

Metabolism modulates network synchrony in the aging brain

Corey Weistuch^{a,b}, Lilianne R Mujica-Parodi^{a,c,d,e,f}, Anar Amgalan^{a,c,e},
Ken A Dill^{a,e,g,*}

^a*Laufer Center for Physical and Quantitative Biology, Stony Brook University, Stony Brook, USA*

^b*Department of Applied Mathematics and Statistics, Stony Brook University, Stony Brook, USA*

^c*Department of Biomedical Engineering, Stony Brook University, Stony Brook, USA*

^d*Program in Neuroscience, Stony Brook University, Stony Brook, USA*

^e*Department of Physics and Astronomy, Stony Brook University, Stony Brook, USA*

^f*Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, USA*

^g*Department of Chemistry, Stony Brook University, Stony Brook, USA*

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.

*Corresponding Author: Ken A Dill, Laufer Center for Physical and Quantitative Biology, Stony Brook University, 100 Nicolls Rd, Stony Brook, USA, 11794; Email, dill@laufercenter.org

Keywords:

fMRI, Aging, Neurometabolism, Synchrony, Ising Model, Criticality

1. Significance Statement

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

2. Introduction

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

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

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

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

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

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

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

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

3. Methods

3.1. Lifespan and metabolic neuroimaging datasets

To identify how the collective features of fMRI change across the lifespan, we analyzed a large-scale 3T fMRI dataset: the Cambridge Centre for Ageing and Neuroscience stage II (Cam-CAN: ages 18-88, $N = 636$) [24]. The Cam-CAN study was designed to identify neural correlates of normal aging and provides a roughly uniform coverage of age groups, allowing comparison between groups as well as a wide array of behavioral measures. While the functional MRI imaging of Cam-CAN stage II included both task and resting state data, we used only resting state data, for which most regions of the brain have roughly similar statistical properties (see *Supplementary Fig. 2*). To relate these changes to energy in the brain, we additionally analyzed 7T fMRI data from the Protecting the Aging Brain (PAgB) database [25]. In a within-subjects experiment, young healthy adults ($N = 12$, $\mu_{age} = 28 \pm 6.73$ years; 4 female) were scanned at resting state under two conditions: (1) *glycolytic*, following their standard diet, without fasting; and (2) *ketogenic*, following a high-fat, moderate-protein, low-carbohydrate (< 50 g/day) diet for one week, by which point all participants were in ketosis (> 0.6 mmol/L ketone blood concentration). For details on the glycolytic and ketogenic dietary regimes, as well as validation of their blood values and neurobiological effects as comparable to calorie-matched administration of glucose and D- β -hydroxybuterate, see previous work [25]. Studies were approved by the Institutional Review Boards of Cambridge University and Massachusetts 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 = $3 \times 3 \times 4.44$ 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 = $2 \times 2 \times 1.5$ 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 = $1.7 \times 1.7 \times 1.5$
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

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

3.3. MRI pre-processing

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

3.4. Ising model

Here we use the principle of maximum entropy [18, 20, 23] to build the 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 quan-
155 tity 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 inde-
157 pendent 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 syn-
164 chrony is most probable. Conversely, when λ is large, $P(s)$ is determined by the
165 interactions between nodes and high synchrony is most probable. In particular,
166 as λ is varied, the relative importance of each of these terms changes. As can be
167 seen in **Fig. 1c**, this causes $P(s)$ to change from a bimodal (left) to a unimodal
168 (right) distribution. The critical point, λ_c , is the value of λ where this shift
169 happens (*i.e.* when these two contributions are balanced). Using the standard
170 approximation of the binomial coefficients, $P(s)$ becomes:

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

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.**

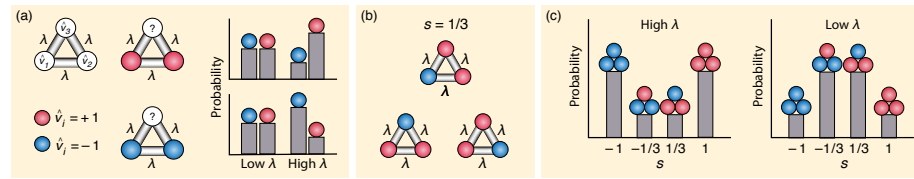


Figure 1 The Ising model predicts network probabilities from interactions between its nodes. **(a)** The Ising model maps binary variables onto a fully-connected network (**left**). Each variable ($i = 1, 2, \dots, N$) is a node with binary weight \hat{v}_i (represented by the colors red and blue), and 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 of neurons [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 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 .

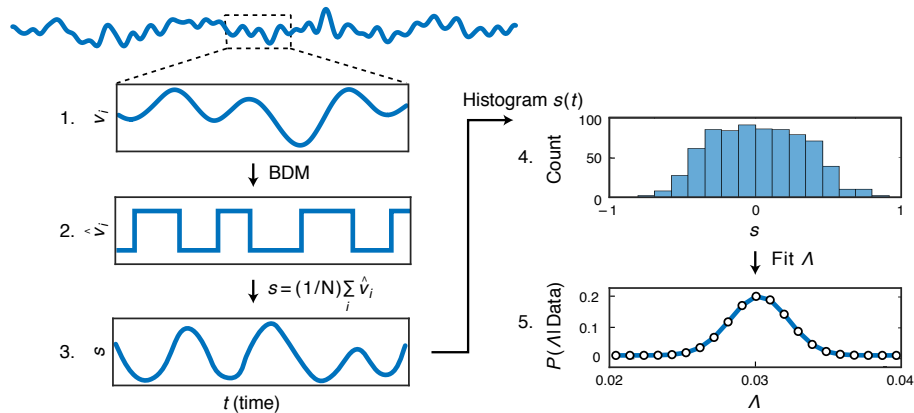


Figure 2 How we obtain the Ising model parameter Λ from fMRI data. [1] shows the fMRI signal $v_i(t)$ from the i th brain region (out of 498), as a function of time t . [2] We binarize it, to give $\hat{v}_i(t)$. [3] The binarized signals are then averaged over all brain regions, giving that individual's 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. $P(\Lambda|\text{Data})$ 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 .

4. Results

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

We are particularly interested in the collective (i.e. regionally-averaged) properties of brain activity. In general, collective properties can often be described using mean-field models, where every component of interest is approximated as being connected to every other component with the same strength [23, 33]. Here the collective property of interest is the observed network synchrony, s , or the average activity across the 498 Willard Atlas brain regions measured in fMRI experiments [30, 23]. The probability distribution of different synchronies can then be described by a mean-field Ising model, with a

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

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

261

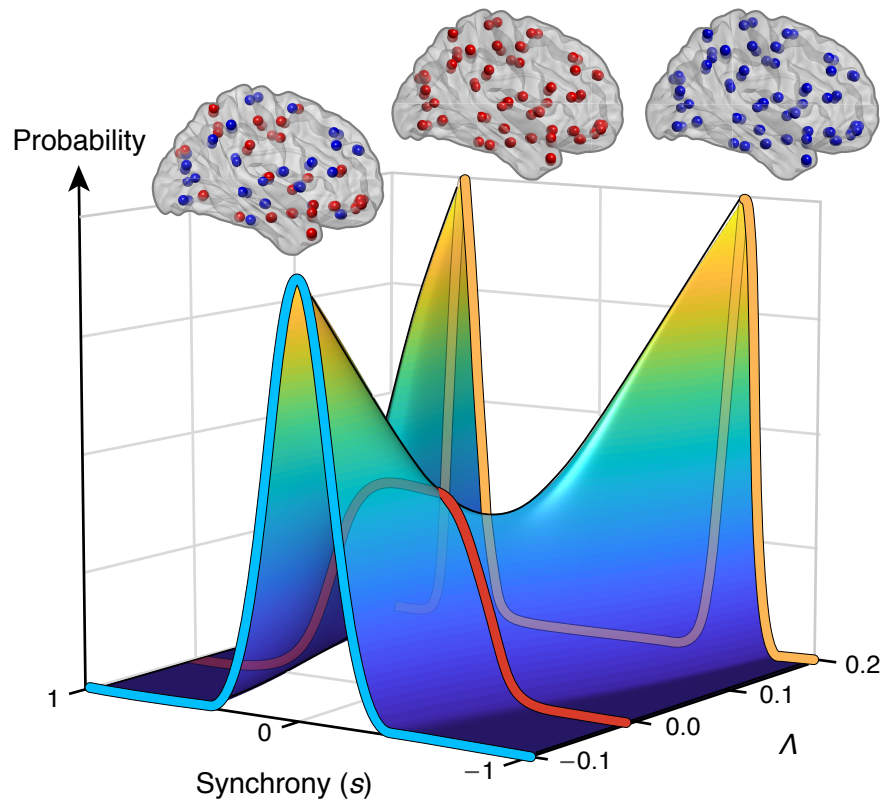


Figure 3 The Ising model applied to brain synchrony. Shown is the probability distribution of different values of synchrony (s) for different values of the dimensionless quantity Λ , reflecting the distance of the actual interaction strength, λ from the critical point λ_c : $\Lambda = (\lambda - \lambda_c)/\lambda_c$. 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, $\Lambda = 0$.

277

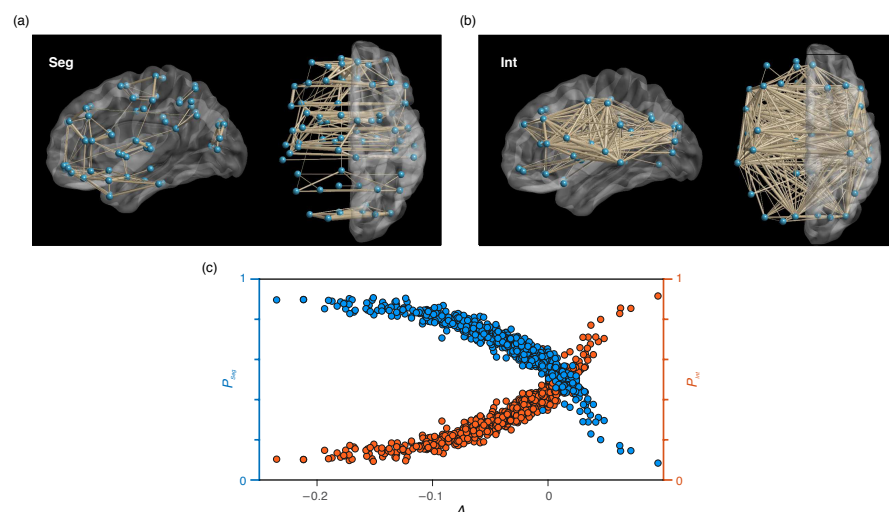


Figure 4 Λ controls the balance between segregated (low s) and integrated (high s) networks. (a,b) Inter-subject average functional connectivity (Pearson Correlation) during low (a) and high (b) synchrony, visualized using the BrainNet Viewer showing the top 10 % of connections [34]. (a) Low synchrony ($s = 0$) 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 .

290

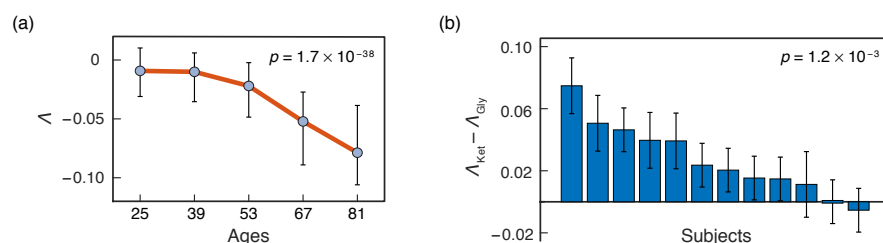


Figure 5 Λ significantly decreases with age (**a**, $p = 1.7 \times 10^{-38}$) and increases on the higher-energy, ketogenic diet (**b**, $p = 1.2 \times 10^{-3}$). (**a**) Each point (as well as the orange curve connecting them) reflects the median best-fit Λ values for each (of 5) equal width (14 years) 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.

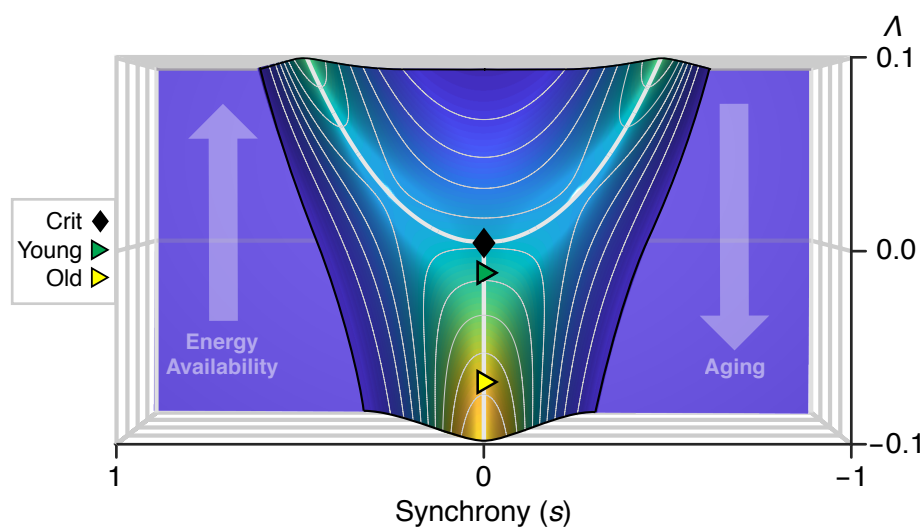


Figure 6 Younger brains are poised at a critical point; this is disrupted by decreasing energy availability. Shown is the probability distribution of synchrony (s) vs Λ , viewed from the top-down. At the critical point ($\Lambda = 0$, black), peak synchrony (indicated by a white line) changes from low ($s = 0$) 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]. Neverthe-
334 less, 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>.

375 *Acknowledgments and Funding*

376 The research was funded by the WM Keck Foundation (LRMP, KD), the
377 NSF BRAIN Initiative (LRMP, KD: ECCS1533257, NCS-FR 1926781), and the
378 Stony Brook University Laufer Center for Physical and Quantitative Biology
379 (KD).

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.

386 **References**

- 387 [1] Lisa Mosconi. Glucose metabolism in normal aging and alzheimers disease:
388 methodological and physiological considerations for pet studies. *Clinical*
389 *and translational imaging*, 1(4):217–233, 2013.
- 390 [2] Manu S Goyal, Andrei G Vlassenko, Tyler M Blazey, Yi Su, Lars E Couture,
391 Tony J Durbin, Randall J Bateman, Tammie L-S Benzinger, John C Morris,
392 and Marcus E Raichle. Loss of brain aerobic glycolysis in normal human
393 aging. *Cell metabolism*, 26(2):353–360, 2017.

- 394 [3] Christian-Alexandre Castellano, Scott Nugent, Nancy Paquet, Sébastien
395 Tremblay, Christian Bocti, Guy Lacombe, Helene Imbeault, Eric Turcotte,
396 Tamas Fulop, and Stephen C Cunnane. Lower brain 18f-fluorodeoxyglucose
397 uptake but normal 11c-acetoacetate metabolism in mild alzheimer’s disease
398 dementia. *Journal of Alzheimer’s Disease*, 43(4):1343–1353, 2015.
- 399 [4] Jessica R Andrews-Hanna, Abraham Z Snyder, Justin L Vincent, Cindy
400 Lustig, Denise Head, Marcus E Raichle, and Randy L Buckner. Disruption
401 of large-scale brain systems in advanced aging. *Neuron*, 56(5):924–935,
402 2007.
- 403 [5] Linda Geerligs, Remco J Renken, Emi Saliasi, Natasha M Maurits, and
404 Monique M Lorst. A brain-wide study of age-related changes in functional
405 connectivity. *Cerebral cortex*, 25(7):1987–1999, 2015.
- 406 [6] Sophie Achard and Ed Bullmore. Efficiency and cost of economical brain
407 functional networks. *PLoS Comput Biol*, 3(2):e17, 2007.
- 408 [7] Ed Bullmore and Olaf Sporns. The economy of brain network organization.
409 *Nature Reviews Neuroscience*, 13(5):336–349, 2012.
- 410 [8] Louis A Profenno, Anton P Porsteinsson, and Stephen V Faraone. Meta-
411 analysis of alzheimer’s disease risk with obesity, diabetes, and related dis-
412 orders. *Biological psychiatry*, 67(6):505–512, 2010.
- 413 [9] Daihong Liu, Lihua Chen, Shanshan Duan, Xuntao Yin, Wu Yang, Yanshu
414 Shi, Jiuquan Zhang, and Jian Wang. Disrupted balance of long-and short-
415 range functional connectivity density in type 2 diabetes mellitus: A resting-
416 state fmri study. *Frontiers in Neuroscience*, 12:875, 2018.
- 417 [10] Andrew Zalesky, Alex Fornito, Luca Cocchi, Leonardo L Gollo, and Michael
418 Breakspear. Time-resolved resting-state brain networks. *Proceedings of the*
419 *National Academy of Sciences*, 111(28):10341–10346, 2014.
- 420 [11] Karl J Friston. Modalities, modes, and models in functional neuroimaging.
421 *Science*, 326(5951):399–403, 2009.

- 422 [12] Olaf Sporns. Network attributes for segregation and integration in the
423 human brain. *Current opinion in neurobiology*, 23(2):162–171, 2013.
- 424 [13] Danielle Smith Bassett and ED Bullmore. Small-world brain networks. *The*
425 *neuroscientist*, 12(6):512–523, 2006.
- 426 [14] Dardo Tomasi, Gene-Jack Wang, and Nora D Volkow. Energetic cost of
427 brain functional connectivity. *Proceedings of the National Academy of Sci-*
428 *ences*, 110(33):13642–13647, 2013.
- 429 [15] Dardo Tomasi and Nora D Volkow. Aging and functional brain networks.
430 *Molecular psychiatry*, 17(5):549–558, 2012.
- 431 [16] Richard F Betzel and Danielle S Bassett. Generative models for network
432 neuroscience: prospects and promise. *Journal of The Royal Society Inter-*
433 *face*, 14(136):20170623, 2017.
- 434 [17] Réka Albert and Albert-László Barabási. Statistical mechanics of complex
435 networks. *Reviews of modern physics*, 74(1):47, 2002.
- 436 [18] Gasper Tkacik, Elad Schneidman, II Berry, J Michael, and William
437 Bialek. Spin glass models for a network of real neurons. *arXiv preprint*
438 *arXiv:0912.5409*, 2009.
- 439 [19] Thierry Mora and William Bialek. Are biological systems poised at criti-
440 cality? *Journal of Statistical Physics*, 144(2):268–302, 2011.
- 441 [20] Elad Schneidman, Michael J Berry, Ronen Segev, and William Bialek.
442 Weak pairwise correlations imply strongly correlated network states in a
443 neural population. *Nature*, 440(7087):1007–1012, 2006.
- 444 [21] Marieke L Schölvinck, Alexander Maier, Q Ye Frank, Jeff H Duyn, and
445 David A Leopold. Neural basis of global resting-state fmri activity. *Pro-*
446 *ceedings of the National Academy of Sciences*, 107(22):10238–10243, 2010.
- 447 [22] Li Zhao, David C Alsop, John A Detre, and Weiyang Dai. Global fluctua-
448 tions of cerebral blood flow indicate a global brain network independent of

- 449 systemic factors. *Journal of Cerebral Blood Flow & Metabolism*, 39(2):302–
450 312, 2019.
- 451 [23] Gašper Tkačik, Olivier Marre, Dario Amodei, Elad Schneidman, William
452 Bialek, Michael J Berry, et al. Searching for collective behavior in a large
453 network of sensory neurons. *PLoS computational biology*, 10(1), 2014.
- 454 [24] Jason R Taylor, Nitin Williams, Rhodri Cusack, Tibor Auer, Meredith A
455 Shafto, Marie Dixon, Lorraine K Tyler, Richard N Henson, et al. The cam-
456 bridge centre for ageing and neuroscience (cam-can) data repository: struc-
457 tural and functional mri, meg, and cognitive data from a cross-sectional
458 adult lifespan sample. *Neuroimage*, 144:262–269, 2017.
- 459 [25] Lilianne R Mujica-Parodi, Anar Amgalan, Syed Fahad Sultan, Botond An-
460 tal, Xiaofei Sun, Steven Skiena, Andrew Lithen, Noor Adra, Eva-Maria
461 Ratai, Corey Weistuch, et al. Diet modulates brain network stability, a
462 biomarker for brain aging, in young adults. *Proceedings of the National
463 Academy of Sciences*, 117(11):6170–6177, 2020.
- 464 [26] Kiyotaka Sato, Y Kashiwaya, CA Keon, N Tsuchiya, MT King, GK Radda,
465 B Chance, K Clarke, and RL Veech. Insulin, ketone bodies, and mitochon-
466 drial energy transduction. *The FASEB Journal*, 9(8):651–658, 1995.
- 467 [27] Daniel J DeDora, Sanja Nedic, Pratha Katti, Shafique Arnab, Lawrence L
468 Wald, Atsushi Takahashi, Koene RA Van Dijk, Helmut H Strey, and Lil-
469 ianne R Mujica-Parodi. Signal fluctuation sensitivity: An improved metric
470 for optimizing detection of resting-state fmri networks. *Frontiers in Neu-
471 roscience*, 10:180, 2016.
- 472 [28] Alexandre Abraham, Fabian Pedregosa, Michael Eickenberg, Philippe
473 Gervais, Andreas Mueller, Jean Kossaifi, Alexandre Gramfort, Bertrand
474 Thirion, and Gaël Varoquaux. Machine learning for neuroimaging with
475 scikit-learn. *Frontiers in neuroinformatics*, 8:14, 2014.

- [29] Jaime S Ide, Sanja Nedic, Kin F Wong, Shmuel L Strey, Elizabeth A Lawson, Bradford C Dickerson, Lawrence L Wald, Giancarlo La Camera, and Lilianne R Mujica-Parodi. Oxytocin attenuates trust as a subset of more general reinforcement learning, with altered reward circuit functional connectivity in males. *Neuroimage*, 174:35–43, 2018.
- [30] Andre Altmann, Bernard Ng, Susan M Landau, William J Jagust, and Michael D Greicius. Regional brain hypometabolism is unrelated to regional amyloid plaque burden. *Brain*, 138(12):3734–3746, 2015.
- [31] R Matthew Hutchison, Thilo Womelsdorf, Elena A Allen, Peter A Bandettini, Vince D Calhoun, Maurizio Corbetta, Stefania Della Penna, Jeff H Duyn, Gary H Glover, Javier Gonzalez-Castillo, et al. Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage*, 80:360–378, 2013.
- [32] James M Shine, Oluwasanmi Koyejo, Peter T Bell, Krzysztof J Gorgolewski, Moran Gilat, and Russell A Poldrack. Estimation of dynamic functional connectivity using multiplication of temporal derivatives. *NeuroImage*, 122:399–407, 2015.
- [33] L.D. Landau and E.M. Lifshitz. *Mechanics*. Number v. 1. Elsevier Science, 1982.
- [34] Mingrui Xia, Jinhui Wang, and Yong He. Brainnet viewer: a network visualization tool for human brain connectomics. *PloS one*, 8(7):e68910, 2013.
- [35] Mark D’Esposito, Leon Y. Deouell, and Adam Gazzaley. Alterations in the bold fmri signal with ageing and disease: a challenge for neuroimaging. *Nature Reviews Neuroscience*, 4(1):9, 2003.
- [36] Meredith A. Shafto, Lorraine K. Tyler, Marie Dixon, Jason R. Taylor, James B. Rowe, Rhodri Cusack, Andrew J. Calder, William D. Marslen-Wilson, John Duncan, Tim Dalgleish, Richard N. Henson, Carol Brayne,

- 504 Fiona E. Matthews, and C. A. N. Cam. The cambridge centre for age-
505 ing and neuroscience (cam-can) study protocol: a cross-sectional, lifespan,
506 multidisciplinary examination of healthy cognitive ageing. *BMC neurology*,
507 14(1):25, 2014.
- 508 [37] Yuri Geinisman, Leyla de Toledo-Morrell, Frank Morrell, Inna S Persina,
509 and Marvin Rossi. Age-related loss of axospinous synapses formed by two
510 afferent systems in the rat dentate gyrus as revealed by the unbiased stere-
511 ological dissector technique. *Hippocampus*, 2(4):437–444, 1992.
- 512 [38] Thomas C Foster and Christopher M Norris. Age-associated changes in
513 ca^{2+} -dependent processes: Relation to hippocampal synaptic plasticity.
514 *Hippocampus*, 7(6):602–612, 1997.
- 515 [39] Julia J Harris, Renaud Jolivet, and David Attwell. Synaptic energy use
516 and supply. *Neuron*, 75(5):762–777, 2012.
- 517 [40] Simonetta Camandola and Mark P Mattson. Brain metabolism in health,
518 aging, and neurodegeneration. *The EMBO journal*, 36(11):1474–1492,
519 2017.
- 520 [41] Fei Yin, Alberto Boveris, and Enrique Cadenas. Mitochondrial energy
521 metabolism and redox signaling in brain aging and neurodegeneration. *Antioxidants & redox signaling*, 20(2):353–371, 2014.
- 523 [42] Dimitrios Kapogiannis and Mark P Mattson. Disrupted energy metabolism
524 and neuronal circuit dysfunction in cognitive impairment and alzheimer’s
525 disease. *The Lancet Neurology*, 10(2):187–198, 2011.
- 526 [43] S. Nedic, S.M. Stufflebeam, C. Rondinoni, T.R. Velasco, A.C. dos Santos,
527 J.P. Leite, A.C. Gargaro, L.R. Mujica-Parodi, and J.S. Ide. Using network
528 dynamic fmri for detection of epileptogenic foci. *BMC Neurology*, 15(1):262,
529 2015.

- 530 [44] Luca Cocchi, Leonardo L Gollo, Andrew Zalesky, and Michael Breakspear.
531 Criticality in the brain: A synthesis of neurobiology, models and cognition.
532 *Progress in neurobiology*, 158:132–152, 2017.
- 533 [45] Dante R Chialvo. Emergent complex neural dynamics. *Nature physics*,
534 6(10):744–750, 2010.
- 535 [46] Jens Wilting and Viola Priesemann. 25 years of criticality in neuro-
536 scienceestablished results, open controversies, novel concepts. *Current opin-
537 ion in neurobiology*, 58:105–111, 2019.
- 538 [47] John M Beggs. The criticality hypothesis: how local cortical networks
539 might optimize information processing. *Philosophical Transactions of
540 the Royal Society A: Mathematical, Physical and Engineering Sciences*,
541 366(1864):329–343, 2008.
- 542 [48] David J Schwab, Ilya Nemenman, and Pankaj Mehta. Zipfs law and crit-
543 icality in multivariate data without fine-tuning. *Physical review letters*,
544 113(6):068102, 2014.