
508 used the Louvain method (Blondel et al., 2008) that attempts to optimize the  
509 "modularity" of a partition of the network. The Louvain algorithm for modularity  
510 maximization is a non-deterministic heuristic, and therefore needs to be initialized  
511 with random seeds. In addition, it depends on the resolution parameter  $\gamma$  which  
512 controls over the size and number of communities found (resolution equal to 1 leads  
513 to the standard Louvain method, whereas higher and lower resolutions produce  
514 larger and smaller number of clusters, respectively). We scanned different resolution  
515 parameters from  $\gamma = 0.5$  to  $\gamma = 1.5$  in increments of 0.1. At each scale, we ran the  
516 Louvain method 250 times to test whether the non-deterministic nature of the method  
517 could produce non-robust results. For all pairs of partitions (250\*249 in total), we  
518 computed their similarity, defined as the z-score of the Rand index (Traub et al.,  
519 2011) and we averaged them across all pairs of partitions. The optimal resolution  
520 parameter  $\gamma$  was associated with the largest average similarity between partitions.  
521 The largest similarity was observed at  $\gamma = 1$ . For  $\gamma = 1$ , we studied the consensus  
522 partition to identify a single representative partition from a set of 250 partitions, based  
523 on statistical testing in comparison to a null model. The representative partition is  
524 obtained by using a generalized Louvain algorithm on the thresholded nodal  
525 association matrix (Bassett et al., 2013). We found that for our FCD matrix at  $\gamma = 1$ ,  
526 the Louvain algorithm is extremely stable and the 250 partitions are all identical.  
527 These graph theoretical analyses were performed using the "Consensus and  
528 Comparison Methods" in the Network Community Toolbox  
529 (<http://commdetect.weebly.com/>).

530           This approach provides a subdivision of non-overlapping communities by  
531 maximizing the number of within-group edges and minimizing the number of  
532 between-group edges. Given that community detection was performed on links, the  
533 detected communities represent link communities where individual brain areas may  
534 participate in multiple overlapping networks. Finally, we computed the mean time-  
535 course of the SFL averaged across all links comprising each link community.

## 536 RESULTS

### 537 Visuomotor-related functional network

538 The brain regions displaying a significant increase in movement-related HGA  
539 with respect to the mean baseline (averaged from -0.5 to -0.1s prior to stimulus  
540 onset) defined the arbitrary visuomotor-related network (Figure 2). For cortical  
541 regions, the largest increase in HGA was observed over the left parietal lobe,  
542 primarily over the dorsal (dorsal intraparietal cortex, IPCd, and the superior parietal  
543 cortex, SPC) and medial (medial superior and medial parietal cortices, SPCm and  
544 PCm, respectively) parietal regions, the dorsal somatosensory areas (Sdl and Sdm)  
545 and the posterior cingulate cortex (PCC). The ventral regions, such as (IPCv and Sv),  
546 displayed a smaller increase relative to the dorsal and medial territories in the left  
547 hemisphere and were not significant in the right hemisphere. Over the motor,  
548 premotor and prefrontal areas, the dorsolateral and dorsomedial regions (PFcdl,  
549 PFcdm, PMdl, PMdm, Mdl and Mdm) showed the most significant increase. In  
550 addition, the mid-cingulate cortex (MCC) showed significant response, bilaterally. The  
551 ventral and ventromedial prefrontal and orbitofrontal cortices did not display a strong  
552 increase in HGA, nor anterior temporal regions. These cortical modulations are  
553 similar to those presented in a previous paper (Auzias et al., 2016), which we  
554 replicate them here for completeness.

555 The novel finding, however, is the presence of significant HGA modulations in  
556 subcortical areas. The strongest response was observed in the left hemisphere in the  
557 dorsal striatum (caudate nucleus and putamen), globus pallidus (GP) and thalamus  
558 (Thal). The thalamus and caudate nucleus displayed a clear bilateral activation,  
559 whereas the GP and putamen showed primarily an activity in the hemisphere  
560 contralateral to the motor response. A significant response was also observed in the  
561 right thalamus and caudate nucleus. No significant increase was seen in other  
562 subcortical areas examined such as the nucleus accumbens, amygdala and  
563 hippocampus.

564

### 565 Visuomotor-related functional connectivity dynamics

566 The analysis of Functional Connectivity Dynamics (FCD) between all pairs of  
567 brain regions of *MarsAtlas* was performed by estimating Pearson's correlation

568 coefficients between pairs of single-trial HGA values over sliding windows of 500  
569 msec, stepped every 10 msec. For each participant, FCD analysis resulted in a 4-  
570 dimensional matrix (i.e., regions x regions x time points x trials) representing the  
571 evolution of linear correlation across all pairs of brain areas from -0.7 to 0.7s around  
572 movement onset. Significant modulations in movement-related FCD with respect to  
573 those in the baseline period from -0.8 to -0.1s prior to stimulus onset using a linear  
574 mixed-effect (LME) approach. Figure 3A shows the connectivity matrix of the average  
575 SFL (i.e., Strength of Functional Link) over time. Note that p-values were thresholded  
576 at  $q < 0.05$  (FDR-corrected) previous to SFL computation, which corresponds to a  
577 threshold value of SFL equal to 2.43. All significant links shows decisive evidence in  
578 FC averaged over time among occipital areas bilaterally with strong links with parietal  
579 regions, in addition to the fronto-parietal network. Subcortical regions, especially in  
580 the left hemisphere, showed a strong FC with the rest of the network. Regions in the  
581 temporal lobes, however, were not found to play a key role in the FC patterns.

582 To better characterize the evolution of the SFL over time, we computed the  
583 mean SFL across pairs of brain regions displaying a significant increase in linear  
584 correlation (Fig. 3B). The mean time course displays two peaks of decisive and  
585 strong evidence at approximately -0.4 and 0.2s around finger movement. The time  
586 intervals around the two peaks represent moments when FC pattern is strongest,  
587 which correspond to the largest increase in linear correlation between HGA time  
588 courses. Given the shape of the group-level HGA responses shown in Figure 2, the  
589 first peak at -0.4s reflects the positive covariation in HGA across the whole network  
590 occurring after stimulus presentation and during movement planning (as early as -  
591 0.55 in visual areas to approximately -0.25s before finger movement). Such common  
592 increase in HGA produces an increase in linear correlation and it reflects the  
593 emergence of the FC network. The second peak occurring at 0.2s reflects a common  
594 return to baseline of the HGA across the whole network after finger movement (from  
595 approximately 0.05s to 0.35s after finger movement). Such global decrease in HGA  
596 from maximal activity produces an increase in linear correlation, but it reflects the  
597 dissolution of the FC network. Thus, the two peaks correspond to the emergence and  
598 dissolution of the FC pattern. The decrease in FC occurring approximately -0.12s to -  
599 0.03s before finger movement corresponds to the positive peak of HGA (Fig. 2). Such  
600 decrease in FC, therefore, does not reflect an absence of HGA, but rather a  
601 maximum of HGA. However, it corresponds to the time interval when FC lacks any

602 significant covariation. Overall, the analysis of the FCD time course reveals two key  
603 processes such as the creation and dissolution of FC network.

604

## 605 Graph theoretical analysis of FC network

606 To gain insight into the properties of the average FC pattern, we performed  
607 graph theoretical analyses of the average SFL matrix shown in Fig. 4A. We  
608 investigated graph theoretical measures of the mean SFL matrices averaged over  
609 time at different thresholds ( $q < 0.001$ ) to non-significant ( $q < 0.99999$ ). Figure 4A  
610 shows the FC network density  $D$  (the ratio between the number of functional links  
611 and the number of possible connections) as a function of threshold  $q$ -values. The  
612 density of the functional network trivially increase as a function of the threshold, i.e.,  
613 the more functional links, the higher is the density. The density values for significant  $q$   
614  $< 0.05$  are less than 10%, meaning that the functional network is not dense, but  
615 sparse. We then computed the density for each time slice of the FCD. Network  
616 density is maximal (approximately 5%) approximately 0.4 s and then displays a  
617 second peak 0.2 after finger movement (2% in density), as shown in Figure 4B.

618 Finally, to identify the most important brain regions in the average SFL graph,  
619 we computed the strength  $S$  (sum of functional links of a region), the eigenvector  
620 centrality  $EC$  and the betweenness centrality  $BC$  at  $q < 0.05$ . The strength of a brain  
621 area is the simplest measure to estimate the importance of a node in a network. A  
622 natural extension of strength centrality is eigenvector centrality  $EC$ , and it stands on  
623 the notion that a node is important if it is linked to by other important nodes. In fact, a  
624 node receiving many links (i.e., high strength) does not necessarily have a high  
625 eigenvector centrality, because it may be linked to node with low strength. Thus,  $EC$   
626 provide additional information, because it computes the centrality of a node as a  
627 function of the centralities of its neighbors. Finally, the betweenness centrality  $BC$  is  
628 equal to the number of shortest paths that pass through a brain region. Thus, a  
629 region with high  $BC$  has the potential to play a key role in the network. Convergence  
630 of these three metrics provides information about the importance of different brain  
631 regions in the network.

632 Table 1 shows the brain regions sorted in a descending order according to  $S$ ,  
633  $EC$ , and  $BC$ . The brain areas that commonly emerge as relevant across the three  
634 measures are the dorsomedial and dorsolateral sensorimotor regions (Mdm, Mdl,



635 Sdm), in addition to dorsolateral premotor area (PMdl), superior parietal regions  
636 (SPC, SPCm) and the caudomedial visual cortex (VCcm).

637

### 638 Dynamic reconfiguration of functional connectivity subnetworks

639 To search for functional subnetworks generating the observed dynamics, we  
640 performed link community analysis. To do so, we first computed the Pearson linear  
641 correlation between significant (at  $q < 0.05$ ) pairs of *SFL* time courses. Then, we  
642 found the optimal subdivision of such link graph into communities of links using an  
643 algorithm that attempts to optimize the "modularity" of a partition of the network,  
644 named the Louvain method (Blondel et al., 2008). This approach provides a  
645 subdivision of non-overlapping communities by maximizing the number of within-  
646 group edges and minimizing the number of between-group edges. Given that  
647 community detection was performed on links, the detected sub-networks represent  
648 link communities, where individual brain areas may participate in multiple overlapping  
649 networks. The analysis revealed the presence of 3 link communities (Figure 5). The  
650 first link community (LC1) primarily included the visual and superior and medial  
651 parietal regions, bilaterally, in addition to the left dorsomedial and dorsolateral  
652 sensorimotor regions (Fig. 5B). These brain regions form a FC subnetwork emerging  
653 approximately 0.5s before finger movement, roughly corresponding to the processing  
654 of the visual cue (Fig. 5A). The second link community (LC2) included the left  
655 dorsolateral and dorsomedial sensorimotor regions and the dorsal fronto-parietal  
656 network. Interestingly, it included the mid and anterior cingulate cortices, the  
657 dorsomedial prefrontal cortex and the dorsal striatum, in the caudate nucleus (Fig.  
658 5C). LC2 emerged later during the trial and its maximum of expansion occurred  
659 approximately 100-150 msec after LC1, that is -0.35s before movement. LC3  
660 involved a larger brain network involving the bilateral sensorimotor regions, the left  
661 fronto-parietal network and visual areas (Fig. 5D). LC3 showed a strongest peak after  
662 finger movement at 0.2s, but displays a peak at -0.4s. The only regions of the  
663 temporal lobe showing significant FC were the superior and mid-temporal cortices in  
664 the left hemisphere. However, these regions displayed a relative weak strength in the  
665 observed networks (Figure 5B, C and D). Overall, the link community analyses  
666 allowed us to identify multiple and spatially overlapping FC patterns that evolve  
667 dynamically during the trial.

668 We can therefore depict the involvement of key brain regions in a given link  
669 community, such as the motor and premotor areas. Figure 6 shows the contribution  
670 of the dorsolateral motor and dorsal premotor areas, Mdl and PMdl, respectively, in  
671 the three subnetworks as it unfolds over time. Around the presentation of the visual  
672 stimulus, the Mdl primarily participates in the LC1, which gradually declines over time  
673 (blue curve in Fig. 6A and B). Then, its involvement in LC2 and LC3 increases in  
674 parallel, but peaks earlier for LC2 (red curve in Fig. 6A and B) rather than for LC3  
675 (green curve). These curves depict the dynamic reconfiguration of the primary motor  
676 area from stimulus onset to motor output. For what concerns the dorsolateral  
677 premotor cortex, its contribution peaking for LC1, followed by LC3 and LC2 (Fig. 6C  
678 and D) confirms that the dynamic engagement in different subnetworks occurs over a  
679 short time scale.

680 Finally, to quantify the dynamics of reconfiguration among the three functional  
681 subnetworks, we inferred the evolution of network “flexibility” (following the same  
682 ideas developed in Braun and collaborators, 2015). We defined the flexibility of a  
683 given brain region as the entropy associated to the probabilities of involvement in the  
684 three LCs (shown in Fig. 6B and D, for Mdl and PMdl, respectively). Accordingly,  
685 node flexibility is maximal for nodes participating with equal probability in the different  
686 LCs and minimal for nodes participating in a single LC. Figure 7A shows the mean  
687 dynamics of network flexibility averaged over nodes. Interestingly, its reconfiguration  
688 shows a single peak occurring at approximately 0.4s before finger movement, which  
689 corresponds to the moment when the three LCs overlap more strongly in time and  
690 space. Figure 7B shows the mean flexibility averaged over time for the first five  
691 strongest brain regions. The parietal regions (SPC, PCm and PPC) display the  
692 largest flexibility together with the dorsal premotor cortex.

693

## 694 Control analyses and intracranial SEEG validation

695 The interpretation of FC measures from non-invasive techniques such as EEG  
696 and MEG may suffer limitations, among which volume conduction and leakage are  
697 potential confounds (Bastos & Schoffelen, 2016). We performed a series of control  
698 analyses to assess the influence of such confounds.

699 First, we studied the relation between the mean SLF for two subcortical  
700 regions displaying a significant increase in HGA and FC with cortical regions, as a

701 function of their respective distance to cortical regions. The rationale was to check  
702 whether volume conduction and leakage effects could have produced the observed  
703 HGA modulations in subcortical regions and the FC patterns between deep sources,  
704 such as the thalamus and caudate nucleus, and cortical areas. Figure 8 shows that a  
705 clear relation between distance and FC measures (as assessed through the mean  
706 SFL) is lacking, neither for the thalamus (Fig., 8A) nor for the caudate nucleus (Fig.  
707 8B).

708         Second, we investigated the dipole orientation of all sources within the  
709 thalamus and caudate nucleus. The rationale was that differences in dipole  
710 orientation of nearby regions may suggest that the estimated HGAs originate from  
711 spatially-separable brain structures. To do so, we computed the average dipole  
712 orientation both for the thalamus and caudate nucleus. Then, we compared the  
713 average dipole orientations by means of the normalized inner product. This measure  
714 equals one for identically-oriented dipoles, minus one for dipoles pointing in opposite  
715 directions, and zero for orthogonal dipoles. The boxplot displayed in Figure 9A  
716 depicts the distribution of normalized inner products between the thalamus and  
717 caudate nucleus across participants. The values of normalized inner products span a  
718 broad range from -0.45 to 0.85, with median value around 0.65. Extremely high  
719 values of raw correlation coefficient between subcortical HGAs would also suggest  
720 strong leakage effects. We thus plotted the Pearson correlation coefficient between  
721 the HGA at the thalamus and caudate nucleus, averaged over sessions and  
722 participants (Figure 9B). The value in the prestimulus interval (i.e., approximately  
723 around -0.8s before finger movement) was 0.615. The corresponding coefficient of  
724 determination  $R^2$  was 37,8%, (i.e.,  $R^2 = 0.615 \times 0.615 = 0.3782$ ), and it equals the  
725 proportion of the variance in HGA shared by the thalamus and caudate nucleus.

726         Finally, to assess the relevance of cortical HGA modulations, we asked three  
727 patients candidate for surgical treatment of drug-resistant epilepsy to perform the  
728 same visuomotor task while recording stereotactic electroencephalography (SEEG)  
729 in multiple brain areas. In fact, high-gamma activity from intracranial recordings in  
730 epileptic patients is largely exploited for cognitive mapping and it represents an  
731 optimal opportunity to validate MEG results. Results from single-patient SEEG cannot  
732 be taken as representative of the population, contrary to group-level MEG results. In  
733 fact, we cannot exclude that across-subject variability is due to either physiological  
734 and/or pathological factors. However, SEEG data provide direct measures of

735 intracranial HGA, free from alteration due to volume conduction or limitation of source  
736 imaging tools. Thus, they provide important additional evidence to support the  
737 significance of the MEG results.

738         Electrodes were localized by combing post-implant CT scans with pre-surgical  
739 anatomical MRI scans, and they were labelled according to *MarsAtlas* (see methods  
740 section). Single-trial HGA for each labelled brain region of *MarsAtlas* was defined as  
741 the mean z-transformed power values averaged across all electrodes within the  
742 same region. To increase the local specificity of SEEG recordings, bipolar derivations  
743 were performed among adjacent contacts. Statistical analyses were performed  
744 separately for each patient. Twelve brain areas across the three patients were found  
745 to display a significant increase in HGA (Table 2) ( $q < 0.05$ ). These included the  
746 dorsomedial and dorsolateral motor cortex, the dorsolateral somatosensory region,  
747 and the dorsal fronto-parietal network (SPC, SPCm, PMdl, PMdm). In patient 2, the  
748 ventral portions of the motor and premotor areas were significantly active. Note that  
749 the SEEG implant did not cover the entire brain, but selected regions in the fronto-  
750 parietal network.

751         We then compared the average time course of single-patient HGA  
752 modulations with those from the MEG group-level analyses (Fig. 10). Seven out of  
753 twelve regions displayed a strong (larger than 0.65) linear correlation between the  
754 group-level MEG results and the single-patient SEEG time courses. The most striking  
755 similarity was observed for brain regions of the sensorimotor cortices and the dorsal  
756 fronto-parietal network. Overall, these results confirm that the increase in HGA  
757 observed in the MEG data over sensorimotor cortices and the dorsal fronto-parietal  
758 network results from area-specific increases in HGA, rather than by leakage from  
759 nearby regions displaying a strong response.

760 **DISCUSSION**

761

762 **Brain network and interactions of visuomotor mapping**

763 Previous analyses of arbitrary visuomotor-related functional connectivity have  
764 shown that parietal areas play a driving role in the network, whereas premotor areas  
765 act as relays from parietal to medial prefrontal cortices, which participate as receivers  
766 (Brovelli et al., 2015). Such approach, however, neither considered the time-evolving  
767 nature of FC patterns, nor analyzed the involvement of subcortical areas. Our whole-  
768 brain and time-dependent brain connectivity analyses showed that visuomotor  
769 mapping resides in three distinct and partly overlapping subnetworks with time-  
770 evolving cortico-cortical and cortico-subcortical interactions. Approximately 0.5s  
771 before finger movement, visual and parietal regions coordinate with sensorimotor and  
772 premotor areas (LC 1 in Fig. 5B; blue curve in Fig. 5A). Subsequently, the  
773 sensorimotor regions, the dorsal fronto-parietal circuit, the medial prefrontal regions,  
774 the basal ganglia and the thalamus (LC 2 in Fig. 5C) dominated the FC pattern. The  
775 dorsal fronto-parietal circuit, known to support visuomotor transformations and goal-  
776 directed attentional processes (Wise et al., 1996; Wise and Murray, 2000; Corbetta  
777 and Shulman, 2002; Culham and Valyear, 2006), is tightly coupled with the  
778 sensorimotor and associative fronto-striatal circuit for a brief period around 0.35s  
779 prior to action (red curve in Fig. 5A). This FC network includes medial prefrontal  
780 areas, such as the dorso-medial prefrontal cortex (PFCdm), mid-cingulate cortex  
781 (MCC), anterior cingulate cortex (ACC) and rostro-medial prefrontal (PFrm), with a  
782 strongest increase in HGA in the MCC and PFCdm (Fig. 2). The involvement of  
783 medial prefrontal areas may correspond to the activation of visuomotor-related neural  
784 populations of the rostral cingulate zone (RCZ), a key node of the human motor  
785 system (Picard and Strick, 1996; Amiez and Petrides, 2014). At the subcortical level,  
786 the dorsal striatum (caudate nucleus and putamen), globus pallidus and thalamus  
787 displayed the strongest HGA, in the hemisphere contralateral to the motor response  
788 (Fig. 2). Indeed, intracranial recordings from patients with motor disorders have  
789 described HGA in the subthalamic nucleus (Amirnovin et al., 2004; Alegre et al.,  
790 2005; Androulidakis et al., 2007; Lalo et al., 2008), globus pallidus (Tsang et al.,  
791 2012a) and thalamus (Brucke et al., 2013) during different types of motor behaviors.  
792 High-gamma oscillatory activity in the sub-thalamic nucleus (STN) and globus

793 pallidus (GPi) has been found to be coherent with cortical activity during voluntary  
794 movement (Cassidy et al., 2002; Brown, 2003). Granger causality analysis also  
795 showed that STN drives activity in M1 (Litvak et al., 2012), thus suggesting that HGA  
796 in motor areas is due to propagating activity from the basal ganglia through the  
797 thalamus (Brucke et al., 2012). Our results showed that the caudate nucleus and  
798 thalamus are coupled with the sensorimotor cortex and the dorsal fronto-parietal  
799 networks (LC 2 in Fig. 5C), thus confirming a dynamic coordination between cortical  
800 and subcortical regions also during visuomotor behaviors most prominently during  
801 the planning phase prior to movement initiation.

802 Several lines of evidence suggest that the reported subcortical activations are  
803 primarily local, rather than due to leakage from cortical areas. First, we observed that  
804 the putamen significantly activated only in the left hemisphere, whereas the thalamus  
805 was activated bilaterally (Fig. 2). If the bilateral activation in the thalamus were due to  
806 leakage from cortical areas, we would have expected a bilateral activation also in the  
807 putamen, given that the thalamus is deeper than the putamen. Second, no significant  
808 correlation was found between the SFL and distance for the thalamus and caudate  
809 nucleus (Fig. 8). Third, the average dipole orientation for the thalamus and caudate  
810 nucleus are significantly different (i.e., the normalized inner product is less than one)  
811 and the distribution of values covers a wide range from -0.45 to approximately 0.85.  
812 This suggests that the thalamus and caudate nucleus lack a systematic similarity in  
813 dipole orientation (Fig. 9A). Forth, the mean Pearson correlation values and the  
814 corresponding coefficient of determination do not saturate at high values and show a  
815 modulation similar to the average time course of FCD (Fig. 9B). This suggests a lack  
816 of strong covariance, as it would be expected if leakage effects were dominating.

817 Nevertheless, we cannot *a priori* exclude that the observed subcortical  
818 increases in HGA and FC patterns may be due to complex configurations of cortical  
819 activations. Indeed, we suggest that HGA estimation at subcortical areas and FC  
820 analysis should not be performed blindly. Rather, the analysis of raw correlations and  
821 dipole orientations provide important insight into the origin of the results.  
822 Experimentally, simultaneous MEG and subcortical measures of HGA from  
823 intracranial recordings would be required to confirm or disprove the ability of MEG to  
824 capture subcortical HGA and FC.

825 Overall, our result suggests that the basal ganglia form a dynamic functional  
826 network, which may allow the coordination within and across different processing

827 streams in the basal ganglia (Brown, 2003) and facilitate motor output (Cheyne and  
828 Ferrari, 2013). The involvement of sensorimotor and associative fronto-striatal  
829 circuits, classically thought to be involved in habits (Yin and Knowlton, 2006;  
830 Graybiel, 2008; Ashby et al., 2010), also suggests that performance of arbitrary  
831 visuomotor mappings can be viewed as a form of acquainted instrumental behavior  
832 (Brovelli et al., 2015), whose gradual consolidation would lead to the formation of  
833 habitual responses (Dickinson, 1985; Dickinson and Balleine, 1993). We therefore  
834 suggest that the FCD pattern observed for LC2 depicts how motor plans circulate in  
835 the sensorimotor and associative cortico-striatal loop in coordination with fronto-  
836 parietal circuits.

837 Finally, a last subnetwork (LC 3 in Fig. 5D) primarily emerging after motor  
838 response peaking around 0.2s (green curve in Fig. 5A), involved the bilateral  
839 sensorimotor regions, the left fronto-parietal network and visual areas. The  
840 involvement of bilateral sensorimotor regions indicates that this network mediates  
841 cortico-cortical interhemispheric coordination processes via the corpus callosum.  
842 Such interhemispheric coupling may support the selective inhibition of inappropriate  
843 responses occurring between motor and premotor cortices across hemispheres in  
844 situations when multiple choices are available (Duque et al., 2013; Burle et al., 2016).  
845 Alternatively, this network may be involved in the processing of the somatosensory  
846 reafference at the end of the movement and/or the processing action's outcome.

847 To exclude potential confounds due to volume conduction or limited spatial  
848 resolution of MEG and beamforming technique (Bastos & Schoffelen, 2016), we  
849 showed that local field potentials derived from SEEG recordings displayed significant  
850 increase in HGA in these regions (Fig. 10, Table 2). We confirmed invasively that  
851 brain regions of the dorsal fronto-parietal network and the sensorimotor and/or  
852 associative fronto-striatal circuits display local increase in HGA, which do not result  
853 from volume conduction effects.

854

## 855 Towards a better understanding of cognitive architectures

856 We computed the density of the thresholded FC and FCD graphs as a function  
857 of significance threshold (Fig. 4) using the FDR-controlling procedure to estimate the  
858 relevant range of  $q$ -values. For  $q < 0.05$ , the density of the visuomotor-related FC  
859 network is less than 10% (approximately 5% for  $q < 0.05$ ). This shows that

860 visuomotor-related FC is not dense, but sparse. Future work on the relation between  
861 structural and functional connectivity may provide clues of how anatomical  
862 connectivity between brain areas shapes how neural information flows and constrains  
863 the dynamics of FC patterns.

864 A second characteristic of FC is its non-stationarity nature. Indeed, fMRI  
865 investigations have shown that resting-state networks (RSNs) display non-stationarity  
866 and dynamically evolve over tens of seconds to minutes (Hutchinson et al., 2013;  
867 Yeo et al., 2013; Allen et al., 2014; Cole et al., 2014; Calhoun et al., 2014; Zalski et  
868 al., 2014; Hansen et al., 2015). Inter-areal phase-synchronisation is known to display  
869 non-stationarity, and to underlie perception and executive functions (e.g., Pesaran et  
870 al., 2008; Hipp et al., 2011; Salazar et al., 2012). Our results further support the  
871 notion that FC is non-stationary and evolves over time scales relevant for visuomotor  
872 integration in the order of tens to hundreds of milliseconds (Fig. 3B and Fig. 5).  
873 Modelling studies of resting-state activity suggest that non-stationarity arises from the  
874 out-of-equilibrium sampling of alternative dynamical modes (Deco & Jirsa, 2012;  
875 Hansen et al., 2015; Deco et al., 2015). Switching between collective dynamical  
876 states have the potential to induce network-wide reorganization of information  
877 sharing and routing patterns and, thus, provides an effective mechanism for flexible  
878 inter-areal communication (Battaglia et al., 2012; Kirst et al., 2016). We suggest that  
879 such underlying mechanisms mediating spontaneous large-scale dynamics may also  
880 underlie task-related activity at shorter time scale. In addition, our results may provide  
881 the basis for linking similar patterns of FCD that have been observed, albeit over  
882 different time scales, during visuomotor learning (Bassett et al., 2011; Heitger et al.,  
883 2012).

884 A third characteristic of FCD is the presence of multiple and spatially  
885 overlapping sub-networks. Each brain area can participate in multiple sub-networks  
886 depending of task demands. In analogy to the concept of cell assembly, where single  
887 neurons can participate in multiple functional populations depending on context, a  
888 sub-network may be viewed as a brain assembly. A brain assembly would constitute  
889 a dynamic entity, whose constituents engage in multiple sub-networks in a time-  
890 dependent manner (Fig. 6). Spatially, areal flexibility was larger for associative  
891 parietal regions, such as the SPC, PCm and PPC together with the dorsal premotor  
892 cortex, which represent the core cortical network for visuomotor transformation (Fig.  
893 7B). Temporally, network flexibility showed a maximum around 0.4s before finger



894 movement, which corresponds to the moment when the three sub-networks interact  
895 more strongly (Fig. 7A). We therefore suggest that visuomotor integration processes  
896 occur in this time interval, when the level of interactions between multiple brain  
897 assemblies is strongest.

898 To conclude, our study confirms that executive functions arise from the  
899 dynamic coordination of neural activity over large-scale networks (Varela et al., 1999;  
900 von der Malsburg et al., 2010; Bressler and Menon, 2010). More precisely, the results  
901 supports the notion that functional specialization is due to the interplay of multiple  
902 and spatially overlapping subnetworks, rather than properties of single brain regions  
903 (Fedorenko and Thompson-Schill, 2014; Petersen and Sporns, 2015). Future work  
904 investigating how subnetworks differently participate depending on tasks demands  
905 may provide a better understanding of the cognitive architectures of executive  
906 functions (Dehaene et al., 2015).

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1174 **FIGURE and TABLE LEGENDS**

1175

1176 **Figure 1.** (A) Arbitrary visuomotor mapping task. (B) *MarsAtlas*: cortical parcellation  
1177 displaying the anatomical gradients both in the rostro-caudal and dorso-ventral directions; for  
1178 a detailed description see Auzias and collaborators (2016). (C) *MarsAtlas*: single-subject  
1179 exemplar volumetric representation displaying subcortical regions included in the atlas:  
1180 nucleus accumbens, amygdala, hippocampus, globus pallidus, putamen, caudate nucleus  
1181 and thalamus.

1182

1183 **Figure 2.** Statistical map displaying the brain areas associated with a significant increases in  
1184 HGA with respect to baseline (time-point and cluster-level threshold were set to  $q < 0.001$   
1185 FDR-corrected). The anatomical labels of subcortical areas are NAc (nucleus accumbens),  
1186 Amyg (amygdala), Hipp (hippocampus), GP (globus pallidus), Put (putamen), Cd (caudate  
1187 nucleus), Thal (thalamus).

1188

1189 **Figure 3.** Strength of the Functional Link (SFL). (A) Mean SFL connectivity matrix averaged  
1190 over time. (B) SFL time course averaged over pairs of areas. The threshold for significant  
1191 SFL was equal to 2.43. Error bars correspond to 95% confidence interval.

1192

1193 **Figure 4.** Graph theoretical measures. (A) Dependence between threshold values (q-values)  
1194 and FC density. (B) Temporal evolution of density D at  $q = 0.05$ .

1195

1196 **Figure 5.** Functional Connectivity Dynamics (FCD). (A) Time course of the average SFL  
1197 (Strength of Functional Link) for the three identified Link Communities (LC). Error bars  
1198 correspond to 95% confidence interval. Spatial patterns for the three LCs are displayed in  
1199 (B), (C) and (D). The thickness of the green links is proportional to the time-averaged SFL  
1200 between areas, whereas the colour and size of nodes is proportional to the mean SFL  
1201 between each area and the rest of the network (i.e., the weight).

1202

1203 **Figure 6.** Exemplar evolution for the dorsolateral motor (A, C) and premotor (B, D) areas. (A)  
1204 and (B) show the involvement of Mdl and PMdl in the three LCs, respectively. (C) and (D)  
1205 depict the involvement in percentage value.

1206

1207 **Figure 7.** Flexibility analysis. (A) Mean evolution of network flexibility (shaded area represent  
1208 standard deviation). (B) Areal flexibility for the five most representative brain regions.

1209

1210 **Figure 8.** Relation between mean FC and distance for the thalamus (A) and caudate nucleus  
1211 (B). Each dot corresponds to a brain area displaying significant FC with the seed regions.

1212

1213 **Figure 9.** Distribution of normalized inner products between the average dipole orientations  
1214 of the left thalamus and caudate nucleus across participants (A). The boxplot depicts  
1215 extreme values (whiskers), first and third quartile (box) and median (red line). (B) Time  
1216 course of mean correlation coefficient.

1217

1218 **Figure 10.** SEEG validation of HGA modulations. Comparison between SEEG single-  
1219 subjects t-value for HGA (blue) and group-level MEG results (red curves). Subject number,  
1220 brain areas and the correlation coefficient between the curves is indicated on the top of each  
1221 panel.

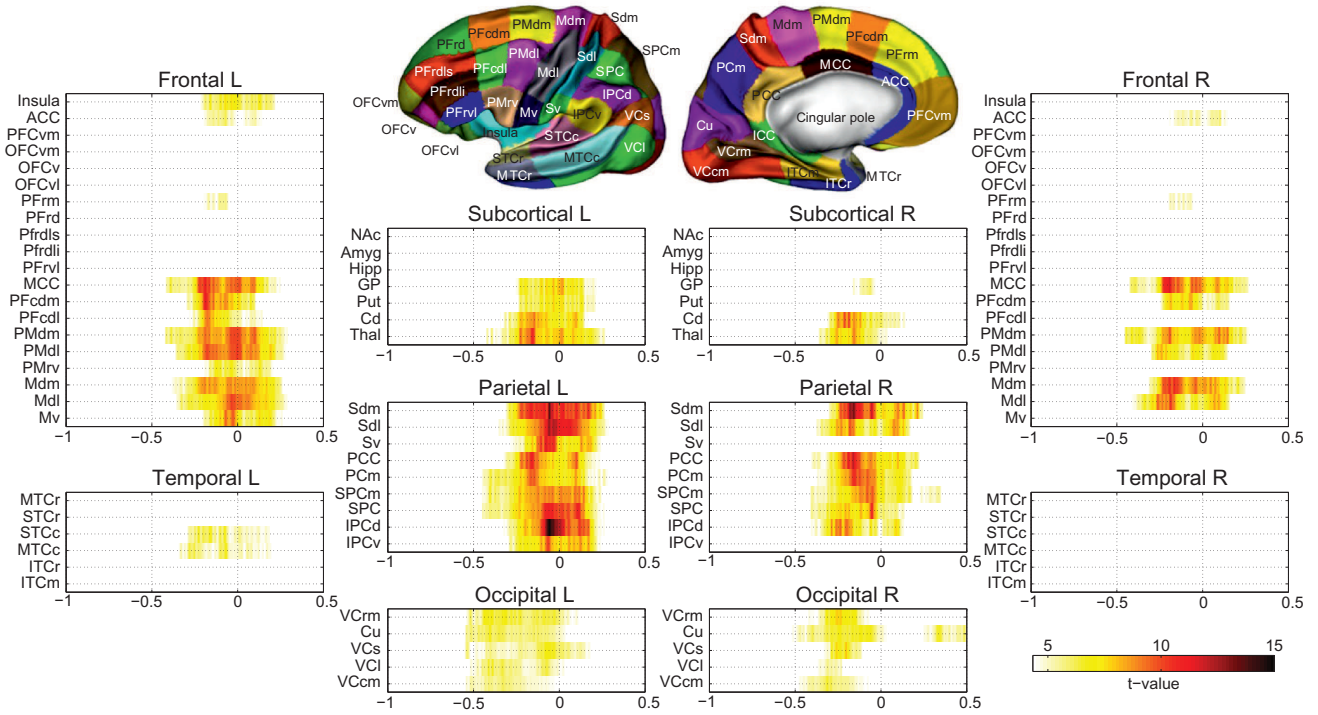
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1223 **Table 1.** Graph theoretical measures.

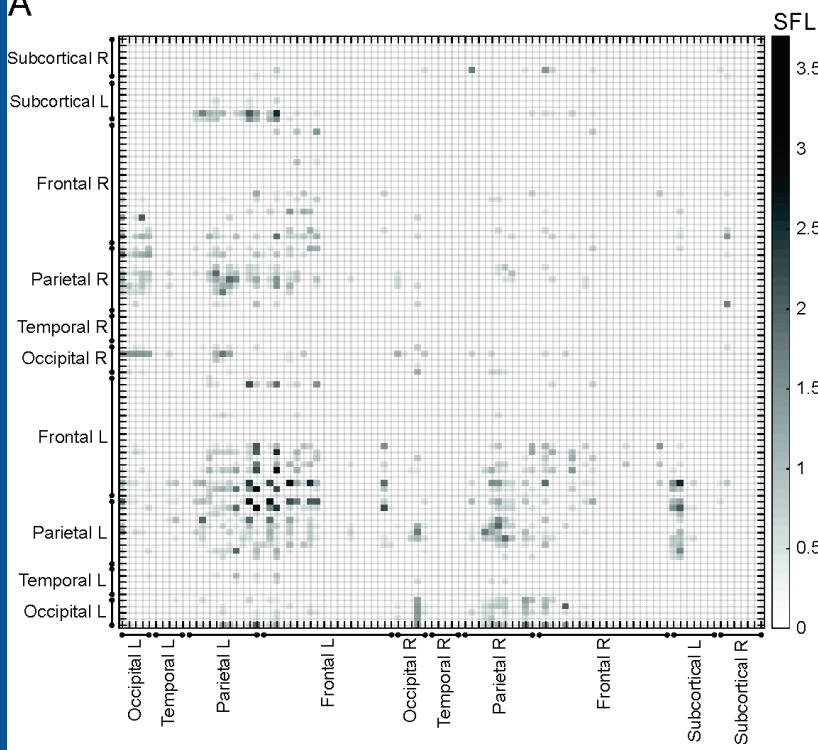
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1225 **Table 2.** SEEG activations

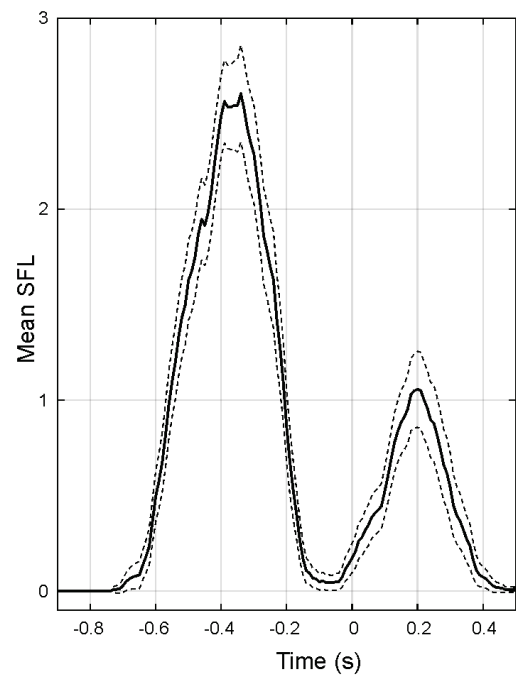


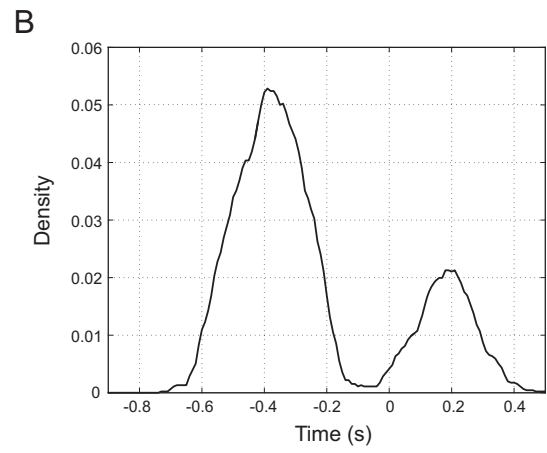
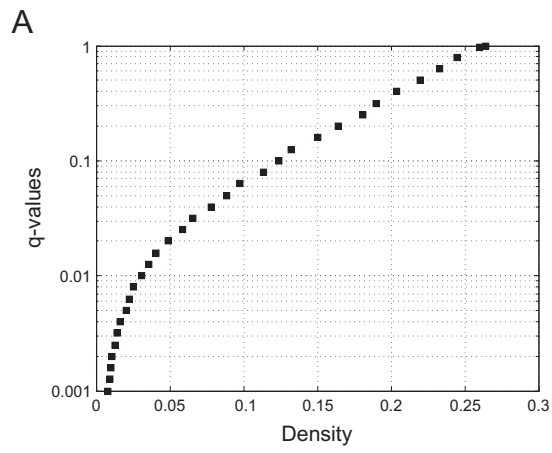


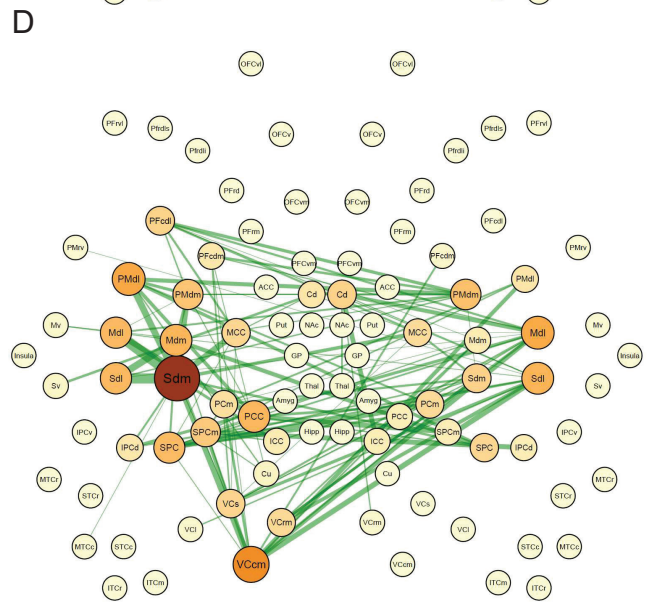
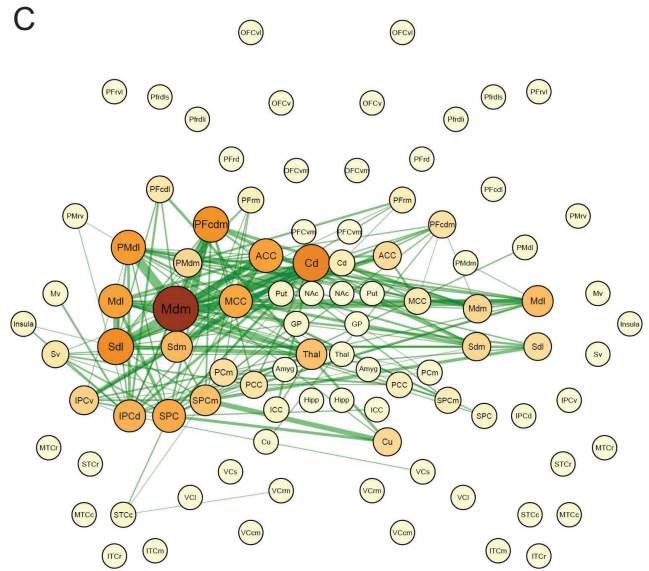
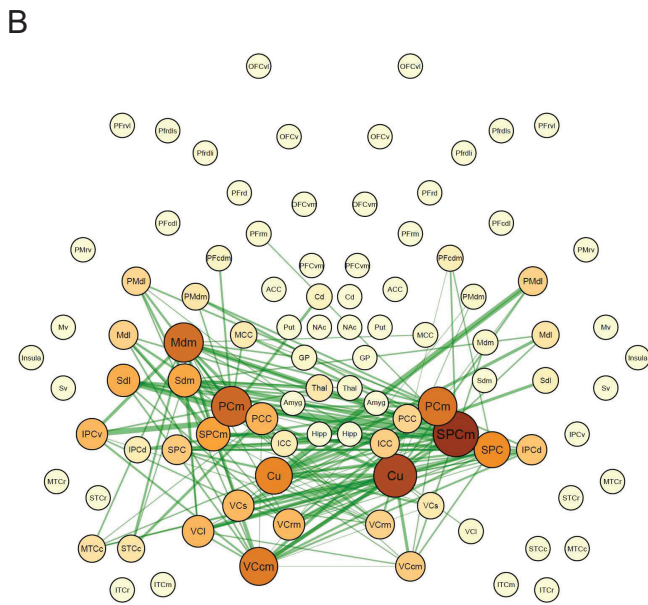
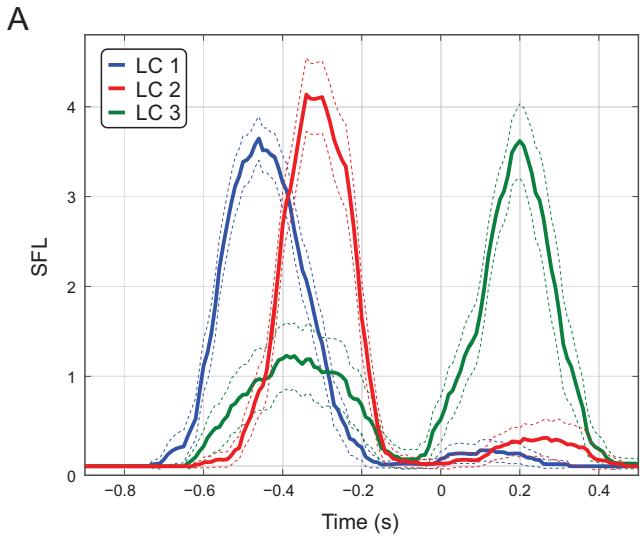
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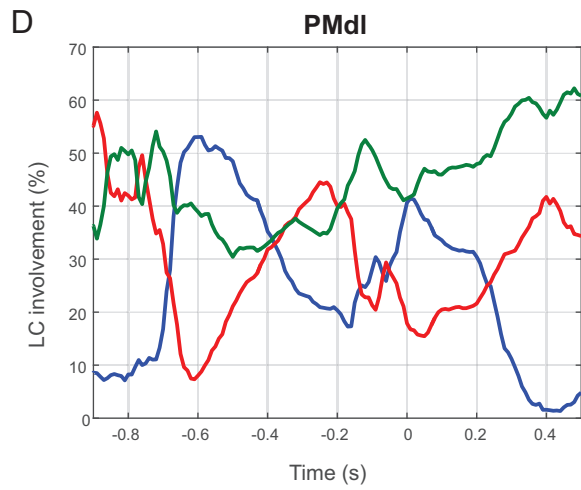
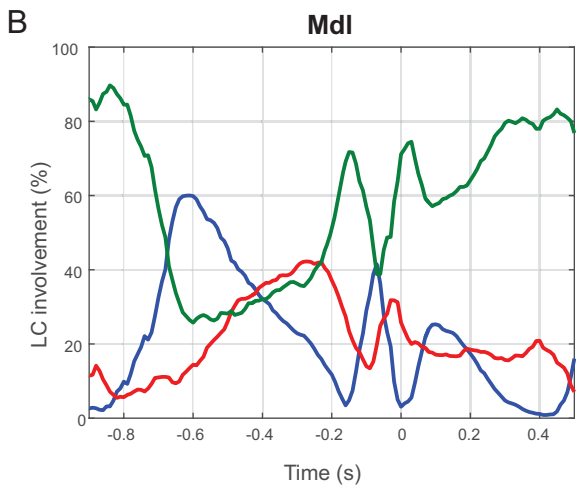
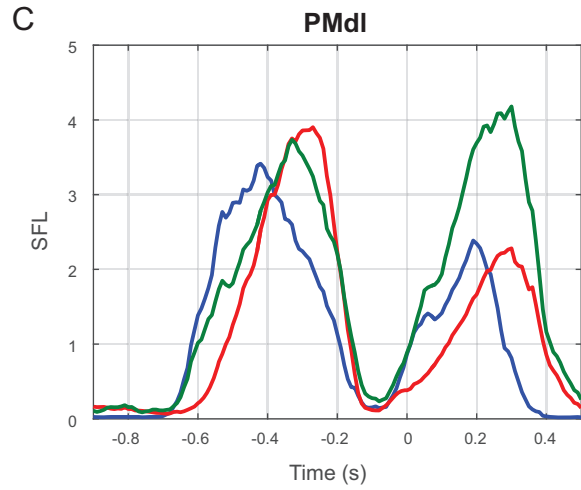
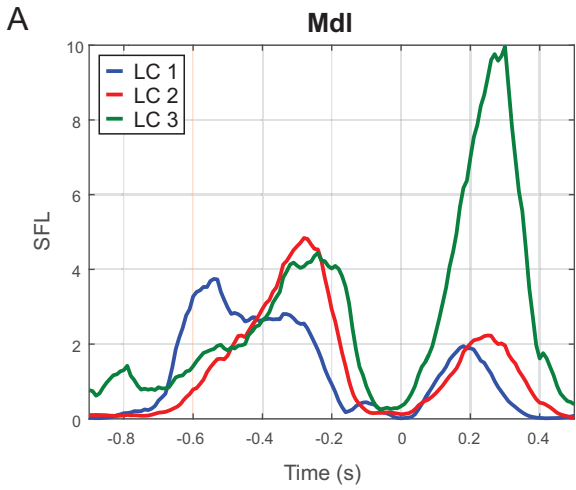
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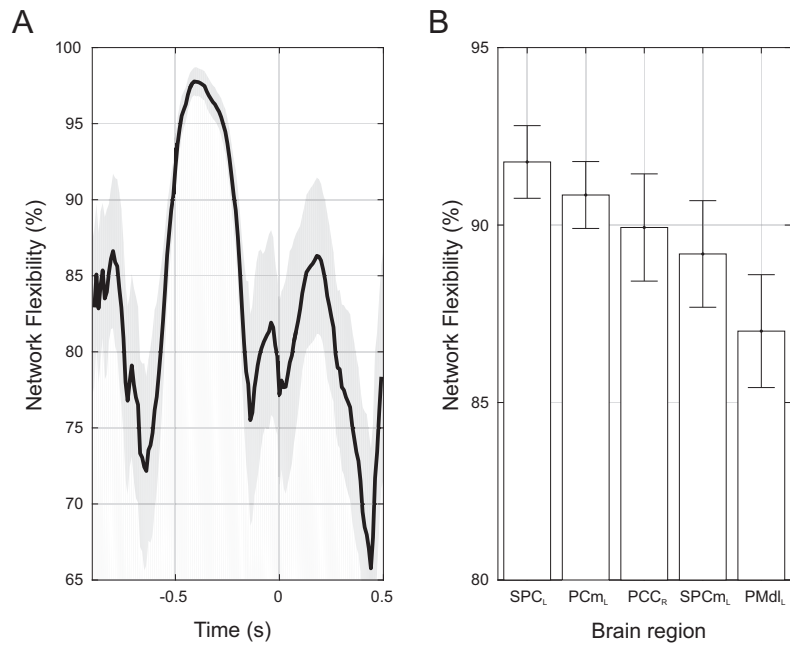


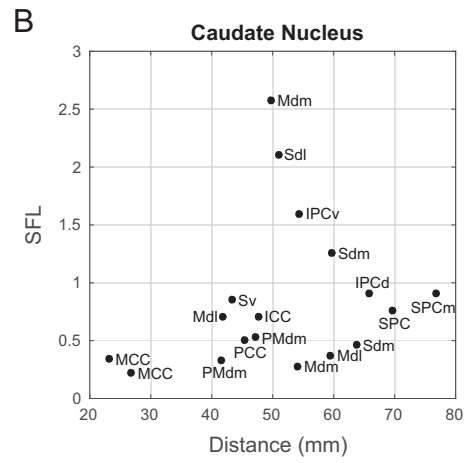
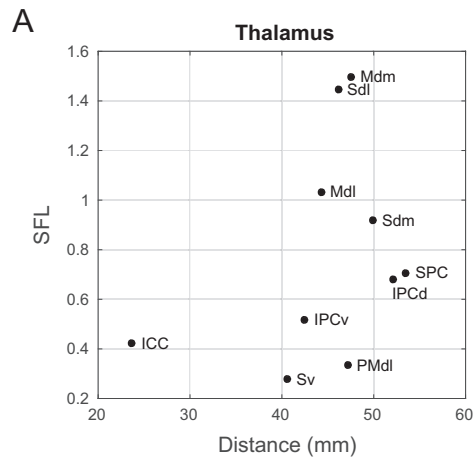


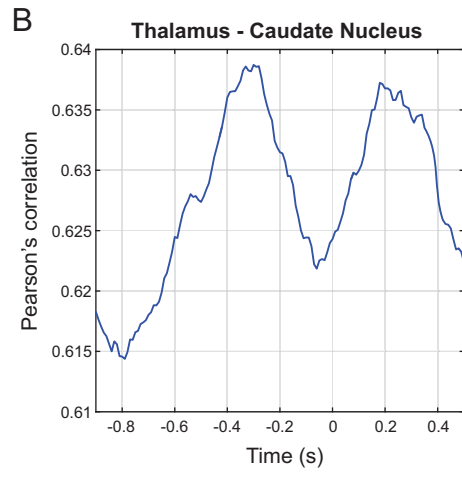
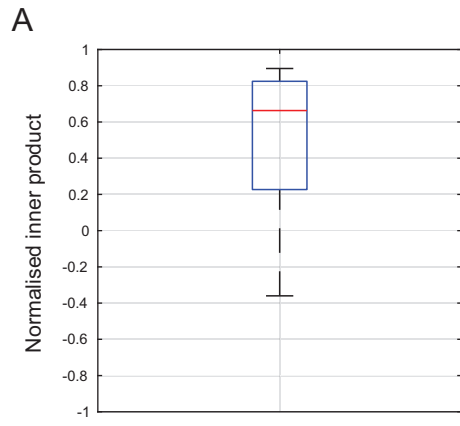


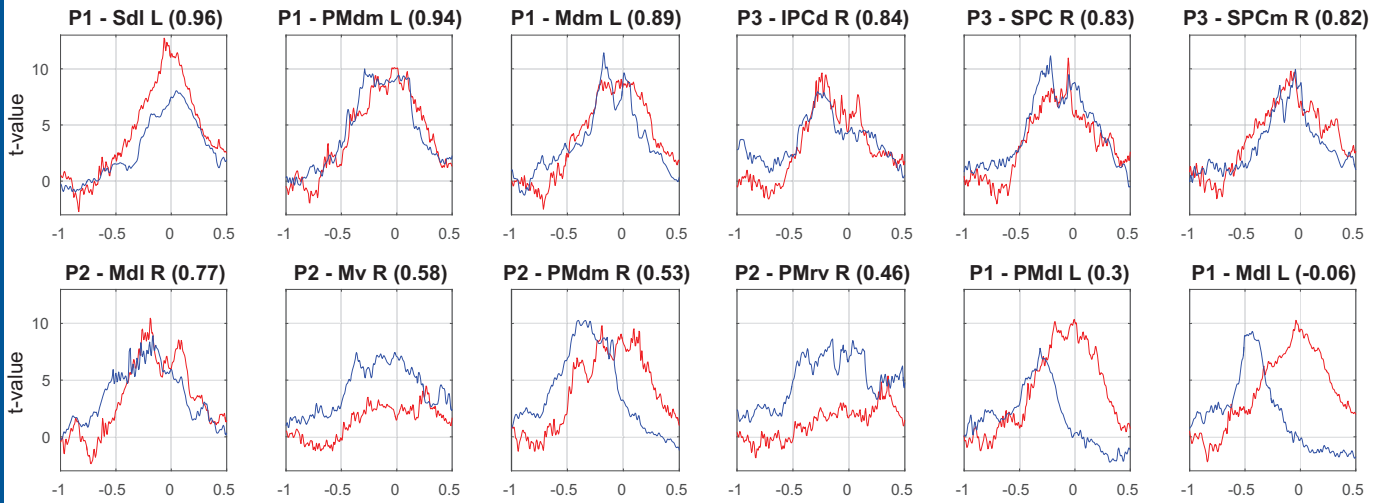












<b>Strength (S)</b>		<b>Eigen Centrality (EC)</b>		<b>Betweenness Centrality (BC)</b>	
<i>Value</i>	<i>Region</i>	<i>Value</i>	<i>Region</i>	<i>Value</i>	<i>Region</i>
7,39	Mdm	6,84	Mdm	16,25	Sdm
6,28	Sdm	6,42	Sdm	13,68	Mdm
4,64	Sdl	5,73	Sdl	9,98	Cu
3,88	PMdl	4,98	Mdl	9,52	VCcm
3,75	VCcm	4,37	PMdl	6,19	Sdl
3,70	Mdl	3,82	Cd	5,81	Mdl
3,34	SPC	3,56	VCcm	4,80	PMdl
3,25	SPCm	3,37	SPCm	4,46	IPCd
3,20	Cu	3,20	PFcdm	3,83	SPC
3,13	Cd	3,05	PCC	3,41	SPCm

Parcel name	Peak <i>p-value</i>	Peak <i>t-value</i>	Peak time (s)	Time interval (s)		Patient number
L Mdm	3,42E-20	11,43	-0,175	-0,28	0,125	1
R SPC	8,76E-20	11,15	-0,22	-0,44	0,2	3
R PMdm	1,41E-17	10,27	-0,34	-0,62	-0,06	2
L PMdm	5,65E-17	10	-0,29	-0,455	0,155	1
R SPCm	4,85E-17	9,96	-0,045	-0,275	0,05	3
L Mdl	2,21E-15	9,29	-0,435	-0,555	-0,315	1
R Mdl	1,52E-14	8,92	-0,165	-0,39	0,055	2
R PMrv	6,70E-14	8,63	-0,145	-0,5	0,155	2
L Sdl	1,29E-12	8,05	0,045	-0,225	0,26	1
R IPCd	1,69E-12	7,96	-0,28	-0,415	-0,135	3
L PMdl	4,22E-12	7,82	-0,315	-0,45	-0,185	1
R Mv	2,78E-11	7,44	-0,02	-0,44	0,18	2
R Mdl	9,89E-08	5,72	-0,475	-0,51	-0,4	2