

Metabolism modulates network synchrony in the aging brain

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Abstract

Brain aging is associated with hypometabolism and associated global changes in functional connectivity. Using fMRI, we show that network synchrony, a collective property of brain activity, decreases with age. Applying quantitative methods from statistical physics, we provide a generative (Ising) model for these changes as a function of the average communication strength between brain regions. In particular, we find healthy brains to be poised at a critical point of this communication strength, enabling a balance between segregated (to functional domains) and integrated (between domains) patterns of synchrony. However, one characteristic of criticality is a high sensitivity to small changes. Thus, minute weakening of pairwise communication between regions, as seen in the aging brain, gives rise to qualitatively abrupt changes in synchrony. Finally, by experimentally modulating metabolic activity in younger adults, we show how metabolism alone—Independent of other changes associated with aging—can provide a mechanism for global changes in synchrony.

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1 1. Significance Statement

2 The brain is a biological machine that utilizes chemical energy to process
3 information. However, the mechanism by which the brain adapts to resource
4 constraints is poorly understood. This is particularly relevant in the aging
5 brain, for which the ability of neurons to utilize their primary energy source,
6 glucose, is diminished. Here, we provide a data-driven quantitative model for
7 how brain-wide activity patterns are controlled by resource availability. This
8 model shows that the brain is poised at a critical point, past which even minute
9 changes in glucose utilization cause communication across the brain to markedly
10 re-configure. Together, our results suggest that the clinical trajectory of cog-
11 nitive changes associated with aging is discontinuous and can be mediated by
12 metabolism.

13 2. Introduction

14 One of the most fundamental questions in neuroscience is how the famili-
15 ar patterns of collective, brain-wide activity arise from the properties of the
16 constituent neurons and their networks. Here, we study how the brain's global
17 activity patterns change with age, and how those changes might arise from the
18 reduced metabolic activity of the constituent regions.

19 We draw on two types of experimental evidence. First, as established us-
20 ing positron emission tomography (PET), older brains show reduced glucose
21 metabolism [1, 2, 3]. Second, as established by functional magnetic resonance
22 imaging (fMRI), aging is associated with weakened *functional connectivity* (FC),
23 *i.e.* reduced communication (on average) between brain regions [4, 5, 6]. Com-
24 bining both observations suggests that impaired glucose metabolism may un-
25 derlie changes in FC [1, 7]. Further supporting this link are studies showing
26 disruptions similar to those seen with aging in Type 2 diabetic subjects [8, 9].

27 In healthy brains, resting-state brain activity (states during which subjects
28 are not engaged in any explicit task) alternates between *segregating* computa-
29 tions to localized functional domains and *integrating* this information across

30 these domains [7, 10, 11, 12, 13]. The metabolic cost of these activities increase
31 in proportion to the number and length of functional connections between pairs
32 of brain regions [14], making highly-connected (integrated) networks more ener-
33 getically costly [10]. Moreover, connections with the highest cost are the first to
34 weaken with age [6, 7, 15]. Thus, it has been hypothesized that declining glucose
35 metabolism in older brains drives the loss of high-cost (integrated) functional
36 activities [14]. Yet the relationship in aging brains, between energetic constraint
37 at the level of individual brain regions and the apparent re-organization of the
38 functional connectome, is still not well understood.

39 Here, we develop a generative model that describes how the probability
40 distribution of FC patterns transforms with changes in global variables (such as
41 age and metabolic activity)[16]. The approach of choice to understand how these
42 changes arise is statistical physics, which interprets the collective properties of
43 complex systems in terms of individual interactions between the underlying
44 parts [17]. In particular, we employ an *Ising model* [18, 19, 20] to describe
45 how pairwise interactions between brain regions give rise to specific profiles of
46 network *synchrony*, a time-dependent average of the activity over the entire
47 brain [21, 22, 23]

48 While the Ising model provides a general tool for describing the collective
49 properties of complex systems, we adapt it to examine the specific relationship
50 between brain aging and metabolic activity. To achieve this, we re-analyzed
51 two fMRI datasets. The first is the *lifespan* Cam-CAN 3T fMRI resting state
52 dataset of 636 individuals, ranging over ages 18-88 [24]. The second, in which
53 we hold age constant in order to isolate the effects of metabolic activity alone,
54 is the PAgB 7T fMRI within-subject experiment of 12 healthy young adults
55 scanned while on glycolytic and ketogenic *diets* [25]. Ketone bodies decrease
56 the relative free energy of ATP production by 27% as compared to glucose [26].
57 This additional efficiency of ketone bodies as a metabolite, observed even in
58 healthy subjects, has been shown to increase both cardiac efficiency [26] as well
59 as brain activity [25].

60 The significance of this work is three-fold. First, in contrast to the tools

61 commonly used to study fMRI networks, our approach provides a predictive
62 mechanism for how FC patterns change, in qualitatively significant ways, as
63 a function of the average interaction between brain regions [16]. Second, we
64 establish a direct link between network synchrony and the relative frequencies of
65 integrated (high-cost) and segregated (low-cost) brain activities [10, 14]. Finally,
66 we illustrate a precise relationship between differences in FC over the lifespan
67 as well as in response to changes in the brain's access to energy.

68 **3. Methods**

69 *3.1. Lifespan and metabolic neuroimaging datasets*

70 To identify how the collective features of fMRI change across the lifespan, we
71 analyzed a large-scale 3T fMRI dataset: the Cambridge Centre for Ageing and
72 Neuroscience stage II (Cam-CAN: ages 18-88, $N = 636$) [24]. The Cam-CAN
73 study was designed to identify neural correlates of normal aging and provides
74 a roughly uniform coverage of age groups, allowing comparison between groups
75 as well as a wide array of behavioral measures. While the functional MRI imag-
76 ing of Cam-CAN stage II included both task and resting state data, we used
77 only resting state data, for which most regions of the brain have roughly similar
78 statistical properties (see *Supplementary Fig. 2*). To relate these changes to en-
79 ergy in the brain, we additionally analyzed 7T fMRI data from the Protecting
80 the Aging Brain (PAgB) database [25]. In a within-subjects experiment, young
81 healthy adults ($N = 12$, $\mu_{age} = 28 \pm 6.73$ years; 4 female) were scanned at
82 resting state under two conditions: (1) *glycolytic*, following their standard diet,
83 without fasting; and (2) *ketogenic*, following a high-fat, moderate-protein, low-
84 carbohydrate (< 50 g/day) diet for one week, by which point all participants
85 were in ketosis (> 0.6 mmol/L ketone blood concentration). For details on the
86 glycolytic and ketogenic dietary regimes, as well as validation of their blood
87 values and neurobiological effects as comparable to calorie-matched administra-
88 tion of glucose and D- β -hydroxybuterate, see previous work [25]. Studies were
89 approved by the Institutional Review Boards of Cambridge University and Mas-
90 sachusetts General Hospital/Partners Healthcare, respectively; all participants

91 provided informed consent.

92 *3.2. MRI acquisition*

93 The Cam-CAN lifespan dataset includes multiple imaging modalities (T1
94 and T2-weighted images, diffusion-weighted images, BOLD EPI images during
95 tasks of three varying levels of cognitive demand, MEG images during two sep-
96 arate cognitive loads and magnetisation-transfer images). Of these, the resting
97 state BOLD EPI fMRI was the focus of our analysis (full dataset documentation
98 at [24]). The Cam-CAN functional imaging was done at 3T field strength over 8
99 min 40 s. The neuroimaging experiments of Cam-CAN study were conducted in
100 Cambridge, UK at the Medical Research Council Cognition and Brain Sciences
101 Unit (MRC-CBSU). Specifics of the BOLD EPI imaging protocol included: TR
102 = 1970 ms, TE = 30 ms, flip angle = 78°, voxel size = 3 × 3 × 4.44 mm, slices =
103 32, number of measurements = 261. The PAgB metabolic dataset was acquired
104 at ultra-high-field (7T) field strength at the Athinoula A. Martinos Center for
105 Biomedical Imaging. Imaging included whole brain BOLD, field map, and T1-
106 weighted structural (MEMPRAGE) images. BOLD images were acquired using
107 a protocol quantitatively optimized, using a dynamic phantom, for detection-
108 sensitivity to resting state networks [27]: SMS slice acceleration factor = 5, R
109 = 2 acceleration in the primary phase encoding direction (48 reference lines)
110 and online GRAPPA image reconstruction, TR = 802 ms, TE = 20 ms, flip
111 angle = 33°, voxel size = 2 × 2 × 1.5 mm, slices = 85, number of measurements
112 = 740 in each resting state session, for a total acquisition time of 10 minutes.
113 Field map images were acquired using the following parameters: TR = 723 ms,
114 TE1 = 4.60 ms, TE2 = 5.62 ms, flip angle = 36°, voxel size = 1.7 × 1.7 × 1.5
115 mm, slices = 89, for a total acquisition time of 3 min 14 s. The whole-brain
116 T1-weighted structural volumes were acquired using a conventional multi-echo
117 MPRAGE (MEMPRAGE) sequence with 1 mm isotropic voxel size and four
118 echoes with the following protocol parameters: TE1 = 1.61 ms, TE2 = 3.47
119 ms, TE3 = 5.33 ms, TE4 = 7.19 ms, TR = 2530 ms, flip angle = 7°, with R =
120 2 acceleration in the primary phase encoding direction (32 reference lines) and

¹²¹ online GRAPPA image reconstruction, for a total volume acquisition time of 6
¹²² min 3 s.

¹²³ *3.3. MRI pre-processing*

¹²⁴ Lifespan dataset pre-processing was conducted in the FMRIB Software Li-
¹²⁵ brary (FSL; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) and FreeSurfer
¹²⁶ (<https://surfer.nmr.mgh.harvard.edu/>): anatomical images were skull-stripped
¹²⁷ using FreeSurfer and co-registered to Montreal Neurological Institute (MNI)
¹²⁸ templates and mean functional images using FLIRT (part of FSL). Functional
¹²⁹ images were motion and fieldmap-corrected (using MCFLIRT and epidewarp),
¹³⁰ brain-extracted (using BET), and co-registered to MNI templates using trans-
¹³¹ formations learned through the anatomical image. Motion parameter as well as
¹³² tissue segmentation-extracted white-matter and CSF confounds (using FAST)
¹³³ were regressed out at ROI-level time series extraction stage using nilearn package
¹³⁴ (<https://nilearn.github.io>) [28]. Metabolic dataset pre-processing used Statisti-
¹³⁵ cal Parametric Mapping 12
¹³⁶ (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) was used as in
¹³⁷ our previous studies conducted at the same acquisition parameters [29], [25].
¹³⁸ Anatomical images (MEMPRAGE) were normalized to MNI templates using
¹³⁹ unified segmentation and registration. Images of each individual participant
¹⁴⁰ were realigned to account for head movements, and fieldmap-corrected (using
¹⁴¹ epidewarp.fsl) for geometric distortions caused by the magnetic field inhom-
¹⁴² geneity. Following normalization, structural images were probabilistically seg-
¹⁴³ mented into three tissues: grey matter, white matter, and cerebral spinal fluid.
¹⁴⁴ We did not apply spatial smoothing or global signal regression to pre-processing
¹⁴⁵ of either dataset. For all datasets, voxelwise data were parceled into the Willard
¹⁴⁶ 498 functional regions of interest (ROI) [30] corresponding entirely to grey mat-
¹⁴⁷ ter voxels.

¹⁴⁸ *3.4. Ising model*

¹⁴⁹ Here we use the principle of maximum entropy [18, 20, 23] to build the
¹⁵⁰ minimally biased probability distribution of N binary (+1 or -1) node weights,

¹⁵¹ $\{\hat{v}_i\}$ satisfying fixed constraints on the mean (0) and variance, $Var(s)$ of the
¹⁵² global property, $s(\{\hat{v}_i\}) = N^{-1} \sum_{i=1}^N \hat{v}_i$ (synchrony). This is given by [23]:

$$P(\{\hat{v}_i\}) = Z^{-1} e^{N^2 \lambda s(\{\hat{v}_i\})^2} \quad (1)$$

¹⁵³ where Z is the partition function and normalizes the distribution. λ represents
¹⁵⁴ the average node-to-node interaction strength and is the basic mechanistic quantity
¹⁵⁵ of our model (**Fig. 1a, left**). Small values of λ describe networks in which
¹⁵⁶ interactions between nodes are weak and in which the node weights are independent
¹⁵⁷ of each other. In contrast, large values of λ describe networks in which
¹⁵⁸ interactions between nodes are strong and node activities are highly correlated
¹⁵⁹ (**Fig. 1a, right**). A given value of synchrony s may be obtained in many
¹⁶⁰ different ways; *i.e.*, it is *degenerate* (**Fig. 1b**). In other words, since there
¹⁶¹ are $\binom{N}{N(1+s)/2}$ different ways to have $s = N^{-1} \sum_i \hat{v}_i$, we find that the total
¹⁶² probability $P(s)$ of different synchronies is:

$$P(\{\hat{v}_i\}) = Z^{-1} \binom{N}{N(1+s)/2} e^{N^2 \lambda s(\{\hat{v}_i\})^2} \quad (2)$$

¹⁶³ Therefore, when λ is small, $P(s)$ is determined by the degeneracy and low synchrony is most probable. Conversely, when λ is large, $P(s)$ is determined by the
¹⁶⁴ interactions between nodes and high synchrony is most probable. In particular,
¹⁶⁵ as λ is varied, the relative importance of each of these terms changes. As can be
¹⁶⁶ seen in **Fig. 1c**, this causes $P(s)$ to change from a bimodal (left) to a unimodal
¹⁶⁷ (right) distribution. The critical point, λ_c , is the value of λ where this shift
¹⁶⁸ happens (*i.e.* when these two contributions are balanced). Using the standard
¹⁶⁹ approximation of the binomial coefficients, $P(s)$ becomes:
¹⁷⁰

$$P(s) \approx Z^{-1} \binom{N}{N/2} e^{[\lambda - \frac{1}{2N}] s^2} \quad (3)$$

¹⁷¹
¹⁷² Conceptually, when $\lambda < \lambda_c$, $P(s)$ opens downwards like a Gaussian; $s = 0$
¹⁷³ is most probable. However, when $\lambda > \lambda_c$, $P(s)$ opens upwards and large values
¹⁷⁴ of s (both positive and negative) are probable. When $N = 498$ (the number of
¹⁷⁵ regions), we find that this critical point is $\lambda_c = \frac{1}{2N} = 1.004 \times 10^{-3}$, coinciding
¹⁷⁶ with the observed transition between unimodal and bimodal synchrony (**Fig.**

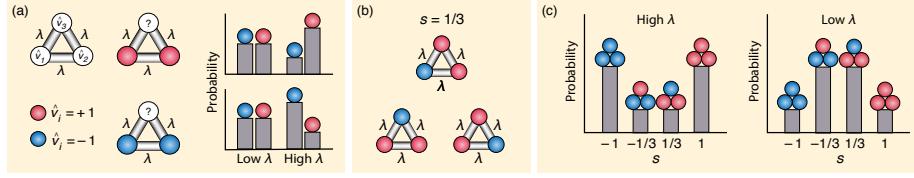


Figure 1 The Ising model predicts network probabilities from interactions between its nodes. (a) The Ising model maps binary variables onto a fully-connected network (left). Each variable ($i = 1, 2, \dots, N$) is a node with binary weight \hat{v}_i (represented by the colors red and blue), and each pair of nodes is connected by an edge with weight λ . Here we show the example of $N = 3$. The value of λ (> 0) describes the average interaction strength between nodes; the larger λ is, the more likely the unknown value of \hat{v}_3 is to be similar to its neighbors (right). (b,c) The probability of each network is determined by its synchrony (s). (b) Multiple graphs give the same value of synchrony. Since there are 3 ways to have 1 blue node and 2 red nodes, there are 3 different graphs that give $s = 1/3$ (red minus blue divided by $N = 3$). This *degeneracy* effectively triples the probability of $s = 1/3$. (c) The probability distribution of s given by the Ising model is a function of λ and degeneracy. When λ (interaction) is large, the probability that $|s| = 1$ is large (left). But, when λ is small, degeneracy wins out and the probability that $|s| = 1/3$ is large (right).

177 **1c).** To simplify our analysis, now refer to the rescaled interaction Λ : $\Lambda =$
 178 $(\lambda - \lambda_c)/\lambda_c$.

179 *3.5. fMRI binarization*

180 In order to access the time-dependent network properties of our data, we
181 first binarize the fMRI time series. This method simplifies time series while pre-
182 serving their functional connectivity (FC) patterns. In particular, the Pearson
183 correlation $\rho(X, Y)$ is widely used to estimate FC between arbitrary pairs of
184 variables (X, Y) :

$$\rho(X, Y) = \frac{Cov(X, Y)}{\sqrt{Var(X)Var(Y)}}. \quad (4)$$

185 Here variables (X and Y for example) are the nodes of a graph and ρ is the
186 weight of the edge between them. However, these connection strengths often
187 change over time [31]. Thus, we calculate ρ over each pair of successive time
188 points, reducing Eq. 4 to:

$$\begin{aligned} \rho^*(X, Y, t) &= \frac{\Delta X(t)\Delta Y(t)}{\sqrt{(\Delta X(t))^2(\Delta Y(t))^2}} = \hat{X}(t)\hat{Y}(t) \\ BDM(X, t) &= \hat{X}(t) \end{aligned} \quad (5)$$

189 where \hat{X} and \hat{Y} are the signs of the time derivatives of X and Y respectively
190 and the time-dependent correlation, ρ^* , is their product. This procedure takes
191 our original time series $X(t)$ and produces a simplified, binarized time series
192 $\hat{X}(t)$ (*Binarized Derivative Method*, BDM). By computing these binarized val-
193 ues for long periods of time, we can ask questions about how the probabilities
194 of different sequences (in time) and patterns (over regions) change with dif-
195 ferent conditions (such as with age and diet). As validation of this method,
196 we find that this simplified representation preserves fMRI FC patterns across
197 time (*Supplementary Fig. 1a*) and for different subjects (*Supplementary Fig.*
198 *1b*). This approach has two key advantages over previous methods [31, 32].
199 First, it simplifies complex, many-variable interactions in terms of dynamical
200 patterns of binary (+1 and -1) variables. Second, it is naturally compatible
201 with Ising-like models, which have been shown to be powerful tools in isolating
202 latent relationships within networks [20, 23].

203 *3.6. Model fitting*

204 We then fit the Ising model to our data (**Fig. 2**). First, we took the fMRI
205 signal $v_i(t)$ for each region i and time t and binarized it using BDM. The model
206 assumes that all nodes have, on average, similar FC strengths. We tested this
207 assumption by computing the total (over all pairs) FC for each region, and we
208 used the subject-averaged (over all diets and ages) FC matrix as our reference
209 (*Supplementary Fig. 2*). From these signals, we found that most nodes are
210 primarily positively correlated, while a few nodes were primarily negatively cor-
211 related with other nodes. For the latter, we flipped ($\hat{v}_i \rightarrow -\hat{v}_i$) for these regions
212 only in order to satisfy the assumptions of our Ising model (*Supplementary Fig.*
213 *2*). For each subject, we then computed the time-dependent *synchrony* $s(t)$ (each
214 TR is a time point) using the binarized fMRI signals from all (498) regions of the
215 brain. We then took the histogram of $s(t)$ for each subject to get a distribution
216 $P(s)$, giving the variation in synchrony per individual. This was then used to
217 obtain Λ by fitting $P(s)$ to the Ising model Eq. 2. This fit is expressed by the
218 Bayesian posterior distribution $P(\Lambda|\text{Data})$, which captures the relative quality
219 of our model. We use a uniform (unbiased) prior distribution of Λ ; thus the
220 posterior is computed directly from the likelihood function $\mathcal{L}(\Lambda|\text{Data})$ of our
221 Ising model **Eq. 2**. In practice, we will summarize this posterior by its peak
222 (the maximum likelihood estimate) and its width (error bars). As fMRI signals
223 are auto-correlated, the data ($s(t)$) are not fully independent. To compensate
224 for this effect, we consider conservative (0.01 likelihood ratio) error bars for Λ .

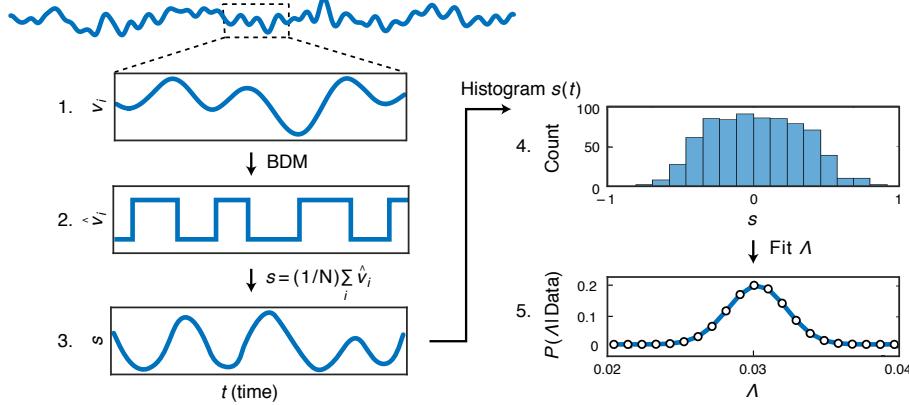


Figure 2 How we obtain the Ising model parameter Λ from fMRI data. [1] shows the fMRI signal $v_i(t)$ from the i th brain region (out of 498), as a function of time t . [2] We binarize it, to give $\hat{v}_i(t)$. [3] The binarized signals are then averaged over all brain regions, giving that individual's time-dependent *synchrony* $s(t)$. [4] We then histogram into $P(s)$ the different s values over time [4], to express the variations in an individual's synchrony levels. [5] We then find the value of Λ that best fits $P(s)$ for each individual. $P(\Lambda|Data)$ expresses the Bayesian posterior probability (with a uniform prior distribution over Λ) that our data $P(s)$ was generated from an Ising model (Eq. 2) with relative interaction strength Λ .

225 **4. Results**

226 To interpret our fMRI data, we developed a generative biophysical approach
 227 based on a network *Ising model* [19, 20]. Widely used in physics, the Ising model
 228 describes how pairwise interactions among microscopic, binary (± 1) elements
 229 give rise to macroscopic behaviors, including correlations ([19], Fig. 1). In
 230 other words, the Ising model allows us to describe time-dependent variability
 231 (probabilities) of different brain states for each subject.

232 We are particularly interested in the collective (i.e. regionally-averaged)
 233 properties of brain activity. In general, collective properties can often be de-
 234 scribed using mean-field models, where every component of interest is approx-
 235 imated as being connected to every other component with the same strength
 236 [23, 33]. Here the collective property of interest is the observed network *syn-
 237 chrony*, s , or the average activity across the 498 Willard Atlas brain regions
 238 measured in fMRI experiments [30, 23]. The probability distribution of dif-
 239 ferent synchronies can then be described by a mean-field Ising model, with a

240 single average interaction strength (assumed positive) between all pairs of brain
241 regions (see *Supplementary Figs. 2 and 3* for further justification). To explore
242 this model, we find the value of the interaction strength, Λ , that best fits the
243 experimentally observed synchrony values for each subject (**Fig. 2**). Thus, each
244 value of s corresponds to the degree of consensus of a particular network pro-
245 duced by the best-fitting Ising model [23]. As further validation for our model,
246 we find that the Ising model, regardless of age and diet, correctly captures the
247 kurtosis of $P(s)$, a higher-order feature that cannot be generally predicted from
248 correlations alone (*Supplementary Fig. 3*).

249 Ising models are useful in understanding how changes in smaller-scale prop-
250 erties (such as the interactions between brain regions) can give rise to abrupt
251 and qualitatively distinct collective phenomena at larger scales. Much like water
252 at its boiling point, which discontinuously changes from liquid to vapor, these
253 changes occur at an intermediate value of the interaction strength, called the
254 *critical point*. Here we use Λ to denote the deviation from the critical interaction
255 strength ($\Lambda = 0$) of the Ising model. Figure 3 illustrates how the distribution
256 of synchronies (with example brain networks shown for comparison) changes as
257 a function of Λ , from unimodal (low synchrony, $s = 0$, blue) when $\Lambda < 0$ to
258 bimodal (high synchrony, $s = \pm 1$, orange) when $\Lambda > 0$. While both low and
259 high synchrony networks are equally likely at the critical point (**Fig. 3**, red,
260 $\Lambda = 0$), small changes in Λ lead to large, abrupt changes in this balance.

261

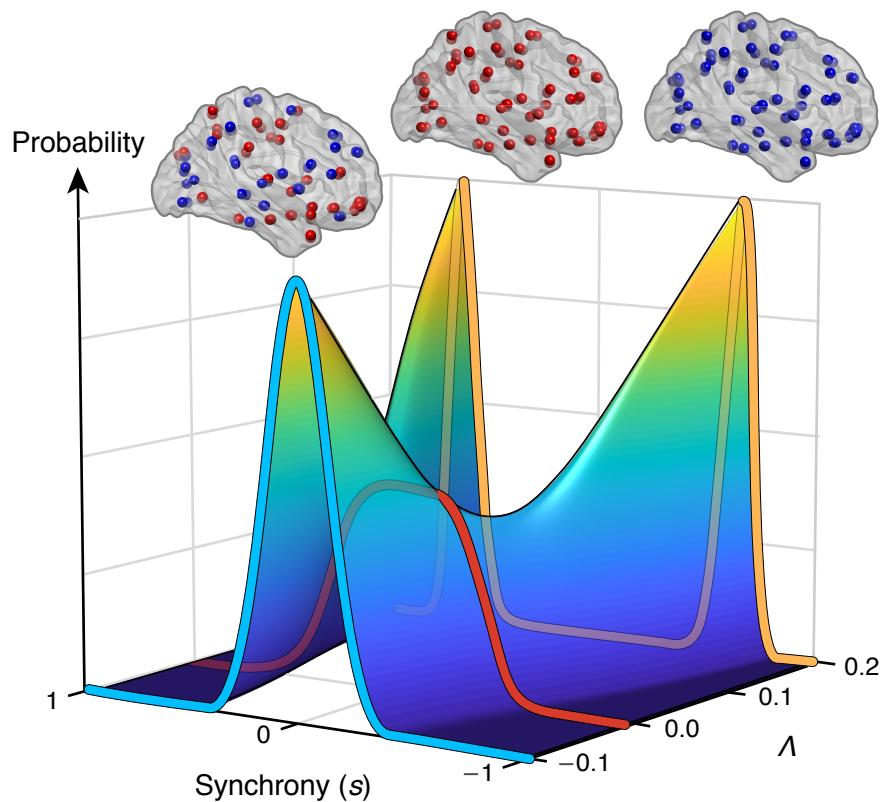


Figure 3 The Ising model applied to brain synchrony. Shown is the probability distribution of different values of synchrony (s) for different values of the dimensionless quantity Λ , reflecting the distance of the actual interaction strength, λ from the critical point λ_c : $\Lambda = (\lambda - \lambda_c)/\lambda_c$. For $\Lambda < 0$ (weak interactions), there is a single unimodal population having a peak at $s = 0$ (blue line). For $\Lambda > 0$ (strong interactions), the population is bimodal, with a peaks at $s \gg 0$ and $s \ll 0$ (orange line). Above each peak is an example network; nodes are brain regions and colors are states (red +1, blue -1). $\Lambda = 0$ defines the critical point, where $s = 0$ changes from a minimum to a maximum and $P(s)$ rapidly changes (red line). At the critical point, low and high synchrony networks are equally probable.

262 To establish the relationship between synchrony and the occupation proba-
263 bilities of specific functional networks, we separately computed the inter-subject
264 average FC matrices during periods of low and high synchrony. During peri-
265 ods of low synchrony, functional connections are found to be sparse, favoring
266 connections between local (segregated) networks of regions (**Fig. 4a**, Seg). In
267 contrast, high synchrony networks are typified by dense connections (integrated)
268 between multiple functional domains across the brain (**Fig. 4b**, Int) [10]. Con-
269 sequently, just as with synchrony (**Fig. 3**), different values of Λ change the
270 relative time spent in segregated (P_{Seg}) and integrated (P_{Int}) networks (**Fig.**
271 **4c**, $R^2 > 0.9$, sigmoidal fit not shown, each colored marker is a subject), inde-
272 pendent of age or diet. The time spent in each pattern was computed as the
273 similarity of each subject's FC to the extracted patterns, Int and Seg. When
274 $\Lambda < 0$, low synchronies (i.e. segregated networks) occur more frequently, while
275 the opposite holds when $\Lambda > 0$. In both cases, this balance rapidly shifts at the
276 critical point, $\Lambda = 0$.

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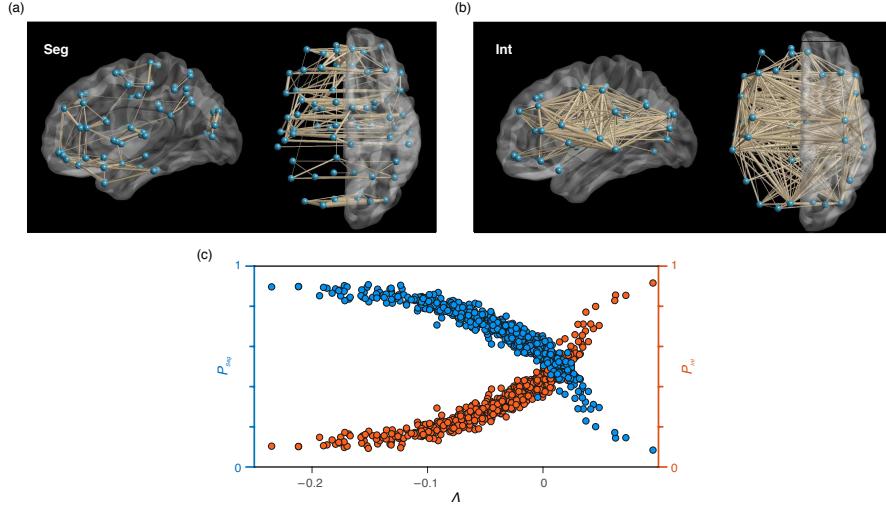


Figure 4 Λ controls the balance between segregated (low s) and integrated (high s) networks. (a,b) Inter-subject average functional connectivity (Pearson Correlation) during low (a) and high (b) synchrony, visualized using the BrainNet Viewer showing the top 10 % of connections [34]. (a) Low synchrony ($|s| = 0$) reflects segregation (Seg). (b) High synchrony ($|s| > 1/2$) reflects integration (Int). (c) The fraction of time each subject (each data point and their specific value of Λ) spends in integrated (P_{Int} , orange) and segregated (P_{Seg} , blue) networks. Time spent was calculated from a bivariate regression of the functional connectivity (here over all s , from each subject) with the patterns, Seg and Int. $\Lambda < 0$ corresponds to large P_{Seg} and small P_{Int} while $\Lambda > 0$ corresponds to the opposite. The cross-over in (c) occurs at the critical point, $\Lambda = 0$.

278 Changes in FC with both age and diet can be described by changes in the
 279 region-region interaction strength Λ . In particular, we find that Λ significantly
 280 decreases with age ($p = 1.7 \times 10^{-38}$, $N = 636$, **Fig. 5a**), suggesting that ag-
 281 ing is associated with a marked shift from integrated towards more segregated
 282 network activities. But, upon switching from a lower-energy glycolytic to a
 283 higher-energy ketogenic diet, Λ increases ($p = 1.2 \times 10^{-3}$, $N = 12$, **Fig. 5b**)
 284 by about 25% to 50% of the decrease seen over the entire lifespan. Thus, by
 285 toggling the relative frequencies of segregated and integrated networks, Λ re-
 286 flects an average cost of functional activity and, as suggested by our metabolic
 287 experiment, the amount of energy available to the brain. Thus one way the
 288 brain may conserve energy when this amount of energy available is decreased,
 289 such as through aging, is by decreasing Λ .

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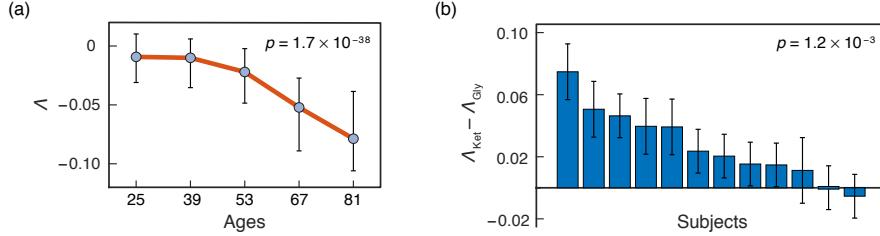


Figure 5 Λ significantly decreases with age (a, $p = 1.7 \times 10^{-38}$) and increases on the higher-energy, ketogenic diet (b, $p = 1.2 \times 10^{-3}$). (a) Each point (as well as the orange curve connecting them) reflects the median best-fit Λ values for each (of 5) equal width (14 years) age groups. Error bars represent the upper and lower quartiles. We used a Spearman-rank Permutation test ($N = 636$, $\rho(634) = -0.48$) to test significance of the nonlinear relationship between Λ and age. (b) Change in Λ for each subject ($N = 12$, $W = 3$) when switching from a lower-energy glucose (glycolytic, Gly) to higher-energy ketone (Ket) metabolism. Error bars reflect a 0.01 likelihood ratio confidence interval. A Wilcoxon 1-sided signed rank test ($N = 12$) was used to test if ketones significantly increased Λ .

291 But why would a small change in Λ lead to the dramatic changes in FC seen
 292 in older age? Precisely because young healthy brains are poised at the critical
 293 point ($\Lambda = 0$), very small changes in the interaction strength between regions
 294 lead to a sharp transition in the ratio of integrated to segregated networks
 295 [19, 20]. **Figure 6** expresses this in terms of the probability distribution of
 296 s , now viewed from the top-down. Here younger brains (green, age 25 ± 7)
 297 are near the critical point (black), allowing them to access both high and low
 298 synchrony networks. But as Λ (a proxy for energy availability, [14]) decreases,
 299 such as observed in older brains (yellow, age 81 ± 7), the probabilities of higher
 300 synchrony networks quickly fall to 0.

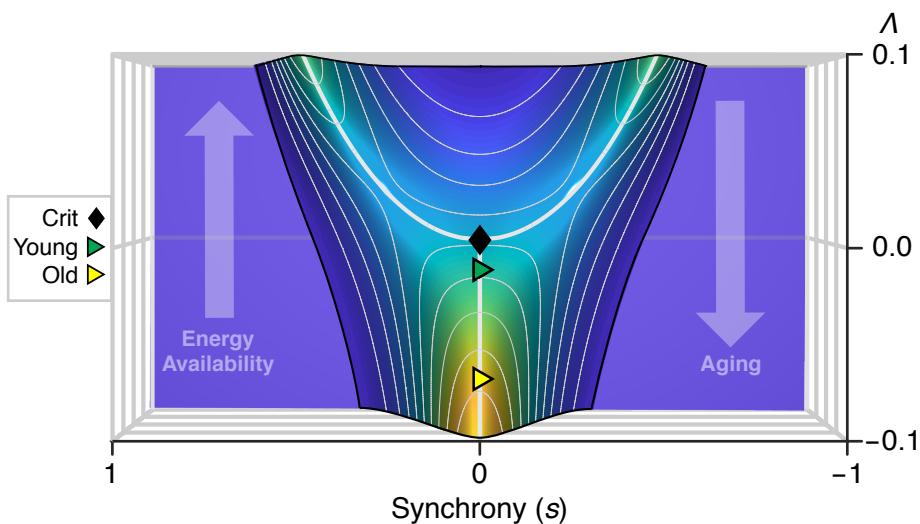


Figure 6 Younger brains are poised at a critical point; this is disrupted by decreasing energy availability. Shown is the probability distribution of synchrony (s) vs Λ , viewed from the top-down. At the critical point ($\Lambda = 0$, black), peak synchrony (indicated by a white line) changes from low ($s = 0$) towards high ($s < 0$ and $s > 0$) values. Near this transition, such as seen in younger brains (Age 25 ± 7 , $N = 85$, green), both low and high synchrony networks can be accessed. Reducing energy availability causes Λ (through associated decreases in FC, [14]) to decrease. Older brains (Age 81 ± 7 , $N = 121$, yellow) have smaller Λ and only access low synchrony networks. The plotted triangles correspond to the Λ values centered at ages 25 (Young) and 81 (Old) (Fig. 5).

301 **5. Discussion**

302 Our results suggest that the principal functional changes associated with
303 aging, in terms of network synchrony, are controlled by an average interaction
304 strength (Λ) between pairs of brain regions. Crucially, unlike graph theoretic
305 features normally used to describe such data[16], Λ encodes *how* the aging brain
306 rewires. We have also shown that Λ governs a trade-off between low-cost, seg-
307 regated and high-cost, integrated activity patterns. Furthermore, as suggested
308 by our findings, we hypothesize that Λ is decreased in older brains to com-
309 pensate for glucose hypometabolism. But, because younger brains are poised
310 near a critical point, this compensation results in sharp changes in functional
311 connectivity.

312 It is important to note that aging and ketosis each exerts independent sys-
313 temic effects that need to be considered in interpreting the results. For exam-
314 ple, older subjects often have cardiovascular changes that affect neurovascular
315 coupling[35] and thus, by extension, the blood oxygen level dependent (BOLD)
316 response measured by fMRI. Likewise, ketosis has systemic effects, such as di-
317 uresis and thus lowered blood pressure, as well as reduced cellular need for
318 oxygen, all of which also could theoretically affect BOLD. However, there are
319 several reasons to suspect that these alternative mechanisms are not the sole
320 causal influence of shifts in Λ . First, to minimize the primary cause of neu-
321 rovascular confounds, the lifespan dataset specifically excluded individuals with
322 cardiovascular disease, including cerebral ischaemia [36]. Moreover, while the
323 impact of arteriosclerosis in reducing the dynamic range of BOLD could reduce
324 signal/noise and therefore reduce the strength of measured connections over-
325 all, it would not discriminate between integrated versus segregated networks
326 and the transitions between them. Second, shifts in λ were observed not only
327 in the aging dataset, but also in the dietary dataset, the latter of which in-
328 cluded only younger individuals and thus eliminated systemic aging effects as
329 a variable. Third, systemic (non-metabolic) effects of ketosis, such as reduced
330 cerebral blood pressure and reduced need for oxygen, should decrease BOLD ac-

331 tivation, while we have previously shown ketosis to increase BOLD activation,
332 both in our dietary dataset as well as an independent dataset in which ketosis
333 was achieved by administering exogenous D- β -hydroxybuterate[25]. Nevertheless,
334 dissociating metabolic from more systemic influences of aging and ketosis
335 is one important direction for our future research.

336 The metabolic cost of connectivity is known to reflect both signaling along
337 axons as well as between synapses. As such, Λ may reflect the average synaptic
338 connectivity across the brain, as suggested by recent evidence linking global
339 resting state fMRI fluctuations to synaptic activity [21]. Indeed, synaptic con-
340 nections weaken with age [37, 38] and are particularly vulnerable to metabolic
341 disruptions [39, 40, 41, 42]. However, the fact that age was associated with a
342 reduced probability of integrated activities (with longer connections) in favor
343 of segregated activities (with shorter connections) suggests that the metabolic
344 cost of axon conductance may also play a key role. Long-range connections
345 are known to be disproportionately diminished not only with age [15] but also
346 epilepsy [43], the latter of which commonly shows improvement with ketosis.

347 That brains at their presumed peak of functionality should be poised so close
348 to a critical point of synchrony may reflect an evolutionary selective advantage.
349 Criticality is not only a widely-observed feature of neural activity[44, 45, 46],
350 but also enables the broadest range of functional patterns while also achieving
351 maximum sensitivity to external drivers (e.g. sensory stimuli) [19, 47]. Some
352 recent work suggests that signatures resembling criticality may be generic fea-
353 tures of systems with many unobserved variables [48]. However, if this were the
354 case, one would find these signatures in both younger and older brains, which
355 is not consistent with our findings.

356 In conclusion, the Ising model provides a data-driven generative model for
357 how the brain adapts to resource constraints, such as progressive glucose hy-
358 pometabolism in aging brains. By simply shifting the balance between integra-
359 tion and segregation away from the critical point, the brain is able to modu-
360 late its fuel efficiency without the need to invest in new synaptic connections
361 [7, 14]. Thus toggling Λ reflects an optimal strategy for the brain, enabling

362 the smoothest adaptation for the smallest energetic cost. At the same time,
363 the brain's protective strategy in conserving energy may produce discontinuous
364 trajectories for cognitive changes associated with aging, both in terms of di-
365 minished sensitivity to sensory stimuli (as predicted by shifts from criticality)
366 as well as cognitive processing associated with flexibility in switching between
367 both segregated and integrated networks.

368 *Data and code availability*

369 Lifespan fMRI data are publicly available from Cam-CAN [24]. Metabolic
370 fMRI data are located at Data Archive for the Brain Initiative (DABI:
371 <https://dabi.loni.usc.edu/explore/project/42>) in the Protecting the Aging Brain
372 (PAgB), Project 1926781 repository. Additional details (including links to cus-
373 tom MATLAB and Python codes used in the processing and analyses of data)
374 can be found at <http://www.lcneuro.org/software-and-instrumentation>.

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380 *CRedit authorship contribution statement*

381 LRMP designed the experiments. AA pre-processed the data. CW did the
382 modeling and designed the methods used. CW, LRMP, and KD wrote and
383 revised the paper.

384 *Declarations of interest*

385 None.

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