

A synergistic core for human brain evolution and cognition

Andrea I. Luppi^{a,b,*}, Pedro A.M. Mediano^c, Fernando E. Rosas^{d,e,f}, Negin Holland^a, Tim D. Fryer^{a,g}, John T. O'Brien^{h,i}, James B. Rowe^{a,i,j}, David K. Menon^{a,g}, Daniel Bor^c, & Emmanuel A. Stamatakis^b

^aDepartment of Clinical Neurosciences, University of Cambridge

^bUniversity Division of Anaesthesia, School of Clinical Medicine, University of Cambridge

^c Department of Psychology, University of Cambridge

^dCenter for Psychedelic Research, Department of Brain Science, Imperial College London

^eCenter for Complexity Science, Imperial College London

^fData Science Institute, Imperial College London

^gWolfson Brain Imaging Centre, University of Cambridge

^h Department of Psychiatry, University of Cambridge

ⁱ Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

^j MRC Cognition and Brain Sciences Unit, University of Cambridge

*Corresponding author: al857@cam.ac.uk

Abstract

A fundamental question in neuroscience is how brain organisation gives rise to humans' unique cognitive abilities. Although complex cognition is widely assumed to rely on frontal and parietal brain regions, the underlying mechanisms remain elusive: current approaches are unable to disentangle different forms of information processing in the brain. Here, we introduce a powerful framework to identify synergistic and redundant contributions to neural information processing and cognition. Leveraging multimodal data including functional MRI, PET, cytoarchitectonics and genetics, we reveal that synergistic interactions are the fundamental drivers of complex human cognition. Whereas redundant information dominates sensorimotor areas, synergistic activity is closely associated with the brain's prefrontal-parietal and default networks; furthermore, meta-analytic results demonstrate a close relationship between high-level cognitive tasks and synergistic information. From an evolutionary perspective, the human brain exhibits higher prevalence of synergistic information than non-human primates. At the macroscale, we demonstrate that high-synergy regions underwent the highest degree of evolutionary cortical expansion. At the microscale, human-accelerated genes promote synergistic interactions by enhancing synaptic transmission. These convergent results provide critical insights that synergistic neural interactions underlie the evolution and functioning of humans' sophisticated cognitive abilities, and demonstrate the power of our widely applicable information decomposition framework.

37 **Synergistic and redundant interactions identify brain networks with distinct**
38 **neurocognitive profiles**

39 In theoretical and cognitive neuroscience, considering the human brain as a distributed
40 information-processing system has proven to be a powerful framework to understand the neural
41 basis of cognition ¹. Crucially, a deeper understanding of any information-processing
42 architecture calls for a more nuanced account of the information that is being processed.

43 As an example, let us consider humans' two main sources of information about the world: the
44 eyes. The information that we still have when we close either eye is called “redundant
45 information” — because it is information that can be conveyed by either source (for instance,
46 information about colour is largely redundant between the two eyes). Redundancy provides
47 robustness: we can still see with one eye closed. However, closing one eye also deprives us of
48 stereoscopic information about depth. This information does not come from either eye alone:
49 one needs both, in order to perceive the third dimension. This is called the “synergistic
50 information” between two sources - the extra advantage that we derive from combining them,
51 which makes them complementary ^{2,3}.

52 Thus, in addition to their own unique information, when multiple sources are considered
53 together their information contribution can be identified as synergistic (only available when
54 both sources are considered together) or redundant (available from either source
55 independently). Every information-processing system — including the human brain — needs
56 to strike a balance between these mutually exclusive kinds of information, and the advantages
57 they provide: robustness and integration, respectively ⁴⁻⁷. Being fundamentally different,
58 synergistic and redundant information cannot be adequately captured by traditional measures
59 of macroscale information exchange (“functional connectivity”) in the human brain, which
60 instead simply quantify the similarity between regional activity ^{2,8}.

61 Here, we reveal the distinct contributions of synergistic and redundant interactions to human
62 cognition, and we delineate their large-scale organisation in the human brain. To this end, we
63 leveraged the partial information decomposition (PID) framework ^{2,3,9} to quantify synergistic
64 and redundant interactions between brain regions (Figure 1A,B), obtained from resting-state
65 functional MRI data from 100 Human Connectome Project subjects (Methods). We ranked
66 each brain region separately in terms of how synergistic and redundant its interactions with
67 other brain regions are; the difference between these ranks (synergy minus redundancy)

91 (Figure S4). In contrast, regions with higher relative importance for synergy predominate in
92 higher-order association cortex, and are affiliated with the default mode (DMN) and fronto-
93 parietal executive control (FPN) subnetworks¹¹ (Figures S3-4).

94 It is noteworthy that synergy, which quantifies the extra information gained by integrating
95 multiple sources^{3,12} is most prevalent in regions belonging to the DMN and FPN. Functionally,
96 these regions are recruited by complex tasks that rely on multimodal information, decoupled
97 from immediate sensorimotor contingencies^{13,14}; anatomically, they receive multimodal inputs
98 from across the brain¹⁵. Therefore, it has been speculated that these networks are devoted to
99 the integration of information^{13,15}. Our findings about regional prevalence of synergy in DMN
100 and FPN provide formal information-theoretic evidence to confirm this long-standing
101 hypothesis. Furthermore, by considering a synergy-redundancy gradient in terms of
102 connections instead of regions, we show that the most synergy-dominated connections
103 correspond to links between DMN/FPN and other subnetworks, whereas redundancy-
104 dominated connections tend to occur within each subnetwork (Figure 1C).

105 The distinct cytoarchitectonic profiles and subnetwork affiliations further suggest that
106 redundant and synergistic interactions may be involved with radically different cognitive
107 domains. To empirically validate this hypothesis, we performed a term-based meta-analysis
108 using NeuroSynth. The redundancy-to-synergy gradient identified in terms of regional rank
109 differences was related to 24 terms pertaining to higher cognitive functions (e.g. attention,
110 working memory, social and numerical cognition) and lower sensorimotor functions (such as
111 eye movement, motion, visual and auditory perception) adopted by previous studies^{13,16}.

112 Supporting the inference from neuroanatomy to cognition, our results reveal that the regional
113 gradient from redundancy to synergy corresponds to a gradient from lower to higher cognitive
114 functions. Specifically, high-redundancy regions loaded strongly onto auditory, visual and
115 multisensory processing and motion. In contrast, high-synergy regions had the strongest
116 loadings onto social and numerical cognition, working memory and cognitive control (Figure
117 1E).

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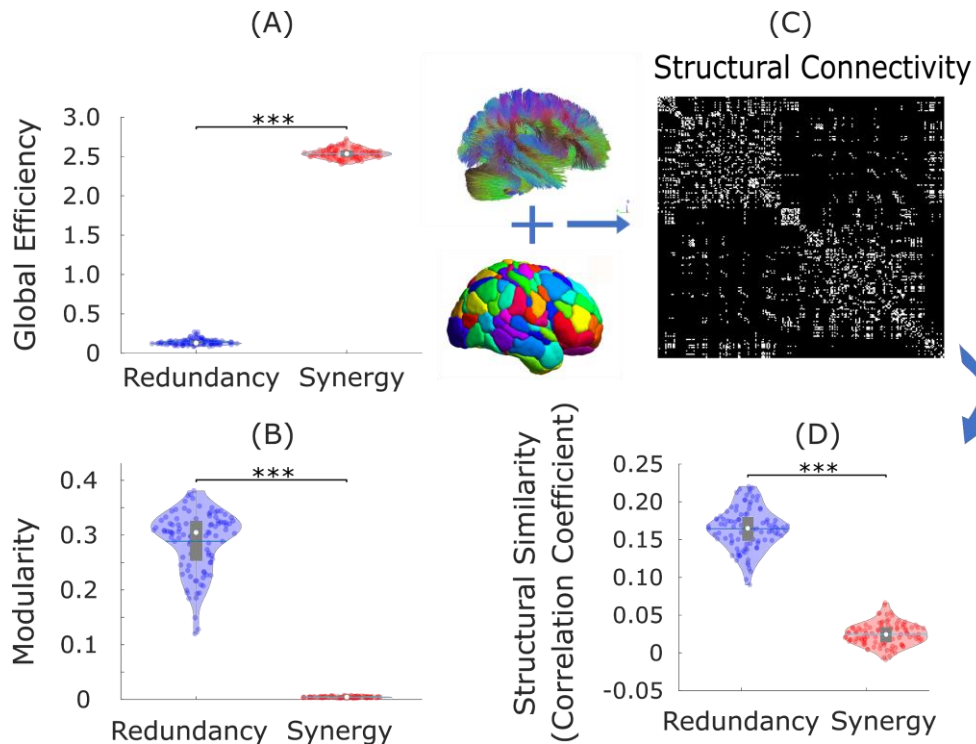
120 **Network organisation of synergy and redundancy support their distinct information-**
121 **processing roles**

122 Sensorimotor and higher-order cognitive functions impose distinct and opposite demands on
123 cognitive architectures: specialised sensory processing benefits from segregation into modules,
124 whereas integration of information demands high levels of interconnectedness^{5,17}. Contrasting
125 the properties of the networks delineated by synergistic and redundant interactions reveals how
126 the human brain resolves this tension.

127 Across individuals, the network of synergistic interactions is more highly interconnected and
128 globally efficient than the network of redundancy (Synergy: $M=2.54$, $SD=0.06$; Redundancy:
129 $M=0.14$, $SD=0.04$; $t(99)=-330.04$, $p<0.001$, Hedge's $g=-46.67$) (Figure 2A). In contrast,
130 redundant interactions delineate a network characterised by a highly modular structure, which
131 is virtually absent in synergistic networks (Synergy: $M=0.005$, $SD=0.001$; Redundancy:
132 $M=0.29$, $SD=0.06$; $t(99)=51.74$, $p<0.001$, Hedge's $g=7.25$) (Figure 2B). Thus, synergistic and
133 redundant interactions exhibit distinct network organisation, supporting integrated and
134 segregated processing, respectively - as demanded by the cognitive functions they support.

135 It is also known that only a subset of regions are directly connected by white matter tracts¹⁸;
136 therefore, we reasoned that the more an organism's survival depends on information exchange
137 between regions X and Y, the more one should expect X and Y to be directly connected. Thus,
138 direct physical connections in the brain reveal where the need for robust communication is
139 highest. Consequently, if redundant interdependencies are representative of robust information
140 exchange, they should be co-located with underlying direct anatomical connections - as
141 quantified using diffusion-weighted imaging (DWI). Our results support this hypothesis: across
142 subjects, the number of white matter streamlines was significantly more correlated with
143 redundant ($M=0.16$, $SD=0.028$) than synergistic interactions between regions ($M=0.025$,
144 $SD=0.015$; $t(99)=39.85$, $p<0.001$, Hedge's $g=6.29$) (Figure 2C,D). These results are replicated
145 using alternative network measures and parcellations (Figures S5-7 and Supplementary Tables
146 1-3).

147 Thus, whereas synergistic interactions are poised to facilitate high-level cognition through
148 global integration, redundant interactions demarcate a structural-functional backbone in the
149 human brain, ensuring robust sensorimotor input-output channels - both critical functions for
150 successful information processing.



151

152 **Figure 2. Synergy is integrated, redundancy is segregated and supported by anatomical connections.** (A)
153 The network organisation of synergistic interactions exhibits significantly higher integrative capacity (global
154 efficiency) than redundant interactions. (B) The network organisation of redundant interactions exhibits
155 significantly higher segregation (modularity) than synergistic interactions. (C) Structural connectivity of each
156 subject was estimated from diffusion MRI, measured as the number of white matter tracts between regions of the
157 232-ROI augmented Schaefer atlas, and Spearman correlation coefficient was used to assess the similarity of
158 redundancy and synergy matrices with structural connectivity, after thresholding to ensure equal numbers of
159 connections. (D) Networks of redundant interactions are significantly more correlated with underlying structural
160 connectivity than synergistic interactions. Violin plots represent the distribution of values across 100 HCP subjects
161 (colored circles). White circle: mean; blue line: median; grey box: interquartile range; *** $p < 0.001$.

162

163 **High-synergy brain regions are selectively potentiated by human evolution**

164 The association between synergistic information processing and higher cognitive functions,
165 raises the intriguing possibility that the human brain may enable humans' uniquely
166 sophisticated cognitive capacities in virtue of its highly synergistic nature. We pursued this
167 hypothesis through three convergent approaches.

168 First, we show that the human brain is especially successful at leveraging synergistic
169 information, compared with the brains of non-human primates. Synergistic interactions account
170 for a higher proportion of total information exchange in the human brain than in the macaque
171 (*Macaca mulatta*); whereas the two species' brains are equal in terms of proportion of total
172 information exchange accounted for by redundancy (Synergy: Human $M=0.478$, $SD=0.003$;

173 Macaque $M=0.466$, $SD=0.005$; $t(117)=14.24$, $p<0.001$, Hedge's $g=3.54$; Figure 3A;
174 Redundancy: Human $M=0.012$, $SD=0.005$; Macaque $M=0.011$, $SD=0.005$; $t(117)=0.90$,
175 $p=0.372$, Hedge's $g=0.22$; Figure 3B).

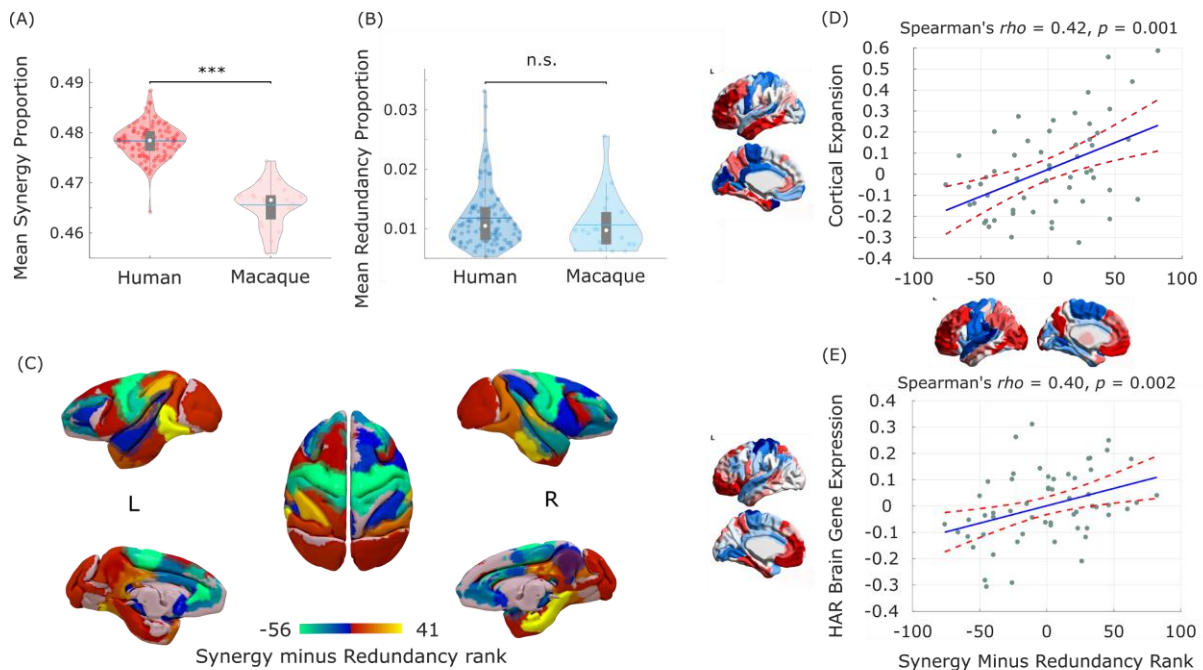
176 The patterns of synergy and redundancy in the macaque brain broadly resemble those observed
177 in humans (Figure S8 and Supplementary Table 7), demonstrating their evolutionary stability
178 - including the expected high redundancy in sensorimotor regions (Figure 3C). However,
179 redundancy is more prevalent than synergy in the prefrontal cortex (PFC) of macaques, despite
180 PFC being among the most synergy-dominated cortices in humans (Figure 3C). Intriguingly,
181 prefrontal cortex underwent substantial cortical expansion in the course of human evolution¹⁹.

182 These findings suggest that the high synergy observed in human brains may be a specific
183 outcome of evolutionary cortical expansion. To explore this hypothesis, we analysed cortical
184 morphometry data from in vivo structural MRI, comparing humans and one of the closest
185 evolutionary relatives of *Homo sapiens*: chimpanzees (*Pan troglodytes*)²⁰. Supporting our
186 hypothesis, we identified a significant positive correlation between relative cortical expansion
187 in humans versus chimpanzees, and the gradient of regional prevalence of synergy previously
188 derived from functional MRI ($\rho = 0.42$, $p = 0.001$; Figure 3D). Thus, these findings suggest
189 that the additional cortical tissue gained through human evolution is primarily dedicated to
190 synergy, rather than redundancy.

191 To provide further support for the evolutionary relevance of synergistic interactions, we
192 capitalised on human adult brain microarray datasets across 57 regions of the left cortical
193 mantle²⁰, made available by the Allen Institute for Brain Science (AIBS)²¹. We demonstrate
194 that regional dominance of synergy correlates with regional expression of genes that are both
195 (i) related to brain development and function, including intelligence and synaptic transmission
196²⁰; and (ii) selectively accelerated in humans versus non-human primates (“HAR-Brain genes”;
197 $\rho = 0.40$, $p = 0.002$; Figure 3E). Thus, the more important a brain region is in terms of synergy,
198 the more likely it is to express brain genes that are uniquely human.

199 Taken together, these findings provide converging evidence for the hypothesis that
200 evolutionary pressures selectively potentiated the role of synergistic interactions in the human
201 brain, both in terms of dedicated genes, (Fig. 3E) dedicated cortical real estate (Fig. 3D), and
202 the end result: higher prevalence of synergy in human brains than non-human primates (Fig.
203 3A,B).

204



205

206 **Figure 3. Human brain evolution favoured high synergy.** (A) The proportion of synergistic information
207 exchange across the brain is significantly higher in humans (*Homo sapiens*) than macaques (*Macaca mulatta*). (B)
208 The proportion of redundant information exchange across the brain is equivalent in humans and macaques. (C)
209 Surface projection of regional redundancy-to-synergy gradient scores for the macaque brain. (D) Significant
210 correlation between human regional redundancy-to-synergy gradient scores and regional cortical expansion from
211 chimpanzee (*Pan troglodytes*) to human (both on left hemisphere of DK-114 cortical atlas). (E) Significant
212 correlation between human regional redundancy-to-synergy gradient scores and regional expression of brain-
213 related human-accelerated (HAR-Brain) genes (both on left hemisphere of DK-114 atlas). The results in (A) and
214 (B) cannot be solely attributed to either the choice of bandpass filter, or the difference in TR between datasets
215 (Figures S9-10). The results in (D) and (E) are also replicated using unadjusted scores (Figure S11).

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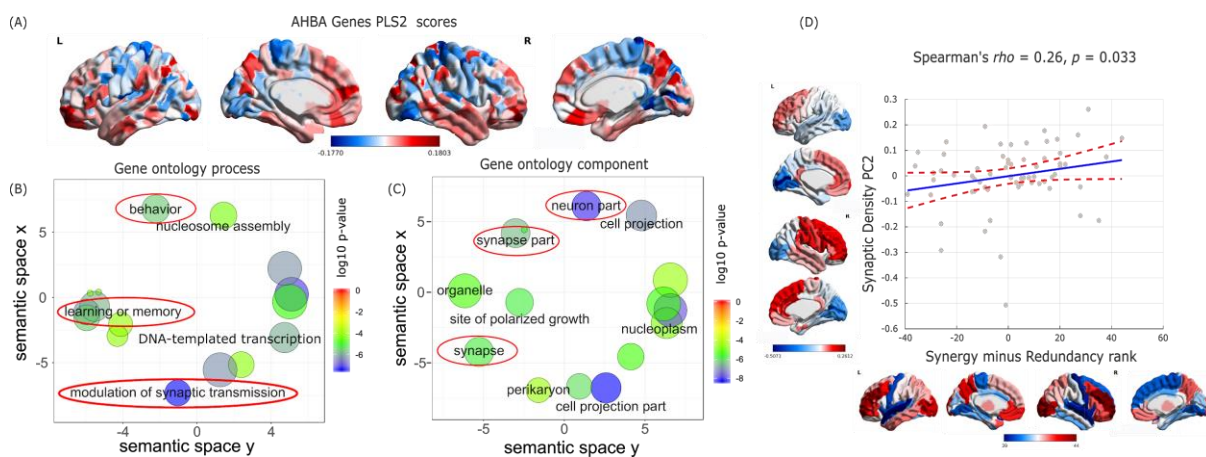
217 Neurobiological origins of synergy in the human brain

218 These observations raise the question of how such high synergy in the human brain could have
219 been attained. To address this question from a neurobiological perspective, we explored the
220 association between the redundancy-to-synergy gradient and regional expression profiles of
221 20,674 genes from AIBS microarray data^{10,22}. Using partial least squares (PLS) regression, we
222 show that the first two PLS components explained 31% of the variance in the regional synergy-
223 redundancy values (Figure S12): significantly more than could be expected by chance
224 (permutation test, $p=0.007$). For both components, gene expression weights were positively
225 correlated with the redundancy-to-synergy regional gradient (PLS1: $\rho = 0.37$, $p<0.001$; PLS2:
226 $\rho = 0.39$, $p<0.001$; Figure 4A and Figure S13). These correlations indicate that a number of

227 genes are overexpressed in regions where synergy dominates over redundancy -- including
228 significant overexpression of HAR-Brain genes, in line with the results presented above (PLS1:
229 $p=0.022$; PLS2: $p<0.001$; Figure S14).

230 We next sought to identify the role played by overexpressed genes related to brain synergy, for
231 each PLS component. Analysis of gene ontology revealed that the transcriptional signature of
232 PLS2 was significantly enriched in genes involved in learning or memory (in line with our
233 meta-analytic results from NeuroSynth), as well as synapses, synapse components and synaptic
234 transmission (all $p<10^{-4}$ for significant enrichment).

235



236

237 **Figure 4. Neurobiological underpinnings of synergy in the human brain.** (A) Second principal component of
238 PLS (PLS2) relating the redundancy-to-synergy regional gradient to 20,647 genes from the Allen Institute for
239 Brain Science, for the 308-ROI subdivision of the Desikan-Killiany cortical parcellation. (B) Dimensionality-
240 reduced gene ontology terms pertaining to biological processes that are significantly enriched in PLS2 (red ovals
241 highlight psychologically- or neurobiologically-relevant terms). (C) Dimensionality-reduced gene ontology terms
242 pertaining to cellular components that are significantly enriched in PLS2 (red ovals highlight psychologically- or
243 neurobiologically-relevant terms). Note that semantic space axes indicate the relative distance between terms in
244 multi-dimensional space, but have no intrinsic meaning. Corresponding gene ontology terms for PLS1 are shown
245 in Figure S15. (D) Significant correlation between regional redundancy-to-synergy gradient scores and an
246 anterior-posterior principal component of synaptic density from [^{11}C]UCB-J PET, for the DK-66 cortical
247 parcellation. Corresponding results for the first principal component of [^{11}C]UCB-J binding potential are shown
248 in Figure S16.

249

250 Synapses are the key structures by which neurons exchange information; therefore they
251 constitute a prime candidate for the neurobiological underpinning of synergistic interactions in
252 the human brain, as suggested by our genetic analysis. To provide a more direct link between
253 synaptic density and regional prevalence of synergy, we used positron emission tomography
254 (PET) to estimate in vivo regional synaptic density based on the binding potential of the

255 synapse-specific radioligand [¹¹C]UCB-J²³. This radioligand has high affinity for the synaptic
256 vesicle glycoprotein 2A (SV2A)²⁴, which is ubiquitously expressed in all synapses throughout
257 the brain²⁵. Supporting the notion that regional brain synergy is related to underlying synaptic
258 density, we found that an anterior-posterior principal component of synaptic density derived
259 from [¹¹C]UCB-J PET is significantly correlated with the regional gradient from redundancy
260 to synergy ($\rho = 0.26$, $p = 0.033$; Figure 4D).

261 Therefore, genetic and molecular evidence converge to indicate synapses and synaptic
262 transmission as key neurobiological underpinnings of synergy in the brain - in line with the
263 notion that synergy quantifies information integration, and its role in supporting higher
264 cognition.

265 Decomposing interactions between brain regions into synergistic and redundant components
266 illuminates how the brain addresses the inherent trade-off between robustness and integration,
267 providing powerful insights that are beyond traditional methods of studying brain interactions
268 (e.g. FC). Having demonstrated the crucial role of synergistic interactions in human cognitive
269 architecture via meta-analytic and graph-theoretical approaches, we proceeded to identify their
270 neurobiological underpinnings by combining genetic, molecular and neuroanatomical
271 evidence.

272 Taken together, our findings reveal that basic sensorimotor functions are supported by a
273 modular backbone of redundant interactions (Fig 1D, 2B). As the brain's input-output systems,
274 reliable sensorimotor channels are vital for survival, warranting the additional robustness
275 provided by redundant interactions — as indicated by our structural-functional analysis (Fig.
276 2D). In contrast, synergistic interactions are ideally poised to act as a global workspace,
277 allowing the integration of complementary information from across the brain in the service of
278 higher cognitive functions (Fig 1D): they bridge across different modules (Fig 1C), form a
279 globally efficient network (Fig 2A), and their neuroanatomical organisation coincides with
280 synapse-rich association cortex (Fig 4D and Supplementary Fig 3).

281 We further discovered that synergistic interactions were specifically enhanced in humans as a
282 result of evolutionary pressures, with dedicated cortical real estate and dedicated genes,
283 including those promoting synaptic transmission. This process resulted in a neural architecture
284 that is capable of leveraging synergistic information to a greater extent than other primates.
285 Our findings suggest that regions of the default mode and executive control (sub)networks may

286 be able to support human higher cognition precisely thanks to their extensive involvement with
287 synergistic processing.

288 Intriguingly, the high-synergy DMN is involved in self-related cognitive processes ^{26,27}, and it
289 is also especially disrupted by loss of consciousness, whether caused by anaesthesia or severe
290 brain injury ²⁸. Indeed, the global workspace theory of consciousness posits that integration of
291 information within a global workspace is necessary for consciousness ²⁹ - and a formal link has
292 also been established between synergy and the measure of consciousness known as integrated
293 information ^{3,30}. Therefore, decomposition of information exchange into synergy and
294 redundancy may also shed light on the emergence of consciousness in the human brain –
295 providing a framework to discover the information-processing principles that govern how
296 mental phenomena emerge from neurobiology.

297

298

299

300

301 MATERIALS AND METHODS

302

303

304 Synergy and Redundancy calculation

305 Shannon's Mutual information (MI) quantifies the interdependence between two random
306 variables X and Y . It is calculated as

$$307 I(X;Y) = H(X) - H(X|Y) = H(X) + H(Y) - H(X,Y) ,$$

308 where $H(X)$ stands for the Shannon entropy of a variable X . Above, the first equality states that
309 the mutual information is equal to the reduction in entropy (i.e. uncertainty) about X after Y
310 becomes accessible. Put simply, the mutual information quantifies the information that one
311 variable provides about another ³¹.

312 Crucially, Williams and Beer (2010)² observed that the information that two source variables
313 X and Y give about a third target variable Z , $I(X, Y; Z)$, should be decomposable in terms of
314 different *types* of information: information provided by one source but not the other (unique
315 information), or by both sources separately (redundant information), or jointly by their
316 combination (synergistic information). Following this intuition, they developed the Partial
317 Information Decomposition (PID²) framework, which leads to the following fundamental
318 decomposition:

$$319 \quad I(X, Y; Z) = \text{Red}(X, Y; Z) + \text{Un}(X; Z|Y) + \text{Un}(Y; Z|X) + \text{Syn}(X, Y; Z).$$

320 Above, *Un* corresponds to the unique information one source but the other doesn't, *Red* is the
321 redundancy between both sources, and *Syn* is their synergy: information that neither X nor Y
322 alone can provide, but that can be obtained by considering X and Y together. It is worth noticing
323 that the unique information is fully determined after synergistic and redundant comments have
324 been accounted for; hence, we focus our analyses on the two latter components.

325 The simplest example of a purely synergistic system is one in which X and Y are independent
326 fair coins, and Z is determined by the exclusive-OR function $Z = \text{XOR}(X, Y)$: i.e., $Z=0$
327 whenever X and Y have the same value, and $Z=1$ otherwise. It can be shown that X and Y are
328 both statistically independent of Z , which implies that neither of them provide - by themselves
329 - information about Z . However, X and Y together fully determine Z : hence, the relationship
330 between Z with X and Y is purely synergistic.

331 While PID provides a formal framework, it does not enforce how the corresponding parts ought
332 to be calculated. While there is ongoing research on the advantages of different decompositions
333 for discrete data, most decompositions converge into the same simple form for the case of
334 continuous Gaussian variables³². Known as *minimum mutual information PID* (MMI-PID),
335 this decomposition quantifies redundancy in terms of the minimum mutual information of each
336 individual source with the target; synergy, then, becomes identified with the additional
337 information provided by the weaker source once the stronger source is known. Since linear-
338 Gaussian models are sufficiently good descriptors of functional MRI timeseries (and more
339 complex, non-linear models offer no advantage³³), here we adopt the MMI-PID
340 decomposition, following previous applications of PID to neuroscientific data³⁴.

341 In a dynamical system such as the brain, one can calculate the amount of information flowing
342 from the system's past to its future, known as time-delayed mutual information

343 (TDMI). Specifically, by denoting the past of variables as $X_{t-\tau}$ and $Y_{t-\tau}$ and treating them as
344 sources, and their joint future state (X_t, Y_t) , as target, one can apply the PID framework and
345 decompose the information flowing from past to future as

$$\begin{aligned} 346 \quad & I(X_{t-\tau}, Y_{t-\tau}; X_t, Y_t) \\ 347 \quad & = \text{Red}(X_{t-\tau}, Y_{t-\tau}; X_t, Y_t) + \text{Un}(X_{t-\tau}; X_t, Y_t | Y_{t-\tau}) \\ 348 \quad & + \text{Un}(Y_{t-\tau}; X_t, Y_t | X_{t-\tau}) + \text{Syn}(X_{t-\tau}, Y_{t-\tau}; X_t, Y_t) \end{aligned}$$

349 Recently, this equation has been refined to also distinguish between redundant, unique, and
350 synergistic information shared with respect to the future variables X_t, Y_t . Importantly, this
351 framework, known as Integrated Information Decomposition (PhiID) ³, has identified
352 $\text{Syn}(X_{t-\tau}, Y_{t-\tau}; X_t, Y_t)$ with the capacity of the system to exhibit emergent behaviour ³⁵ [CITE
353 emergence]. Furthermore, PhiID introduced a stronger notion of redundancy, in which
354 information is shared by X and Y in both past and future. Accordingly, using the MMI-PhiID
355 decomposition for Gaussian variables, we use

$$356 \quad \text{Red}(X, Y) = \min\{I(X_{t-\tau}; X_t), I(X_{t-\tau}; Y_t), I(Y_{t-\tau}; X_t), I(Y_{t-\tau}; Y_t)\}$$

$$357 \quad \text{Syn}(X, Y) = I(X_{t-\tau}, Y_{t-\tau}; X_t, Y_t) - \max\{I(X_{t-\tau}; X_t, Y_t), I(Y_{t-\tau}; X_t, Y_t)\}$$

358

359

360 Here, we used the Gaussian solver implemented in the JIDT toolbox ³⁶ to obtain TDMI, synergy
361 and redundancy between each pair of brain regions, based on their HRF-deconvolved BOLD
362 signal timeseries (Supplementary Methods).

363

364 **Gradient of redundancy-to-synergy relative importance**

365 After building networks of synergistic and redundant interactions between each pair of regions
366 of interest (ROIs), we determined the role of each ROI in terms of its relative engagement in
367 synergistic or redundant interactions. We first calculated the nodal strength of each brain region
368 as the sum of all its connections in the group-averaged matrix. Then, we ranked all 232 regions
369 based on their nodal strength (with higher-strength regions having higher ranks). This

370 procedure was done separately for networks of synergy and redundancy. Subtracting each
371 region's redundancy rank from its synergy rank yielded a gradient from negative (i.e. ranking
372 higher in terms of redundancy than synergy) to positive (i.e. having a synergy rank higher than
373 the corresponding redundancy rank); note that the sign is arbitrary.

374 It is important to note that the gradient is based on relative - rather than absolute - differences
375 between regional synergy and redundancy. Consequently, a positive rank difference does not
376 necessarily mean that the region's synergy is greater than its redundancy; rather, it indicates
377 that the balance between its synergy and redundancy relative to the rest of the brain is in favour
378 of synergy - and *vice versa* for a negative gradient.

379 The same procedure was also repeated for network edges (instead of nodes), using their weights
380 to rank them separately in terms of synergy and redundancy and then calculating their
381 difference. This produced a single connectivity matrix where each edge's weight represents its
382 relative importance, being higher for synergy (positive edges) or redundancy (negative edges).

383

384 **NeuroSynth term-based meta-analysis of redundancy-to-synergy gradient**

385 The regional redundancy-to-synergy gradient identified in terms of nodal rank differences was
386 related to specific words using NeuroSynth, an online platform for large-scale, automated
387 synthesis of fMRI data [<https://neurosynth.org/>]. For our analyses we employ 24 topic terms
388 used by previous studies^{13,16}, which range from lower sensorimotor functions (such as eye
389 movement, motion, visual and auditory perception) to higher cognitive functions (e.g.
390 attention, working memory, social and numerical cognition).

391 A meta-analysis analogous to the one implemented by previous studies^{13,16}, was conducted to
392 identify topic terms associated with the redundancy-to-synergy gradient. Twenty binary brain
393 masks were obtained by splitting the values of the redundancy-to-synergy gradient into five-
394 percentile increments. These brain masks served as input for the meta-analysis, based on the
395 chosen 24 topic terms. For visualisation, terms were ordered according to the weighted mean
396 of the resulting Z-statistics. Note that the term "visual semantics" was excluded from
397 visualisation, because it failed to reach the significance threshold of $Z > 3.1$, leaving 23 terms
398 (Figure 1). The analyses were carried out using modified code made freely available at
399 [https://www.github.com/gpreti/GSP_StructuralDecouplingIndex].

400 **Measures of network integration and segregation**

401

402 We quantified global integration in the networks of synergistic and redundant connections
403 computing the networks *global efficiency*, a well-known measure that quantifies the ease of
404 parallel information transfer in the network. More precisely, the global efficiency of a network
405 corresponds to the average of the inverse of the shortest path length between each pair of nodes
406 ³⁷.

407

$$408 \quad Ge = \frac{1}{n} \sum_i^n \frac{\sum_{j \neq i}^n (d_{ij})^{-1}}{n-1}$$

409 Following Cruzat et al (2018) ³⁸, segregation of brain networks was quantified by means of
410 network modularity. Put simply, the modularity function quantifies the extent to which a
411 network can be partitioned such that the number of within-group edges is maximised and the
412 density of between-group edges is minimised. We employed an implementation of Newman's
413 spectral modularity algorithm ³⁹ available in the Brain Connectivity Toolbox (BCT; ^{37,40}.

414

415 **Structural-Functional Similarity**

416 Matrices of synergy and redundancy were thresholded proportionally using the same network
417 density as the structural connectivity matrix of the same subject. This procedure was selected
418 in order to ensure that the same number of edges would be present in both matrices, so that the
419 two matrices can be compared. Then, the upper triangular portion of each connectivity matrix
420 (structural and synergy/redundancy) was flattened into a vector, and the Spearman correlation
421 coefficient between these two vectors was computed. We use this correlation as a measure of
422 similarity between synergy or redundancy and structural connectivity.

423 **HAR-BRAIN genes.**

424 The maps of regional expression of human-accelerated genes for the DK-114 atlas were made
425 available by Wei et al (2019), where the reader can find detailed information about how these
426 data were generated. Briefly, genes located in a total of 2737 human accelerated regions
427 (HARs) of the genome were taken as presented by comparative genome analysis representing

428 genomic loci with accelerated divergence in humans⁴¹. Out of 2143 HAR-associated genes
429 identified from this procedure, 1711 were described in the Allen Human Brain Atlas (AHBA)
430 microarray dataset (human.brain-map.org)²¹ and were used in the analyses by Wei and
431 colleagues, referred to as HAR genes.

432 HAR genes were subsequently subdivided into HAR-BRAIN and HAR-NonBRAIN genes.
433 BRAIN genes were selected as the set of genes commonly expressed in human brain tissue
434 using the Genotype-Tissue Expression (GTEx) database (data source: GTEx Analysis Release
435 V6p; <https://www.gtexportal.org/>), which includes 56,238 gene expression profiles in 53 body
436 sites collected from 7333 postmortem samples in 449 individuals. From these 56,238 genes, a
437 total number of 2823 genes were identified as BRAIN genes showing significantly higher
438 expressions in brain sites than non-brain sites (one-sided t-test and an FDR corrected $q < 0.05$
439 were used). HAR-BRAIN genes were identified as the 405 genes that overlapped between the
440 2823 BRAIN genes and the 1711 HAR genes, whereas the remaining HAR genes were labelled
441 as HAR-NonBRAIN genes. Finally, the HAR gene expression data were mapped to the 114-
442 region subdivision of the Desikan-Killiany atlas [DK-114]^{42,43}. Since only two of the six AHBA
443 donors have data for the right hemisphere, Wei et al (2019) only considered HAR gene expression
444 patterns for the left hemisphere.

445

446 **Cortical expansion**

447 The maps of evolutionary cortical expansion were made available by Wei et al (2019),²⁰ who
448 describe in detail how these data were generated. Briefly, Wei and colleagues analysed in-vivo
449 MRI data from 29 adult chimpanzees, as well as 30 adult human subjects from the Human
450 Connectome Project. Pial surface reconstructions of chimpanzee and human T1-weighted MRI
451 scans (processed with FreeSurfer v5.3.0; <https://surfer.nmr.mgh.harvard.edu/>) were used for
452 both vertex-to-vertex mapping across chimpanzee and humans and also for subsequent
453 computation of region-wise expansion for cortical morphometry. A regional-level cortical
454 surface area (S_i) was computed by summing up face areas within each cortical region, for all
455 regions of the DK-114 atlas^{42,43}. Normalized cortical area was obtained by dividing the
456 regional area by the area of the whole cortex. Cortical expansion between every pair of
457 chimpanzee and human subjects was calculated based on both the raw (“unadjusted”) and
458 normalized (“adjusted”) cortical surface area by

459
$$E_{i,j} = \frac{S_{human,i} - S_{chimp,j}}{S_{chimp,j}}$$

460 with $E_{i,j}$ denoting the expansion from chimpanzee j to human i . A group-level region-wise
461 cortical expansion map was calculated by taking averages over the 870 chimpanzee-to-human
462 comparisons.

463

464 **AIBS gene expression analysis**

465 Regional gene expression levels for 20,647 human genes were obtained from transcriptomic
466 measurements in six post-mortem adult brains (age: 24-57 years), made available by the AIBS
467 (human.brain-map.org) ²¹. We used code made freely available by Morgan et al (2019) ¹⁰
468 https://github.com/SarahMorgan/Morphometric_Similarity_SZ) to obtain a 308 x 20,647 regional
469 transcription matrix, matching gene expression data to each cortical region of the DK-308 atlas
470 ^{10,22,44,45} (Supplementary Methods). Each tissue sample was assigned to a cortical region using the
471 AIBS MRI data for each donor, pooling samples between bilaterally homologous regions ^{10,45}.

472

473 **Partial Least Squares**

474 To explore the association between the redundancy-to-synergy regional gradient and all 20,647
475 genes measured in the AHBA microarrays, at each of 308 regions, we used partial least squares
476 (PLS) as a dimensionality reduction technique ^{10,22,44,46}. PLS finds components from the predictor
477 variables (308 × 20,647 matrix of regional gene expression scores) that have maximum covariance
478 with the response variables (308 × 1 matrix of regional redundancy-to-synergy gradient). The PLS
479 components (i.e. linear combinations of the weighted gene expression scores) are ranked by
480 covariance between predictor and response variables, so that the first few PLS components provide
481 a low-dimensional representation of the covariance between the higher dimensional data matrices.

482 Goodness of fit of low-dimensional PLS components was tested non-parametrically by repeating
483 the analysis 1000 times after shuffling the regional labels. The error on the PLS weights associated
484 with each gene were tested by resampling with replacement of 308 ROIs (bootstrapping); the ratio
485 of the weight of each gene to its bootstrap standard error was used to Z-score the genes and rank
486 their contributions to each PLS component ^{10,22,44}.

487

488 **Gene ontology and enrichment analysis**

489 We used GOrilla for enrichment analysis of the first two PLS components^{22,47} GOrilla identifies
490 enriched gene ontology (GO) terms in ranked gene list, leveraging a large online database of gene
491 annotations corresponding to ‘biological processes’ and ‘cellular components’⁴⁷ We identified GO
492 terms that were over-represented among the genes with the strongest positive weightings on each
493 PLS component (i.e. those most strongly associated with dominance of synergy over redundancy).
494 For our analyses on the online GOrilla platform (<http://cbl-gorilla.cs.technion.ac.il>) we unchecked
495 the “Run GOrilla in fast mode” option and used the “P-value threshold 10⁻⁴” setting in order to
496 best approximate FDR correction with $\alpha = 0.05$ ²².

497 We then used the online tool REViGO (<http://revigo.irb.hr>) to summarize the list of significant GO
498 terms and visualize the results of whole-genome enrichment analysis. First, REViGO employs
499 measures of semantic similarity between terms⁴⁸ to identify representative clusters of genes. Then,
500 REViGO plots significant GO terms in semantic space, where semantically similar GO terms are
501 represented clustered near one another and labelled in a representative manner.

502 For our hypothesis-driven analysis, testing for enrichment of HAR-Brain genes, we also used non-
503 parametric permutation testing. Specifically, we randomly drew 1000 samples of the same number
504 of genes and estimated their PLS weighting, and compared the PLS weights of the HAR-Brain
505 genes to this permutation distribution. This provided an estimate of the probability of HAR-Brain
506 gene enrichment of each PLS component under the null hypothesis^{10,22}. We note that this
507 permutation procedure does not take into account the correlation between HAR-Brain genes; more
508 sophisticated null models for permutation testing that controlled for these or other characteristics
509 of candidate genes will be important to develop for computational inference in future studies.

510

511

512 **Synaptic Density from Positron Emission Tomography**

513 In-vivo estimates of regional synaptic density in the human brain were obtained from positron
514 emission tomography (PET) with the radioligand [¹¹C]UCB-J ((R)-1-((3-(methyl-¹¹C)pyridin-
515 4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one)⁴⁹. This ligand quantifies synaptic

516 density²³ based on its affinity for the presynaptic vesicle glycoprotein 2A (SV2A)²⁴ which is
517 ubiquitously expressed in all brain synapses²⁵.

518

519 PET/MR imaging protocol

520 The research protocol was approved by an NHS Research Ethics Committee (REC:
521 18/EE/0059) and the Administration of Radioactive Substances Advisory Committee
522 (ARSAC), and all participants provided written informed consent in accordance with the
523 Declaration of Helsinki. Participant recruitment and exclusion criteria are described in detail
524 in the original publication⁴⁹. Here, we included data from the healthy volunteers (N=15, 8
525 females; age: 68 ± 7 years).

526 The radioligand [¹¹C]UCB-J was synthesised at the Radiopharmacy Unit, Wolfson Brain
527 Imaging Centre, Cambridge University, using the methodology previously described²⁴. All
528 participants underwent simultaneous 3T MRI and [¹¹C]UCB-J PET on a GE SIGNA PET/MR
529 (GE Healthcare, Waukesha, USA). Dynamic PET data acquisition was performed for 90
530 minutes starting immediately after [¹¹C]UCB-J injection (median (range) injected activity: 408
531 (192-523) MBq, injected UCB-J mass $\leq 10 \mu\text{g}$). Attenuation correction included the use of a
532 multi-subject atlas method⁵⁰ and improvements to the MRI brain coil component⁵¹. Each
533 emission image series was aligned using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/)
534 then rigidly registered to a T1-weighted MRI acquired during PET data acquisition (TR = 3.6
535 msec, TE = 9.2 msec, 192 sagittal slices, in plane resolution 0.55 x 0.55 mm (subsequently
536 interpolated to 1.0 x 1.0 mm); slice thickness 1.0 mm). Regional time-activity curves were
537 extracted following the application of geometric transfer matrix partial volume correction⁵¹ to
538 each of the dynamic PET images. To quantify SV2A density (and therefore synaptic density),
539 regional [¹¹C]UCB-J non-displaceable binding potential (BP_{ND}) was determined for a 66-ROI
540 subdivision of the Desikan-Killiany cortical atlas (DK-66), using a basis function
541 implementation of the simplified reference tissue model⁵², with the reference tissue defined in
542 the centrum semiovale^{53,54}.

543

544 Principal components of synaptic density

545 Principal Components Analysis (PCA) was subsequently employed to derive the principal
546 components that explain most of the variance in regional [¹¹C]UCB-J BP_{ND} across volunteers.
547 Components were selected if their associated eigenvalue was greater than unity; two principal
548 components satisfied this criterion, explaining 45% and 16% of the variance, respectively.

549

550 Acknowledgements

551

552 Funding

553 This work was supported by grants from the National Institute for Health Research (NIHR,
554 UK), Cambridge Biomedical Research Centre and NIHR Senior Investigator Awards [to
555 DKM]; the British Oxygen Professorship of the Royal College of Anaesthetists [to DKM]; the
556 Stephen Erskine Fellowship (Queens' College, Cambridge), [to EAS]; and the Gates
557 Cambridge Trust (to AIL). PAM and DB are funded by the Wellcome Trust (grant no.
558 210920/Z/18/Z). FR is funded by the Ad Astra Chandaria foundation. Computing
559 infrastructure at the Wolfson Brain Imaging Centre (WBIC-HPHI) was funded by the
560 MRC research infrastructure award (MR/M009041/1).

561 The PET study was funded by the Cambridge University Centre for Parkinson-Plus; the
562 National Institute for Health Research Cambridge Biomedical Research Centre (146281); the
563 Wellcome Trust (103838) and the Association of British Neurologists, Patrick Berthoud
564 Charitable Trust (RG99368).

565 Data were provided [in part] by the Human Connectome Project, WU-Minn Consortium
566 (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the
567 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and
568 by the McDonnell Center for Systems Neuroscience at Washington University.

569 For the macaque data, primary support for the work by Newcastle University was provided by
570 Wellcome Trust (WT091681MA, WT092606AIA), National Centre for 3Rs (Project grant
571 NC/K000802/1; Pilot grant NC/K000608/1), and BBSRC (grant number BB/J009849/1).

572 We express our gratitude to the Primate neuroimaging Data- Exchange (PRIME-DE) initiative,
573 to the organizers and managers of PRIME-DE and to all the institutions that contributed to the
574 PRIME-DE dataset (http://fcon_1000.projects.nitrc.org/indi/indiPRIME.html), with special
575 thanks to the Newcastle team. We are also grateful to Anoine Grigis, Jordy Tasserie and Bechir
576 Jarraya for their help with the Pypreclin code, and Rodrigo Romero-Garcia for generating and
577 sharing the 500mm2 subparcellation of the DK atlas, and the corresponding Von Economo
578 cytoarchitectonics map. We are also grateful to Yongbin Wei and colleagues for generating
579 and making available the data pertaining to HAR genes and cortical expansion. We are grateful
580 to UCB Pharma for providing the precursor for the radioligand used in PET imaging.

581

582

Author Contributions

583 AIL: conceived the study; analysed data; wrote first draft of the manuscript. PAM: conceived
584 the study; contributed to data analysis; reviewed and edited the manuscript. FR: contributed to
585 data analysis; reviewed and edited the manuscript. NH: acquired PET data; reviewed PET
586 analysis; reviewed the manuscript. TDF: preprocessed PET data; reviewed the manuscript.
587 JOB: conceived the PET project; reviewed PET analysis; reviewed the manuscript. JBR:
588 conceived the PET project; reviewed PET analysis; reviewed the manuscript. DKM: reviewed
589 the manuscript. DB: conceived the study; reviewed and edited the manuscript. EAS: conceived
590 the study; reviewed and edited the manuscript.

591

592

Competing Interests

593 JBR serves as an associate editor to Brain, and is a non-remunerated trustee of the Guarantors
594 of Brain and the PSP Association (UK). He provides consultancy to Asceneuron, Biogen and
595 UCB and has research grants from AZ-Medimmune, Janssen and Lilly as industry partners in
596 the Dementias Platform UK. All other authors declare no conflicts of interest.

597

598

Data Availability

599 The HCP DWI data in SRC format are available online
600 (<http://brain.labsolver.org/diffusion-mri-data/hcp-dmri-data>). The HCP fMRI data are
601 available online (<https://www.humanconnectome.org/study/hcp-young-adult/data-releases>).

602

603 Macaque MRI data are available from the PRIMatE Data Exchange (PRIME-DE) through the
604 Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC;
605 http://fcon_1000.projects.nitrc.org/indi/indiPRIME.html).

606

607 The PET data that support the findings of this study are available from author NH
608 (nda26@medschl.cam.ac.uk), upon reasonable request for academic (non-commercial)
609 purposes.

610

611 The macaque connectome is available online on Zenodo:

612 <https://zenodo.org/record/1471588#.X2JCjdZuJPY>

613

614 Cortical gene expression patterns were taken from the transcriptomic data of the Allen Human
615 Brain Atlas (AHBA, <http://human.brain-map.org/static/download>).

616 Region-wise maps of chimpanzee-to-human cortical expansion and HAR gene expression are
617 available as Supplementary Materials from Wei et al (2019) ²⁰.

618 The NMT anatomical volume and associated probabilistic tissue segmentation maps (GM,
619 WM and CSF) are freely available online: [https://afni.nimh.nih.gov/pub/
620 dist/atlas/macaque/nmt](https://afni.nimh.nih.gov/pub/dist/atlas/macaque/nmt) and <http://github.com/jms290/NMT>.

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Code Availability

625

626 The Java Information Dynamics Toolbox is freely available online:

627 (<https://github.com/jlazier/jidt>).

628 The CONN toolbox is freely available online (<http://www.nitrc.org/projects/conn>).

629 DSI Studio is freely available online (www.dsi-studio.labsolver.org).

630 The Brain Connectivity Toolbox code used for graph-theoretical analyses is freely available

631 online (<https://sites.google.com/site/bctnet/>).

632 The code used for NeuroSynth meta-analysis is freely available online:

633 (https://www.github.com/gpreti/GSP_StructuralDecouplingIndex).

634 The HRF deconvolution toolbox is freely available online:

635 (<https://www.nitrc.org/projects/rshrf>).

636 The Pypreclin pipeline code is freely available at GitHub

637 (<https://github.com/neurospin/pypreclin>).

638 The code for PLS analysis of gene expression profiles is freely available online:

639 https://github.com/SarahMorgan/Morphometric_Similarity_SZ.

640

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