Brain hothubs and dark functional networks: Correlation analysis between amplitude and connectivity for Broca's aphasia

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Source localization and functional brain network modeling are methods of identifying critical regions during cognitive tasks. The first activity estimates the relative differences of the signal amplitudes in regions of interest (ROI) and the second activity measures the statistical dependence among signal fluctuations. We hypothesized that the source amplitude–functional connectivity relationship decouples or reverses in persons having brain impairments. Five Broca's aphasics with five matched cognitively healthy controls underwent overt picture-naming magnetoencephalography scans. The gamma-band (30–45 Hz) phase-locking values were calculated as connections among the ROIs. We calculated the partial correlation coefficients between the amplitudes and network measures and detected four node types, including hothubs with high amplitude and high connectivity, coldhubs with high connectivity but lower amplitude, non-hub hotspots, and non-hub coldspots. The results indicate that the high-amplitude regions are not necessarily highly connected hubs. Furthermore, the Broca aphasics utilized different hothub sets for the naming task. Both groups had dark functional networks composed of coldhubs. Thus, source amplitude–functional connectivity relationships could help reveal functional reorganizations in patients. The amplitude–connectivity combination provides a new perspective for pathological studies of the brain's dark functional networks.

Brain Hothubs and Dark Functional Networks: Correlation Analysis Between Amplitude and Connectivity for Broca's Aphasia

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Abstract

22 Source localization and functional brain network modeling are methods of identifying critical

23 regions during cognitive tasks. The first activity estimates the relative differences of the signal

24 amplitudes in regions of interest (ROI) and the second activity measures the statistical

25 dependence among signal fluctuations. We hypothesized that the source amplitude–functional

26 connectivity relationship decouples or reverses in persons having brain impairments. Five

27 Broca's aphasics with five matched cognitively healthy controls underwent overt picture-naming

28 magnetoencephalography scans. The gamma-band (30–45 Hz) phase-locking values were

29 calculated as connections among the ROIs. We calculated the partial correlation coefficients

30 between the amplitudes and network measures and detected four node types, including hothubs

31 with high amplitude and high connectivity, coldhubs with high connectivity but lower amplitude,

32 non-hub hotspots, and non-hub coldspots. The results indicate that the high-amplitude regions

33 are not necessarily highly connected hubs. Furthermore, the Broca aphasics utilized different

34 hothub sets for the naming task. Both groups had dark functional networks composed of

35 coldhubs. Thus, source amplitude–functional connectivity relationships could help reveal

36 functional reorganizations in patients. The amplitude–connectivity combination provides a new

37 perspective for pathological studies of the brain's dark functional networks.

38

Introduction

40   In functional brain-imaging studies, there are two strategies can be utilized to identify a

41 brain region as a responsible position for a certain task (e.g., picture naming) or event (e.g.,

42 seizure) (Youssofzadeh & Babajani-Feremi, 2019; van den Heuvel & Sporns, 2013;

43 Daffertshofer & van Wijk, 2011; Michel & Brunet, 2019; Biswal, 2012; Raichle, 2006; Salmelin,

44 Hari, Lounasmaa, & Sams, 1994). The first strategy utilizes source localization to, for example,

45 find activations that can be quantified by measurements, such as blood-oxygen-level-dependent

46 signals detected through functional magnetic resonance imaging (fMRI) or current densities

47 estimated via electroencephalography or magnetoencephalography (MEG) (Bassett, Khambhati,

48 & Grafton, 2017; Bassett & Sporns, 2017; De Vico Fallani, Richiardi, Chavez, & Achard, 2014;

49 Lewis, 2009). The second strategy utilizes connectivity estimation to, for example, calculate

50 connections that represent statistical dependencies, such as synchronizations or causal

51 relationships among brain regions (Farahani, Karwowski, & Lighthall, 2019; Medaglia, 2017;

52 Bassett & Sporns, 2017; Friston, 2011; Lewis, 2009; O. Sporns, 2002). It is possible to detect

53   statistical dependencies among regions regardless of whether the regions are highly activated.

54   This yields an inevitable but not fully understood question regarding the relationship between

55   "amplitude" and "connectivity."

56   In functional brain imaging, brain regions having large amplitudes are usually exhibited as

57   hotspots, and other low-amplitude regions are considered coldspots. Considering this

58   visualization tradition, van den Heuvel and Sporns (2013) raised a question of whether or not the

59   highly connected functional hubs were potential hotspots for developing diagnostic biomarkers

60   or therapeutic targets. If we view the relationships between amplitude (i.e., hotspots and

61   coldspots) and connectivity (i.e., hubs and non-hubs), there are four possible types of brain

62   regions, including hothubs, coldhubs, non-hub hotspots, and non-hub coldspots. Hassan et al.

63   (2015) reported that the deletion of regions of interest (ROI) having no more than 50% of the

64   highest activations removed the temporal lobe from the brain networks of picture naming. Their

65   findings implied that there were potential coldhubs in functional brain networks and that the

66   possible contribution of "low-energy" regions should be further studied.

67   To the best of our knowledge, the relationship between activation and functional

68   connectivity remains unexplored regarding task-related functional brain imaging. Few studies

69   have investigated whether highly activated regions are also hubs in the task-related brain

70   network. There are also limited reports of the pathological changes of activation-connectivity

71   relations, and whether non-trivial activation-connection relations exist. In this study, we

72   **hypothesize that** activation–connection coupling patterns exist for the performance of a naming

73   task (i.e., significantly negative or positive correlations by healthy persons). We also **propose**

74   **that** persons having post-stroke aphasia also have uncoupling patterns or opposite coupling

75   patterns compared with healthy persons. The term "**coupling**" means that there is a significant

76   correlation. The term "**uncoupling**" means there is a non-significant correlation. The term

77   "**opposite coupling**" means that both correlations are significant, but their coefficients have a

78   different sign. Based on a picture-naming task requiring MEG scanning, we investigate whether

79   the highly connected regions are associated with low or high amplitudes. This allows detection

80   of regions having both high activations and critical positions in brain networks (viz., hothubs).

81   Moreover, we also explore the subnetworks comprising the coldhubs. Because such subnetworks

82   are shown as dark parts in functional brain imaging, we call them **dark functional networks**.

83

Materials & Methods

85   Five male persons having Broca's aphasia were recruited from the Rehabilitation Medical

86   Center of the First Affiliated Hospital of Nanjing Medical University. The inclusion criteria were

87 as follows: (1) a single left-hemisphere stroke confirmed by computed tomography or magnetic
88 resonance imaging (MRI); (2) Broca's aphasia determined by the Mandarin version of the
89 Western Aphasia Battery (WAB); and (3) native right-handed speakers of mandarin Chinese.
90 The exclusion criteria were as follows: (1) severe vision or hearing impairment; (2) any
91 neurological or psychiatric complications other than stroke, including but not limited to the
92 diagnosis of mild cognitive impairment or dementia before stroke; and (3) contradictions with
93 MRI testing. Five healthy volunteers (four males and one female) were enrolled in the control
94 group. All participants performed the picture-naming task in a single session. The demographics
95 are listed in **Table 1**. All participants signed an informed consent form that was approved by the
96 Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (No.2011-
97 SRFA-025). All examinations were carried out under the guidance of the Declaration of
98 Helsinki. Before the MEG test, all participants completed the WAB, which includes spontaneous
99 speech, auditory comprehension, repetition, and naming tasks. The WAB suggests aphasia
100 diagnosis for an aphasia quotient (AQ) <93.8. The WAB results can also be used to categorize
101 the aphasia into different subtypes, such as Broca's or Wernicke's aphasia. All stroke
102 participants in our study were diagnosed with Broca's aphasia.
103
104 **Experiment paradigm**
105   The participants lay supine on the MEG scanner bed. A set of pictures was randomly
106 presented onto a screen for the naming task. The stimuli consisted of 40 black-and-white outline
107 drawings presented on a white background (see *Supplementary File S1*). They were from the 100
108 words of the Kent–Rosanoff word association test (Kent & Rosanoff, 1910). All selected stimuli
109 were a picturable noun or had a noun part of the meaning. They were both emotionally neutral
110 and with high frequency (Wang, Bing, & Hou, 2010). We modified a previously reported
111 delayed naming task (Laganaro, Morand, Schwitter, Zimmermann, & Schnider, 2008) based on
112 the paradigm of Levelt et al. (Levelt, Praamstra, Meyer, Helenius, & Salmelin, 1998). Before the
113 experiment, participants were trained to name aloud each picture correctly. This was done to
114 confirm that the participants could perform the naming task in the scanning session (Ellis,
115 Burani, Izura, Bromiley, & Venneri, 2006). Each trial comprised the following procedures
116 (**Figure 1**): a picture was shown on the screen for 200 ms, followed by a blank white screen for
117 1000 ms. Next, a white question mark on a black background was shown for 2,000 ms. This was
118 followed by a 1,000 ms black interval preceding the next trial. During the target-picture
119 presentation, the participants were expected to perform overt naming. The question mark was a
120 warning for the participants, indicating that they would soon be expected to perform overt

121   naming. The 40 stimuli were randomly arranged as a sequence. The original design of this study
122   was to let the participants do three runs in each experiment, and each run completed the
123   sequence. However, our preliminary test showed that the patients could not tolerate a long test
124   procedure, particularly when they were required to stay alone in a closed room without any tasks,
125   waiting for the next run. We finally allowed all the participants to execute only a run of 100 trials
126   (i.e., two-and-a-half sequences). There were no close distances of the same pictures in the run.
127   The voices were transmitted outside the shielded room via a plastic tube and were recorded by
128   researchers. The records were then classified as correct responses (i.e., target word or suitable
129   alternatives) and incorrect responses (i.e., no-response or unsuitable words), according to the
130   works of Feng Lin, Shao-Qiang Cheng, and Dong-Qing Qi. Only the consensuses would then
131   become the final decisions. Then, the trials having correct responses were selected for further
132   analyses.
133
134   **Data acquisition**
135   Using a CTF-275 whole-head MEG scanner (VSM Canadian Medical Technology
136   Company), available from the MEG Center of the Affiliated Brain Hospital of Nanjing Medical
137   University, raw files of magnetic fields were recorded within the 0.03–100-Hz band. The sample
138   rate was 1,200 Hz. The participants lay relaxed with their heads fixed under the sensory matrix.
139   They were trained to avoid limb movements, head movements, and frequent blinking during the
140   test. The pictures were delivered in a pseudorandom sequence using BrainX6.0 (Cincinnati
141   Children's Hospital Medical Center, OH, USA) (Dinga et al., 2018; Xiang, Wilson, Otsubo, Ishii,
142   & Chuang, 2001). The pictures were projected through an aperture onto a mirror, which, in turn
143   projected the beam onto a screen. The horizontal and vertical visual angles were 3–4° and 1–2°,
144   respectively. The space between the screen and the nasion of each participant was adjusted to a
145   comfortable distance of 35–45 cm. The head positions were measured at the beginning and end
146   of each session. Trials exhibiting motions greater than 0.5 cm were excluded.
147   After the MEG test, the participants underwent an MRI session for lesion delineation and
148   source localization. The MRI data were acquired on a Signa (GE Medical Systems, USA) 1.5-T
149   scanner capable of producing a high-resolution T1-weighted anatomical volume image (TR: 33
150   ms; TE: 9 ms; recording matrix: 256×256 pixels; excitation: 1; the field of view: 240 mm; and
151   slice thickness: 1.4 mm). Transformation of the MEG coordinate system into MRI-defined space
152   was achieved with the aid of three fiduciary points marked on the nasion and the right and left
153   pre-auricular points with MRI markers, which were identical to the positions of the coils used in
154   the MEG.

155

Data processing

157   Brainsuite18a was used for MRI segmentation. Cortical surfaces were extracted from the T1

158 MRI data. The surface and volume registration was established based on the USCBrain Atlas,

159 which has a total of 65 cortical regions per hemisphere (i.e., the cortex has 130 **original scouts**)

160 (see *Supplementary Table S1)* (Joshi et al., 2017). The anatomic data, including the MRI results

161 and the registered surface files with their corresponding MEG data, were imported into

162 Brainstorm (Tadel et al., 2019; Baillet, 2017; Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011).

163 The recordings were preprocessed using DC-offset correction, linear trend removal, 1–45-Hz

164 band-pass filtering, and 50-Hz notch filtering. Artifacts were detected via signal-space projection

165 and independent component analysis. The raw MEG files were epoched from –200 to 600 ms

166 with a reduced sample rate of 600 Hz. As shown in **Figure 1**, the epoched time window

167 contained the word generation stages rather than the overt speaking actions. The pronouncing

168 periods were only used to ensure that the participants paid attention to and were involved in the

169 task. Although the control participants produced correct responses for all trials, the aphasics had

170 incorrect responses. After discarding the bad trials having incorrect responses or unremovable

171 artifacts, we uniformly resampled the trails into 60 correct ones for each participant for further

172 analyses of the source-space functional connectivity. Although there were repetitions of some

173 pictures, all participants provided corresponding trails during the run. Source reconstruction was

174 performed using weighted minimum-norm estimation (WMNE) on a current density map and

175 constrained dipole orientations (Hincapié et al., 2017). Each original scout was subdivided into

176 six sub-regions. The final subdivided atlas had 776 **refined scouts**. Trials were averaged on the

177 source level for each person using the weighted arithmetic average. The source data for each

178 person were projected onto the USCBrain_BrainSuite_2017 template. We further averaged the

179 projected source files on the group level, finally obtaining one source file per group. Following

180 the previous work of Hassan et al. (2015), we extracted six picture-naming stages: t1 (0–119 ms,

181 visual feature extraction); t2 (120–150 ms, object recognition); t3 (151–190 ms, memory access);

182 t4 (191–320 ms, semantic processing); t5 (321–480 ms, phonological encoding); and t6 (481–

183 535 ms, articulation). Phase-locking values (PLV) among the 776 refined scouts were estimated

184 for each stage on the gamma frequency band of 30–45 Hz. As reported by Hassan et al. (2015),

185 to reduce confounding factors from correlations of adjacent regions, all PLVs were normalized

186 by the mean and standard deviation matrix of the baseline (-200ms–0ms) time-window.

187

Graph modeling

189  We use graph theory terminology (de Nooy, Mrvar, & Batagelj, 2018) and the expressions

190 from the work of Rubinov and Sporns (2010) for brain network analyses. A node is a scout of the

191 brain region, and an edge is an undirected line. Size refers to the number of nodes in a network.

192 A cluster refers to a subnetwork of the entire network. In this study, the nodes were the 776

193 refined scouts, and the edge weights were normalized PLV scores larger than 1.96. We

194 established six undirected refined networks on the subdivided USCBrain Atlas for each person.

195 These personal networks were utilized for further within-subjects and inter-group permutation t-

196 tests. We also established refined networks on the averaged source files for each group. These

197 averaged original networks were applied for further hothub and coldhub detection. The

198 amplitude of each refined scout was measured according to the estimated electric density in a

199 physical unit of picoampere. The scouts were partitioned using a functional scheme (see

200 *Supplementary Table S1*) that included eight systems (Muldoon et al., 2016; Gu et al., 2015): 1)

201 frontoparietal, 2) medial default mode, 3) visual, 4) ventral temporal association, 5) attention, 6)

202 cingulo-opercular, 7) motor and somatosensory, and 8) auditory. By partitioning the functional

203 systems into the left and right hemispheres, the final scheme contained 16 functional modules. In

204 our descriptions, the term "strongly connected" indicates the weight strength of connections. The

205 term "highly connected" is known as the number of connections. The term "heavily connected"

206 implies to the measures concerning both weights and numbers of connections. The term "highly

207 activated" identifies the amplitude of a node.

208

209 **Network thresholding**

210  To find nontrivial functional connections and get robust findings, Hassan and Wendling

211 (2018) suggested the reduction of the edges in a graph using a series of threshold values. In this

212 work, we utilized the island decomposition technique embedded in Pajek 5.07 to perform fast

213 thresholding operations (Mrvar & Batagelj, 2016). Pajek is a network analysis software package

214 that can achieve fast speed and memory-efficient calculations for large and densely structured

215 graphs (Pavlopoulos, Paez-Espino, Kyrpides, & Iliopoulos, 2017). The island decomposition

216 defines an island as a cluster with highly weighted within-cluster edges. In particular, the weights

217 inside the cluster must be larger than the weights to neighboring nodes outside the cluster. Pajek

218 called for two inputs to control the island thresholding processes: the minimum and maximum

219 island sizes. In this study, the former was fixed to three. This is the minimum graph size that can

220 support calculating clustering coefficients. We shifted the maximum size from 50 to 750 in

221 increments of 50. Given the half nodes of each hemisphere and the total nodes of the entire

222 network, we also set 388 and 776 as candidate maximum island sizes. These numbers determined

223   the possible size of the main components in the obtained networks. At each naming stage, the
224   island decomposition generated a series of m-island graphs (where m denotes the maximum
225   island size).
226
227   **Graph measures**
228   The refined networks and their thresholded networks were weighted undirected graphs
229   lacking loops and multiple edges. Based on these graphs, we calculated nine variables for each
230   node (de Nooy et al., 2018; Olaf Sporns, 2016; Rubinov & Sporns, 2010).
231   The first six variables were calculated without utilizing the network partitions of the 16
232   functional modules. The **degree centrality** of a node in its weighted definition is the sum of the
233   edge weights connected to the node. This is a measure of the strength of the node in the range of
234   its firstly connected neighbors. The largely weighted degree centrality indicates that the node is
235   heavily connected. The **betweenness centrality** of a node in its weighted definition is the
236   number of weighted shortest paths going through it. This is a measure of the key connector role
237   of the node in transferring information or its role as a bottleneck in blocking information flowing
238   through the graph paths. **Transitivity** is the probability that the first-connected neighbors of a
239   node are also connected. Barrat et al. (Barrat, Barthelemy, Pastor-Satorras, & Vespignani, 2004)
240   reported that the weighted definition of transitivity was the local clustering coefficient having
241   constant edge weights between the target and adjacent nodes. The **k-coreness** of a node was
242   derived from a thresholding method called the "k-core decomposition". This method reduces the
243   graph to a maximal subgraph in which each node has at least a degree, k. A valid k-coreness
244   means that a node belongs to the k-core but not to the $(k+1)$-core, and the k-coreness measures
245   whether a node involves the highly connected core of the brain graph. The **Laplacian centrality**
246   is a measure that concerns the possible destructive effects of deactivating or deleting a node from
247   a graph (Qi et al., 2013). The higher the Laplacian centrality of a node, the more indispensable it
248   is. Note that the k-coreness and Laplacian centrality algorithms do not consider the edge weights.
249   Finally, the **eigenvector centrality** of a node is assigned based on whether the node connects to
250   many other nodes and/or to highly connected nodes. Highly scored nodes are highly connected
251   with highly connected neighbors. That is, they are hubs of the graph (de Nooy et al., 2018).
252   Weighted definitions were applied to the eigenvector centralities obtained in this study.
253   To measure the distribution of a node's connections across modules, we also calculated
254   three variables that depend on the network partitions. We used 16 functional modules, as detailed
255   in *Supplementary Table S1*. The **participation coefficient** of a node measures the distribution of
256   its inter-modular connections. If a node is only connected to nodes in the same module, the

257 participation coefficient is zero. If the node is equally connected to all other modules, the

258 participation coefficient is one. The **gateway coefficient** of a node refers to both its inter-

259 modular and within-modular connections (Vargas & Wahl, 2014). If a node links to the hub

260 within its module and occupies most of the outer connections from other modules to its module,

261 this node has a larger gateway coefficient. As described by Vargas and Wahl (2014), this

262 coefficient makes it feasible to identify nodes with unique inter-modular connections. The

263 **within-module-degree z-score** of a node is its normalized number of edges that connect to other

264 nodes in the same module of the target node.

265   In this work, all graph measures were calculated using the undirected definitions (Hassan &

266 Wendling, 2018; Rubinov & Sporns, 2010). The degree, betweenness, transitivity, *k*-coreness,

267 and eigenvector centrality were calculated using the igraph 1.2.4.1 package (Csardi & Nepusz,

268 2006) of the R software. The Laplacian centrality was calculated using Pajek 5.07 (Mrvar &

269 Batagelj, 2016). The within-module-degree z-score, participation coefficient, and gateway

270 coefficient were obtained using the brainGraph 2.2.0 package (Watson, 2019) of the R software.

271

272 **Hub and hotspot detection**

273   The z-scores of the amplitudes were calculated for both subdivided and original scouts by

274 comparing the baseline of –200 ms. At each stage, the refined scouts were categorized into

275 hotspots or coldspots depending on whether their amplitudes were larger than the mean plus

276 standard deviation (Hassan et al., 2015). The network hubs were detected using Pajek 5.07. As

277 defined by de Nooy et al. (2018), hubs are nodes with top-level eigenvector centralities.

278 However, there is no optimal strategy to determine the top-level cutoff value. In this study, the

279 number of hubs was set to the number of hotspots in each graph. This is an arbitrary selection

280 that includes 11.86%-16.37% nodes. This strategy followed a rule of thumb (de Nooy et al.,

281 2018) and did not exceed the arbitrary threshold of 30% (Youssofzadeh & Babajani-Feremi,

282 2019). Finally, all nodes were categorized into four types: **hothubs**, **coldhubs**, non-hub

283 coldspots, and non-hub hotspots.

284

285 **Statistical analysis**

286   **Figure 2** shows the data-processing workflow. Inter-group permutation t-tests for the

287 amplitude z-scores on the 130 scouts at each naming stage were processed using Brainstorm

288 (Tadel et al., 2019, 2011), with p<0.05 as the level of significance. Within-subject Pearson

289 coefficients were calculated between the amplitude (i.e., electric densities in a unit of

290 picoamperes) and each of the graph measures on the refined 776 scouts. These were partial

291 correlations with the effect of subjects removed. Thus, the individuals were regarded as a third

292 variable that should be adjusted when comparing the amplitude with a graph measure. The 95%

293 confidence intervals and significances of the Pearson coefficients were estimated using the psych

294 1.8.12 package (Revelle, 2019) of the R software. To explore the entire continuum of m-island

295 graphs and select an optimal m value, we plotted all coefficients on a coordinate system for

296 which the x-axis denoted the maximum island size (see *Supplementary Figures S1, S2*). The left

297 pole included m-island graphs having small but strongly connected clusters (i.e., the "rich-club"

298 structures). The right pole contained m-island graphs having both large and highly connected

299 clusters (i.e., large island structures with a wide range of edge weights from weak to strong). If a

300 correlation were significant ($p<0.05$), it could be regarded as a **coupling correlation**.

301 Conversely, a non-significant correlation could be termed an **uncoupling correlation.** We also

302 did a permutation test on inter-group correlation coefficients with 1,000 randomizations by

303 shuffling the group assignments of individuals [i.e., the 10 individuals in a permutation were

304 randomly reassigned into two groups (5 ones per group) without replacement]. For each

305 permutation, an inter-group difference value of partial correlation coefficients were calculated.

306 The 1,000 values formed an estimation for the distribution of inter-group differences. The

307 statistics of correlation coefficients followed the estimation approach with 95% confidence

308 intervals (Calin-Jageman & Cumming, 2019). The brain networks were visualized using Pajek

309 5.07 (Mrvar & Batagelj, 2016) and VOSviewer 1.6.13 (van Eck & Waltman, 2009).

310

311 **Results**

312

313 **Amplitude–connectivity analysis**

314   **Figures 3 and 4** show the Pearson correlation coefficients between the ROI amplitudes and

315 their graph measures, for measures independent of and dependent on the brain modules,

316 respectively. A positive significant coefficient suggests that the regions having higher activation

317 levels tend to have high values of the corresponding graph measure. That is, hotter spots occupy

318 pivotal network positions. Conversely, a negative significant coefficient suggests that the regions

319 having lower activation levels tend to have high values of the corresponding graph measure (i.e.,

320 colder spots are positioned at important network locations). **Figure 3** shows coefficients in

321 m776-islands, and **Figure 4** shows coefficients in m388-islands. The selection of m values in the

322 two figures was determined by methods summarized in *Supplementary Figures S1, S2*. There are

323 two positions on the x-axis that optimally separate the inter-group distribution of coefficients

324 (see vertical dashed lines in *Supplementary Figures S1, S2*). *Supplementary Figures S3 and S4*

325   support the significant inter-group differences of Pearson coefficients by showing the 95%

326   confidence intervals of 1,000 random permutations.

327   **Figures 3 and 4** provide two obvious findings. First, the healthy controls had positive

328   significant coefficients, especially at t4, t5, and t6 (**Figure 3**). Second, the coefficients of the two

329   groups deviated from each other with two types of deviation. For Type-I, the two groups had

330   significant but opposite coefficients (i.e., there was a deviation between the two coupling

331   correlations, and the degree results for t4 and 5 are shown in **Figure 3**). For Type-II, one group

332   had significant coefficients, but the other group showed no correlation significance (i.e., the

333   coupling and uncoupling correlations differed, and the degree results for t1, t3 and t6 are shown

334   in **Figure 3**). For the Broca-group view results, Type-I means that significant differences in

335   amplitude–connectivity patterns were noted between the Broca aphasics and the control group,

336   and the Type-II deviation implies emergence or vanishing of amplitude–connectivity patterns in

337   the Broca group.

338   In **Figure 3**, Stages t4 (semantic processing) and t5 (phonological encoding): the degree,

339   transitivity, k-coreness, and Laplace show Type-I deviation with positive significant coefficients

340   in the Broca group. Type-I deviations having positive coefficients in the Broca group occurred at

341   t1 of the eigenvector, t2 of the transitivity, k-coreness, Laplace, and eigenvector, t3 of the k-

342   coreness, Laplace, and eigenvector, t5 of the betweenness, and t6 of the eigenvector. Type-I

343   deviations having negative coefficients in the Broca group occurred at t1 and t3 of the degree, t1

344   of the transitivity, k-coreness, and Laplace. Type-I deviations having positive coefficients in the

345   control group occurred at t4 and t6 of the betweenness. Type-I deviations having negative

346   coefficients in the control group occurred at t4 of the eigenvector, and t6 of the transitivity, k-

347   coreness, and Laplace. In **Figure 4**, within-module-degree z-score shows no significant

348   correlations for each group. The t1, t2, and t3 show significant positive correlations in the Broca

349   group. The t3, t4, t5, and t6 show a significant negative correlation in the control group.

350

351   **Hotspot and hothub analysis**

352   Although there were different possible categories for the six subdivided scouts in the same

353   130 original ones, we reported the hothubs on the level of the original 130 scouts (**Figure 5**) if

354   there was at least one hothub on the level of the 776 subdivided scouts. This was because most

355   previous reports did not interpret functional brain activities on a resolution as did the level of the

356   776 refined scouts (as shown in *Supplementary Table S2*). Therefore, **Figure 5** reports the

357   regions in which hothubs occurred. We also marked eight functional systems in this figure using

358   different colors. As detailed in **Figure 5**, the Broca group scores for InfOcciGyr_VenPst_R

359   (right inferior occipital gyrus ventroposterior), PreCune_Sup_R (right precuneus superior), and

360   MidOcciGyr_DsoAnt_L (left middle occipital gyrus dorsal anterior) had significantly lower

361   amplitude z-scores (cells with superscript a). However, they remain in the list of hothubs.

362   Compared with the control group, the Broca group did not use the cingulo-opercular hothubs

363   (yellow cells) across all stages, and the hothubs in the medial default mode (green cells) were

364   absent at t3. They required more visual system regions at each stage (white cells) and resorted to

365   the attention system in the last three stages (pink cells). For the control-group t4 and the Broca-

366   group t5, most hothubs were from the frontoparietal system.

367

368   **Brain network visualizations**

369   We visualized the m776 islands by showing their hotspots and hubs. **Figure 6** provides a

370   visualization of the brain networks for the semantic processing stage of t4. This figure presents

371   two aspects of the brain networks by changing the node size according to both amplitude and

372   linking strengths. Four colors are used in this figure: red (hothubs), green (coldhubs), yellow

373   (non-hub hotspots), and blue (non-hub coldspots). The full set of visualizations is provided in

374   *Supplementary Figure S5*.

375

376   # Discussion

377   **Thinking about amplitude, connectivity, hothubs, and coldhubs**

378   In the last two decades, a new trend known as functional brain network analysis, which

379   involves identification of critically connected positions as specific regions for a certain task or

380   event, has been developed (Farahani et al., 2019; Medaglia, 2017; Bassett & Sporns, 2017;

381   Lewis, 2009; O. Sporns, 2002). The new principle based on connectivity challenges the

382   traditional paradigm that identifies critical regions by their levels of activation/amplitude. It is

383   thus necessary to clarify whether or not a highly/heavily connected region also has a high

384   activation level. Although there is a growing number of reports about either or both of the two

385   aspects, few studies have considered the relationship between them. By using resting-state and

386   finger tapping fMRI tests, Zhou et al. (2014) explored the fractional amplitudes of the lower-

387   frequency fluctuations and the thalamic seed-based functional connectivity in persons affected

388   by mild traumatic brain injuries. Although these researchers did not provide quantitative

389   measurements for the amplitude–connectivity relations, their side-by-side comparison revealed

390   co-occurring amplitude and connectivity decreases. This finding suggests that the target patients

391   had attenuated thalamocortical networks (Zhou et al., 2014). Furthermore, based on resting-state

392   fMRI tests, Zhang et al. (2015) defined the amplitude–connectivity coupling strength as the

393   correlation coefficients between the amplitude of the low-frequency fluctuation and the

394   functional connectivity density. Compared with healthy controls, the amplitude–connectivity

395   coupling strengths in persons having mesial temporal lobe epilepsy were found to be

396   significantly lower in the mesial temporal structures and significantly higher in the default-mode

397   regions. This suggests that the amplitude–connectivity uncoupling pattern can be used for

398   differentiating patients with healthy controls. Base on a picture-naming test via MEG scanning,

399   the present study investigated the task-state amplitude–connectivity correlation. We expanded

400   the field by answering the following two questions.

401   First, do amplitude–connectivity relationships exist across scales? This question considers

402   whether amplitude–connectivity relationships occur in different spaces and at different times. For

403   the second aspect, we utilized a MEG naming test with a six-stages of separation (see **Figures 3,**

404   **4, and 5**) (Hassan et al., 2015). For the first aspect, we adopted island decomposition(de Nooy et

405   al., 2018) as the thresholding method for brain graph modeling. This method establishes

406   continuums for brain graphs and allows distributions of amplitude–connectivity patterns in the

407   continuums to be found (see *Supplementary Figures S1, S2*).

408   Second, how can the most important brain regions be identified? In the amplitude

409   dimension, the hotspots having high activity levels are responsible for the task performance. In

410   the connectivity dimension, the highly connected hubs are pivotal to signal processing. Based on

411   both dimensions, we classified brain regions into four categories: hothubs, non-hub hotspots,

412   coldhubs, non-hub coldspots. If the correlation of amplitude–connectivity is significant ($p<0.05$)

413   and strong (with coefficients approaching 1 or -1), there should be only hothubs or coldhubs. If

414   the correlations are non-significant or significant with weak coefficients, there should be four

415   types of nodes in functional brain networks, and the hothubs should be the most important

416   position, because they match both amplitude and connectivity principles.

417   **Coupling and uncoupling amplitude–connectivity patterns in Broca and control groups**

418   The coefficients were distributed in a similar pattern at different stages and with different

419   graph measures (see **Figures 3, 4**, and *Supplementary Figures S1, S2*). For the Type-I deviations,

420   the 95% confidence intervals of the two groups seldom overlapped along the island continuums.

421   This suggests that, although both groups had amplitude–connectivity coupling relationships, their

422   patterns were opposite. The Type-II deviations revealed the differences in the coupling and

423   uncoupling patterns of the different groups. The controls tended to have negative values, whereas

424   the Broca persons tended to have positive coefficients. **Figure 3** also showed that the Broca

425   group had more coupling relationships than did the control group. For example, the t2 and t3 of

426   the *k*-coreness, Laplace, and eigenvector had Type-II deviations with positive correlations in the

427   Broca group. These findings suggest that, at the object recognition (t2) and memory-access (t3)

428   stage, the regions having high activation levels tended to be hubs (by eigenvector centrality) in

429   core structures (by *k*-coreness), and they occupied critical positions (by Laplacian centrality) in

430   the Broca aphasics. However, the interesting findings of our study were that the healthy controls

431   had uncoupling or opposite patterns, compared with the Broca patients. This implies that the

432   amplitude and connectivity of healthy persons are usually independent (as indicated by the

433   uncoupling pattern) or negatively related to each other (as indicated by the coupling pattern with

434   negative coefficients). We can thus theorize that a healthy brain follows the principle of least

435   effort. That is, to perform a task without requesting more resources, the highly activated regions

436   tend to run without unnecessary weak connections.

437   Close analysis of the coefficient distributions in **Figure 3** (and *Supplementary Figures S1*)

438   yielded further detailed findings. Betweenness appears to be a measure that is usually uncoupled

439   with amplitude, especially in islands having small m-values (see *Supplementary Figures S1*),

440   suggesting that the highly activated regions did not necessarily work to transport information

441   between other regions. The transitivity shows mixed distribution patterns for the coefficients

442   across all naming stages. As the transitivity measures the clustering possibility of a node's first

443   neighbors, it seems that healthy persons tended to form highly clustered structures of low

444   activation regions during t3 to t6 in islands having large m values(see **Figure 3** and

445   *Supplementary Figures S1*). The Broca persons considered in this study exhibited the opposite

446   distribution (i.e., the low activation regions had lower neighborhood clustering coefficients).

447   This suggests that, during memory access (t3), semantic processing (t4), phonological encoding

448   (t5), and articulation (t6), the low-activation regions in the patient's brain lost their internal

449   organizations, and their highly excited regions formed a greater number of connections among

450   their neighbors for task performance. That is, the impaired brain recruited more local-neighbor

451   resources to perform the same tasks (Medaglia, 2017).

452   The weighted degree, *k*-coreness, and Laplacian centrality indicated negative coefficients in

453   the m776 islands during t1 (see **Figure 3**), but they showed positive coefficients in most m-

454   islands (see *Supplementary Figures S1*). This suggests that weakly weighted edges (indicated by

455   the m776 islands, see **Figure 3**) in the Broca group supported low activation regions while being

456   central (by the weighted degree), core (by the *k*-coreness), and critical (by the Laplacian

457   centrality). However, most edges (in m-islands other than m=776, see *Supplementary Figures

458   S1*) allowed the highly activated regions to be central (by the weighted degree), core (by the *k*-

459   coreness), and critical (by the Laplacian centrality). Moreover, the *k*-coreness and Laplacian

460   centrality result from t2 to t5 show consistent forms of the positive coefficients (see **Figure 3**),

461 suggesting that most edges supported the highly activated regions while being core (by the *k*-
462 coreness) and critical (by the Laplacian centrality). A similar pattern was obtained for the degree
463 from t4 to t5, for the *k*-coreness and Laplacian centrality. Given the language production problem
464 exhibited by the Broca persons, we can infer that these patients required more resources to
465 reconstruct compensatory brain areas as task-specific regions. **Figure 4** (and *Supplementary*
466 *Figure S2*) supports this conclusion, because, among the Broca persons, the highly activated
467 regions tended to participate in more functional systems during the first three stages.
468
469 **Hothubs interpretation**
470   The hub detection method with participation coefficients should identify the optimal
471 functional module partition scheme(Muldoon et al., 2016; van den Heuvel & Sporns, 2013; Gu et
472 al., 2015; Medaglia, 2017). The eigenvector centralities allow the detection of hubs in the
473 network without considering partition schemes(de Nooy et al., 2018). To avoid the controversy
474 regarding partition schemes, we used the eigenvector centralities to self-consistently define the
475 network hubs. As shown in **Figure 3**, the Broca-group, t1, t2, t3, and t6, had positive coefficients
476 on the eigenvector centralities in m776-islands, suggesting that these patients tended to use
477 highly activated regions as hubs. However, uncoupling distributions were apparent for t4 and t5,
478 suggesting that the highly activated regions were not necessarily to be hubs in patients. In other
479 words, the inference of hubs based on the region's activation level during the semantic
480 processing and phonological encoding stage of the naming task was uncertain for the Broca
481 group. Interestingly, the control-group t4 stage had a negative correlation, implying significant
482 coldhubs at this stage.
483   We identified the hothubs in the averaged brain of each group. The regions in **Figure 5**
484 were both hotspots having amplitudes exceeding the mean-plus-one standard deviation and hubs
485 having top-level eigenvector centralities for the same number of hotspots. First, the results
486 suggest that there were only several intersections between the two groups. That is, the patients
487 reorganized their functional brain networks using different sets of regions as their hothubs in
488 response to the naming task. The hothubs in **Figure 5** were mostly reported as naming specific
489 regions (as shown in *Supplementary Table S2*). Note that some regions support cognitive
490 functions related to naming tasks, such as visual recognition, long-term memory processing, and
491 object configuration by the right posterior fusiform gyrus(Song, Peng, Liu, & Wang, 2019).
492 Second, the significantly attenuated regions, such as InfOcciGyr_VenPst_R (right inferior
493 occipital gyrus ventroposterior) in t1, and MidOcciGyr_DsoAnt_L (left middle occipital gyrus
494 dorsal anterior) and PreCune_Sup_R (right precuneus superior) in t2, also acted as hothubs in the

495   Broca group. However, during the entire naming process, the Broca group used specific hothubs
496   for which the activation levels did not differ from the control group. Third, both groups
497   commanded more than one functional system at each stage. This suggests that naming should be
498   a cross-modular task. Because our Broca participants were tested at least 5 months after their
499   onset (see **Table 1**), we can infer that our observations were the results of functional
500   reorganizations. The different hothubs and functional systems in each group (as detailed in
501   **Figure 5**) suggest that there were both intrasystem and intersystem reorganizations in the Broca
502   group.

503   **Network visualizations and coldhubs exploration**

504   For more detailed inspections of these reorganizations, we visualized each graph by
505   categorizing the refined 776 regions into four types (as shown in **Figure 6** and *Supplementary*
506   *Figure S5*). **Figure 6** is an example of amplitude and linking-strength distributions in t4.
507   Coldhubs are always present in each graph. For example, the left SupFrtGyr_Pst (superior frontal
508   gyrus posterior, see **Fig.6 arrow a**) and MidTempGyr_Mid (middle temporal gyrus middle, see
509   **Fig.6 arrow b**) are coldhubs occupying critical positions on the dorsal and ventral stream at the
510   semantic processing stage. These coldhubs cannot be visualized by the traditional imaging
511   strategy that depends on the scout activation level. Focusing on the linking-strength panels could
512   reveal that the coldhubs (green nodes) exhibit a different functional brain network landscape.
513   From these findings, a partial answer to the question raised by Heuvel and Sporns on whether
514   brain hubs are potential hot spots with clinical meaning could be derived (van den Heuvel &
515   Sporns, 2013). Network hubs are possible but not necessarily bound to be hot spots. Patients and
516   their healthy controls differed both in the hothubs and in the coldhubs. The dark functional
517   networks formed by coldhubs deserve more considerations in future studies.

518   **Methodological considerations, limitations, and clinical implications**

519   Our study has several limitations. First, the connectivity modeling in MEG has spatial
520   leakage problems (J. Matias Palva et al., 2018; Colclough et al., 2016; Brookes, Woolrich, &
521   Barnes, 2012). PLV is a method lacking leakage correction (Colclough et al., 2016). Palva et al.
522   recommended that researchers perform the full source-space interaction mapping rather than
523   applying a seed-based approach (J. Matias Palva et al., 2018). We utilized the connectivity
524   strategy to interpret undirected graphs based on PLVs across the whole cerebral cortex. Hassan
525   et al. (2015) previously used such graphs for studying picture-naming. They constructed an atlas
526   with 1000 scouts covering the whole cortex, calculated PLVs based on the source space
527   estimated by the WMNE method, and normalized PLVs to reduce artefactual inflated
528   connectivity. We constructed 776 scouts covering the whole cortex, calculated PLVs based on

529   WMNE, and also normalized PLVs as connection weights. According to Hincapié et al., if the
530   interacting sources were extended patches having several dipoles in them, the minimum-norm
531   estimation would provides better connectivity estimation than would the beamformer (Hincapié
532   et al., 2017). We know that these considerations might not fully resolve the controversy about
533   using PLV. This is an ongoing issue. Rizkallah et al. reported that PLV metrics of MEGs were
534   significantly correlated with fMRI networks compared with other zero-lag corrected methods
535   (Rizkallah, Amoud, Fraschini, Wendling, & Hassan, 2020). Our report encourages us to explore
536   more types of functional and effective connectivity in future works. For example, the phase-
537   transfer entropy will establish directed graphs for detailed inspections of information flows in the
538   brain (Engels et al., 2017).
539   Second, the estimated source values of the WMNE tended to be reduced with increasing
540   depths, varying significantly between subjects. The Brainstorm's guides recommended using the
541   current density map for computing connectivity measures. Although the coupling patterns
542   explored by our study were based on within-subject analyses, we still reported findings based on
543   the raw current density values in the unit of picoamperes. We also projected all source spaces
544   into the same template to reduce the influences of inter-individual differences.
545   Third, we are aware of our small participant sample and the inconsistencies of stroke
546   victims. One of the participants (B5) was significantly younger than the others. Although this is a
547   possible confounding factor, the maximum variation strategy provides another view (Patton,
548   2014). If there any patterns were to emerge, despite the great variation, the patterns would have
549   value in capturing the essential impacts of a program. Therefore, the amplitude–connectivity
550   correlation patterns found in this study made sense for our original hypothesis. On the other
551   hand, the effects of individuals were adjusted via partial correlation analysis. That was, we
552   treated the individuals as the third variable when calculating the amplitude–connectivity
553   correlation coefficients.
554   Fourth, the stroked structure should be considered in the study. There were brain volumes
555   with encephalomalacia that could influence the results of source reconstruction. This is a
556   technical problem without a satisfactory solution in the head-modeling and brain parcellation.
557   The stroked-out areas remained part of the source space. Therefore, the results of stroke persons
558   were estimates based on virtual structures of the brain. Nevertheless, the control group should
559   not be influenced by this problem, and results from them should make sense for our hypothesis.
560   Besides, the amplitude–connectivity relationships between groups remained unchanged after
561   removing the stroked left hemisphere in both groups (see *Supplementary Figures S6 and S7*).
562   Moreover, clinical applications of transcranial brain stimulation (e.g., repetitive transcranial

563   magnetic stimulation) usually inject electric currents into the brain by inversely assuming the
564   source space of stimulation (Biou et al., 2019; Norise & Hamilton, 2017; Coslett, 2016). With
565   the rapid expansion of non-invasive brain stimulation technology, the effective target region
566   location is an issue strongly associated with clinical application. Therapists should decide to use
567   one of two opposite strategies to execute stimulation (viz., to excite or inhibit a target position)
568   (Biou et al., 2019; Norise & Hamilton, 2017; Polania, Nitsche, & Ruff, 2018). Essentially, their
569   decisions related to excitatory or inhibitory stimulation protocols are related to the hot or cold
570   spots. The amplitude–connectivity correlation study reported herein presents a new perspective
571   on this question by revealing the dark functional networks with coldhubs in the reconstructed
572   source space. The effects of brain stimulation on the cold and hot hubs may differ and require
573   more study. Further study should include more participants to confirm the cross-scale deviation
574   patterns of the amplitude–connectivity relationships.

575   Apart from the perspective of brain stimulation, speech-language therapy is another field
576   related to our findings. Picture-naming is a widely used therapy task in speech-language therapy.
577   However, various variables can influence the outcomes of linguistic therapy, including but not
578   limited to semantic and phonological factors in picture-naming (Nakagawa, Sano, Funayama, &
579   Kato, 2019; Shrubsole, Worrall, Power, & O'Connor, 2017). One future direction is to find links
580   between graph measures and behavioral performances (Meier, Johnson, & Kiran, 2018; Meier,
581   Kapse, & Kiran, 2016; J. M. Palva, Monto, Kulashekhar, & Palva, 2010). Another future work is
582   to find associations between variables embedded in stimuli, such as semantic components based
583   on semantic feature norms (Feng LIN, 2015), and graph measures of hothubs and coldhubs.
584   Then, the speech-language pathologist would be able to arrange brain modifying stimuli during
585   therapy.

586

Conclusions

588   In this study, we investigated the activation–connection correlations for the performance of
589   naming tasks by persons having post-stroke aphasia compared with healthy subjects. Although
590   this study observed a small sample of participants with regards to a simple naming paradigm, it
591   expanded our knowledge of hothubs by integrating both the activation and connection. The
592   results reveal that the examined patients utilized different activation–connection coupling
593   patterns and different sets of hothubs as healthy participants to perform the same task, thereby
594   functionally reorganizing their brains. The findings also indicate that there were hubs with low
595   activations in functional brain networks. Thus, dark functional networks must be considered in
596   functional brain-imaging studies. The operational concepts of "hothubs" and "dark functional

597 networks" will promote further development of target-selection approaches to therapeutic brain
598 stimulation.
599

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603

Data Availability

605   The following information was supplied regarding data availability:
606   Zenodo database: Functional Brain Networks of Picture Naming in Broca's Aphasia and
607 Healthy Controls. ID: 3831117. https://doi.org/10.5281/zenodo.3831117
608

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782

Figure 1

Experiment paradigm

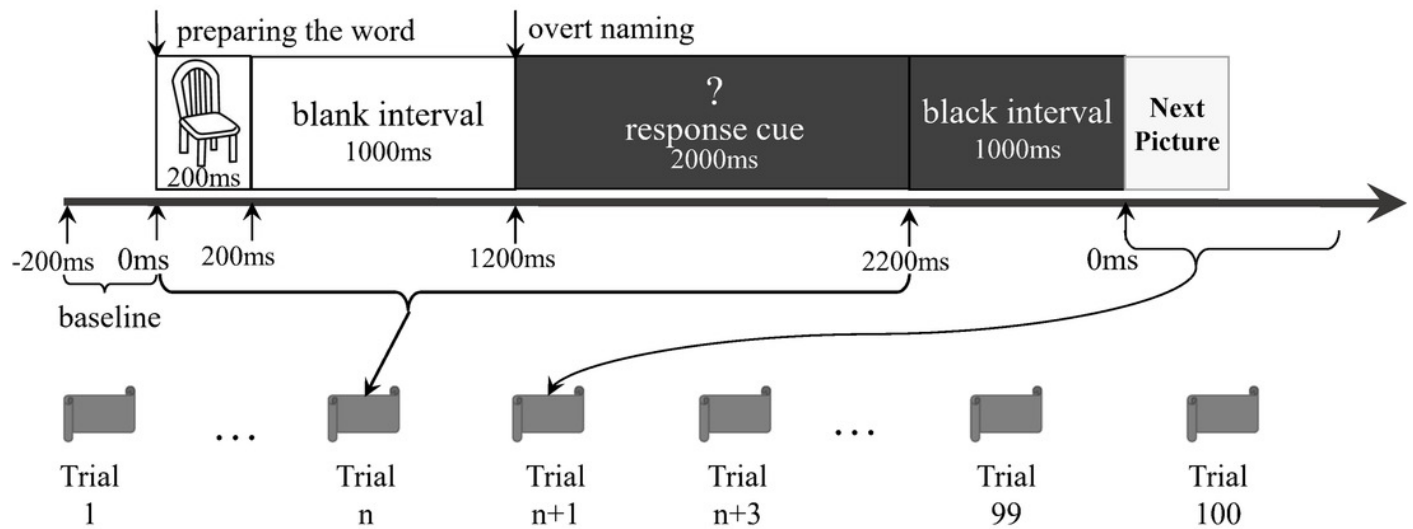



Figure 2

Data processing workflow

The dashed curved arrow denotes that the final reported m776 and m388 islands are selected from a series of m values by interpreting the *Supplementary Figures S1, S2*. MEG: magnetoencephalography; MRI: magnetic resonance imaging.

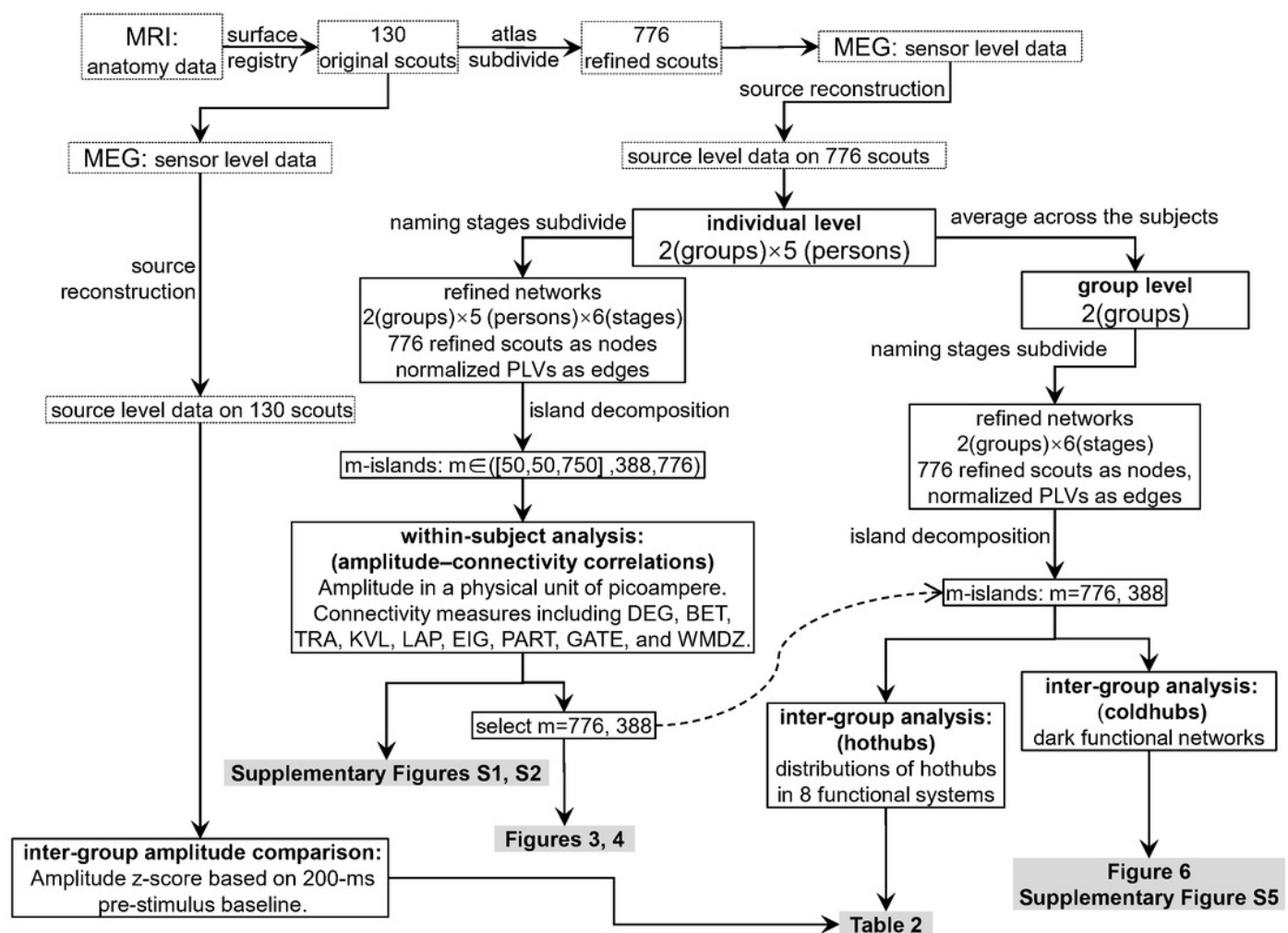



Figure 3

Relations between activations (picoampere) and module-independent graph measures in m776-islands

Activations are the estimated electric densities (in a physical unit of picoampere) in the source space. The partial Pearson coefficients between the activations and graph measures are calculated for m776-islands at different stages. The significant coefficients ($p<0.05$) are marked with asterisks. The 95% confidence intervals having significant coefficients are marked by transparent colored bars. DEG: weighted degree; BET: weighted betweenness; TRA: weighted transitivity; KVL: k-value of coreness; LAP: Laplacian centrality; EIG: eigenvector centrality; t1: 0–119 ms, visual feature extraction; t2: 120–150 ms, object recognition; t3: 151–190 ms, memory access; t4: 191–320 ms, semantic processing; t5: 321–480 ms, phonological encoding; t6: 481–535 ms, articulation. A positive coefficient marked with an asterisk denotes that strongly activated brain regions are more likely to be highly connected hubs. A negative coefficient marked with an asterisk suggests that highly connected hubs are more likely to be with weak intensities of activation. The separation of the confidence intervals having opposite values of coefficients infers that the two groups have significantly different amplitude–connectivity relationships. One significant correlation having another nonsignificant correlation also implies that there are interconditional differences of amplitude–connectivity relationships.

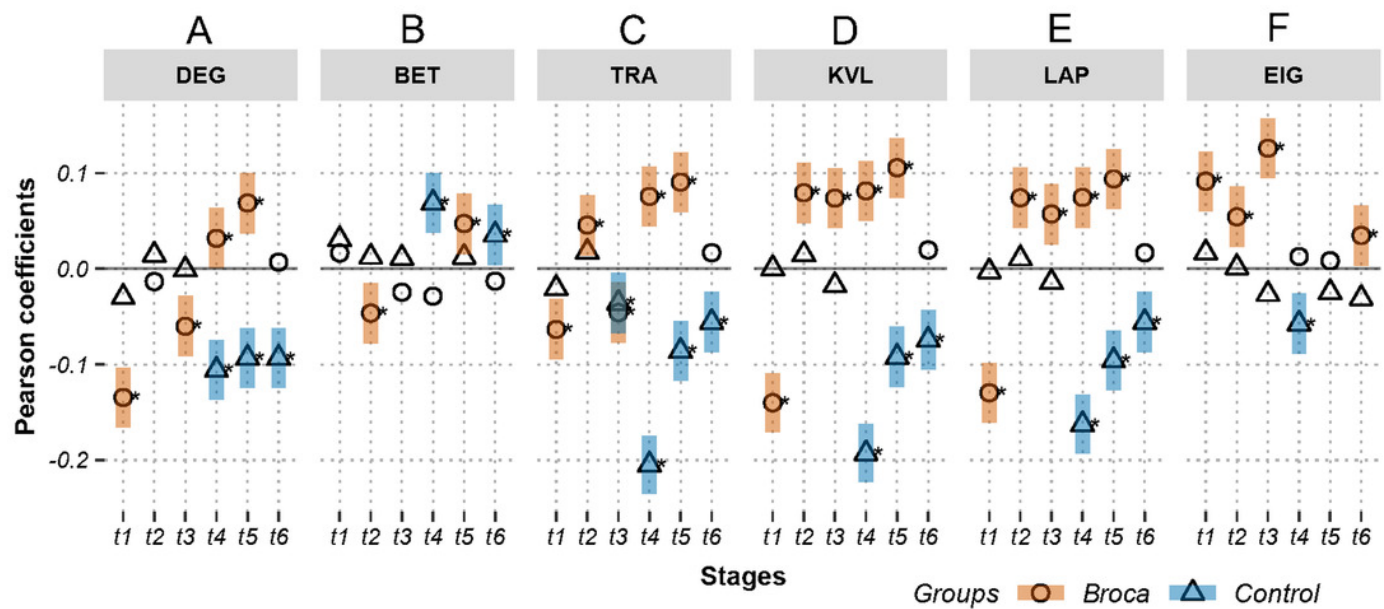



Figure 4

Relations between activations (picoampere) and module-dependent graph measures in m388-islands

Activations are the estimated electric densities (in a physical unit of picoampere) in the source space. The partial Pearson coefficients between the activations and graph measures are calculated for m388-islands at different stages. The significant coefficients ($p < 0.05$) are marked with asterisks. The 95% confidence intervals having significant coefficients are marked by transparent colored bars. PART: participation coefficient; GATE: gateway coefficient; WMDZ: within module degree z-score; t1: 0–119 ms, visual feature extraction; t2: 120–150 ms, object recognition; t3: 151–190 ms, memory access; t4: 191–320 ms, semantic processing; t5: 321–480 ms, phonological encoding; t6: 481–535 ms, articulation. A positive coefficient marked with an asterisk denotes that strongly activated brain regions are more likely to be highly connected hubs. A negative coefficient marked with an asterisk suggests that highly connected hubs are more likely to be with weak intensities of activation. The separation of the confidence intervals with opposite values of coefficients infers that the two groups have significantly different amplitude–connectivity relationships. One significant correlation with another nonsignificant correlation also implies that there are interconditional differences of amplitude–connectivity relationships.

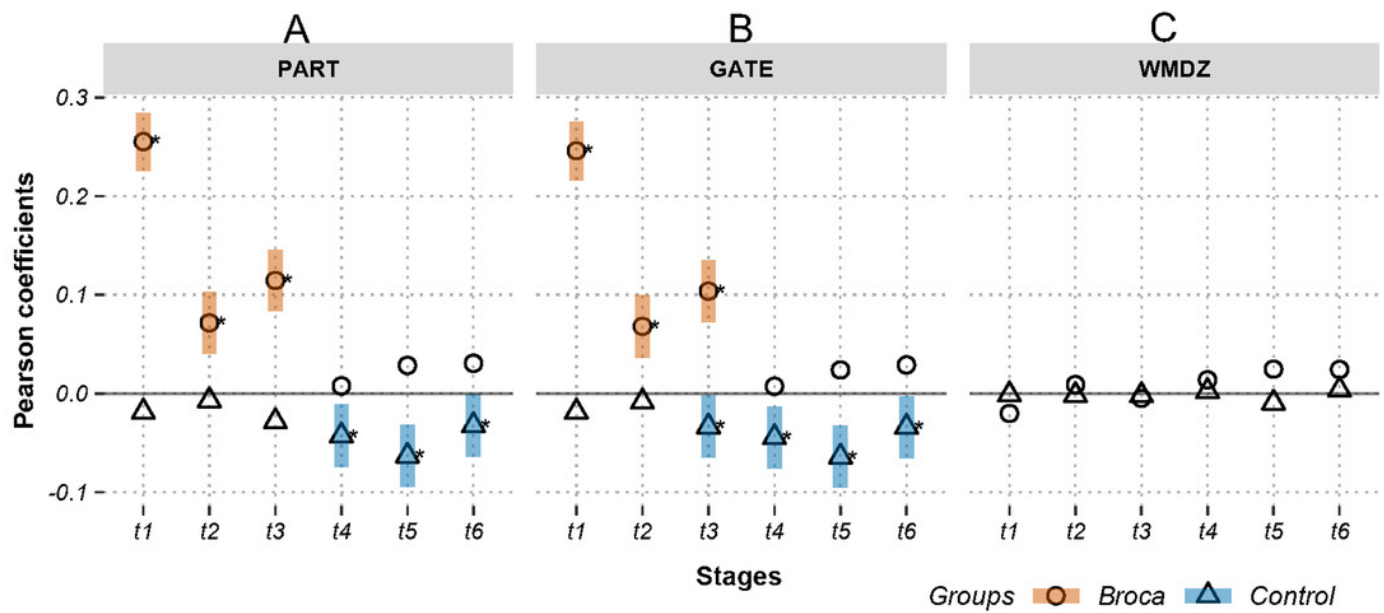



Figure 5

Hothubs in m776-islands

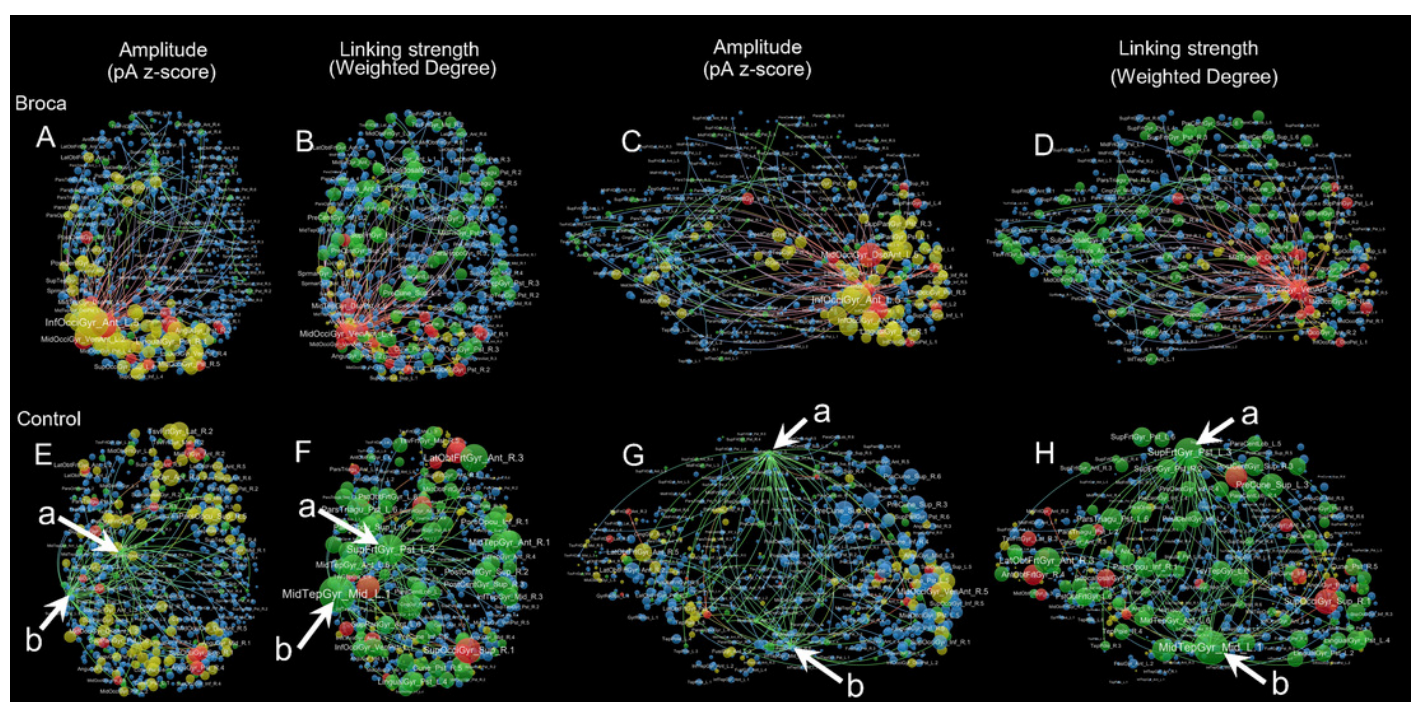
a: Significantly lower z-scores for amplitudes of Broca group than those of the control group (permutation t-test, 1,000 randomizations). b: Significantly higher z-scores for amplitudes of control group than those of Broca group (permutation t-test, 1,000 randomizations). t1: InfOcciGyr_VenPst_R (p=0.016), SupPariGyr_Pst_R (p=0.008), PreCune_Sup_L (p=0.02). t2: PreCune_Sup_R (p=0.046), MidOcciGyr_DsoAnt_L (p=0.004). t3: SupPariGyr_Ant_R (p=0.016), PreCune_Sup_L (p=0.024), PreCune_Sup_R (p=0.017), SupFrtGyr_Ant_L (p=0.039). Colors for functional modules: Pink: attention; orange: auditory; yellow: cinguloopercular; blue: frontoparietal; green: medial default mode; grey: motor and somatosensory; lilac: ventral temporal association; white: visual.

	A	B	C	D	E	F
	t1	t2	t3	t4	t5	t6
Broca	SupTepGyr-Pst-L AnguGyr-Pst-R Insula-Ant-R MidOcciGyr-VenAnt-L Cune-Pst-R InfOcciGyr-VenPst-R [a] LingualGyr-Pst-R SupOcciGyr-Inf-L SupOcciGyr-Sup-R	ParsOrbitalis-R PreCune-Sup-R [a] PreCentGyr-Sup-L Cune-Pst-L&R LingualGyr-Ant-R MidOcciGyr-DsoAnt-L [a] MidOcciGyr-VenAnt-L SupOcciGyr-Sup-L	LatObtFrtGyr-Pst-L SupPariGyr-Pst-L TsvTepGyr-L ParsOrbitalis-R GyrRectus-R MidObtFrtGyr-R Cune-Ant-R InfOcciGyr-Ant-R InfOcciGyr-VenPst-R LingualGyr-Ant-R MidOcciGyr-DsoAnt-L MidOcciGyr-VenAnt-L	SupPariGyr-Pst-L AnguGyr-Mid-L PreCune-Inf-R PostCentGyr-Inf-L MidTepGyr-DsoPst-L Cune-Ant-R InfOcciGyr-Ant-R InfOcciGyr-DsoPst-L LingualGyr-Ant-R LingualGyr-Pst-R MidOcciGyr-Pst-R MidOcciGyr-VenAnt-L	LatObtFrtGyr-Pst-R AnguGyr-Mid-R GyrRectus-L&R Insula-Ant-L MidObtFrtGyr-L ParsTriagu-Mid-L TsvFrtGyr-Lat-R PstObtFrtGyr-L MidTepGyr-DsoPst-L LingualGyr-Ant-R MidOcciGyr-DsoAnt-L	LatObtFrtGyr-Pst-L&R SupTepGyr-Pst-L ParsOpcu-Inf-R AnguGyr-Ant-L AnguGyr-Mid-L Insula-Ant-L ParsTriagu-Mid-L PreCentGyr-Inf-L MidTepGyr-DsoPst-L MidTepGyr-VenPst-L InfOcciGyr-Ant-L LingualGyr-Pst-R MidOcciGyr-DsoAnt-L MidOcciGyr-VenAnt-L
Control	LatObtFrtGyr-Pst-L SupPariGyr-Pst-R [b] MidFrtGyr-Ant-R AntObtFrtGyr-R TsvFrtGyr-Msl-R PstObtFrtGyr-R TepPole-L Cune-Pst-L MidOcciGyr-VenAnt-R SupOcciGyr-Sup-R	MidFrtGyr-Ant-R AnguGyr-Pst-R Cune-Ant-L Cune-Pst-R SupOcciGyr-Inf-R SupOcciGyr-Sup-R	LatObtFrtGyr-Ant-R SupPariGyr-Ant-R [b] SupPariGyr-Pst-R ParsOpcu-Sup-L AnguGyr-Mid-L MidFrtGyr-Pst-R PstObtFrtGyr-R CingGyr-Mid-L PreCune-Sup-L&R [b] SupFrtGyr-Ant-L [b] PreCune-Inf-L InfTepGyr-Mid-R MidTepGyr-Ant-L Cune-Ant-L Cune-Pst-L&R InfOcciGyr-DsoPst-R SupOcciGyr-Inf-L&R SupOcciGyr-Sup-R	SupTepGyr-Ant-L TsvTepGyr-L MidFrtGyr-Ant-R AnguGyr-Ant-L AnguGyr-Pst-L&R AntObtFrtGyr-R MidObtFrtGyr-R ParsTriagu-Ant-L ParsTriagu-Pst-L TsvFrtGyr-Lat-R [b] SubcallosalGyr-R PostCentGyr-Sup-L SupOcciGyr-Sup-R	MidFrtGyr-Ant-R FusiGyr-Pst-R InfTepGyr-Ant-L InfOcciGyr-Ant-L SupOcciGyr-Sup-L	CingGyr-Ant-R SprmarGyr-Pst-R AntObtFrtGyr-R ParsTriagu-Ant-R SupFrtGyr-Pst-R PreCentGyr-Inf-R FusiGyr-Pst-R MidTepGyr-Ant-R
Intersection	PreCune-Sup-L [b] InfOcciGyr-VenPst-L MidOcciGyr-Pst-R	SupPariGyr-Pst-R InfOcciGyr-DsoPst-L	AnguGyr-Pst-R	MidOcciGyr-DsoAnt-L	LatObtFrtGyr-Ant-R MidOcciGyr-VenAnt-L	

Legend:
- attention
- auditory
- cinguloopercular
- frontoparietal
- medial default mode
- motor and somatosensory
- ventral temporal association
- visual

Figure 6

Sample amplitude and linking strength distributions in t4

Hotspots are identified based on their amplitudes that exceeded the mean-plus-one standard deviation. Hubs are identified based on their eigenvector centralities as defined in Pajek, with the same number of hotspots at each stage. For each viewpoint, node areas on the left panel are in proportion to the z-scores of their amplitudes, whereas those on the right panel are in proportion to the total linking strengths (i.e., weighted degrees). Arrow a: Left SupFrtGyr_Pst (left superior frontal gyrus posterior). Arrow b: Left MidTempGyr_Mid (left middle temporal gyrus middle). The top-weighted 100 edges are plotted, and the edges are colored according to their terminals. There are four node types: hothubs (red), coldhubs (green), non-hub hotspots (yellow), and non-hub coldspots (blue). The t4 is the semantic processing window of 191–320 ms. The amplitude weighted layouts (left panels in each viewpoint) are remarkably different from the linking strength weighted layouts (right panels in each viewpoint), suggesting that it is necessary to reconsider the role of coldhubs in functioning brain.

Demographic characteristics

AQ: aphasia quotient; B: persons with Broca's aphasia; C: control subjects; F: frontal lobe; T: temporal lobe; P: parietal lobe; O: occipital lobe; WAB: Western Aphasia Battery. T-tests between control group and Broca's aphasics with *P=0.30; **P=0.24; ***P=0.00092.

1 **Table 1: Demographic characteristics.**

Subjects	B1	B2	B3	B4	B5	C1	C2	C3	C4	C5
Gender (Male/Female)	Male	Male	Male	Male	Male	Female	Male	Male	Male	Male
Handedness (R/L)	R	R	R	R	R	R	R	R	R	R
Age at onset (years)[*]	71	50	48	55	19	68	55	55	54	70
Education duration (years)[**]	7	10	10	16	9	8	8	9	12	9
Time after onset (months)	8	5	5	42.7	9.4	-	-	-	-	-
Stroke type	hemorrhage	hemorrhage	infarction	hemorrhage	infarction	-	-	-	-	-
Lesion locations	left (F, T, P, O)	left (basal ganglia)	left (F, T, P)	left (basal ganglia)	left (F, T, P)	-	-	-	-	-
WAB AQ[***]	31.4	64.6	43.8	53.5	58.3	98	99.4	99.4	99.6	99.8
Spontaneous speech	6	12	8	10	12	19	20	20	20	20
Auditory comprehension	90	138	154	129	133	200	194	200	198	198
Repetition	29	70	49	64	57	100	100	97	100	100
Naming	23	54	13	39	48	100	100	100	100	100