

1 **Common Fronto-temporal Effective Connectivity in Humans and Monkeys**

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22 **Highlights**

- 23 • Privileged human auditory to inferior frontal connectivity, linked to monkeys
24 • Common auditory to parahippocampal effective connectivity in both species
25 • Greater lateralization in human effective connectivity, more symmetrical in monkeys
26 • Human fronto-temporal network function rooted in evolutionarily conserved signature

27

28 **eTOC short summary**

29 Functional connectivity between regions crucial for language and declarative memory is thought to
30 have substantially differentiated in humans. Using a new technique to similarly visualize directional
31 effective connectivity in humans and monkeys, we found remarkably comparable connectivity patterns
32 in both species between fronto-temporal regions crucial for cognition.

33

34 **Keywords**

35 Language, cognition, declarative memory, evolution, neurophysiology, neuroimaging

36 **ABSTRACT**

37 Cognitive pathways supporting human language and declarative memory are thought to have uniquely
38 evolutionarily differentiated in our species. However, cross-species comparisons are missing on site-
39 specific effective connectivity between regions important for cognition. We harnessed a new approach
40 using functional imaging to visualize the impact of direct electrical brain stimulation in human
41 neurosurgery patients. Applying the same approach with macaque monkeys, we found remarkably
42 comparable patterns of effective connectivity between auditory cortex and ventro-lateral prefrontal
43 cortex (vIPFC) and parahippocampal cortex in both species. Moreover, in humans electrical
44 tractography revealed rapid evoked potentials in vIPFC from stimulating auditory cortex and speech
45 sounds drove vIPFC, consistent with prior evidence in monkeys of direct projections from auditory
46 cortex to vocalization responsive regions in vIPFC. The results identify a common effective
47 connectivity signature that from auditory cortex is equally direct to vIPFC and indirect to the
48 hippocampus (via parahippocampal cortex) in human and nonhuman primates.

49 INTRODUCTION

50 Brain networks adapted for specialized functions typically show direct, rapid or effective connectivity
51 between regions crucial for behavior. Finding such connectivity, alongside evidence for evolutionary
52 homology, convergence or divergence, can be of substantial theoretical significance: Within the motor
53 domain, human and nonhuman primates have direct cortico-spinal projections subserving fine
54 movement control that are indirect in rodents¹. Also, human laryngeal motor cortex projects directly to
55 a brain stem nucleus (ambiguous) controlling laryngeal muscles². Such projections for vocal production
56 are more indirect in nonhuman primates³ and rodents⁴, shedding light on human speech evolution⁵.

57 Language defines us as a species and because of its prominent role in declarative memory
58 substantial evolutionary differentiation of human cognitive pathways is expected. Comparative studies
59 often see considerable levels of evolutionary conservation alongside insights on species-specific
60 differences⁶⁻¹². Yet, certain cross-species comparisons are missing, such as on the impact of directed
61 effective connectivity with the required precision of site-specific perturbation that can be applied to
62 both human and nonhuman primates. Thereby, the question on the extent of differentiation versus
63 conservation in primate fronto-temporal systems—although crucial for understanding which aspects of
64 human language and cognition can find realistic nonhuman animal models—remains open.

65 Speech and language are supported by a fronto-temporal network, including auditory and
66 ventro-lateral prefrontal cortex (vIPFC) areas interconnected via white matter pathways⁹. Left
67 hemisphere areas posterior to Heschl's gyrus (HG; an anatomical landmark associated with primary
68 auditory cortex) are interconnected with Brodmann areas 44 and 45 in vIPFC by way of the dorsal
69 arcuate fasciculus pathway¹³. There is now evidence for an auditory homolog in chimpanzees and
70 macaques, with its left hemisphere lateralization as a prominent human-specific difference⁸. In
71 monkeys, vIPFC neurons respond to vocalization sounds¹⁴, and single neuron tractography has shown
72 evidence for directional connectivity between non-primary auditory (lateral belt) areas and vIPFC¹⁵.
73 Whether similar auditory to inferior frontal interconnectivity exists in humans is however unclear^{7,16,17}.
74 Based on the notion of human vIPFC areas 44 and 45 having functionally differentiated for language⁹,
75 one prediction is that human auditory cortex would have a greater effective connectivity impact on
76 areas 44/45. By contrast, the impact on the adjacent frontal operculum (FOP) could be similar in
77 humans and monkeys¹⁸.

78 Sensory input to the medial temporal lobe (MTL) in humans is important for declarative
79 memory and may also have differentiated in humans. Monkey recognition memory for sounds is
80 surprisingly more fleeting than for visual items¹⁹. Also, studies in nonhuman animals (rodents, cats and
81 monkeys) show primarily indirect projections from auditory cortex to the hippocampus²⁰ via
82 parahippocampal/perirhinal cortex^{21,22}. However, human neuroimaging studies have not been able to

83 demonstrate direct auditory to hippocampal connectivity, with the current data suggesting indirect
84 interconnectivity with auditory cortex (via parahippocampal cortex)²³, as seen in other species. Thus,
85 another prediction, given that human language allows naming and conceptualizing sounds and thereby
86 better remembering them²⁴, is that the auditory-to-MTL memory circuit may be largely evolutionarily
87 conserved.

88 New approaches for assessing effective connectivity similarly across the species could shed
89 light on human cognitive pathway specialization or primate origins. In monkeys, electrical stimulation
90 combined with functional magnetic resonance imaging (esfMRI) was developed to visualize the impact
91 of site-specific stimulation on regional effective connectivity²⁵. Direct electrical brain stimulation is a
92 common treatment for debilitating brain disorders, thus following safety testing the esfMRI method
93 was recently translated to human patients being monitored for neurosurgery²⁶. We conducted a
94 comparative study of esfMRI effects obtained by stimulating auditory cortex in humans and macaques.
95 Electrical stimulation of auditory cortex induced differential esfMRI activity in several vIPFC (areas
96 44, 45 and FOP) and MTL subregions (including parahippocampal and hippocampal areas). We found
97 largely comparable effective connectivity patterns across the species. In humans, we also studied
98 electrical stimulation tractography to assess the latency of interconnectivity between auditory cortex,
99 vIPFC and MTL. Finally, we observed strong neurophysiological responses to speech sounds in human
100 vIPFC and establish directional effective interconnectivity with auditory cortex.

101 RESULTS

102 *Auditory cortex esfMRI in macaques*

103 We first studied the esfMRI response from stimulation of auditory cortical sites in the right hemisphere
104 of two macaques. Auditory cortex esfMRI induced significantly stronger activity relative to non-
105 stimulation trials (Fig. 1; $p < 0.05$, cluster corrected, $Z > 2.8$) in areas including auditory cortex,
106 prefrontal and MTL regions (Table 1). The prefrontal pattern involving area 8 and areas 44/45 is
107 generally similar to prefrontal neuronal tractography from auditory lateral belt in macaques^{15,27} (Table
108 1). MTL activation included parahippocampal gyrus²⁰.

109 Grouping of stimulation sites was conducted across two tonotopically organized fields ('core'
110 Site 1 and 'belt' Site 2; Suppl. Fig. 1). However, esfMRI results from stimulating these sites were
111 statistically indistinguishable (no significant voxels surviving the $p < 0.05$ cluster-corrected threshold
112 for the Site 1 versus Site 2 contrast, or vice versa). We suspected that this might arise because of
113 partially overlapping stimulation, which we confirmed by estimating the passive current spread using
114 the formula $r = 2\sqrt{\frac{I}{K}}$, where I is current in mA, and K a constant of pyramidal cell excitability for a
115 200 μs pulse (1.3 mA/mm²). The resulting radius (r) of passive current spread is 0.9 mm, confirming
116 that stimulating core auditory cortex sites also likely passively electrically stimulates portions of the
117 adjoining auditory belt, and vice versa, an important consideration for interpreting the esfMRI results.

118 *Auditory cortex esfMRI in humans*

119 We assessed the esfMRI activity in response to human auditory cortex electrical stimulation of depth
120 electrodes at medial or lateral sites in either left or right Heschl's gyrus (HG; Fig. 2A; Suppl. Fig. S2
121 shows individual subject contact locations). Stimulation sites were subdivided into Site 1 (medHG),
122 grouping contacts in medial HG areas where significant phase-locking to high-repetition click sound
123 rates occur (Methods), and Site 2, grouping lateral HG and planum temporale contacts (latHG + PT)
124 lacking high click rate neural phase locking (Suppl. Fig. S3). Suppl. Fig. S4 shows the amount of data
125 retained following removal of neurosurgically resected sites and loss of data around electrode contacts.

126 Significant esfMRI effects (Fig. 2C; cluster corrected $p < 0.05$) from stimulating Site 1
127 (medHG) included auditory cortex (superior temporal gyrus, STG) and vIPFC (inferior frontal gyrus;
128 Table 2). Site 2 (latHG+PT) stimulation activated areas including STG and MTL (Fig. 2D). In some
129 individual participants, the activity response was significant in vIPFC (Suppl. Fig. S5) and MTL (Suppl.
130 Fig. S6). The strength of the esfMRI response in vIPFC and MTL overlaid on the stimulated HG
131 contacts that produced it is shown in Suppl. Fig. S7.

132 Unlike the monkey esfMRI results, which did not significantly differ between the two auditory
133 cortex stimulation sites, effects from stimulating the two sites in humans differed. We calculated the
134 passive current spread as above: resulting in a 3 mm radius around the stimulation contact pairs, which
135 are separated by 5-10 mm. The analytical group contrast of Site 1 (medHG) vs Site 2 (latHG+PT)
136 showed stronger vIPFC activity from stimulating Site 1 (Fig. 3; Table 2). Site 1 stimulation also resulted
137 in stronger activity in more posterior temporal and parietal areas (e.g., supramarginal gyrus). Site 2
138 stimulation resulted in stronger activity in anterior temporal areas (Table 2).

139 *Differential macaque esfMRI effects in vIPFC and MTL subregions*

140 We assessed whether macaque auditory cortex stimulation differentially activates anatomically defined
141 areas 44, 45 and the FOP in the vIPFC (Fig. 4A-B). Region of interest (ROI) effects were tested with
142 a mixed-design analysis of variance (ANOVA): between-subjects factor of Monkeys, within-subjects
143 factors of Activated hemisphere (left or right), ROI (area 44, 45 or FOP) and Stimulation site as
144 covariate (Site 1 or 2). Model assumptions for this and all subsequent reported analyses were met or
145 corrected as indicated. Planned post-hoc tests were used to identify differential effects across the ROIs.

146 The overall magnitude of the fMRI signal in the vIPFC ROIs was stronger in macaque 1 (M1;
147 significant Monkey factor: $F_{1,34} = 7.34$, $p = 0.010$), but there were no interactions with other factors,
148 suggesting a similar pattern of esfMRI effects across the monkeys. The two Sites of stimulation did not
149 differentially affect the vIPFC fMRI response, consistent with the whole-brain results. The macaque
150 vIPFC ROI effects were also statistically indistinguishable across the two hemispheres (no significant
151 Hemisphere effect). The ROIs showed a trend towards a differential fMRI response ($F_{2,33} = 3.04$, $p =$
152 0.054), and the planned post-hoc comparisons identified stronger esfMRI activity in the FOP over areas
153 45 and 44 in that order (all $p < 0.002$, Bonferroni corrected; Fig. 4A-B).

154 Monkey MTL subregions showed differential esfMRI activity during auditory cortex
155 stimulation (Fig. 4C). A mixed-design ANOVA including the seven anatomically delineated MTL
156 subregions showed that esfMRI activity in these ROIs did not differ between monkeys. Effects also
157 did not differ across the two stimulation sites, or across the two hemispheres. The MTL ROIs differed
158 nonlinearly in their fMRI activity response (cubic effect: $F_{1,34} = 4.27$, $p = 0.028$; Fig. 4A, C). The
159 planned post-hoc comparisons showed stronger esfMRI activity in parahippocampal gyrus (PHG) than
160 entorhinal cortex (EC) and CA4 ($p < 0.003$, Bonferroni corrected). Subiculum (Sub), dentate gyrus
161 (DG), CA1 and CA3 also had stronger activity than CA4 (all $p < 0.015$, Bonferroni corrected).

162 *Differential human auditory cortex esfMRI effects in vIPFC and MTL*

163 We studied the human vIPFC and MTL effects in anatomically defined ROIs. Effects were tested with
164 mixed-design ANOVA (between-subjects factor: Human subject; within-subject factors: ROI
165 subregion, Activated hemisphere, left or right; Site of stimulation and Stimulated hemisphere, left or
166 right, as covariates). The vast majority of subjects were left hemisphere language dominant (Table 3).

167 For vIPFC, we observed differential activity of areas 44, 45 and FOP ($F_{1,21} = 5.26$, $p = 0.032$;
168 Fig. 4B) in a similar pattern as in the monkeys. The post-hoc tests showed a stronger FOP response
169 than in areas 45 and 44 ($p < 0.003$, Bonferroni corrected) with a trend for stronger area 45 than area 44
170 activity ($p = 0.070$). Site of stimulation (Site 1 vs Site 2) effects on vIPFC were a trend ($F_{1,21} = 3.14$, p
171 $= 0.090$), with a borderline weaker Site 2 (latHG+PT) esfMRI effect on the vIPFC subregions (Fig.
172 4A). Hemispheric differences for certain ROIs were evident: visualized in Fig. 4D as a stronger FOP
173 response on the left, with the right hemisphere showing similar activity across the three ROIs. Activated
174 hemisphere effects did not interact with vIPFC ROI but did with Site of stimulation (Site 1 vs Site 2 by
175 hemisphere interaction: $F_{1,21} = 7.23$, $p = 0.014$) and Stimulated hemisphere (Stimulated hemisphere by
176 Activated hemisphere interaction: $F_{1,21} = 4.68$, $p = 0.042$; Fig. 4E).

177 For the human MTL ROI effects, the ANOVA did not show significant differential activation
178 between the ROIs, although the albeit weaker pattern was similar to that seen in monkeys with the
179 following post-hoc comparisons: The PHG had a stronger esfMRI response than CA4 ($p = 0.016$,
180 Bonferroni corrected) and DG ($p = 0.026$, corrected), and the subiculum response was stronger than
181 CA4 ($p = 0.034$, corrected). MTL ROI effects showed a trend for Activated hemisphere ($F_{1,10} = 3.35$,
182 $p = 0.097$), seen in Fig. 4D as a slight right hemisphere bias particularly for entorhinal cortex (Fig. 4D-
183 E). No other significant effects or interactions were observed.

184 *Cross-species auditory cortex esfMRI comparisons*

185 We conducted cross-species esfMRI comparisons of the vIPFC and MTL ROI responses (Fig. 4 shows
186 the anatomically-delineated ROIs in both species). Statistical testing included Species as a between-
187 subjects factor.

188 For the vIPFC cross-species comparison, both monkey and human esfMRI results showed
189 stronger FOP responses than area 45 (ROI effect: $F_{1,57} = 9.68$, $p = 0.003$). There was no significant
190 species difference in the vIPFC ROI effects ($p = 0.139$), showing statistically indistinguishable vIPFC
191 ROI response patterns across the species (Fig. 4A-B). An effect was found for Activated hemisphere
192 (left stronger than right, $F_{1,57} = 4.21$, $p = 0.045$) but did not significantly interact with Species. There
193 were higher order interactions with species, including hemispheric differences (vIPFC ROIs by
194 Species: $F_{1,57} = 4.97$, $p = 0.010$; ROIs by Activated hemisphere by Species: $F_{2,57} = 7.11$, $p = 0.002$).

195 For the MTL, the overall esfMRI activity level differed across the Species (Fig. 4D, $F_{2,46} =$
196 $10.55, p < 0.001$). The ROIs did not differ in their fMRI response pattern but interacted with Species
197 (Greenhouse Geisser corrected: $F_{7.63,175.52} = 3.05, p = 0.004, \epsilon = 0.636$), and stronger hemispheric
198 lateralization was seen in humans (Species by Activated hemisphere interaction; Greenhouse Geisser
199 corrected: $F_{8.70,200.16} = 2.175, p = 0.027, \epsilon = 0.725$). For instance, entorhinal cortex shows greater right
200 hemisphere activation (Fig. 4D), and this region was relatively more activated when the left auditory
201 cortex was stimulated (Fig. 4E). By contrast, the monkey effects were statistically indistinguishable
202 across the two hemispheres. No other effects or higher-order interactions were significant.

203 *Human electrical stimulation tractography (esT)*

204 In the human patients, clinical electrode coverage could include vIPFC, auditory cortex and
205 hippocampus. We studied neurophysiological connectivity with esT between auditory cortex, vIPFC
206 and hippocampus (Figs. 5A, F-H show the stimulation sites and recording contacts).

207 Auditory cortex Site 1 (MedHG) and Site 2 (latHG+PT) stimulation induced
208 neurophysiological potentials in vIPFC (Fig. 5B-C) as soon as they could be measured after the 0-3 ms
209 electrical stimulation artifact (Fig. 5D; Suppl. Movies 1-6). We assessed the polarity and latency of
210 stimulation-induced responses using spatial Laplacian correction to reduce volume conduction effects
211 and spurious cross-channel correlated responses. Response waveforms in vIPFC showed positive and
212 negative components at different latencies (Fig. E-H). Our labelling convention follows prior
213 reports^{16,28}, identifying positivities (P) and negativities (N) by latency (early: a ; later: b).

214 Auditory cortex stimulation induced an early vIPFC positivity ($P(a)$: average latency: 5.3 and
215 6.8 ms, respectively from stimulating medHG or latHG+PT) followed by an early negativity, $N(a)$, and
216 later positivity and negativity (Fig. 5E). Notably, the early positivity is as early as reported from
217 stimulating medial HG and recording in postero-lateral STG²⁸ (Suppl. Fig. S8 shows replication).

218 Effects from stimulating vIPFC while recording in HG indicate that connectivity appears to be
219 bi-directional, evident as the presence of both sets of positivities and negativities: compare Fig. 5F with
220 stimulation in the opposite direction in Fig. 5E. However, the waveforms do differ particularly in the
221 latencies of some of the components which are earlier for the HG to vIPFC direction. An ANOVA
222 (within-subjects factor: Potential latency across recordings, between-subjects factors: Stimulation sites
223 and Subjects) substantiated this, showing a significant interaction of Stimulation site with Potential
224 latency (Greenhouse Geisser corrected: $F_{1.467,77.742} = 45.641, p < 0.001, \epsilon = 0.489$). No other effects or
225 interactions were found.

226 Next we studied esT effects between hippocampus and auditory cortex. The waveforms
227 recorded in the hippocampus after stimulation of HG, or vice versa, were also distinctly different in
228 shape, with later components much more variable in latency depending on the direction of stimulation
229 (compare $N(b)$ latencies in Fig. 5G-H). There was a significant interaction of Stimulation site with
230 Potential latency (Greenhouse Geisser corrected: $F_{1,407,45.034} = 9.399$, $p < 0.001$, $\epsilon = 0.469$). No other
231 significant effects or interactions were found.

232 Testing only the earliest $P(a)$ component (excluding the others), showed it to be significantly
233 earlier when stimulating HG and recording in vIPFC than any of the other combinations of directions
234 or stimulation/recording sites (all comparisons relative to stimulating HG and recording in vIPFC, $p <$
235 0.001 , Bonferroni-corrected). Notably, this early latency response in vIPFC resulting from stimulating
236 HG appears as early as reported from potentials recorded in the posterior STG when stimulating HG²⁸
237 or when recording in vIPFC and stimulating STG¹⁶.

238 *Human vIPFC speech responses and directional connectivity with auditory cortex*

239 Lastly, we studied whether speech sounds induce neurophysiological responses in human vIPFC or
240 MTL and the directionality of neurophysiological interactions using state-space Conditional Granger
241 Causality (CGC). Expectedly, auditory (HG and STG) sites showed strong broad-band speech-driven
242 responses (Fig. 6A), including power decreases in low frequencies after speech onset²⁹. Individual
243 contacts showed significant speech responses in PHG and hippocampus, although responses in these
244 areas were weak in the group average results. By comparison, vIPFC responses to speech sounds was
245 much more substantial in individual and group results (Fig. 6A), evident as increases in lower
246 frequency (theta) power with suppression in alpha and beta bands.

247 Directional frequency-resolved CGC analyses were conducted between pairs of contacts with
248 the results conditioned on non-specific effects across all contacts during the neurophysiological
249 responses to speech (subject 429, Fig. 6B). Expected HG and STG directional interactions were
250 observed (Fig. 6B). In this subject there were no hippocampal contacts, but the available PHG contact
251 only showed significant directional interconnectivity with vIPFC; PHG connectivity with auditory
252 cortex was weak. By comparison, the vIPFC showed strong bi-directional interactions with the auditory
253 sites (Fig. 6B).

254 **DISCUSSION**

255 In monkeys, neuronal tractography has shown both direct projections from non-primary auditory cortex
256 to vocalization sensitive vIPFC neurons^{14,15,27} and indirect projections from auditory cortex to the
257 hippocampus via parahippocampal cortex^{20,21,30,31}. In humans, because of language and declarative
258 memory the corresponding pathways are expected to have specialized in our species. Amidst
259 comparative insights on differentiation involving language pathways^{7-9,32}, there is surprisingly little
260 evidence for a privileged auditory to vIPFC pathway in humans^{7,16,17,33} as in macaques^{14,15,27}. Also,
261 human resting-state data is suggestive of indirect auditory to hippocampal functional connectivity^{23,34},
262 as in other species, with the only evidence for direct projections between hippocampus proper and
263 hierarchically earlier auditory fields having been obtained in rodents²².

264 We harnessed a new approach for similarly assessing effective connectivity in humans and
265 monkeys, using combined electrical stimulation and functional MRI (esfMRI)^{26,35}. We found
266 comparable fronto-temporal effective connectivity in both species from stimulating auditory cortex in
267 several vIPFC and MTL subregions. More subtle differences in human hemispheric lateralization were
268 seen, relative to more bilaterally symmetrical effects in monkeys. In humans, we also obtained evidence
269 for rapid electrically-induced neurophysiological responses in vIPFC from stimulating auditory cortex,
270 with shorter latency in the first measurable potential than that seen in the opposite direction (stimulating
271 vIPFC and recording in the auditory HG), or for interactions between HG and hippocampus. Also, we
272 identified a speech responsive region in human vIPFC with directional effective connectivity with
273 auditory cortex. The findings show human auditory pathways that appear to be as direct to vIPFC and
274 indirect to the hippocampus (via parahippocampal cortex) as in nonhuman primates, illuminating the
275 primate origins of fronto-temporal pathways for cognition.

276 *Common auditory esfMRI fronto-temporal effective connectivity*

277 The comparison of esfMRI effects in humans and monkeys supports the notion of fronto-temporal
278 networks including auditory cortex, vIPFC and MTL being based on a largely evolutionarily conserved
279 effective connectivity signature. In both species, we observed stronger frontal operculum (FOP)
280 responses than in vIPFC areas 44 and 45, with some hemispheric difference in humans, evident as a
281 more balanced response across these regions in the human right hemisphere. Also in both species,
282 auditory cortex stimulation induced stronger activation in PHG than other MTL subregions.

283 The strong FOP effect is interesting because this region ventral to vIPFC areas 44 and 45 has
284 been implicated in initial syntactic processes in humans, based on its involvement in processing local
285 relationships such as those between adjacent words in a sentence⁹. Comparative human and monkey
286 fMRI using a sequence learning task has shown that the FOP, in particular, similarly responds in these

287 species to adjacent sequencing relationships³⁶. Also, the FOP is part of a fronto-temporal saliency in
288 attention or task control network that appears to be evolutionarily conserved in primates³⁷.

289 The comparably stronger esfMRI effect in monkeys and humans from stimulating auditory
290 cortex seen in the PHG, which was stronger than certain hippocampal subregions, suggests an equally
291 indirect auditory cortical projection to the hippocampal memory circuit across these species. This
292 observation is not inconsistent with impressions from human resting-state connectivity, including ultra-
293 high-resolution data^{33,34}. The current findings challenge the notion that monkeys have a less direct
294 auditory effective interconnectivity with the MTL memory system than humans. Our language abilities
295 allows us to name, conceptualize and thus better remember sounds²⁴, but, as our observations suggest,
296 possibly with a largely evolutionarily conserved MTL system.

297 The mode of action of esfMRI remains poorly understood. A prior monkey esfMRI study
298 showed that electrical stimulation of the visual thalamus elicits an fMRI response in primary visual
299 cortex (V1) with inhibitory neurons reducing signal propagation to other areas³⁸. However, some
300 propagation to multi-synaptically connected sites appears to be evident in the form of graded fMRI
301 responses. Namely, our pattern of graded MTL ROI effects are generally consistent with known
302 parahippocampal and hippocampal subregion multi-synaptic connectivity^{39,40}.

303 *Cross-species differences in esfMRI effects*

304 Evidence for human differentiation was clearest in the form of hemispheric lateralization. By contrast,
305 the monkey esfMRI effects were largely bilateral (even though it was only possible to stimulate the
306 right hemisphere in the monkeys). The human results showed hemispheric lateralization effects for
307 vlPFC and MTL subregions, almost independently of which hemisphere was stimulated (Fig. 4D).

308 There were also differences in effects between humans and monkeys by auditory cortical site
309 of stimulation. We initially stimulated auditory ‘core’ and ‘belt’ areas in the monkeys aiming to identify
310 distinctly different esfMRI effects, given that belt neurons are known to project to prefrontal cortex⁴¹.
311 However, the monkey results were statistically indistinguishable from stimulation of these two adjacent
312 auditory sites, potentially because passive current spread was estimated to be ~1 mm radius around the
313 stimulating electrode (Results). The human results were distinctly different between the two
314 stimulation sites, one of which was identified by its auditory click following response⁴². Passive current
315 spread in the human results is also worth considering, with ~2.5 mm radius around the stimulating
316 contacts, indicating that some of the human medHG effects can involve stimulation of adjacent areas.

317 *Considerations in relation to white matter pathways and monkey anterograde tractography*

318 The effective connectivity approach we used is agnostic to the white matter tracts that interconnect
319 auditory cortex with the fronto-temporal sites. Human diffusion MRI and monkey anterograde
320 tractography indicate that the FOP is interconnected with auditory cortex via the ventral extreme-
321 capsule or uncinate fasciculus pathway⁴³. Human area 44 is interconnected with areas caudal to
322 auditory cortex via the dorsal arcuate fasciculus pathway¹³. A recent comparative study showed a
323 homolog of this dorsal auditory pathway in macaques⁸ projecting from caudo-medial regions near to
324 those that we electrically stimulated, which elicited vIPFC activity.

325 Is it unexpected that our esfMRI results from stimulating posterior auditory cortical sites show
326 effects in vIPFC? Namely, monkey anterograde tractography results from caudal auditory belt areas
327 (like area CL) show denser *dorso-lateral* prefrontal cortex axonal bouton labelling^{15,27}. Although
328 mesoscopic effects such as those measured by esfMRI lack the specificity of single neuron
329 tractography, our results do recapitulate key patterns shown with macaque anterograde tractography,
330 such as both anterior and posterior auditory belt neuronal tracer injections labelling axonal boutons in
331 vIPFC¹⁵. Also, in relation to a prior macaque esfMRI study, our results are more similar to their effects
332 from stimulating posterior lateral belt (area ML) than those from stimulating the anterior lateral belt
333 (RTL)⁴⁴. In that study there was one auditory cortical field separation between the two stimulated sites.
334 In our study, there was no such buffer region between the two stimulated sites, which may be why our
335 effects from stimulating the two sites were statistically indistinguishable. Another consideration is the
336 inherent differences in how the monkeys and humans were studied (e.g., different scanners, electrodes,
337 parameters). However, amidst all such differences, it is remarkable how similar the esfMRI effects in
338 vIPFC and MTL were across the species.

339 *Rapid human auditory cortical to vIPFC electrical tractography*

340 The study provides evidence for a rapid electrical-tractography response in vIPFC following HG
341 stimulation. An early vIPFC positive potential occurred as soon as we could measure after the
342 stimulation artifact, peaking ~5-7 ms after HG stimulation. Auditory cortex and the vIPFC are separated
343 by ~10 cm via the arcuate fasciculus. The latency of this early positivity was significantly longer in the
344 opposite direction (stimulating vIPFC and recording in HG) and between HG and the hippocampus in
345 either direction (Fig. 5E-H). The estimated conduction velocity, based on axonal diameter and
346 conduction speeds^{45,46} including within fronto-temporal pathways⁴⁷, is 10-30 m/s. Thus, the expected
347 latency of the first potentials from auditory cortex arriving in vIPFC is between ~3-10 ms. Our HG to
348 vIPFC latency results are remarkably similar in latency to the reported ~6 ms peak of the initial
349 positivity recorded in auditory posterior STG sites after medial HG stimulation²⁸; the two sites are
350 separated by 1-2 cm. The authors in that study could not exclude the possibility of a monosynaptic
351 connection between medial HG and the STG, because, surprisingly, stimulation of a lateral HG site

352 expected to be an intermediary elicited weaker recorded potentials in the STG. In another study,
353 stimulation of the posterior STG while recording in vIPFC resulted in an early negativity (the study
354 focused on negative potentials) with an average vIPFC response latency of ~ 13.5 ms¹⁶, which is similar
355 to our first negativity latency in vIPFC from stimulating HG ($N(a)$; Fig. 5E). Even longer first negativity
356 latencies in vIPFC can be seen from stimulating various temporal lobe sites¹⁷.

357 Thereby, our electrical tractography effects from HG to vIPFC are notably similar to those
358 reported from recording in vIPFC after stimulating STG¹⁶. The results raise the possibility that the HG
359 to vIPFC connection is as rapid as the one from posterior STG to vIPFC. Although we cannot exclude
360 multi-synaptic effects, it is possible that if medial or lateral HG sites require additional synaptic
361 connections in the STG, that the vIPFC early positivity (or negativity) could peak later. Moreover,
362 although HG and vIPFC effective connectivity appeared to be bidirectional, there were key differences
363 in the shape of waveforms in both directions and the early positivity was earlier when stimulating HG
364 and recording in vIPFC than in the opposite direction. The early positive potential between the HG and
365 hippocampus in either direction was also later than the one observed between HG and vIPFC. Our
366 latencies between HG and the hippocampus are however within the range of those reported from
367 recording in various temporal lobe sites after entorhinal cortex stimulation⁴⁸. The results provide
368 support for privileged HG to vIPFC effective connectivity that differs in the opposite direction and
369 from results involving the hippocampus.

370 *Human speech responsive vIPFC region with directional auditory cortex effective connectivity*

371 We observed considerable speech sound driven neurophysiological responses in vIPFC and show
372 conditional Granger causality results on bidirectional effective connectivity between HG and vIPFC.
373 Speech responses in vIPFC are not unexpected, typically being evident during active speech recognition
374 or difficult listening conditions⁴⁹. Spoken speech or reading can also elicit responses from the human
375 hippocampus⁵⁰ (see Fig. 6). The conditional Granger causality results showing interconnectivity
376 between vIPFC and HG during speech processing is further evidence for a privileged auditory to vIPFC
377 pathway in the human brain.

378 In summary, the findings demonstrate largely comparable effective connectivity signatures
379 between human and macaque auditory cortex, vIPFC and MTL. The auditory system as the model
380 sensory system under study here is expected to show human-specific specialization for speech,
381 language and declarative memory. However, even these results involving auditory cortex show
382 considerable correspondence in fronto-temporal effective connectivity across these species. Future
383 studies in other species or sensory modalities could further support or refute our observations.

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391

392 **AUTHOR CONTRIBUTIONS**

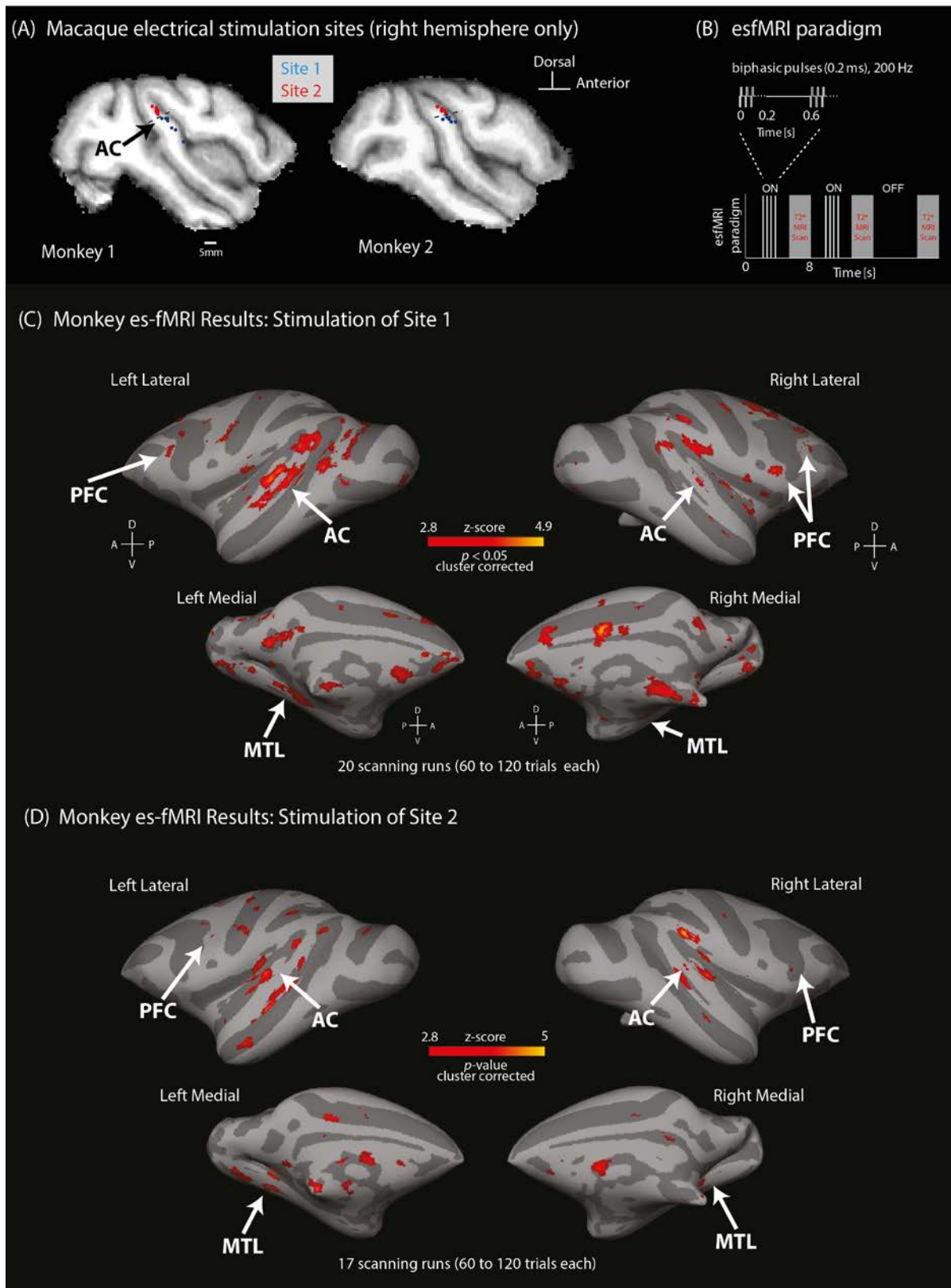
393 Conceptualization: CIP, MAH, TDG. Investigation: FR, HO, FB, AER, KVN, MS, YK, HK, CIP.
394 Formal Analysis: FR, HO, ZK, RJ, CIP. Resources: FB, AB, CKK, KVN, YK, BJD, HK, RA, JDWG,
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396 AB, ZK, RJ, KVN, YK, BJD, RA, JDWG, TDG, MAH, CIP. Supervision: MAH & CIP. Project
397 administration: HO, FR, FB, AER, KVN, MAH, CIP. Funding acquisition: RA, JDWG, TDG, MAH,
398 CIP.

399

400 **DECLARATION OF INTERESTS**

401 The authors declare no competing or financial interests.

402 **FIGURES**



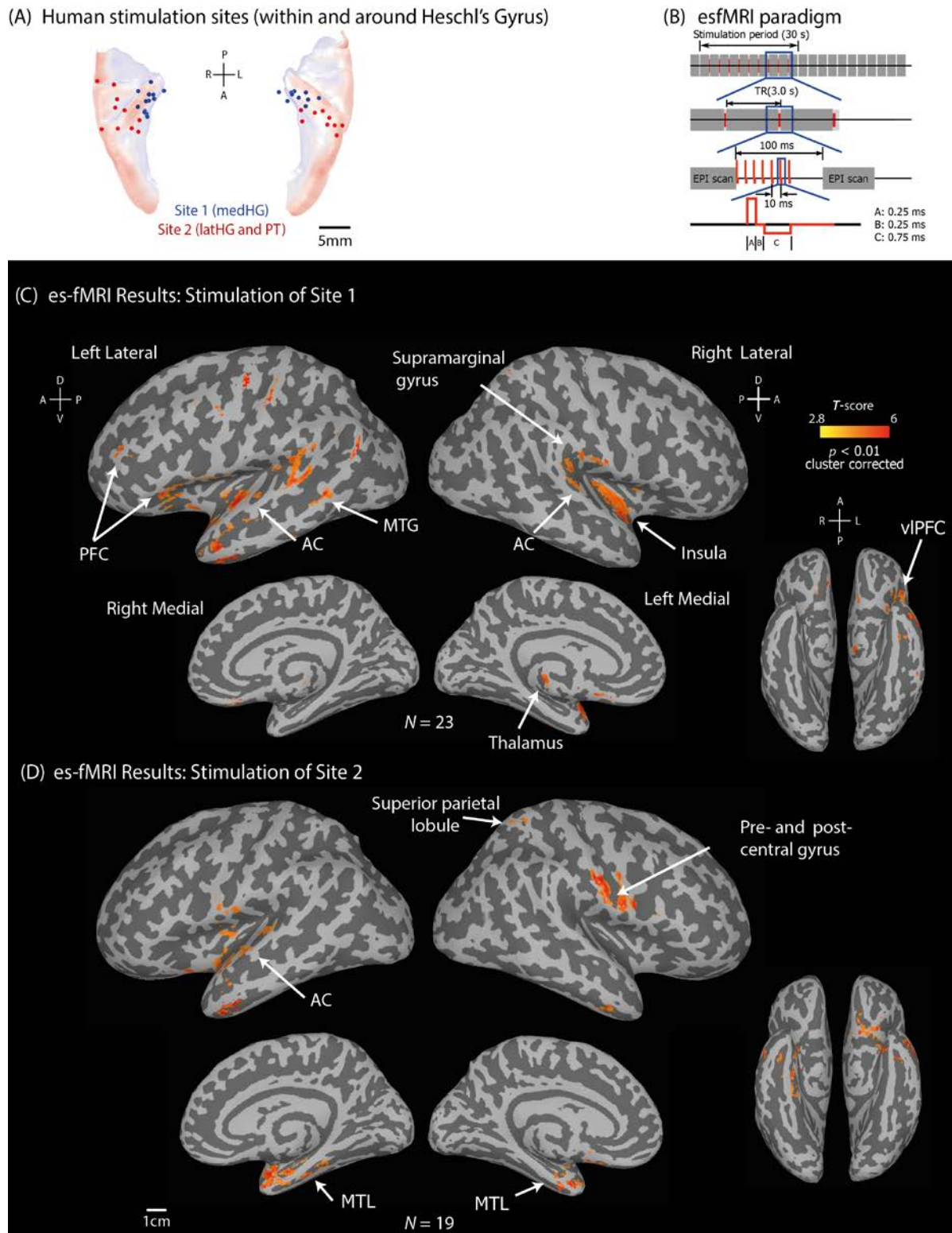
403

404 **Figure 1. Macaque monkey auditory cortex electrical stimulation sites and esfMRI results.** (A)

405 Stimulation sites 1 (blue) and 2 (red) auditory cortex of the right hemisphere in the two macaques (M1

406 and M2). (B) esfMRI paradigm timing. (C-D) Macaque esfMRI group results showing significantly

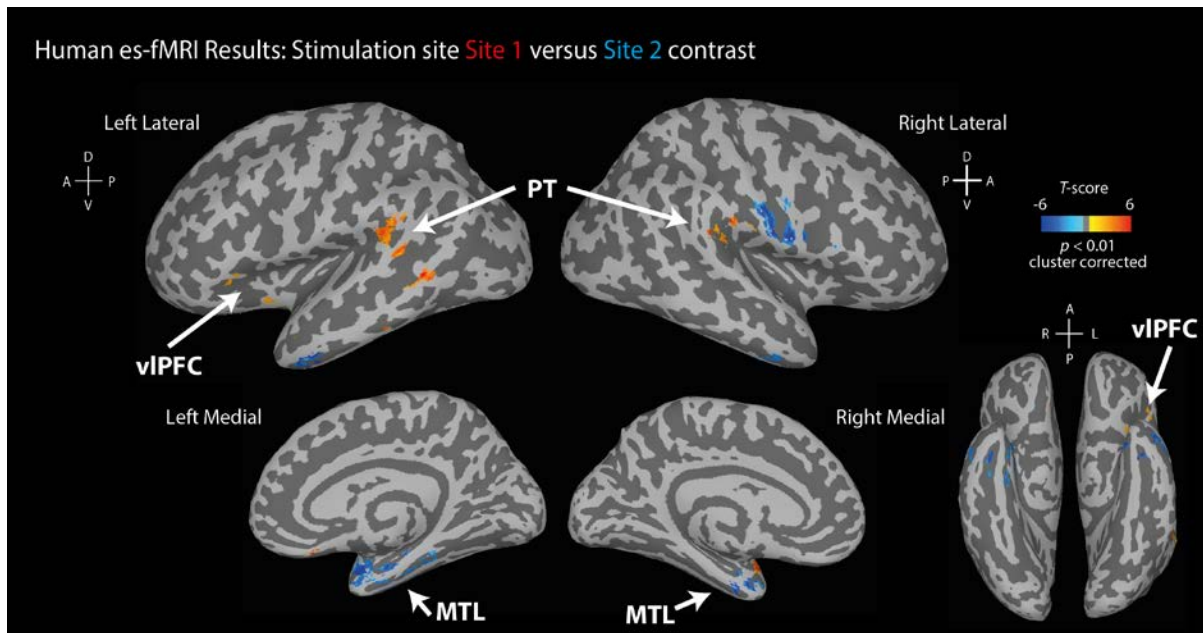
407 activated voxels relative to no-stimulation trials in response to electrical stimulation of the auditory
408 cortex sites: Site 1 (C) and Site 2 (D), cluster-corrected $p < 0.05$, $Z > 2.8$ (see Table 1 for list of activated
409 anatomical regions). Results projected to the surface-rendered standard macaque template brain.
410 Abbreviations: auditory cortex (AC), prefrontal cortex (PFC) and medial temporal lobe (MTL).



411

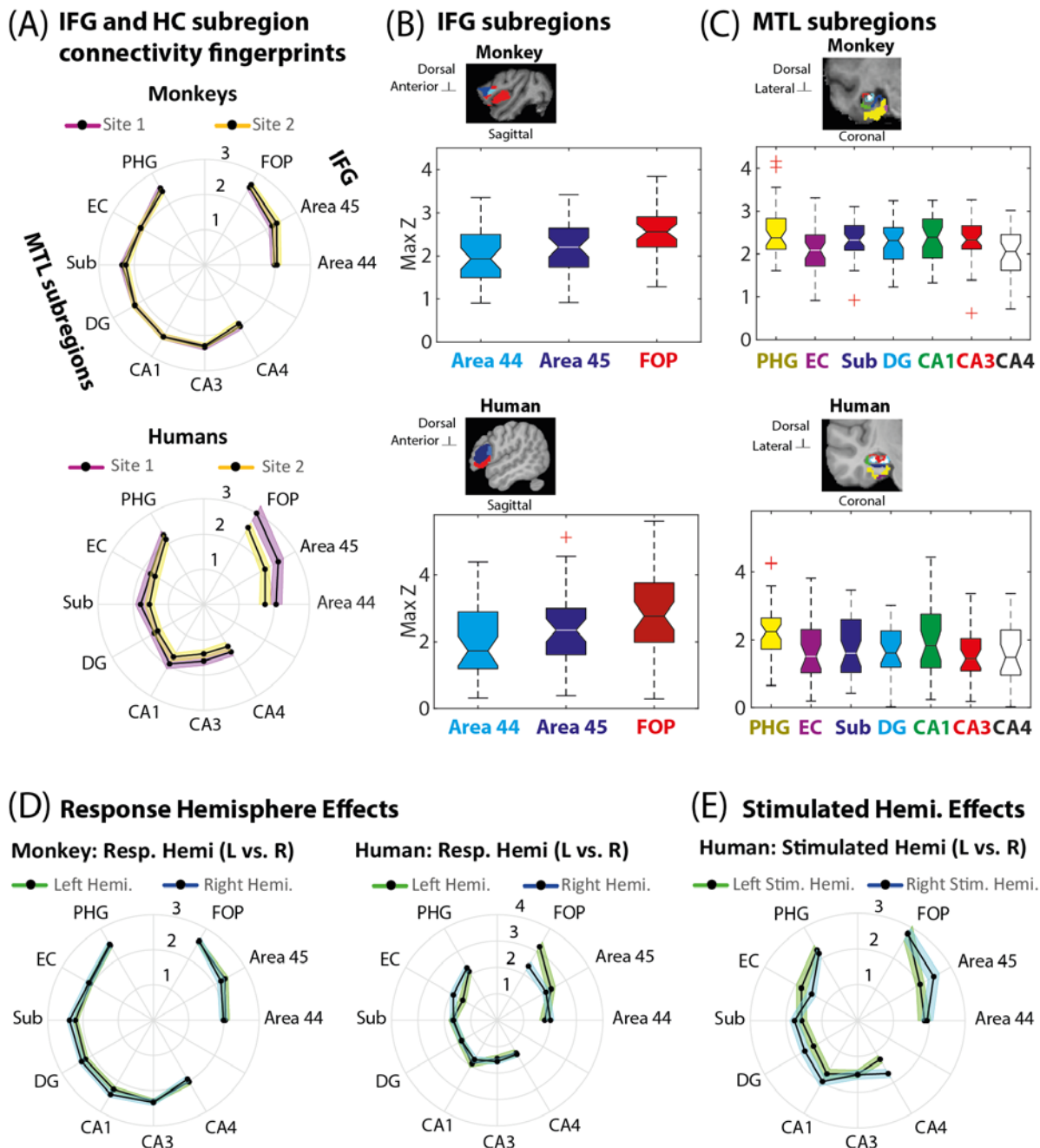
412 **Figure 2. Human auditory cortex electrical stimulation sites and esfMRI results.** (A) Stimulation
 413 of depth electrodes in the transverse temporal gyrus (Heschl's gyrus; HG). Human auditory stimulation
 414 Sites 1 and 2 shown looking down on the superior temporal plane. Stimulation sites are identified at
 415 the center of the adjacent contacts used for stimulation (Suppl. Fig. S2 shows actual contact location
 416 in each participant). (B) esfMRI paradigm timing. (C-D) Human esfMRI group results shown as
 417 significantly activated voxels relative to no-stimulation trials (cluster corrected, $T = 2.8$, $p < 0.01$) in

418 response to electrical stimulation of Site 1 (C) or Site 2 (D), shown on the surface-rendered Montreal
419 Neurological Institute human standard brain.



420

421 **Figure 3. Human results contrasting Site 1 versus Site 2 esfMRI effects.** Same format as in Fig.
422 2C-D, showing statistically significant ($p < 0.01$ cluster-corrected) effects where either Site 1 (red color
423 map) or Site 2 (blue color map) were stronger. The corresponding contrast in monkeys yielded no
424 cluster-corrected differences.



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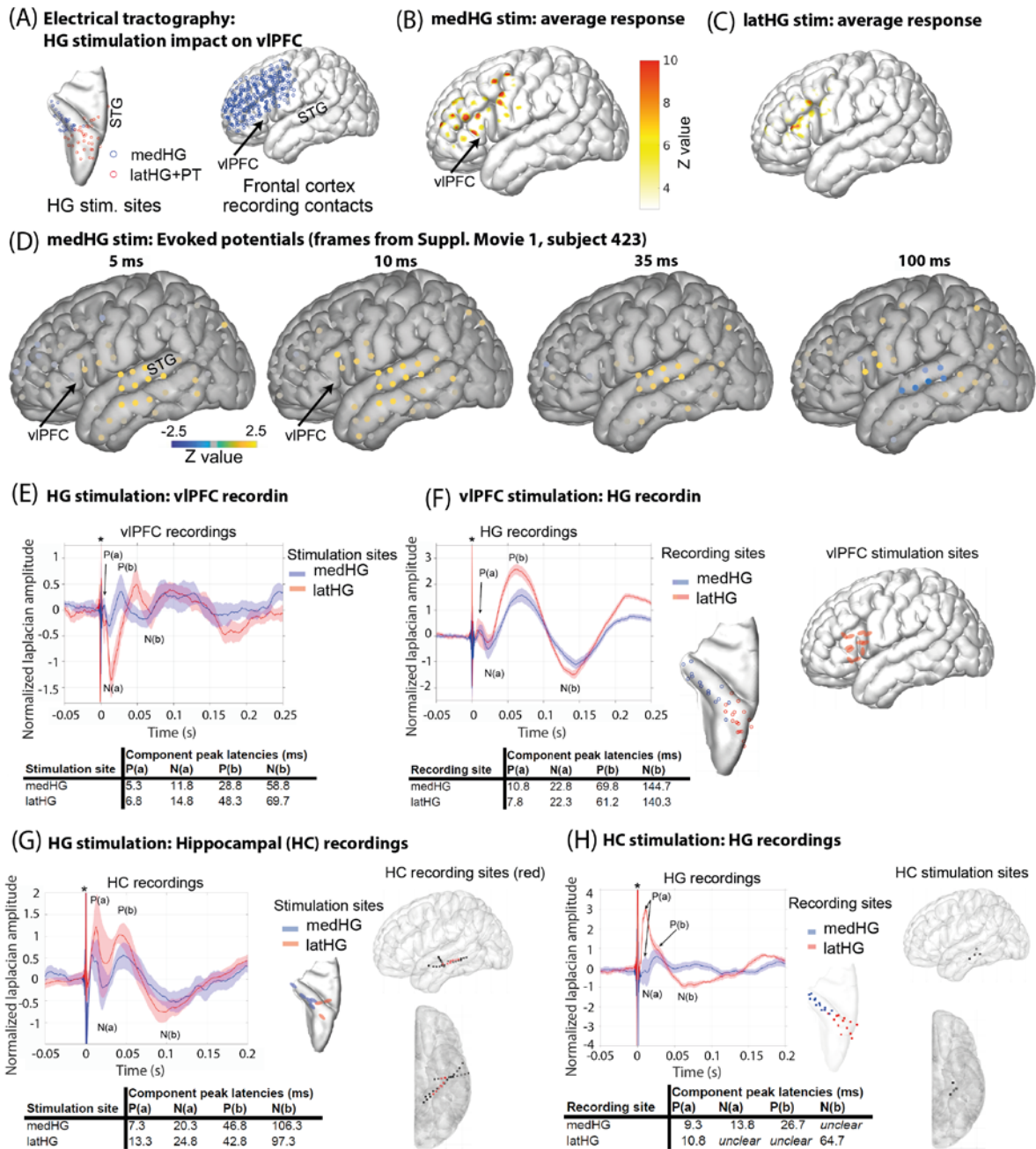
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Figure 4. Human and macaque vIPFC and MTL connectivity profiles. (A) vIPFC and MTL subregion esfMRI effects displayed as polar plots. Shown are the across scanning runs peak z-values and variability (+/-SEM, standard error of the mean). Top plot in (A) shows monkey results, bottom human results. (B-C) whisker plots of vIPFC (B) and MTL (C) esfMRI activity responses (across scanning runs, peak z-value; central mark identifies the median, edges of box are 25th and 75th percentiles, whiskers extend to extreme ends of data not including outliers in red crosses; non-overlapping notches are significantly different at $p < 0.05$). Also shown are sagittal and coronal slices in each species with the anatomically localized ROIs used for the analysis. (D) effects by response

434 hemisphere (monkeys left, humans right). (E) human effects by stimulated hemisphere; only right
435 hemisphere was stimulated in the monkeys.



436

437 **Figure 5. Human electrical tractography.** (A) Human HG stimulation sites and vIPFC recording

438 electrode locations. (B-C) average gamma band evoked response from the recording contacts shown

439 by medHG (B) or latHG+PT (C) stimulation. (D) frames at 5, 10, 35 and 100 ms post-electrical pulse

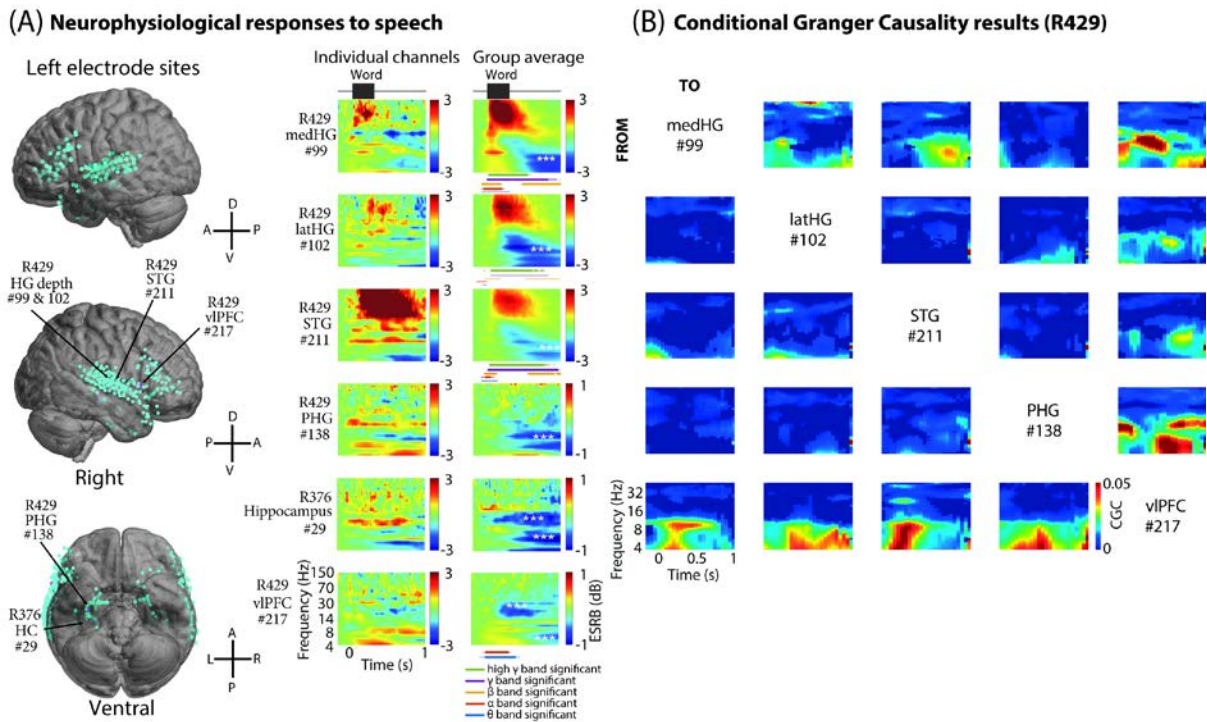
440 stimulation from Supplementary Movie 1 (subject 423) during medHG stimulation. (E) average

441 neurophysiological evoked potentials in vIPFC from stimulating the HG sites, showing the peak latency

442 (ms) for each component. (F) vIPFC stimulation and recording in HG; same format as in (E); location

443 of stimulation and recording contacts shown on right. (G) stimulation of HG during recordings in

444 hippocampus (HC). (H) stimulation of HC during recordings in HG.



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Figure 6. Human vIPFC responses to speech and conditional Granger causality interconnectivity with auditory cortex. (A) left, electrode locations across all participants ($N = 8$) projected on the left and right lateral and ventral view a template brain across all the participants. Right, time-frequency resolved responses to speech sounds (common words). Shown are single subject individual channels (left column) and group average (right column) within Heschl's gyrus (HG), superior temporal gyrus (STG), parahippocampal gyrus (PHG), hippocampus (HC) and vIPFC. Subject 429 did not have hippocampal coverage, therefore the responses from another subject (376) are shown for this region. Below the group results we identify significant responses subdivided by frequency bands (thin > 2 SD; thick > 4 SD relative to the pre-word baseline variability). White *** symbols inset in the group plots identify significant suppression. (B) state-space Conditional Granger Causality (CGC) results showing directional neurophysiological interactions during speech sound presentation. Directions of influence are shown from regions of interest (rows) to recipient regions (columns) active during speech presentation. Subthreshold (not significant) regions of time-frequency CGC were set to 0 and are masked in dark blue. Note the strong dynamic directional influences particularly between vIPFC and auditory sites such as HG.

461 **REFERENCES**

- 462 1. Lemon, R.N. Descending pathways in motor control, *Annu Rev Neurosci* **31**, 195-218 (2008).
- 463 2. Simonyan, K. & Horwitz, B. Laryngeal motor cortex and control of speech in humans,
464 *Neuroscientist* **17**, 197-208 (2011).
- 465 3. Petkov, C.I. & Jarvis, E.D. Birds, primates, and spoken language origins: behavioral phenotypes
466 and neurobiological substrates, *Front Evol Neurosci* **4**, 12 (2012).
- 467 4. Arriaga, G., *et al.* Of mice, birds, and men: the mouse ultrasonic song system has some features
468 similar to humans and song-learning birds, *PLoS one* **7**, e46610 (2012).
- 469 5. Boë, L.-J., *et al.* Which way to the dawn of speech?: Reanalyzing half a century of debates and data
470 in light of speech science, *Science Advances* **5**, eaaw3916 (2019).
- 471 6. Eichert, N., *et al.* What is special about the human arcuate fasciculus? Lateralization, projections,
472 and expansion, *Cortex* (2018).
- 473 7. Neubert, F.X., *et al.* Comparison of human ventral frontal cortex areas for cognitive control and
474 language with areas in monkey frontal cortex, *Neuron* **81**, 700-713 (2014).
- 475 8. Balezeau, F., *et al.* Primate auditory prototype in the evolution of the arcuate fasciculus, *Nature*
476 *Neuroscience* (in press).
- 477 9. Friederici, A.D. *Language in our brain: The origins of a uniquely human capacity* (MIT Press,
478 2017).
- 479 10. Pryluk, R., *et al.* A tradeoff in the neural code across regions and species, *Cell* **176**, 597-609. e518
480 (2019).
- 481 11. Flinker, A. & Knight, R.T. Broca's area in comprehension and production, insights from
482 intracranial studies in humans, *Current opinion in behavioral sciences* **21**, 170-175 (2018).
- 483 12. Donahue, C.J., *et al.* Quantitative assessment of prefrontal cortex in humans relative to nonhuman
484 primates, *Proceedings of the National Academy of Sciences* **115**, E5183-E5192 (2018).
- 485 13. Catani, M. & Jones, D.K. Perisylvian language networks of the human brain, *Annals of neurology*
486 **57**, 8-16 (2005).
- 487 14. Romanski, L.M. & Goldman-Rakic, P.S. An auditory domain in primate prefrontal cortex, *Nat*
488 *Neurosci* **5**, 15-16 (2002).
- 489 15. Romanski, L.M., *et al.* Dual streams of auditory afferents target multiple domains in the primate
490 prefrontal cortex, *Nat Neurosci* **2**, 1131-1136 (1999).
- 491 16. Garell, P., *et al.* Functional connection between posterior superior temporal gyrus and ventrolateral
492 prefrontal cortex in human, *Cerebral Cortex* **23**, 2309-2321 (2012).
- 493 17. Nakae, T., *et al.* Connectivity Gradient in the Human Left Inferior Frontal Gyrus: Intraoperative
494 Cortico-Cortical Evoked Potential Study, *bioRxiv*, 702753 (2019).
- 495 18. Wilson, B., *et al.* Conserved Sequence Processing in Primate Frontal Cortex, *Trends in*
496 *Neurosciences* (2017).
- 497 19. Fritz, J., *et al.* In search of an auditory engram, *Proc Natl Acad Sci U S A* **102**, 9359-9364 (2005).

- 498 20. Munoz-Lopez, M.M., *et al.* Anatomical pathways for auditory memory in primates, *Front*
499 *Neuroanat* **4**, 129 (2010).
- 500 21. Insausti, R. & Amaral, D.G. Entorhinal cortex of the monkey: IV. Topographical and laminar
501 organization of cortical afferents, *Journal of Comparative Neurology* **509**, 608-641 (2008).
- 502 22. Cenquizca, L.A. & Swanson, L.W. Spatial organization of direct hippocampal field CA1 axonal
503 projections to the rest of the cerebral cortex, *Brain research reviews* **56**, 1-26 (2007).
- 504 23. Maller, J.J., *et al.* Revealing the Hippocampal Connectome through Super-Resolution 1150-
505 Direction Diffusion MRI, *Scientific reports* **9**, 2418 (2019).
- 506 24. Schulze, K., *et al.* Test of a motor theory of long-term auditory memory, *Proceedings of the*
507 *National Academy of Sciences* **109**, 7121-7125 (2012).
- 508 25. Tolias, A.S., *et al.* Mapping cortical activity elicited with electrical microstimulation using fMRI
509 in the macaque, *Neuron* **48**, 901-911 (2005).
- 510 26. Oya, H., *et al.* Mapping effective connectivity in the human brain with concurrent intracranial
511 electrical stimulation and BOLD-fMRI, *Journal of Neuroscience Methods* **277**, 101-112 (2017).
- 512 27. Romanski, L.M., *et al.* Auditory belt and parabelt projections to the prefrontal cortex in the rhesus
513 monkey, *Journal of Comparative Neurology* **403**, 141-157 (1999).
- 514 28. Brugge, J.F., *et al.* Functional connections between auditory cortex on Heschl's gyrus and on the
515 lateral superior temporal gyrus in humans, *Journal of Neurophysiology* **90**, 3750-3763 (2003).
- 516 29. Billig, A.J., *et al.* A Sound-Sensitive Source of Alpha Oscillations in Human Non-Primary
517 Auditory Cortex, *The Journal of neuroscience : the official journal of the Society for Neuroscience*
518 **39**, 8679-8689 (2019).
- 519 30. Amaral, D.G., *et al.* Evidence for a direct projection from the superior temporal gyrus to the
520 entorhinal cortex in the monkey, *Brain Research* **275**, 263-277 (1983).
- 521 31. Munoz, M. & Insausti, R. Cortical efferents of the entorhinal cortex and the adjacent
522 parahippocampal region in the monkey (*Macaca fascicularis*), *Eur J Neurosci* **22**, 1368-1388
523 (2005).
- 524 32. Mars, R.B., *et al.* Connectivity and the search for specializations in the language-capable brain,
525 *Current Opinion in Behavioral Sciences* **21**, 19-26 (2018).
- 526 33. Baker, C.M., *et al.* A Connectomic Atlas of the Human Cerebrum—Chapter 5: The Insula and
527 Opercular Cortex, *Operative Neurosurgery* **15**, S175-S244 (2018).
- 528 34. Baker, C.M., *et al.* A Connectomic Atlas of the Human Cerebrum—Chapter 6: The Temporal
529 Lobe, *Operative Neurosurgery* **15**, S245-S294 (2018).
- 530 35. Jones, S.E., *et al.* Functional magnetic resonance imaging networks induced by intracranial
531 stimulation may help defining the epileptogenic zone, *Brain connectivity* **4**, 286-298 (2014).
- 532 36. Wilson, B., *et al.* Auditory sequence processing reveals evolutionarily conserved regions of frontal
533 cortex in macaques and humans, *Nat Commun* **6**, 8901 (2015).
- 534 37. Higo, T., *et al.* Distributed and causal influence of frontal operculum in task control, *Proceedings*
535 *of the National Academy of Sciences* **108**, 4230-4235 (2011).

- 536 38. Logothetis, N.K., *et al.* The effects of electrical microstimulation on cortical signal propagation,
537 *Nat Neurosci* **13**, 1283-1291 (2010).
- 538 39. Witter, M.P. Organization of the entorhinal—hippocampal system: A review of current anatomical
539 data, *Hippocampus* **3**, 33-44 (1993).
- 540 40. Jinno, S. Structural organization of long-range GABAergic projection system of the hippocampus,
541 *Frontiers in neuroanatomy* **3**, 13 (2009).
- 542 41. Diehl, M. & Romanski, L. Representation and Integration of Faces and Vocalizations in the
543 Primate Ventral Prefrontal Cortex. in *Integrating Face and Voice in Person Perception* (ed. P.
544 Belin, S. Campanella & T. Ethofer) 45-69 (Springer New York, 2013).
- 545 42. Brugge, J.F., *et al.* Functional localization of auditory cortical fields of human: click-train
546 stimulation, *Hearing Research* **238**, 12-24 (2008).
- 547 43. Rilling, J.K., *et al.* The evolution of the arcuate fasciculus revealed with comparative DTI, *Nat*
548 *Neurosci* **11**, 426-428 (2008).
- 549 44. Petkov, C.I., *et al.* Different forms of effective connectivity in primate frontotemporal pathways
550 (vol 6, 6000, 2015), *Nature Communications* **6** (2015).
- 551 45. Caminiti, R., *et al.* Diameter, length, speed, and conduction delay of callosal axons in macaque
552 monkeys and humans: comparing data from histology and magnetic resonance imaging diffusion
553 tractography, *Journal Of Neuroscience* **33**, 14501-14511 (2013).
- 554 46. Bishop, G.H. & Smith, J.M. The sizes of nerve fibers supplying cerebral cortex, *Experimental*
555 *Neurology* **9**, 483-501 (1964).
- 556 47. Greenlee, J.D., *et al.* A functional connection between inferior frontal gyrus and orofacial motor
557 cortex in human, *Journal of Neurophysiology* **92**, 1153-1164 (2004).
- 558 48. Takeyama, H., *et al.* Human entorhinal cortex electrical stimulation evoked short-latency potentials
559 in the broad neocortical regions: Evidence from cortico-cortical evoked potential recordings, *Brain*
560 *and behavior* (2019).
- 561 49. Davis, M.H., *et al.* Dissociating speech perception and comprehension at reduced levels of
562 awareness, *Proc Natl Acad Sci U S A* **104**, 16032-16037 (2007).
- 563 50. Jafarpour, A., *et al.* Human hippocampal pre-activation predicts behavior, *Scientific reports* **7**, 5959
564 (2017).

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566 **ONLINE METHODS**

567 *Macaque procedures*

568 All the nonhuman animal work and procedures were approved by the university Animal Welfare and
569 Ethical Review Body and UK Home Office. The work complies with the revised UK Animal Scientific
570 Procedures Act (1986), the US National Institutes of Health Guidelines for the Care and Use of Animals
571 for Experimental Procedures and with the European Directive on the protection of animals used in
572 research (2010/63/EU). We support the principles on reporting animal research stated in the consortium
573 on Animal Research Reporting of In Vivo Experiments (ARRIVE). All persons involved in animal
574 handling and procedures were certified and the work was strictly regulated by the UK Home Office.

575 Two male rhesus macaques (*macaca mulatta*) from a group-housed colony were scanned
576 awake with combined electrical stimulation and fMRI (M1 and M2, 10 and 12 years old, weighing 12.2
577 and 12.6 kg, respectively). The pen sizes in the colony range from 130 x 240 cm to 215 x 240 cm. All
578 are 230 cm high, and hatches between neighboring cages are used to increase the space available to the
579 animals. Given the ethical sensitivities involved in studying nonhuman primates and the 3Rs principles
580 (one of which is on the Reduction of animal numbers), our work requires using the fewest monkeys
581 possible. A sample size of two is common in neuroscience work with macaques provided that results
582 are robust with each individual and that the effects generalize beyond one animal. Given that our results
583 from several hundred trials and many scanning runs with each animal are statistically robust and
584 consistent in the overall pattern of effects between the animals (i.e., no significant interactions of
585 monkeys as a factor with the reported patterns of esfMRI results) there was little ethical justification
586 to test additional monkeys.

587 *Macaque electrical stimulation procedure*

588 The electrical stimulation procedure used in this work is based on methodology developed in prior
589 macaques esfMRI studies^{25,38,44,51}. Here the procedure was conducted on awake monkeys in absence of
590 alterations due to anesthetics^{52,53} to allow more direct comparison with awake human esfMRI data.

591 Prior to the experiments, an MRI-compatible PEEK head post and chamber were implanted
592 stereotaxically during an aseptic procedure under general anesthesia. The chamber was positioned over
593 the right hemisphere to provide access to posterior auditory cortex, including fMRI tonotopically
594 localized fields A1 and the posterior area adjoining the border between belt fields CL and CM (Suppl.
595 Fig. 1).

596 During each scanning session, a custom-made PEEK microdrive was used to advance the
597 stimulating electrode to auditory cortex. Electrical stimulation was induced through platinum/iridium

598 microelectrodes coated in parylene-C (Microprobes, Gaithersburg, Germany), with a typical
599 impedance of 100-200 k Ω (electrodes with impedance below 75 k Ω were not used). The stimulating
600 electrode location in auditory cortex was confirmed via MRI structural scans and sound-evoked
601 neurophysiological responses as in previous studies⁴⁴, using a TDT system running Synapse (Tucker-
602 Davis Technologies, Alachua, FL). The experiment was controlled by Matlab software (MathWorks,
603 Natick, Massachusetts, US) running the Psychophysics Toolbox, interacting with the hardware
604 connected via a LabJack interface device (www.labjack.com). The experimental computer triggered
605 each EPI scan.

606 The target areas were electrically stimulated using a World Precision Instruments (DS8000)
607 waveform generator with an electrical stimulus isolator unit (DLS 100). The system delivered a
608 constant-current, charge-balanced electrical pulse of either 0.5 or 1 mA (fixed within a stimulation
609 session) at a repetition rate of 200 Hz (within 4 pulse periods; Fig. 1A). Each biphasic-square-wave
610 pulse had 0.2 ms duration. The stimulation and MRI scanning timing paradigm are shown in Fig. 1B.
611 Electrical stimulation was randomly induced in 50-70% of the scanning trials with the others containing
612 no stimulation, as a baseline point of reference.

613 *Macaque fMRI*

614 Functional MRI measured the blood oxygen level dependent (BOLD) signal, using an actively
615 shielded vertical primate-dedicated 4.7 Tesla MRI scanner (Bruker BioSpin, Ettlingen, Germany). The
616 monkeys had been slowly acclimated over several months with reinforcement training to work in the
617 primate scanning chair and with the required periods of head immobilization during fMRI⁵⁴. They were
618 scanned awake under head immobilisation while conducting a visual spot fixation task³⁶.

619 A custom 4-channel surface receiver coil array and a saddle transmitter coil were used for MRI
620 acquisition (WK Scientific, California USA). Functional data were obtained using a gradient-recalled
621 echo planar imaging (GE-EPI) sequence, with the following parameters: echo time (TE) = 20 ms;
622 volume acquisition time (TR) = 2000 ms; flip angle = 90 degrees; 32 slices, in plane with a field of
623 view (FOV) of 10.7 \times 10.7 cm², on a grid of 88 \times 88 voxels. Voxel resolution was 1.2 \times 1.2 \times 1.3 mm³
624 covering much of the brain. A sparse fMRI acquisition paradigm was used to minimize the interference
625 caused by the scanner noise on the auditory cortex response^{55,56}; a single T2* weighted MRI volume
626 was acquired after the electrical stimulation or no-stimulation periods for each trial. The onset of the
627 volume lagged by ~4 s to account for the lag in the hemodynamic response⁵⁷. The number of trials
628 obtained per scanning run for each animal were 60 for M1 and 120 for M2 and the numbers of scanning
629 runs analyzed were 20 (9 in M1; 11 in M2) for Site 1 stimulation and 17 (8 in M1; 9 in M2) for Site 2,
630 see Fig. 1.

631 Anatomical images, including those for helping to visualize the electrode position, were
632 acquired at the beginning and end of each experimental testing session using magnetization-prepared
633 rapid gradient-echo (MP-RAGE) sequences. Typical sequence parameters were: TE = 20 ms; inversion
634 time, TI = 750 ms; TR = 2000 ms; 50 slices with in-plane field of view: $10.7 \times 10.7 \text{ cm}^2$ on a grid of
635 140×140 voxels. The voxel resolution was $0.75 \times 0.75 \times 0.75 \text{ mm}^3$.

636 *Macaque fMRI data analysis*

637 We performed General Linear Analysis using FEAT in FSL^{58,59}. We contrasted the BOLD responses
638 during stimulation and non-stimulation trials. Each scanning volume in this sparse imaging paradigm
639 was assigned to either the stimulation or no-stimulation conditions. Brain extraction used the BET
640 function in FSL, and the fMRI image series were motion corrected within a given testing session using
641 FLIRT (typically 9 or 12 degrees of freedom affine transformation with the normalized mutual
642 information option). The motion parameters were used as regressors of no interest in the fMRI analyses.
643 The data were smoothed with a Gaussian kernel 2 mm Full Width Half Maximum (FWHM). For
644 registration of the fMRI time series, the T2-weighted scans were registered to the animal's session full-
645 brain mean functional scan. This scan was then registered to the animal's session anatomical and then
646 to its high-resolution anatomical scan. Finally these scans were registered to a macaque template
647 brain⁶⁰, which is in register to a macaque atlas in stereotactic coordinates⁶¹.

648 *General Linear Modelling:* We first preprocessed each scanning run using first-level analyses.
649 Individual scanning runs with little evidence of the expected electrically induced activity (at a liberal
650 uncorrected threshold $Z > 2.3$) in auditory areas around the electrode or in auditory cortex in the
651 opposite hemisphere were not analyzed further. Group higher-level analyses were conducted
652 combining all of the viable scanning runs grouped by stimulation site (Site 1 or 2). Higher-level
653 analyses were conducted using FLAME in FSL with a significance threshold at a cluster corrected (p
654 < 0.05 , $Z > 2.8$) level. FreeSurfer was used to project the results onto a surface-rendered macaque
655 template brain⁶². Table 1 shows the anatomical regions with significant electrically-induced esfMRI
656 activity (x, y, z in the macaque atlas brain space) resulting from Site 1 or 2 stimulation. The contrast
657 between Site 1 and Site 2 did not result in any cluster corrected ($p < 0.05$) voxels.

658 *Region of Interest analyses:* ROI analyses used anatomically defined regions from the macaque
659 atlas⁶¹ registered to the macaque template brain⁶⁰ and to each animal's dataset. For vIPFC subregion
660 analyses, we used anatomically delineated areas 44 and 45 from the atlas and FOP from prior work³⁶.
661 The MTL subregion analyses used anatomical regions corresponding to the PHG, entorhinal cortex
662 (EC), subiculum (Sub), dentate gyrus (DG) and the CA1, 3 and 4 subregions (CA2 was not available
663 in the human brain atlas). No voxels overlapped between ROIs. Polar plots using the ROIs (Fig. 4)
664 show the average positive BOLD peak Z-value across the scanning runs.

665 *Statistical tests:* Mixed-design ANOVA models were used to examine ROI effects. The
666 statistical test was implemented in SPSS 24 (IBM Corp, USA) and used scanning run ROI peak Z-
667 values as the dependent variable, with between-subject factors of Monkey (M1, M2) and Species (in
668 the cross-species comparison: Macaque), within-subjects factors of ROI (vIPFC or MTL ROIs),
669 Hemisphere (left or right) and Stimulation site (Site 1 or 2) as covariate. We ensured that the data fit
670 normality and equality of variance assumptions by using rank-based normalization and reporting
671 Greenhouse-Geisser corrected results as required.

672 *Human subjects*

673 Patients with intractable epilepsy requiring chronic invasive monitoring as part of their clinical
674 treatment participated: $N = 29$; male = 19, female = 10; age range: 13 - 59 years old; median age = 34
675 years; handedness: right dominant = 21, left = 6, mixed = 2. All experimental procedures were
676 approved by university IRB and written informed consent was obtained from all subjects. Depth and
677 subdural surface platinum electrodes (Ad-Tech Medical Instruments) had been implanted for clinical
678 monitoring. The patients' demographic information and treatment outcomes are shown in Tables 3-4.

679 *Human esfMRI procedure*

680 Details of the human esfMRI procedure and safety testing are available elsewhere²⁶. In this study, we
681 focused on data from auditory cortex stimulation with combined fMRI. Pre-electrode clinical
682 implantation T1-weighted and T2-weighted structural MRI images were obtained at 3 Tesla (GE
683 Discovery 750W scanner, 32 channel head coil): T1w inversion recovery fast spoiled gradient recalled
684 (BRAVO) sequence, $1.0 \times 1.0 \times 0.8 \text{ mm}^3$ voxel size, TE = 3.28 ms, TR = 8.49 ms, TI = 450 ms, FOV
685 = 240 mm^3 , flip angle = 12 degrees; T2w: 3-D fast spin-echo (CUBE) sequence, $1.0 \times 1.0 \times 1.0 \text{ mm}^3$
686 voxel size, TE = 77.21 ms, TR = 3200 ms, TI = 450 ms, FOV = 256 mm^3 , flip angle = 90 degrees.

687 During esfMRI scanning sessions, structural T1-weighted images were obtained using a
688 Siemens Skyra 3 Tesla scanner (MPRAGE sequence with $1.0 \times 1.0 \times 1.0 \text{ mm}^3$ resolution, TE = 3.34
689 ms, TR = 2530 ms, TI = 1100 ms, FOV = 256 mm^3). A transmit and receive head coil was used for
690 esfMRI sessions and for the session structural and functional scans. Gradient-echo, echo-planar
691 imaging (GE-EPI) was used to obtain the T2* weighted BOLD scans (TR = 3.0 s, TE = 30 ms, slice
692 thickness = 3.0 mm, FOV = 220 mm^3 , flip angle = 90 degrees, matrix size 68 mm^3).

693 Stimulus isolators were used for electrical stimulation, connected to two of the available
694 intracranial electrode contacts. Stimulus waveforms were computer controlled and electrical
695 stimulation was induced via an optically isolated stimulation unit (AM Systems, Model 2200). The
696 control computer received and timed the electrical stimulation via a trigger from the scanner indicating
697 the start of each EPI volume acquisition. Stimulation was bipolar using adjacent contacts (inter-contact

698 distance was 5 or 10 mm) with stimulus intensity between 9-12 mA using constant-current electrical
699 stimulation. In-vivo impedance of the electrode contacts ranged from 1.5 k Ω to 5.5 k Ω at 100 Hz for
700 both depth (cylindrical) and surface (disk) electrode contacts. Electrical stimulus waveforms were
701 charge-balanced biphasic square waves (0.2 and 0.6 ms duration) with a 0.2 ms inter-stimulation pulse
702 period at 100 Hz repetition as illustrated in Fig. 2B. Stimulation was delivered in blocks of 7 or 9 pulses
703 repeated for 10 consecutive TRs followed by a 30 s no-stimulation baseline period. Each scanning run
704 contained 10 stimulation and 11 no-stimulation blocks. Overall, 42 esfMRI runs in 19 patients were
705 available for this study (Table 3). Stimulated sites in all of the individual brain are shown in Suppl. Fig.
706 S2.

707 *Stimulation site categorization procedure:* The stimulation sites in the human esfMRI (and the
708 electrical tractography, see below) were divided into two categories: 1) postero-medial HG sites
709 (medHG); and 2) antero-lateral HG sites which included some sites on the planum temporale
710 (latHG+PT). The number of esfMRI runs with Site 1 stimulation and Site 2 stimulation were 23 and
711 19, respectively.

712 The two sites were categorized according to the electrophysiological responses to click sounds
713 presented at different rates⁴². Click trains of various repetition rates (0.2 ms square pulse, 25, 50, 100,
714 150 and 200 Hz, 50 presentations for each condition) were presented to the subject through earphones
715 (ER4B Etymotic Research) binaurally fitted in custom-made ear-molds. The intracranial
716 neurophysiological signal was recorded with an ATLAS system (NeuraLynx) at a sampling rate of 2
717 kHz (0.1 - 500 Hz acquisition filter). Raw (wideband) averaged potentials were calculated. The
718 wideband averaged potentials were subsequently bandpass filtered centered at the click repetition rate
719 (Windowed FIR filter with tap length of 250 sampling points, passband width 8 Hz). If averaged evoked
720 potentials in response to click trains showed short-latency (<20 ms) waveform components and a
721 frequency-following response to the 50 Hz or higher click rate, that contact was categorized as Site 1
722 (medHG) since the typical distribution of these sites are typically in the posterior to medial part of
723 HG⁴². If the click-train induced averaged potentials showed clear wideband auditory evoked potentials
724 but failed to show a strong frequency-following response, that site was categorized as Site 2
725 (latHG+PT); these types of responses are more typical in higher-order auditory regions including the
726 antero-lateral parts of HG and planum temporale, see Suppl. Fig. S3.

727 *Electrode localization procedure:* The location of the implanted electrodes was determined by
728 comparing pre- and post- electrode implantation structural T1w MRI scans. To compensate for
729 potentially significant displacement of the electrode due to postoperative brain shift, post-implantation
730 volumes were non-linearly warped into pre-implantation MRI volume space using a thin-plate spline
731 (TPS) procedure with manually selected control points for the electrodes in three-dimensional
732 space^{26,63}. Between 50 and 100 control points throughout the brain are typically selected in this step.

733 Contact coordinates in the subject's original space were transformed to standard MNI space using
734 affine transformation and surface-based non-linear transformation implemented in FreeSurfer⁶².

735 For surface grid electrodes, the locations of all grid contacts were identified in a postoperative
736 CT scan. This was accomplished by manually identifying the location of a subset of contacts in the grid
737 on the basis of the characteristic hyper-intense radiological artifacts. Identified contacts included the
738 depth electrode contacts or the full 64- or 96-grid fitted to these locations by TPS warping, using a
739 negligibly small regularization parameter. Applying TPS allowed the non-linear deformation of the
740 grid to be approximated. Accuracy of fitting was evaluated by visually comparing fitted contact
741 locations with the contact artifacts in the CT and by verifying that inter-contact spacing fell within 0.2
742 mm of the expected 5-10 mm contact spacing.

743 After the initial grid locations were determined using CT, these were further corrected using a
744 pre-explantation MR scan. Because displacement of brain parenchyma related to electrode mass-effect
745 and post-operative swelling is often difficult to evaluate accurately on the CT scan, the results of CT-
746 based localization were compared against a T1w MR scan obtained shortly before explantation. When
747 significant discrepancy (greater than approximately 2 mm) was observed between CT-derived contact
748 locations and corresponding magnetic susceptibility artifacts in the MR scan, a rigid linear transform
749 was used to adjust grid positioning on the basis of clearly identifiable electrode-related artifacts in the
750 MRI scan. The corner contacts were used as control points in this transformation. Individual T1w
751 structural volumes were warped onto the CIT168 template brain (registered in MNI space,
752 <https://osf.io/hksa6/>) with ANTs symmetric normalization algorithm^{64,65} and the contact coordinates in
753 the original space warped onto the CIT168 template yielded the MNI coordinates used in this study.

754 *Human esfMRI data processing*

755 The anatomical and functional imaging data were pre-processed using the fMRIPrep pipeline⁶⁶.

756 *Anatomical image preprocessing:* The high resolution T1w image was corrected for intensity
757 non-uniformity using `N4BiasFieldCorrection`` and was used as a reference image throughout the
758 workflow. The T1w-reference was then skull-stripped using `antsBrainExtraction.sh`` (ANTs 2.2.0)
759 using the OASIS template as a target⁶⁴. Spatial normalization to the ICBM 152 Nonlinear
760 Asymmetrical template version (2009c) was performed through nonlinear registration with
761 `antsRegistration``, using brain-extracted versions of both the T1w and template brains. Brain tissue
762 segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed
763 on the brain-extracted T1w using FAST in FSL.

764 The subject's pre-electrode implantation structural MRI and the template brain (MNI-152-
765 NonLinear-2009c Asymmetrical brain) were processed with FreeSurfer 'recon-all' procedure to create

766 the surface mesh. For improved pial surface reconstruction, cortical parcellation was facilitated via the
767 T2w structural scans ($1.0 \times 1.0 \times 1.0 \text{ mm}^3$) obtained during the same imaging session whenever
768 possible. For mapping the BOLD and electrophysiological response onto the brain surface, the
769 FreeSurfer surface meshes were further processed with AFNI's @SUMA_Make_Spec_FS to create
770 standard icosahedron surfaces with various mesh densities.

771 *Functional data preprocessing:* For each of the esfMRI runs per subject, first a reference
772 volume and its skull-stripped version were generated using fMRIPrep. The T2*-weighted reference
773 was then co-registered to the T1w reference using FLIRT in FSL with the boundary-based registration
774 cost-function. Co-registration was configured with nine degrees of freedom to account for T2*w
775 distortions. Head-motion parameters with respect to the BOLD reference (transformation matrices, and
776 the six rotation and translation parameters) were estimated before any spatiotemporal filtering using
777 FLIRT in FSL. EPI scans were slice-time corrected using `3dTshift` from AFNI⁶⁴. The BOLD time-
778 series (including slice-timing correction when applied) were resampled onto their original, native space
779 by applying a single, composite transform to correct for head-motion and susceptibility distortions. The
780 BOLD time-series were then resampled to the MNI-152-NonLinear-2009cAsymmetrical standard
781 space. Several confounding time-series were calculated based on the preprocessed BOLD: framewise
782 displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for
783 each functional run, both using the implementation in Nipype @power_fd_dvars.

784 The three global signals, CSF, WM and whole-brain masks were extracted, though not used as
785 nuisance regressors. Additionally, a set of physiological regressors were extracted to allow for
786 component-based noise correction (CompCor). Principal components were estimated after high-pass
787 filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128 s cut-off). We also
788 defined two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). Six tCompCor
789 components were also calculated from the top 5% voxel variability within a mask covering subcortical
790 regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does
791 not include cortical gray matter. The head-motion estimates calculated in the motion correction step
792 were also added to the confounding variables file. All resampling was then performed using a single
793 interpolation step by composing all the pertinent transformations (i.e., head-motion transform matrices,
794 susceptibility distortion correction, when available, and co-registration information to anatomical and
795 template spaces). Gridded volumetric resampling was performed using `antsApplyTransforms`
796 (ANTs), configured with Lanczos interpolation to minimize smoothing effects (@lanczos).

797 The above fMRIPrep processing pipeline generally yielded good registration between
798 anatomical and functional imaging data, even with signal dropout due to the intracranial electrodes. If
799 misalignment was obvious in the visual inspection of EPI to T1w registration or as reported in
800 fMRIPrep, AFNI's coregistration program discarded parts of the functional data that had significant

801 signal dropout. Here, the functional data was clipped in the sagittal plane and this volume was used for
802 finding the coregistration parameters using AFNI's 'align_epi_anat.py' program with normalized
803 mutual information as a cost function. During this step, the part of the brain contaminated with the
804 intracranial electrodes was not used for coregistration.

805 *General Linear Modelling:* The preprocessed functional datasets were subjected to univariate
806 general linear model (GLM) analysis using AFNI's 3dDeconvolve routine. For the GLM analysis,
807 functional data is spatially smoothed with a Gaussian kernel (FWHM = 6.0 mm). Stimulus times were
808 convolved with a 1-parameter gamma function. Baseline detrending was applied with a Legendre
809 polynomial (5 degrees). Volumes (TRs) that showed large levels of motion (FD > 1.0 mm) and adjacent
810 TRs were discarded. The six tCompCor components extracted above and the FD time-series were
811 added to the baseline model as nuisance regressors.

812 A brain mask was created before spatial smoothing using intensity thresholded EPIs excluding
813 areas of signal dropout from the electrodes contributing to the fMRI analyses. The clinically determined
814 seizure onset zone (SOZ) was also excluded from the brain mask. If the SOZ affected any part of an
815 ROI, the result for that run and ROI was excluded from further analysis. We show an incidence map
816 in Suppl. Fig. S3 showing the data across the brain that were included.

817 For the higher-level group analysis we used AFNI's '3dREMLfit'⁶⁴. Datasets showing
818 evidence of a response anywhere within the brain mask (false-discovery rate corrected, $Z > 2$) were
819 submitted to higher-level analysis. Resulting statistical maps were subjected to multi-level mixed-
820 effects analysis using '3dMEMA'. The first- and higher-level GLMs were conducted in standard space
821 (MNI-152-NonLinear-2009c Asymmetrical).

822 *ROI analyses:* Regions of interest analyses of the vIPFC and MTL used anatomically defined
823 ROIs from standard anatomical atlases of the human brain. The vIPFC subregion analyses included as
824 ROIs areas 44 and 45, and the frontal operculum (FOP). For area 44 and 45, the parcellation is based
825 on the Jülich histological (cyto- and myelo-architectonic) atlas using a 25% probability threshold⁶⁷.
826 The human FOP ROI is based on prior work³⁶. The MTL subregion analyses used anatomical regions
827 corresponding to the following subregions: subiculum (Sub), dentate gyrus (DG) and the CA1, 3 and
828 4 subregions, using FreeSurfer's hippocampal subfield segmentation (v6.0)⁶⁸. For the entorhinal cortex
829 (EC) and parahippocampal gyrus (PHG), we used FreeSurfer's cortical segmentation (aparc+aseg files)
830 from the Desikan-Killiany atlas. No ROIs had overlapping voxels. Polar plots (Fig. 4) show the average
831 positive BOLD peak Z -value, with variability across the scanning runs in the humans.

832 *Statistical tests:* Mixed-design ANOVA models were used to examine ROI effects. The
833 statistical test used scanning run ROI peak Z -values as the dependent variable, with between-subject

834 factors of Human and Species (in the cross-species comparison: Human), within-subjects factors of
835 ROI (vIPFC or MTL ROIs), Hemisphere of activation (left or right) and Stimulation site (Site 1 or 2)
836 and Stimulated hemisphere (left or right) as covariates. We ensured that the data fit normality and
837 equality of variance assumptions of the models or transformed the data to achieve normal distribution
838 and report Greenhouse-Geisser corrected results, as required.

839 *Electrical stimulation tract-tracing (esT)*

840 Electrical stimulation neurophysiological tractography (esT) was conducted in human patients ($N = 13$,
841 Table 3) according to general methods described previously^{16,28}. Here, we used a single constant current
842 electrical stimulation pulse (biphasic charge-balanced square wave, duration = 0.2 ms/phase, 9 or 12
843 mA). The electrical pulses were delivered through stimulus isolators connected to the intracranial
844 electrodes in a bipolar configuration (always connected to adjacent contacts). The inter-stimulus
845 interval was set to 2 s and repeated 60 times. The intracranial EEG signal was recorded using the
846 ATLAS system (NeuraLynx) with a sampling frequency of 8 kHz. A disk contact in the subgaleal space
847 was used as a reference electrode for the recordings. Stimulated sites included HG, STG, vIPFC and
848 hippocampal contacts. Average potentials were calculated for each contact after rejecting trials that
849 contained large amplitude non-physiological signals after applying a high-pass filter (4th order
850 Chebyshev type 2, -6 dB roll-off at 3 Hz) and de-meaning the potentials. The trial exclusion criterion
851 for rejection was a signal greater than 3 times the interquartile range above the 75th percentile of the
852 amplitude distribution.

853 *Spline-Laplacian correction:* A Laplacian procedure was applied to reduce non-specific
854 neurophysiological or electrical stimulation effects evident as cross-correlated potentials common to
855 many electrodes from a common source or far-field potentials^{69,70}. This procedure spatially corrects the
856 average potentials after spline interpolation. The Laplacian operation is a spatial high-pass filter
857 (second derivative) and the resulting potentials are reference independent and de-emphasize far-field
858 effects or those from volume conduction. For depth electrode potentials, a 1-dimensional spline-
859 Laplacian was calculated using the inter-contact distance information to calculate a spherical spline-
860 laplacian⁷¹⁻⁷³. For potentials from surface grids and strip electrodes, we used the spherical coordinates
861 corresponding to each contact's MNI coordinates based on FreeSurfer's spherical surface mapping⁶².
862 The regularization parameter for spherical surface spline-Laplacian computation was determined by
863 generalized cross-validation⁷² and the spline-flexibility parameter was set to 3. The magnitude of esT
864 responses was quantified by comparing the root mean square (RMS) values of the Laplacian
865 transformed waveforms between the post-stimulation period (10 - 200 ms after stimulation onset) and
866 pre-stimulation period (-500 to -10 ms) prior to the electrical stimulation pulse.

867 *esT movie creation method:* To make the movies, continuous intracranial recordings were cut
868 into trials (-1 to 1 s around electrical stimulation). The following procedure that we used yields similar
869 results to one extracting high-frequency power (gamma and high-gamma band), but it avoids the need
870 for temporal band-pass filtering and frequency decomposition. Stimulation artifacts (-5 to 5 ms from
871 stimulation) were first replaced with the time-reversed waveform of the same length (10 ms) during an
872 artifact free pre-stimulus period (-10 to -5 ms). Then a peri-stimulus waveform of 12 ms duration (-6
873 to 6 ms) was smoothed twice with median filters (length 3 ms, followed by 5 ms). This process was
874 done for all single-trial waveforms. The trials were then re-referenced to the average of the surface grid
875 contacts, to reduce the volume conducted artifact waveforms common across the recording surface
876 grid. To extract induced responses (not phase-locked components), each channel's averaged potential
877 in the re-referenced signal was subtracted from the single trials in that channel⁷⁴. Induced response
878 magnitude was calculated by taking the trial average of the full-wave rectified signal.

879 The magnitude of stimulation-induced responses was calculated by taking the logarithm of the
880 ratio of the magnitude in the pre-stimulus period (0.5 to 0.3 s before stimulus onset) and post-stimulus
881 period. This yields the relative magnitude change with respect to the pre-stimulus period in dB. To
882 make the movies, averaged induced responses of the surface contacts were calculated for non-
883 overlapping temporal windows (length 5 ms), then color-coded and plotted onto the MNI template
884 brain for each experimental run and temporal window. We employed bootstrapping (1000 iterations)
885 of the mean activity within 5 ms temporal windows from the pre-stimulus period (55 to 7.5 ms before
886 stimulation onset) and thresholded the response at the lower and upper 2.5 % points. Responses not
887 exceeding this threshold were set to 0 and thus were not mapped to the brain surface. For patients who
888 had multiple esT sessions for either medHG or latHG sites, we averaged responses for each site
889 separately to create the movies (Suppl. Movies 1-6).

890 *Speech sound recording experiment and Granger Causality analyses.*

891 To examine the brain's effective connectivity under a natural sensory stimulation setting, we examined
892 neurophysiological responses to speech sounds. Many of the subjects were the same neurosurgical
893 patients ($N = 8$) who took part in the electrical tractography study (Table 3-4).

894 *Speech stimuli:* The experiment used a speech presentation paradigm previously described^{75,76}.
895 The speech sounds were common monosyllabic consonant-vowel-consonant English words, e.g., “cat”,
896 “dog”. All sounds were normalized to the same root mean square amplitude and edited to be 300 ms in
897 duration with 5 ms amplitude rise and fall times. Sounds were delivered binaurally via insert earphones
898 (ER4B, Etymotic Research, Elk Grove Village, IL, USA) integrated into custom-fit ear molds. Sound
899 delivery was controlled using Presentation software (Version 16.5 Neurobehavioral Systems).
900 Altogether 80 presentation trials were presented during two experimental blocks. The subjects were

901 asked to press a button when they heard a target word (only non-target word responses analyzed here)
902 using their index fingers ipsilateral to the hemisphere from which the recordings were made.

903 *Event-related spectral analysis of LFP:* Intracranial recording data were downsampled to 1000
904 Hz. The analysis of the neurophysiological responses focused on five frequency bands: theta (4-8 Hz),
905 alpha (8-14 Hz), beta (14-30 Hz), gamma (30-70 Hz) and high gamma (70-150 Hz) denoised using a
906 demodulated band transform-based algorithm⁷⁷. Event-related spectral perturbations were calculated
907 by log-transforming the power for each center frequency and normalizing it to the baseline (mean
908 power in the pre-stimulus reference interval of -200 ms to -100 ms before stimulus onset). The
909 waveforms were then averaged across trials.

910 *State-space Conditional Granger Causality (CGC) analysis:* CGC was used to investigate the
911 directional influence between brain regions during speech processing. The method is multivariate and
912 conditional, in the sense that simultaneous time series from a collection of electrodes are included in
913 order to account for both direct and indirect influences between contacts. Intracranial recordings were
914 downsampled to 100 Hz and sectioned into trials from -200 to 1000 ms relative to sound onset.
915 Intuitively, CGC tests if activity in a source area can be used to predict subsequent activity on a target
916 area. We estimated spectral CGC in 500 ms sliding windows in steps of 50ms to construct trial-
917 averaged time-frequency CGC representations between selected pairs of electrodes⁷⁸. Prior to time-
918 frequency CGC analysis, the mean at individual time points across trials was subtracted from the single
919 trial responses and then scaled by the standard deviation.

920 Several significant problems arise in applying standard Vector Auto-Regressive (VAR) based
921 CGC models to intracranial recordings, which are related to downsampling and nonstationarities⁷⁹.
922 Most of these recorded time-series contain a moving-average (MA) component that may not be
923 adequately modeled using VAR due to the intractably large model order necessary to handle the MA
924 component. It has been shown that spectral CGC estimates can be obtained with high computational
925 reliability using estimation approaches based on single model-fits. The state-space model addresses a
926 number of theoretical and practical problems related to spectral CGC estimation, e.g., see⁸⁰. Spectral
927 CGC was directly computed using Geweke's formulations based on the estimated state-space
928 innovations covariance matrix^{81,82}, cross-spectral densities and transfer functions^{83,84}.

929 State-space models use state variables to describe a system by a set of first-order differential
930 or difference equations, rather than by one or more VAR n th-order differential or difference equations.
931 State variables can be reconstructed from the measured recordings but are not themselves measured
932 during an experiment. For modeling directional influence in the brain, it is possible to directly express
933 the interactions between different regional signal time series as a state-space model defined by:

934
$$\vec{x}(t + 1) = A \vec{x}(t) + K \vec{\epsilon}(t) \text{ state transition equation} \quad (1)$$

935
$$\vec{y}(t) = C \vec{x}(t) + \vec{\epsilon}(t) \quad \text{observation equation} \quad (2)$$

936 where $\vec{x}(t)$ is an unobserved (latent) m -dimensional state vector, and $\vec{\epsilon}(t)$ is the vector of the
937 innovations or prediction errors. The observed vector of time-series $\vec{y}(t)$ corresponds to the recordings
938 from regions in the targeted network. The state transition matrix A , observation matrix C and the steady-
939 state Kalman gain matrix K are estimated using a subspace method⁸⁵. Subspace methods are optimal
940 for state-space model parameter estimation, especially for high-order multivariable systems⁸⁶. The
941 order of the state-space model was 25, which corresponds to the vector size of $\vec{x}(t)$.

942 To statistically evaluate the reliability of the connectivity results we used a phase-
943 randomization surrogate data technique to construct a null distribution^{87,88}. This method consists of
944 randomly shuffling the Fourier phases of each of the intracranial recordings, which generates
945 uncorrelated data with preserved autocorrelation properties. For each original data set, 500 surrogates
946 were generated, and CGC values that exceeded the 95% threshold were unmasked in the time-
947 frequency representations.

948 **METHODS REFERENCES**

- 949 51. Tehovnik, E.J., *et al.* Direct and indirect activation of cortical neurons by electrical
950 microstimulation, *J Neurophysiol* **96**, 512-521 (2006).
- 951 52. Moeller, S., *et al.* Patches with links: a unified system for processing faces in the macaque temporal
952 lobe, *Science* **320**, 1355-1359 (2008).
- 953 53. Ekstrom, L.B., *et al.* Bottom-up dependent gating of frontal signals in early visual cortex, *Science*
954 **321**, 414-417 (2008).
- 955 54. Rinne, T., *et al.* Functional imaging of audio–visual selective attention in monkeys and humans:
956 How do lapses in monkey performance affect cross-species correspondences?, *Cerebral Cortex* **27**,
957 3471-3484 (2017).
- 958 55. Hall, D.A., *et al.* "Sparse" temporal sampling in auditory fMRI, *Hum Brain Mapp* **7**, 213-223
959 (1999).
- 960 56. Petkov, C.I., *et al.* Optimizing the imaging of the monkey auditory cortex: sparse vs. continuous
961 fMRI, *Magn Reson Imaging* **27**, 1065-1073 (2009).
- 962 57. Baumann, S., *et al.* Characterisation of the BOLD response time course at different levels of the
963 auditory pathway in non-human primates, *Neuroimage* **50**, 1099-1108 (2010).
- 964 58. Smith, S.M., *et al.* Advances in functional and structural MR image analysis and implementation as
965 FSL, *Neuroimage* **23 Suppl 1**, S208-219 (2004).
- 966 59. Woolrich, M.W., *et al.* Bayesian analysis of neuroimaging data in FSL, *Neuroimage* **45**, S173-186
967 (2009).
- 968 60. McLaren, D.G., *et al.* A population-average MRI-based atlas collection of the rhesus macaque,
969 *Neuroimage* **45**, 52-59 (2009).
- 970 61. Saleem, K.S. & Logothetis, N.K. *A combined MRI and histology atlas of the rhesus monkey brain*
971 *in stereotaxic coordinates* (Academic Press, 2012).
- 972 62. Fischl, B. FreeSurfer, *Neuroimage* **62**, 774-781 (2012).
- 973 63. Oya, H., *et al.* Neural phase locking predicts BOLD response in human auditory cortex,
974 *Neuroimage* **169**, 286-301 (2018).
- 975 64. Cox, R.W. AFNI: software for analysis and visualization of functional magnetic resonance
976 neuroimages, *Computers and Biomedical research* **29**, 162-173 (1996).
- 977 65. Tyszka, J.M. & Pauli, W.M. In vivo delineation of subdivisions of the human amygdaloid complex
978 in a high-resolution group template, *Human brain mapping* **37**, 3979-3998 (2016).
- 979 66. Esteban, O., *et al.* fMRIPrep: a robust preprocessing pipeline for functional MRI, *Nature methods*
980 **16**, 111 (2019).
- 981 67. Eickhoff, S.B., *et al.* A new SPM toolbox for combining probabilistic cytoarchitectonic maps and
982 functional imaging data, *Neuroimage* **25**, 1325-1335 (2005).
- 983 68. Iglesias, J.E. & Sabuncu, M.R. Multi-atlas segmentation of biomedical images: a survey, *Medical*
984 *image analysis* **24**, 205-219 (2015).

- 985 69. Nunez, P.L. & Pilgreen, K.L. The spline-Laplacian in clinical neurophysiology: a method to
986 improve EEG spatial resolution, *Journal of clinical neurophysiology: official publication of the*
987 *American Electroencephalographic Society* **8**, 397-413 (1991).
- 988 70. Nourski, K.V., *et al.* Coding of repetitive transients by auditory cortex on posterolateral superior
989 temporal gyrus in humans: an intracranial electrophysiology study, *Journal of Neurophysiology*
990 **109**, 1283-1295 (2012).
- 991 71. Kayser, J. & Tenke, C.E. On the benefits of using surface Laplacian (current source density)
992 methodology in electrophysiology, *International journal of psychophysiology: official journal of*
993 *the International Organization of Psychophysiology* **97**, 171 (2015).
- 994 72. Carvalhaes, C. & de Barros, J.A. The surface Laplacian technique in EEG: Theory and methods,
995 *International Journal of Psychophysiology* **97**, 174-188 (2015).
- 996 73. Perrin, F., *et al.* Spherical splines for scalp potential and current density mapping,
997 *Electroencephalography and Clinical Neurophysiology* **72**, 184-187 (1989).
- 998 74. Sinai, A., *et al.* Intracranial mapping of auditory perception: event-related responses and
999 electrocortical stimulation, *Clinical Neurophysiology* **120**, 140-149 (2009).
- 1000 75. Steinschneider, M., *et al.* Differential activation of human core, non-core and auditory-related
1001 cortex during speech categorization tasks as revealed by intracranial recordings, *Frontiers in*
1002 *neuroscience* **8**, 240 (2014).
- 1003 76. Nourski, K.V., *et al.* Intracranial electrophysiology of auditory selective attention associated with
1004 speech classification tasks, *Frontiers in human neuroscience* **10**, 691 (2017).
- 1005 77. Kovach, C.K. & Gander, P.E. The demodulated band transform, *Journal of neuroscience methods*
1006 **261**, 135-154 (2016).
- 1007 78. Jenison, R.L. Directional influence between the human amygdala and orbitofrontal cortex at the
1008 time of decision-making, *PloS one* **9**, e109689 (2014).
- 1009 79. Seth, A.K., *et al.* Granger causality analysis in neuroscience and neuroimaging, *Journal Of*
1010 *Neuroscience* **35**, 3293-3297 (2015).
- 1011 80. Barnett, L., *et al.* Solved problems for Granger causality in neuroscience: A response to Stokes and
1012 Purdon, *Neuroimage* **178**, 744-748 (2018).
- 1013 81. Geweke, J.F. Measures of conditional linear dependence and feedback between time series, *Journal*
1014 *of the American Statistical Association* **79**, 907-915 (1984).
- 1015 82. Geweke, J. Measurement of linear dependence and feedback between multiple time series, *Journal*
1016 *of the American statistical association* **77**, 304-313 (1982).
- 1017 83. Barnett, L. & Seth, A.K. Granger causality for state-space models, *Physical Review E* **91**, 040101
1018 (2015).
- 1019 84. Solo, V. State-space analysis of Granger-Geweke causality measures with application to fMRI,
1020 *Neural computation* **28**, 914-949 (2016).
- 1021 85. Van Overschee, P. & De Moor, B. Subspace algorithms for the stochastic identification problem,
1022 *Automatica* **29**, 649-660 (1993).

- 1023 86. Becker, C.O., *et al.* Large-scale dynamic modeling of task-fMRI signals via subspace system
1024 identification, *Journal of neural engineering* **15**, 066016 (2018).
- 1025 87. Lancaster, G., *et al.* Surrogate data for hypothesis testing of physical systems, *Physics Reports* **748**,
1026 1-60 (2018).
- 1027 88. Prichard, D. & Theiler, J. Generating surrogate data for time series with several simultaneously
1028 measured variables, *Physical review letters* **73**, 951 (1994).
1029

EXTENDED DATA

Table 1. Macaque esfMRI results as significant activation in the listed anatomical regions. Shown are the macaque brain regions in reference to the macaque atlas⁶¹ (x,y,z stereotactic coordinates), the peak voxel Z-value in the region and the number of voxels above $Z > 2.8$ corrected significance threshold. Right (rt.) and left (lt.) hemispheres are identified.

Site 1 esfMRI macaque group results

size (voxels)	peak z-score	x y z	
<i>Temporal-Occipital Cortex</i>			
1350	3.89	6 -13 17	rt. Primary/Secondary Visual Cortex (e.g., V2, V1)
1296	4.19	-4 -6 21	lt. Primary/Secondary Visual Cortex (e.g., V2, V1)
268	3.93	-24 6 20	lt. Superior Temporal Sulcus STS, dorsal (TAa)
185	3.70	-24 3 20	lt. Inferior Temporal Cortex (TEO)
118	4.10	-24 9 18	lt. Koniocortex (Primary Auditory)
86	3.29	22 9 23	rt. Koniocortex (Primary Auditory)
86	3.30	-14 -11 29	lt. Higher Visual Cortex (V3a)
77	3.30	23 13 17	rt. Auditory Core, field R
61	3.38	15 2 7	rt. Higher Visual Cortex (V4v)
55	3.74	10 0 15	rt. Medial Occipital area (V2)
46	3.19	-21 -3 19	lt. Fundus of Superior Temporal Sulcus (FST)
44	3.48	27 11 19	rt. Auditory Non-primary Cortex
39	3.43	-12 3 7	lt. Higher Visual Cortex (V4v)
36	3.60	-22 10 16	lt. Auditory Core, field R
33	3.09	-15 -11 27	lt. Higher Visual Area, dorsal (V3d)
31	3.36	-27 12 13	lt. Rostral Auditory Para-Belt (RPB)
21	3.08	-18 7 13	lt. STS fundus (IPa)
21	2.98	3 -12 31	rt. Higher Visual Cortex (V6av)
18	3.37	-5 -11 27	lt. Higher Visual Area (V6)
16	3.01	1 -12 25	rt. Higher Visual Area (V6)
11	3.15	17 17 6	rt. STS fundus (IPa)
<i>Frontal cortex</i>			
699	4.02	12 23 33	rt. Frontal Eye Fields (area 8av)
369	4.08	1 28 32	rt. Supplementary Motor Area (SMA)
349	3.55	-9 -4 12	lt. Area 10
298	4.00	5 32 23	rt. Area 11

291	3.92	21 22 10	rt. Frontal-Operculum
270	3.77	-6 31 32	lt. Frontal Eye Fields (area 8av)
252	3.63	11 1 10	rt. Area 10
238	3.37	-21 20 25	lt. Primary Motor Cortex (4/F1)
214	3.97	2 33 12	rt. Medial Prefrontal Cortex (10m)
167	3.74	8 33 26	rt. Dorso-Lateral Prefrontal Cortex (8b)
150	3.65	-3 34 13	lt. Medial Prefrontal Cortex (10m)
145	3.70	13 16 30	rt. Primary Motor Cortex (4/F1)
129	3.59	-19 29 23	lt. Frontal Eye Fields (area 8av)
119	3.57	2 38 30	rt. Dorso-Lateral Prefrontal Cortex (8bd)
114	3.39	-6 32 31	lt. Premotor Area, dorsal 6dr
112	3.80	4 34 12	rt. Orbito-frontal (13l)
108	3.37	-20 16 16	lt. Frontal-Operculum
85	3.59	2 37 31	rt. Premotor Area, dorsal 6dr
63	3.49	-1 29 32	lt. Supplementary Motor Area (SMA)
57	3.21	-4 37 15	lt. Orbito-prefrontal (13m)
48	3.49	24 27 16	rt. Premotor Area, ventral (6Va)
44	3.26	20 20 8	rt. Area 46
31	3.44	13 33 15	rt. Orbito-prefrontal (13m)
27	3.19	-15 26 25	lt. Premotor Area, ventral (6Va)
27	3.32	-19 29 22	lt. Ventro-Lateral Prefrontal Cortex (45b)
26	3.23	-14 26 24	lt. Dorso-Lateral Prefrontal Cortex (8b)
16	3.12	-10 33 12	lt. Orbito-frontal (13l)
15	3.05	15 25 7	rt. Agranular Insular, lateral (Ial)
15	3.34	13 31 18	rt. Area 44
10	2.98	14 29 19	rt. Area 45
7	3.13	-19 29 22	lt. Area 45

size (voxels)	peak z-score	x y z	<i>Medial Temporal Lobe</i>
129	3.49	15 -1 13	rt. Hippocampus (CA1)
118	3.58	-9 6 7	lt. Parahippocampal Cortex (TFO)
90	3.50	-10 6 8	lt. Parahippocampal Cortex (TH)
73	3.39	9 6 8	rt. Parahippocampal Cortex (TFO)
59	3.45	16 1 13	rt. Hippocampus (CA3)
52	3.44	12 2 12	rt. Subiculum
44	3.52	10 7 6	rt. Parahippocampal Cortex (TH)
40	3.16	16 8 7	rt. Dentate Gyrus
38	3.60	11 3 12	rt. Prosubiculum
36	3.54	-16 8 6	lt. Dentate Gyrus

35	3.68	-17 9 6	lt. Hippocampus (CA3)
34	3.16	15 8 7	rt. Hippocampus (CA4)
25	3.37	-13 3 8	lt. Hippocampus (CA1)
25	3.23	-12 5 8	lt. Subiculum
22	3.56	16 0 14	rt. Hippocampus (CA2)
21	3.38	-12 3 9	lt. Prosubiculum
14	3.23	-15 9 6	lt. Hippocampus (CA4)
10	3.42	-17 9 6	lt. Hippocampus (CA2)
10	3.14	-9 7 6	lt. Parahippocampal Cortex (TF)

size (voxels)	peak z-score	x y z	<i>Cingulate Cortex</i>
460	4.94	4 19 28	rt. Anterior Cingulate Cortex (24c)
145	3.62	3 14 27	rt. Posterior Cingulate Cortex (23c)
94	3.48	1 2 26	rt. Posterior Cingulate Cortex (23b)
90	3.82	1 34 21	rt. Anterior Cingulate Cortex (24a)
83	4.25	2 18 27	rt. Anterior Cingulate Cortex (24b)
38	3.64	-1 35 20	lt. Anterior Cingulate Cortex (24a)
29	3.12	-6 24 30	lt. Anterior Cingulate Cortex (24c)
11	2.97	-1 3 26	lt. Posterior Cingulate Cortex (23b)
11	3.02	-3 -1 26	lt. Posterior Cingulate Cortex (31)
10	3.20	-2 -6 22	lt. Posterior Cingulate Cortex (v23b)

size (voxels)	peak z-score	x y z	<i>Parietal Cortex</i>
384	3.70	-21 15 19	lt. Somatosensory Area secondary (SII)
315	3.55	22 10 23	rt. Somatosensory Area secondary (SII)
189	3.29	4 -8 27	rt. Medial Parietal Area (7m/PGm)
143	3.75	-6 -10 28	lt. Medial Intraparietal Area (MIP)
124	3.17	16 4 35	rt. Intraparietal Area (LIPd)
56	3.09	26 14 17	rt. Somatosensory Cortex (areas 1-2)
14	3.00	7 -11 28	rt. Medial Intraparietal Area (MIP)
10	3.05	-11 -7 33	lt. Inferior Parietal Lobule, posterior (7a/Opt/PG)

size (voxels)	peak z-score	x y z	<i>Other Areas</i>
1148	4.11	9 16 22	rt. Striatum
843	4.05	-2 25 14	lt. Striatum
570	4.03	21 21 10	rt. Thalamus
286	3.95	18 13 14	rt. Claustrum
229	3.69	-21 15 17	lt. Granular Insular Cortex
227	3.67	5 7 15	rt. Superior Colliculus

208	3.40	19 13 16	rt. Granular Insular Cortex
181	3.73	4 5 11	rt. Inferior Colliculus
137	3.93	8 4 18	rt. Medial Pulvinar
67	3.40	-4 5 9	lt. Inferior Colliculus
42	3.44	10 4 19	rt. Lateral Pulvinar
29	3.73	15 14 12	rt. Globus Pallidus (GPe/Gpi)
28	3.03	-4 5 10	lt. Superior Colliculus
27	3.28	11 5 12	rt. Inferior Pulvinar
21	3.05	-17 13 12	lt. Claustrum
13	3.04	-8 3 14	lt. Lateral Pulvinar
11	3.21	8 16 3	rt. Nucleus Accumbens
10	3.15	4 29 9	rt. Anterior Olfactory Nucleus (AONd/m)
10	2.93	7 20 6	rt. Nucleus of Lateral Olfactory Tract (NLOT)

Site 2 esfMRI macaque group results

size (voxels)	peak z-score	x y z	<i>Temporal-Occipital Cortex</i>
652	4.16	-14 -5 18	lt. Secondary Visual Cortex (V2)
155	3.96	21 10 19	rt. Koniocortex (Primary Auditory)
154	3.89	12 -1 13	rt. Secondary Visual Cortex (V2)
132	4.32	27 6 22	rt. Superior Temporal Sulcus STS, dorsal (TAa)
66	3.86	27 8 23	rt. Auditory Non-primary Cortex
57	3.30	-7 0 17	lt. Medial Occipital area (V2)
56	3.58	-18 15 3	lt. STS fundus (IPa)
30	3.10	18 11 7	rt. STS fundus (IPa)
29	3.65	22 11 17	rt. Auditory Core, field R
20	3.36	-24 9 14	lt. Superior Temporal Sulcus STS, dorsal (TAa)
14	3.51	-22 9 17	lt. Koniocortex (Primary Auditory)
13	3.53	-14 -5 11	lt. Higher Visual Cortex (V4v)
13	3.36	23 -3 29	rt. Higher Visual Cortex (V4t)
size (voxels)	peak z-score	x y z	<i>Frontal cortex</i>
523	4.30	23 2 28	rt. Area 11
263	3.98	-14 -7 11	lt. Area 10
114	3.68	-17 19 25	lt. Primary Motor Cortex (4/F1)
29	3.18	-11 12 32	rt. Area 46
15	3.20	-18 15 16	lt. Frontal_Operculum
7	3.10	21 15 16	rt. Frontal_Operculum

3 2.99 19 29 16 rt. Area 44

size (voxels)	peak z-score	x y z	<i>Medial Temporal Lobe</i>
88	3.51	-7 3 11	lt. Parahippocampal Cortex (TFO)
38	3.75	-14 -1 15	rt. Hippocampus (CA3)
26	3.48	8 3 12	rt. Parahippocampal Cortex (TFO)
14	3.34	13 -1 14	rt. Subiculum
13	3.54	-10 3 12	lt. Prosubiculum
11	3.24	-14 -2 13	lt. Hippocampus (CA1)

size (voxels)	peak z-score	x y z	<i>Parietal Cortex</i>
74	3.55	-18 13 22	lt. Somatosensory Area secondary (SII)
73	3.19	23 12 18	rt. Somatosensory Area secondary (SII)
42	3.40	22 -3 30	rt. Inferior Parietal Lobule, posterior (7a/Opt/PG)

size (voxels)	peak z-score	x y z	<i>Other Areas</i>
408	3.96	4 29 18	rt. Striatum
304	3.97	20 12 17	rt. Granular Insular Cortex
295	4.38	-2 5 11	lt. Inferior Colliculus
226	3.87	-2 26 18	lt. Striatum
199	3.73	-4 5 10	lt. Superior Colliculus
197	4.64	27 6 23	rt. Thalamus
157	3.51	-17 11 19	lt. Granular Insular Cortex
58	3.31	-9 3 14	lt. Lateral Pulvinar
45	3.70	-6 7 12	lt. Medial Geniculate, magnocellular
44	3.20	-18 15 16	lt. Claustrum
28	3.36	14 25 11	rt. Claustrum
26	3.31	-7 7 12	lt. Medial Geniculate, ventral
16	3.47	-10 4 13	lt. Inferior Pulvinar
12	3.09	7 3 12	rt. Inferior Colliculus
10	3.04	-13 15 16	lt. Globus Pallidus (GPe/Gpi)

Table 2. Human esfMRI results, as significant activation in the listed anatomical regions. Shown are the human brain regions in reference to the human atlas⁶⁷ in MNI x,y,z coordinates, the peak voxel value in the region and the number of voxels above the corrected significance threshold (cluster-wise alpha < 0.05 with primary $p < 0.005$).

Site 1 (medHG) esfMRI human group results:

size (voxel)	peak T	MNI coordinates (mm)			Brain structure
		x	y	z	
831	7.38	54.5	0.5	-28.5	lt. middle temporal gyrus
327	7.10	66.5	56.5	13.5	lt. superior temporal gyrus
291	5.77	-41.5	4.5	-12.5	rt. insula
241	5.62	-65.5	26.5	27.5	rt. supramarginal gyrus
166	4.97	42.5	-29.5	1.5	lt. inferior frontal gyrus
149	6.54	2.5	26.5	-4.5	lt. thalamus
123	4.57	-32.5	-18.5	-2.5	rt. putamen
84	5.26	32.5	-47.5	21.5	lt. middle frontal gyrus

Site 2 (latHG + PT) esfMRI human group results:

size (voxel)	peak T	MNI coordinates (mm)			Brain structure
		x	y	z	
696	7.29	-23.5	-5.5	-26.5	rt. parahippocampal gyrus
600	7.77	46.5	2.5	-30.5	lt. inferior temporal gyrus
377	7.19	-63.5	10.5	37.5	rt. postcentral gyrus
173	7.34	58.5	-11.5	-6.5	lt. superior temporal gyrus
140	7.58	-31.5	64.5	65.5	rt. superior parietal lobule
104	4.68	-15.5	21.5	-17.5	lt. superior orbital gyrus

Site 1 versus Site 2 esfMRI human group results:

size (voxel)	peak T	MNI coordinates (mm)			Brain structure
		x	y	z	
430	7.21	66.5	56.5	13.5	lt. middle and superior temporal gyrus
196	7.17	-63.5	28.5	25.5	rt. supramarginal gyrus
106	5.39	48.5	-15.5	1.5	lt. inferior frontal gyrus

Site 2 versus Site 1 esfMRI human group results:

size (voxel)	peak T	MNI coordinates (mm)			Brain structure
		x	y	z	

971	5.65	-35.5	-19.5	-28.5	rt. ATL (incl. entorhinal cortex, parahippocampal gyrus, temporal pole & amygdala)
283	5.60	22.5	-5.5	-28.5	lt. ATL (incl. entorhinal cortex & amygdala)
262	5.71	-63.5	6.5	21.5	lt. precentral gyrus

Table 3. Human patient demographics

Patient ID	Age	Sex	Handedness	Language dominance (Wada test)	esfMRI	esT	Speech
292	50	F	L	L	Yes (Y)		
302	47	F	R	**	Y		
307	30	M	R	L	Y		
314	30	F	R	L	Y		
316	31	F	R	**	Y		
320	50	F	R	**	Y		
330	43	M	L	**	Y		
331	35	M	R	**	Y		
334	39	M	L	L	Y		
335	31	M	R	L	Y		
339	45	M	R	**	Y		
352	31	M	Mixed	**	Y		
357	36	M	R	L	Y		Y
369	30	M	R	L	Y	Y	Y
372	34	M	R	L	Y	Y	Y
376	48	F	R	L	Y	Y	Y
384	37	M	R	L		Y	
394	23	M	L	L		Y	Y
395	13	M	R	**	Y		
399	22	F	R	L	Y	Y	Y
400	59	M	L	L	Y		
403	56	F	R	L	Y		
405	19	M	R	L	Y	Y	Y
413	22	M	L	R	Y	Y	
418	25	F	R	L		Y	
423	49	M	R	L		Y	Y
427	17	M	Mixed	**		Y	
429	32	F	R	**		Y	Y
457	18	M	R	**			Y
460	52	M	R	L (fMRI)		Y	

** (not done)

Table 4. Human patient clinical observations and surgical resection sites

Patient ID	Clinical MRI finding	Surgery	Seizure onset zone
292	Left frontal focal encephalomalacia	left ATL+ left frontal seizure focus resection	Left mesial temporal lobe + left frontal lobe
302	Left MTS	Left ATL	Left mesial temporal lobe
307	Left insular cavernoma	Cavernoma resection	Left insula
314	Left occipital cortical dysplasia	No resection	Bilateral mesial temporal lobe
316	Right MTS	Right ATL	Right mesial temporal lobe
320	Right MTS	Right ATL	Right hippocampus
330	Right occipital cortical dysplasia	Right occipital lesionectomy	Left occipital lobe
331	Right MTS	No resection	Left mesial temporal lobe
334	Right temporal ganglioglioma	Right ATL	Right temporal pole, ventral surface of temporal lobe
335	Left MTS	No resection	Bilateral medial temporal lobe
339	Normal	No resection	Not determined
352	Left frontal cystic lesion	Left frontal regionectomy	Left frontal cystic mass
357	Normal	Left ATL	Left mesial temporal lobe
369	Right basal ganglia venous anomaly	Right ATL	Right mesial temporal lobe
372	Normal	Left ATL	Left temporal pole
376	Normal	Right ATL	Right mesial temporal lobe
384	Normal	Right ATL, Right frontal pole resection	Right mesial temporal lobe, Right frontal pole
394	Right temporal lobe cavernoma	Right ATL	Right amygdala
395	Left frontal lobe cavernoma	Left mesial frontal lobe resection including left frontal cavernoma	Left frontal lobe
399	Normal	Right ATL+ right ventral frontal seizure focus resection	Right mesial temporal lobe + possible right basal frontal lobe
400	Left MTS	Left ATL	Left mesial temporal lobe
403	Normal	Left ATL	Left mesial temporal lobe
405	Left frontal encephalomalacia	Left frontal regionectomy	Left frontal encephalomalacia
413	Normal	Right ATL	Right mesial temporal lobe
418	Right inferior temporal dysplasia	Right ATL	Right mesial temporal lobe
423	Normal	Left ATL	Left mesial temporal lobe
427	Right frontal encephalomalacia	Right frontal lobectomy	Right frontal lobe
429	Normal	Left ATL	Left mesial temporal lobe
457	Normal	Left ATL	Left mesial temporal lobe
460	Normal	Left ATL	Left mesial temporal lobe

MTS: Mesial temporal sclerosis

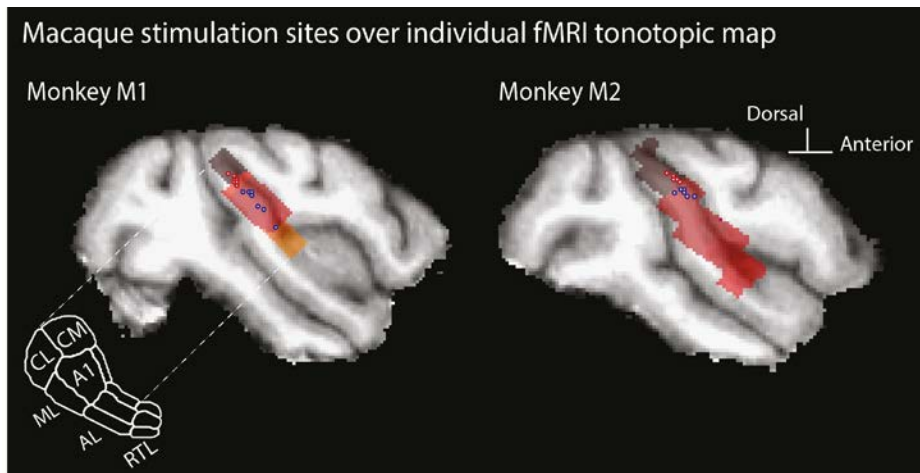
ATL: Anterior temporal lobectomy

SUPPLEMENTARY MATERIALS

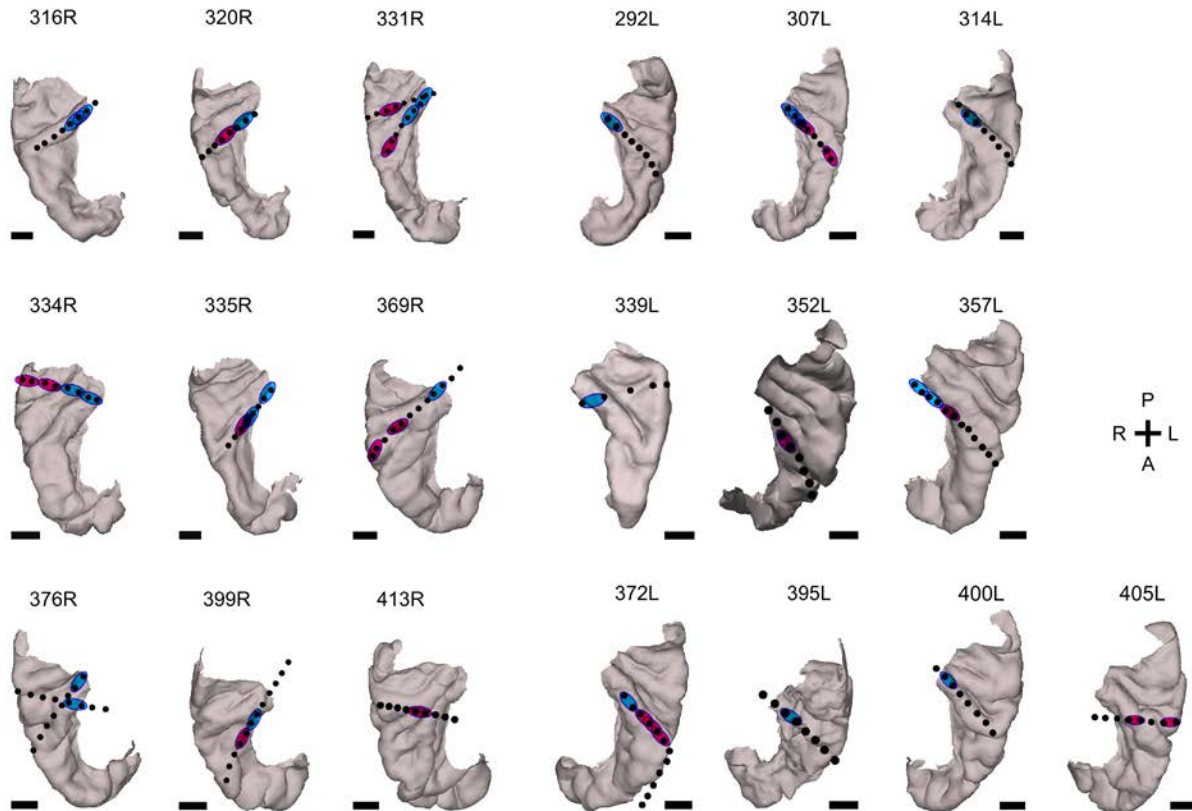
Supplementary Figures list

- S1. Macaque stimulation sites overlaid on individual animal fMRI tonotopic maps
- S2. Individual human depth electrode contact locations for esfMRI
- S3. Click frequency following response used to identify Site 1 (medHG) sites in humans
- S4. Human electrode contact locations affecting fMRI signal: preserved fMRI signal map
- S5. Individual human es-fMRI activation results involving vIPFC
- S6. Individual human es-fMRI results involving MTL
- S7. Impact of stimulation sites on the MTL and vIPFC contact sites
- S8. Impact of medHG stimulation on STG evoked responses in subject 369

M1-6: Movies 1-6

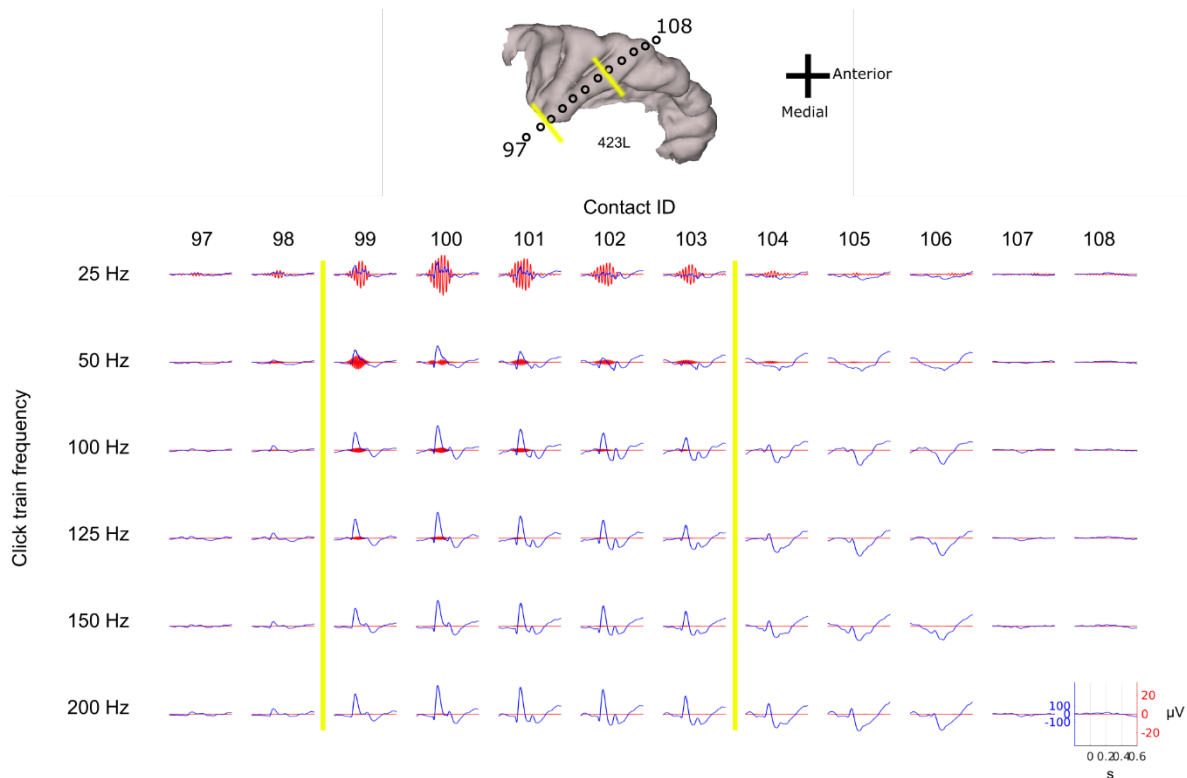


Supplementary Figure S1. Macaque stimulation sites overlaid on individual animal fMRI tonotopic maps. Shows the stimulation sites (Site 1 blue circles; Site 2 red circles) in the two macaques with an overlaid individual animal fMRI tonotopical map (gray to orange shading).

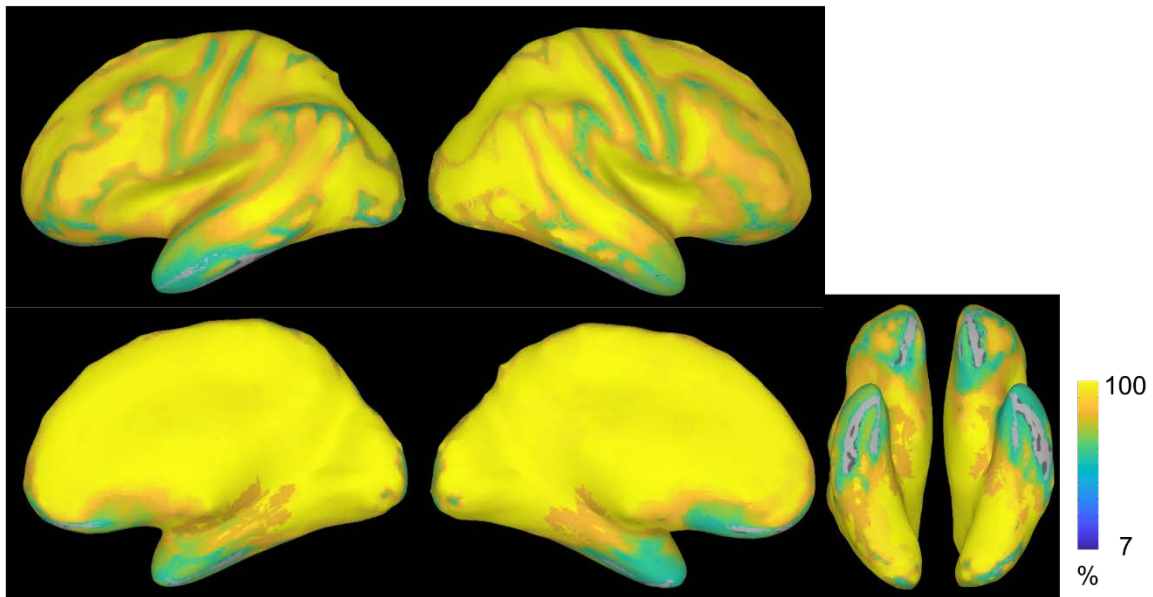


Supplementary Figure S2. Individual human depth electrode contact locations for esfMRI.

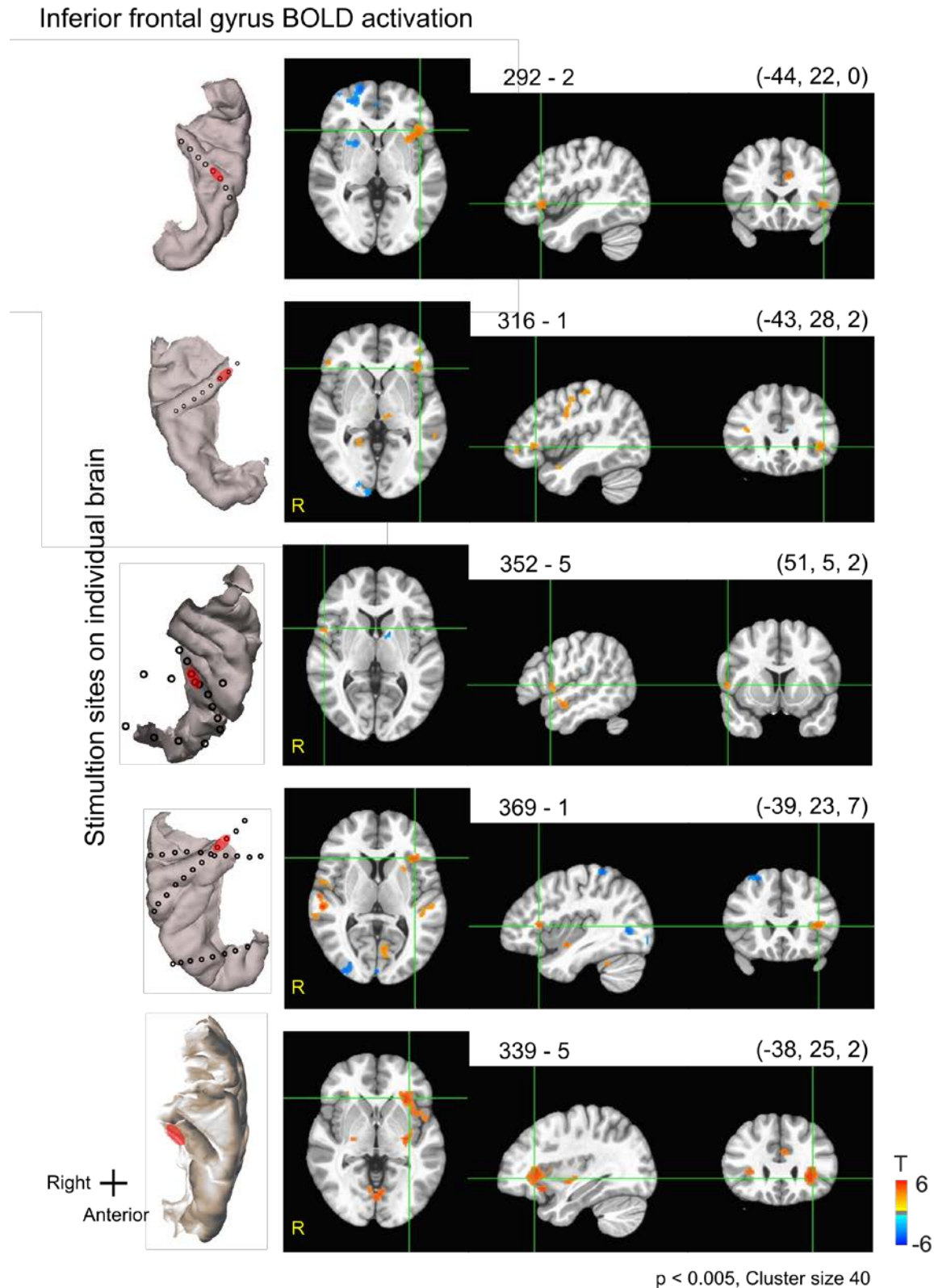
Shown are views looking down on the superior temporal plane. Black circles identify the clinically placed contacts and the blue/red regions the two contacts used for bipolar stimulation, respectively in the medHG or latHG+PT sites, shown on each individual's anatomy. Whenever more than two contacts are shown in red is an indication of other pairs of adjacent contacts that were stimulated in a separate testing run. Scale bars 10 mm.



Supplementary Figure S3. Click frequency following response used to identify Site 1 (medHG) sites in humans. Shown is how the click evoked neurophysiological response was used to identify medial HG contacts by their click-frequency following response. In this example, traces in blue show the auditory evoked potentials. Traces in red are the high-pass filtered frequency following response. Contacts between the two yellow lines show a strong frequency following response to 25-100Hz and were thus assigned to medHG. Contacts on the right are assigned to Site 2 (latHG+PT) because they respond to the sounds but do not show a clear high frequency following response. The non-responsive contacts at the flanks of these were not used.

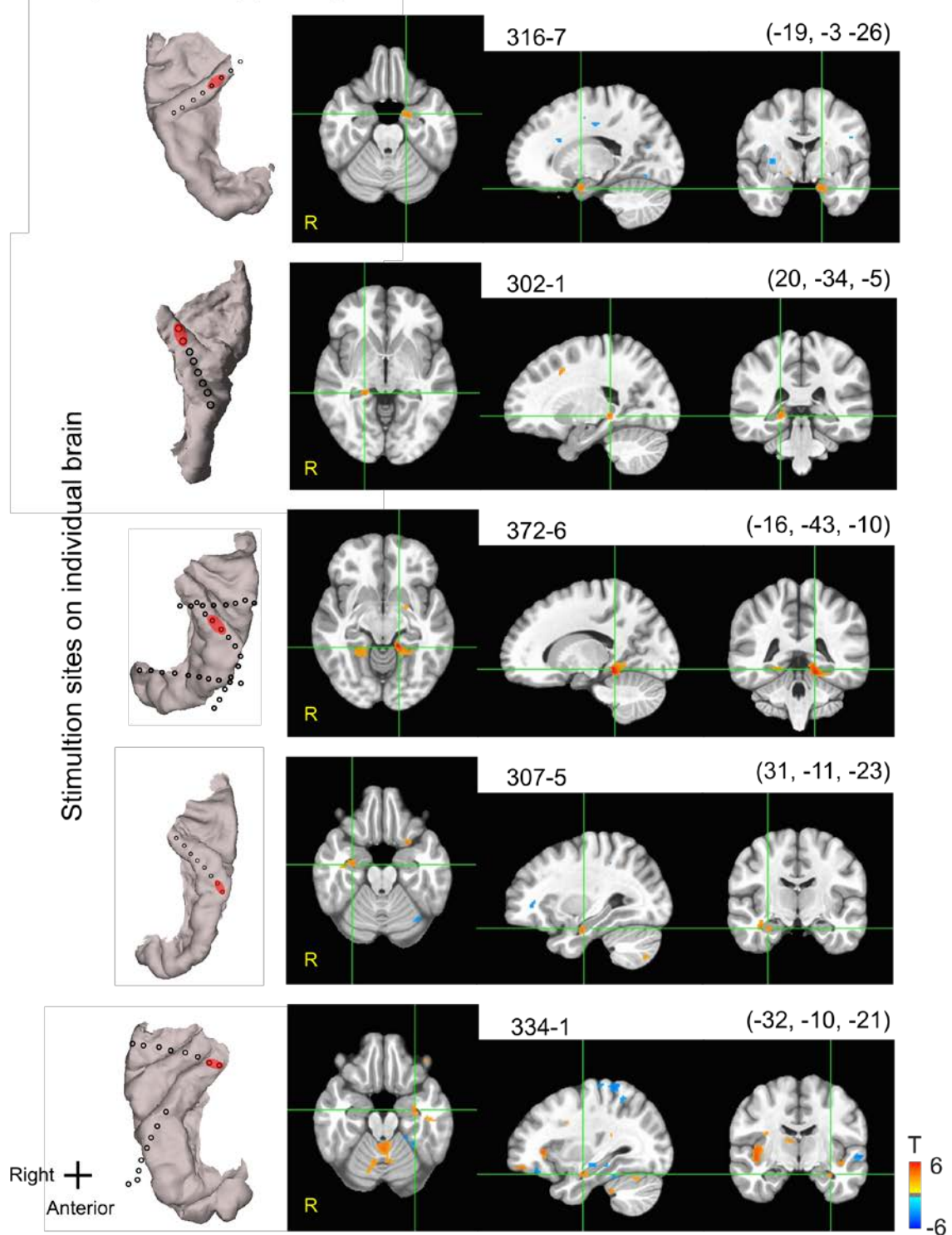


Supplementary Figure S4. Human electrode contact locations affecting fMRI signal: preserved fMRI signal map. Regions where the fMRI signal was contaminated by the electrodes were masked and excluded from analysis. We also excluded regions that were resected, typically in the anterior medial temporal lobe (Table 4). Here is show an incidence map identifying the regions most affected by signal drop out (blue and green colored regions), which includes areas where the fMRI signal is also affected by sinuses (orbitofrontal cortex). Orange to yellow color shows the percentage of human esfMRI runs that were available for analysis (not masked by intracranial electrodes, weak signal or outside of the epileptic foci regions).



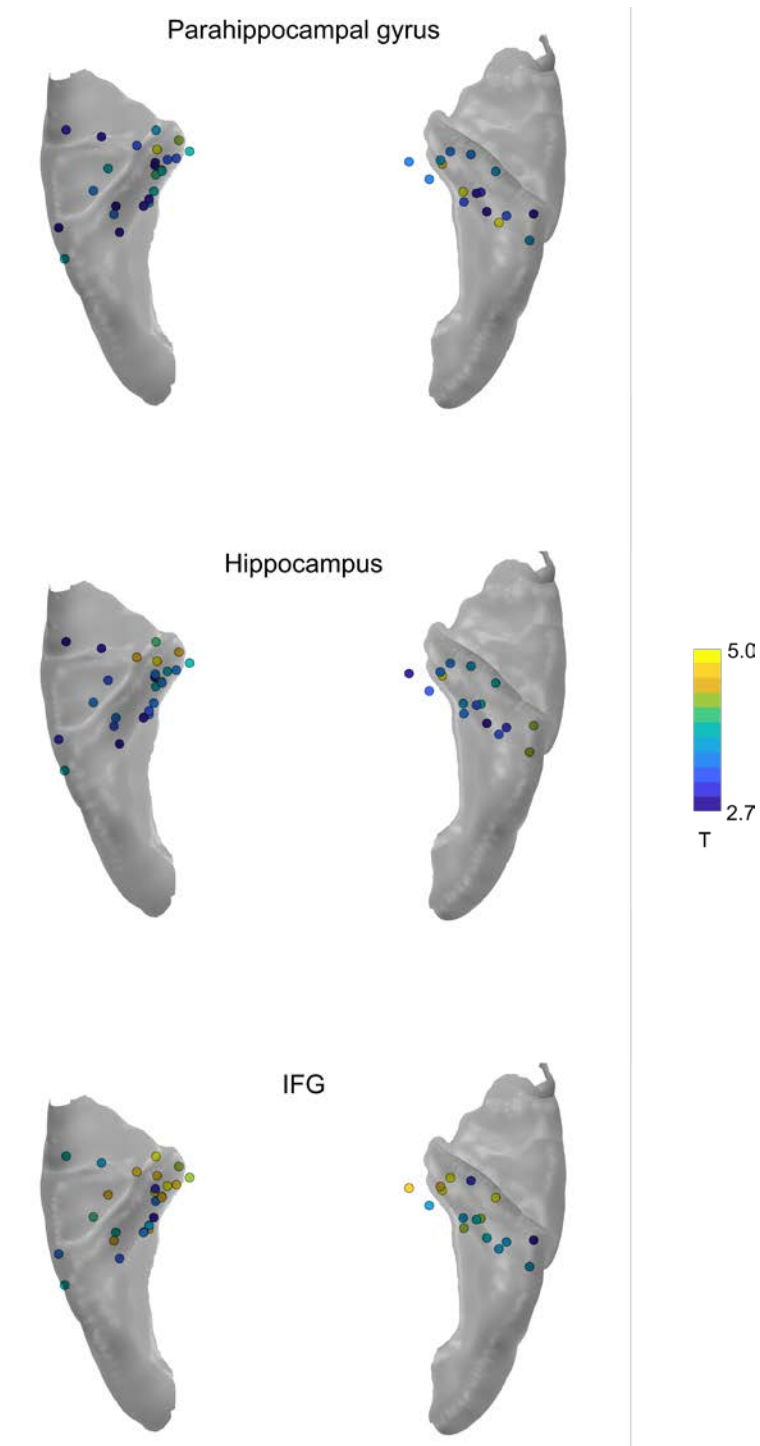
Supplementary Figure S5. Individual human es-fMRI activation results involving vIPFC. Shown are several individual human results showing substantial vIPFC (inferior frontal cortex/gyrus) activation $p < 0.005$, cluster size = 40. Numbers above the panels indicate the subject number and testing run, followed by MNI x, y, z coordinates at the cross-hairs.

Hippocampus / Parahippocampal area BOLD activation



$p < 0.005$, Cluster size 40

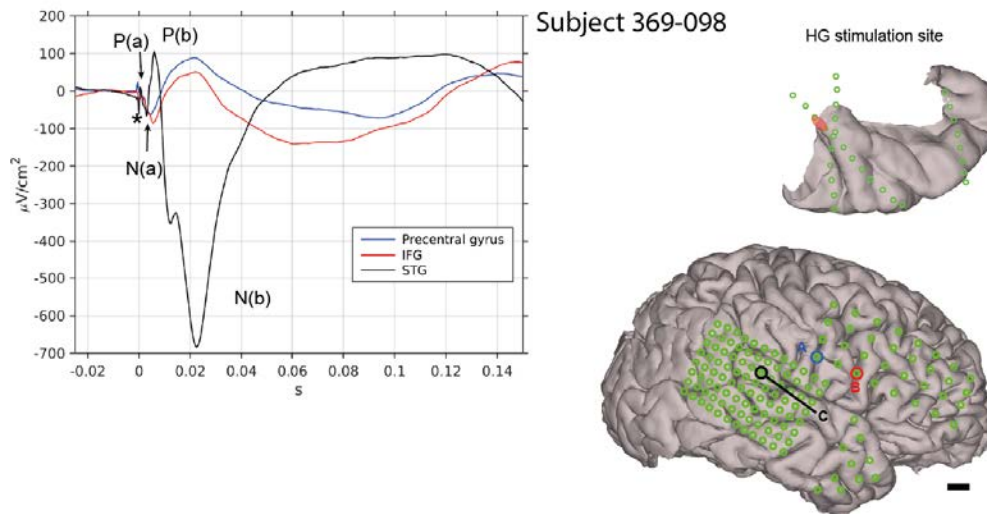
Supplementary Figure S6. Individual human es-fMRI results involving medial temporal lobe (MTL). Shown are several individual human results showing substantial MTL activation, $p < 0.005$, cluster size = 40. Format as in Suppl. Fig. S5.



Supplementary Figure S7. Impact of stimulation sites on the MTL and vIPFC contact sites.

Shown are the auditory cortex regions that when stimulated resulted in the displayed strength of fMRI responses on vIPFC (inferior frontal gyrus: IFG) and MTL regions. Auditory cortex (Heschl's gyrus) stimulation sites are color coded from blue to yellow color map according to the strength of the fMRI BOLD response elicited in the parahippocampal, hippocampal, or vIPFC (IFG) regions. Although stronger responses tend to be seen from the more medial HG contacts, there are also contacts bordering other regions that also elicit strong responses and passive current spread is a factor, see manuscript text discussion.

medHG stim: Evoked STG, IFG and Precentral waveforms



Supplementary Figure S8. Impact of medHG stimulation on STG evoked responses in subject 369. The early positivity P(a) and negativity N(a) in this subject at least qualitatively replicate the effects reported previously of medHG stimulation impact on the latency of the recorded potentials in the STG (Brugge et al., 2003). Upper right image shows the adjacent stimulation contacts in HG (shaded red area). Lower right shows the recording contact electrode locations and potentials evoked in inferior frontal gyrus (IFG) within vIPFC and the precentral gyrus, see manuscript text. Scale bar in bottom right of figure is 8 mm for top image and 1 cm for whole brain.

Supplementary Movies M1-M6. Electrical tractography (esT) results: impact of Heschl's Gyrus stimulation on high gamma responses in the brain, as a function of time. Induced high gamma power results from electrically stimulating contacts in medial or lateral Heschl's gyrus are shown in three subjects.

- **M1: Movie_1_AEP-Ave-medHG_movie_estt_423:** Subject 423 stimulation of medHG
- **M2: Movie_2_AEP-Ave-latHG_movie_estt_423:** Subject 423 stimulation of latHG+PT
- **M3: Movie_3_AEP-Ave-medHG_movie_estt_384:** Subject 384 stimulation of medHG
- **M4: Movie_4_AEP-Ave-latHG_movie_estt_384:** Subject 384 stimulation of latHG+PT
- **M5: Movie_5_AEP-Ave-medHG_movie_estt_372:** Subject 372 stimulation of medHG
- **M6: Movie_6_AEP-Ave-latHG_movie_estt_372:** Subject 372 stimulation of latHG+PT