1 **Full title: Identifying optimal working points of individual Virtual Brains: A large-scale brain**
2 **network modelling study**

3 **Short title: Optimal working points of individual Virtual Brains**

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18 **Abstract**

19 Using The Virtual Brain (TVB, thevirtualbrian.org) simulation platform, we explored for 50 individual adult human
20 brains (ages 18-80), how personalized connectome based brain network modelling captures various empirical
21 observations as measured by functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). We
22 compare simulated activity based on individual structural connectomes (SC) inferred from diffusion weighted imaging
23 with fMRI and EEG in the resting state. We systematically explore the role of the following model parameters:
24 conduction velocity, global coupling and graph theoretical features of individual SC. First, a subspace of the parameter
25 space is identified for each subject that results in realistic brain activity, i.e. reproducing the following prominent
26 features of empirical EEG-fMRI activity: topology of resting-state fMRI functional connectivity (FC), functional
27 connectivity dynamics (FCD), electrophysiological oscillations in the delta (3-4 Hz) and alpha (8-12 Hz) frequency
28 range and their bimodality, i.e. low and high energy modes. Interestingly, FCD fit, bimodality and static FC fit are
29 highly correlated. They all show their optimum in the same range of global coupling. In other words, only when our
30 local model is in a bistable regime we are able to generate switching of modes in our global network. Second, our
31 simulations reveal the explicit network mechanisms that lead to electrophysiological oscillations, their bimodal
32 behaviour and inter-regional differences. Third, we discuss biological interpretability of the Stefanescu-Jirsa-
33 Hindmarsh-Rose-3D model when embedded inside the large-scale brain network and mechanisms underlying the
34 emergence of bimodality of the neural signal.

35 With the present study, we set the cornerstone for a systematic catalogue of spatiotemporal brain activity regimes
36 generated with the connectome-based brain simulation platform The Virtual Brain.

37 **Author Summary**

38 In order to understand brain dynamics we use numerical simulations of brain network models. Combining the structural
39 backbone of the brain, that is the white matter fibres connecting distinct regions in the grey matter, with dynamical
40 systems describing the activity of neural populations we are able to simulate brain function on a large scale. In order to
41 make accurate prediction with this network, it is crucial to determine optimal model parameters. We here use an
42 explorative approach to adjust model parameters to individual brain activity, showing that subjects have their own
43 optimal point in the parameter space, depending on their brain structure and function. At the same time, we investigate
44 the relation between bistable phenomena on the scale of neural populations and the changed in functional connectivity
45 on the brain network scale. Our results are important for future modelling approaches trying to make accurate
46 predictions of brain function.

47 **Introduction**

48 Brain network models allow us to investigate how realistic neural behaviour arises as a function of variations in specific
49 neural parameters. Large-scale brain network models combine empirical data from multiple modalities into a
50 framework where we can test predictions using non-invasive techniques in humans (1). These models take as input
51 imaging data, for instance the structural connectivity (SC) map of white matter pathways derived from diffusion
52 weighted imaging, and predict brain behaviour. Models are used to estimate how this behaviour arises as a function of
53 the anatomical connectome taking into account features such as noise (stochastic fluctuations in the signal due to
54 internal and external factors), transmission delays (the speed with which the signal travels along physical pathways), or
55 connectivity weighting (the strength of pathways between regions). Realistic values of these features in the brain are
56 then estimated by fitting the simulated signal to the empirical signal.

57 ***The Virtual Brain***

58 The Virtual Brain (TVB; thevirtualbrain.org) is a simulation platform that integrates local neural mass models with
59 large-scale long-range global connectivity dynamics driven by individual SC(2–7). A unique feature of TVB is the
60 ability to model “personalized virtual brains”, whereby an individual’s DTI derived SC, optionally combined with
61 directionality information from CoCoMac, constrains the inter-regional interactions. This allows researchers to make
62 subject-specific hypotheses, and to investigate individual differences in parameter values (i.e. of conduction speed, etc.)
63 that may lead to biologically significant neural activity. TVB has previously been used, for example, to model
64 biophysical correlates of recovery after stroke in adults(8,9), and children(10), or brain activity dynamics pre and post
65 surgery in brain tumor patients(11,12) with the goal of aiding the design of therapeutic interventions(13), or to identify
66 biophysical mechanisms underlying seizure dynamics, with the ability to accurately predict spatial spread of the
67 epileptic seizure (14,15). With the healthy connectome, TVB has been used for instance to study the timing of cognition
68 neural behaviour during transcranial direct current stimulation (16), effects of plasticity and learning(17) or to
69 understand individual structure-function relations in healthy individuals(18).

70 (See <http://www.thevirtualbrain.org/tvb/zwei/neuroscience-publications> for a full list of publications).

71 The TVB model combines local (at the level of neural populations) and global (network-level) features to capture the
72 dynamics of the neural system. A local model, for example the Stefanescu-Jirsa Hindmarsh-Rose 3D (SJHMR3D)(19)
73 defines the mean-field behaviour at the nodal level (see below for a detailed description). Local dynamics are then

integrated across the system via the long-range fibers represented by the individual's SC and global parameters such as conduction speed and long-range coupling, which describe the structural-temporal integration across the cortex. Optimal model fit (simulated FC to empirical FC) is highly dependent on the global coupling and conduction speed values. (8,9,13,18,20–23). See equation 1 in Methods for a mathematical description of these parameters.

Conduction Velocity: Conduction velocity describes the speed with which the signal travels between the nodes, and is used to estimate time delays based on distances derived from an individual's diffusion tractography. Thus, propagation of neural signal will be faster for dense, myelinated neural fibers compared to smaller fibers for the same distance (24). With a fixed distance, a large conduction velocity will result in a short time delay; a small conduction velocity will result in a large time delay and slower system. Conduction velocity in TVB and similar models has been associated with important features of healthy and diseased brains (9,21,22).

Global coupling: Long-range global coupling describes the balance of local and global dynamics, and consequently has an effect on the resulting efficiency of the system(8). The long-range coupling is a scaling factor for the individual's tractography-derived connectivity weights. Higher long-range global coupling describes a system where the local (intra-regional) dynamics have a stronger influence on a region's activity compared to the global (inter-regional) dynamics. That is, the inputs from within the regions play a stronger role than the input from other regions. Conversely, a low global coupling means that global dynamics have a stronger influence compared to local dynamics. Long-range coupling parameter values in TVB may serve as relevant biomarkers to identify clinical populations (8). Specifically, long-range global coupling in TVB has been associated with important neural mechanisms in health as well as disease. For example: tuning the network close to a bifurcation point (25), exploration of the dynamical landscape (21), motor recovery in stroke (8–10), seizure activity (26), Alzheimer's disease (27–29) efficiency of the system in the pathological brain(8). Moreover, alpha band power in an MEG model was a function of transmission delays and global cortical coupling(30). Optimal global parameters have been shown to give rise to a number of empirical resting-state behaviours such as network synchronization(31), fluctuations in the stability of the system leading to the emergence of new resting-state networks (RSN)(25), changes in the attractor landscape(32), the engagement and disengagement of various subnetworks (33), and realistic alpha band activity(30). An optimal point in these parameters defines the manifestation of these behaviours.

Previous TVB Studies

Several studies with TVB are limited by the number of metrics fitted (often a single metric such as FC fit), modalities simulated, sample size, and/or are focused on pathological changes in these neural parameters lacking a full

103 investigation of the healthy brain. The following are a few examples. We are focusing here on what our present study
 104 provides beyond state-of the art. Thereby we acknowledge the value of these previous publications on which our present
 105 study builds to further extend our present scope of understanding Falcon et al (2015, 2016) investigated stroke in TVB
 106 have a sample size of 30 (31) subjects. These authors explored global coupling, conduction velocity, and local coupling
 107 (K12, K11 and K21) of the SJHMR3D model (8,9). The simulated data was validated by comparing to empirical in
 108 terms of amplitude, frequency and FC. The parameters were optimized in a stepwise manner, rather than exploring the
 109 full grid of all parameter combinations as done in the present study. Another study on exclusively healthy subjects used
 110 the same local model and the SC of 9 individuals to fit simulated FCs to their empirical counterpart (18). This
 111 procedure was also used in another study when varying global coupling to simulate 42 virtual brains (10). In the study
 112 of Kunze et al., the standard SC provided by TVB was used to assess the effect of transcranial direct current stimulation
 113 (tDCS) on frequency, FC and postsynaptic potentials of pyramidal cells (16). These authors varied the parameters global
 114 coupling and maximum voltage scaling of the tDCS. In another study, the effect of different parcellation size and short-
 115 range connectivity on simulation results was investigated using 10 random connectomes of the human connectome
 116 project (14). Different number of regions, global and local coupling parameters and different local models (Reduced
 117 Wong-Wang and FitzHugh-Nagumo) were simulated and later analysed with graphtheoretical measures, entropy and
 118 principal component analysis. A Hopf-Bifurcation model was used in the study of Deco et al. fitting simulated blood
 119 oxygenation level dependent (BOLD) signal to empirical FC and FCD (34). The optimal fit was found tuning a local
 120 bifurcation parameter and global coupling. Tuning of a single excitability parameter of the Epileptor model was used to
 121 model individual epileptic brains for 1 and 15 patients, respectively (14,15). The simulated data was fitted to determine
 122 clinical epilepsy propagation zones. TVB was also used to simulate rat brains (35) and macaque brains(36). With an
 123 evolutionary optimization algorithm and the Generic 2D oscillator the simulated FC was tuned to fit its empirical
 124 counterpart.

125 In sum, parameter grid-search explorations and FC fitting are a common approach in brain modelling. In the present
 126 study, we utilize a larger sample size (N = 50) of healthy subjects across the full age spectrum, and a more detailed
 127 description of the effects from parameters on neural and BOLD signal, as well as the convergence across several fitting
 128 metrics.

129 **Present Study**

130 We conduct a comprehensive parameter exploration of personalized brain network models in a sample of 50 healthy

131 human brains (18 to 80 years of age, mean 41.12 ± 18.20 ; 30 females and 20 males) using TVB. The goal is to show
132 that there exists a specific set of neural parameters for which virtual brains operate in a biologically realistic manner in
133 the resting-state, and that these parameters converge at a particular, unique, point for each individual across several
134 metrics. Typically, a single correlation metric for comparison of FCs, for a single modality, is used to assess model fit in
135 simulations studies. Yet, the assessment across multiple modalities and metrics is critical in order to validate how
136 optimal models are.

137 We show that there exists a particular subset in the parameter space, unique to each individual, where several metrics
138 converge to produce the best fit of the simulated to the empirical data, and reproduce important empirical features of
139 EEG and fMRI. The results are shown for alpha as well as delta frequency electrophysiological activity. Specifically, we
140 show that this optimal fit parameter subset is similar for the following metrics: 1) the correlation between empirical and
141 simulated BOLD FC, 2) fit of simulated to the empirical BOLD FCD 3) frequency of the mean neural signal, as well as
142 4) a bimodal power distribution of the neural signal at an alpha frequency, a feature that has been observed in
143 empirical(37–41), and simulated (42,43) EEG data(44,45). Our simulations reveal the mechanisms that lead to the
144 bimodal behaviour, as well as inter-regional differences in bimodality.

145 High-power alpha-frequency oscillations are a robust finding in resting-state electroencephalography (EEG) of the
146 human brain(39–41,44,46–48). Bimodality in the distribution of the power in the alpha frequency band refers to the
147 bursting between two distinct modes that is observed in the empirical signal (37,38)and has also been modelled as a
148 function of noise(42). The characterization of the power distribution provides more information about the temporal
149 behaviour of the system than the traditional power spectrum, which reports only the mean power. The bimodality that is
150 observed in the empirical signal demarcates a switching, or bimodality, between low and high amplitude alpha
151 oscillations arising from a dynamical instability of the system in the presence of stochastic noise (37,38,42). In recent
152 work, TVB simulations have demonstrated feasibility to simulate alpha oscillations (17,18). To date its capability to
153 reproduce bimodality of alpha has not been explored.

154 We here investigate how empirical-simulated fMRI FC correlations and the electrophysiological alpha frequency power
155 distribution vary as a function of conduction velocity and long-range coupling. We focus on the global parameters of
156 conduction velocity and long-range coupling because these variables have an influence on the large-scale
157 spatiotemporal dynamics. In addition, we will also report the effect of local inhibitory and excitatory synaptic coupling

158 parameters (parameters K12 = inhibitory on excitatory, K11 = recurrent excitatory, K21 = excitatory on inhibitory) (19)
 159 within a single (i.e. unconnected) population model.

160 **Methods**

161 ***Data acquisition***

162 Simultaneous EEG-fMRI data, dwMRI, and structural MRI were recorded from 50 healthy adult subjects at Berlin
163 Center for Advanced Imaging, Charité University Medicine, Berlin, Germany (18 to 80 years of age, mean $41.12 \pm$
164 18.20 ; 30 females and 20 males). Subjects were voluntarily recruited, and had no self-reported history of cognitive,
165 neurological or psychiatric conditions. Informed consent was provided to subjects before participating in the study, and
166 the research was conducted in accordance with the Code of Ethics of the World Medical Association Declaration of
167 Helsinki, and approved by the local ethics community at Charité University. The data acquisition procedures are those
168 reported by our colleagues (18) and are summarized here.

169 Images were acquired on a Siemens Tim Trio MR scanner (12-channel Siemens head coil). Anatomical and dwMRI
170 acquisition was performed first, after which subjects were taken out of the scanner to have their EEG cap set up.
171 Subjects then returned to the scanner for simultaneous EEG-fMRI measurements. Subjects lay in the scanner with their
172 eyes closed and were asked not to fall asleep.

173 High resolution $1 \times 1 \times 1$ mm T1-weighted scans were acquired with an MPRAGE sequence: repetition time (TR) =
174 1900ms, echo time (TE) = 2.25ms, flip angle (FA) = 98, field of view (FoV) = 256mm, 256 matrix, 192 sagittal slices,
175 slice thickness = 1mm. EEG and fMRI were recorded for 22 minutes at resting state. We used an echo planar imaging
176 (EPI) T2* sequence: 666 volumes, TR = 1940 ms, TE = 30ms, FA = 78, FoV = 192, 64 matrix, voxel size = $3 \times 3 \times 3$
177 mm^3 , 32 transversal slices, slice thickness = 3mm. The first five images of the blood oxygen level dependent (BOLD)
178 fMRI series were removed to prevent disturbance from saturation effects. Diffusion-weighted MR echo-planar
179 measurements were conducted with: TR = 7500ms, TE = 86ms, FoV = 220mm, 96 matrix, voxel size =
180 $2.3 \times 2.3 \times 2.3$ mm, 61 transversal slices, slice thickness = 2mm; 64 diffusion gradient directions with b-values = 1000
181 s/mm^2 .

182 ***Brain imaging data preprocessing***

183 Preprocessing of anatomical, diffusion and functional data was performed using our pipeline for derivation of individual
184 connectomes (49). The preprocessing steps are described in detail there, and more briefly below. Preprocessing of T1-
185 weighted images included the following: motion correction, intensity normalization, extraction of non-brain tissue,
186 brain mask generation, and segmentation of cortical and subcortical grey matter. We used the parcellation from the
187 Desikan-Killiany Atlas (50) implemented in FREESURFER to divide the cortex into 68 regions of interest. A quality
188 check of the parcellation of individual high-resolution T1-weighted scans was performed manually.

189 The dwMRI data was preprocessed as follows: motion and eddy current correction, linear registration of b0 image to

individual T1-weighted image. The anatomical cortical parcellations were transformed to individual diffusion space, where probabilistic tractography was conducted. Spherical deconvolution was applied to constrain tractography, using MRTrix streaming method, which has the ability to identify crossing fibers (FA threshold = 0.1)(51). The gray matter – white matter interface was exhaustively sampled, streamlining up to 200,000 times from each voxel (radius of curvature = 1mm, maximum length = 300mm). Binary connections for each region pair, based on the Desikan-Killiany atlas, were then aggregated, and a 68 by 68 SC was obtained. The region labels are listed in Table S1. A weights and distance matrix was calculated for each subject. Weights matrices were the number of voxel pairs between two ROIs with at least one track found. We modified the weights matrix by using the common logarithm of its values and then normalizing to its highest value. Distance matrices were the mean track length of fibers between each pair of ROIs, measured in mm. In brief, the functional data was preprocessed as follows: motion correction, brain extraction, high-pass filter (100s), registration to individual T1-weighted anatomical scans to apply high-resolution parcellation mask to the fMRI. Additionally, quality of BOLD signal was analyzed with temporal signal to noise to maps (52).. BOLD signal was averaged across voxels within brain regions. Functional connectivities were computed using a Pearson's linear correlation coefficient on the BOLD data of each region pair.

204 *The TVB Model: Local and Global Dynamics*

205 *Global Dynamics*

206 The global behaviour of the system is driven by interactions between individual nodes, as described by the conduction
207 velocity and long-range coupling.

208 The local dynamics at a node i can be described by **Eq. 1**

$$x_i(t+1) = x_i(t) + f(x_i(t))dt + c \sum_{j=1}^N w_{ij} x_j(t - \Delta t_{ij})dt + \sqrt{2*D} + \sqrt{dt} + \eta(t) \quad 1$$

209 **Eq. 1** Global equation of TVB

210 The local mean-field potential of node i is integrated across time $t=1:T$ by taking the sum of its current potential $x_i(t)$,
211 the derivative of the local model $f(x_i(t))dt$, the scaled input of all other nodes $j=1:N$ and the influence of noise. The
212 parameter D scales the dispersion of the gaussian distribution from which random values are drawn $\eta(t)$. Connectivity
213 weights (i.e. individual diffusion tractography derived structural connectivity weights combined with optional
214 CoCoMac directionality information(53)) are defined here as w_{ij} , where the connection weight scales the influence of
215 node j on node i . The time delays of signal propagation, $\Delta t_{ij} = d_{ij}/v$ are influenced by distances, d_{ij} (ie diffusion

tractography derived distances between regions), and conduction velocity, v . The long-range coupling factor, c , does an additional scaling of influence (15).

Simulations and global parameters

The simulations were performed with TVB v1.5. TVB input was the individual SC, and a combination of local and global parameters describing the nodal and network level dynamics. Different parameter combinations were simulated in two sets for each individual subject, with global and local parameters described in Table 1 and 2 respectively. The neural signal in the first set of simulation oscillated with a frequency of around 2-5 Hz whereas in the second set around 8-12Hz. We will call them delta and alpha sets respectively. All computations described in the following section were performed on a high performance computer consisting of multicore CPUs at a clock rate of ~ 2.50 GHz per CPU core and 8GB RAM per core. The time per simulation was approximately 10h (1.6h) for integration step size 0.01220703125 ms (0.05ms) for the delta (alpha) set. In total we tested 1615 parameter combinations for each subject resulting in 80750 simulations with a total simulation length of ~ 6554 h. The total computation time was ~ 230000 h.

Table 1: Global parameters for delta and alpha sets.

Parameters	Delta set	Alpha set
Global coupling	linear	linear
a (multiplicative)	[0.05:0.01:0.25]	[0.025:0.0001:0.04]
b (additive)	0	0
Conduction speed	[20:20:100]	[10:10:100]
Integrator Integration step size Additive noise	HeunStochastic dt = 0.01220703125 ms D = 1.0	HeunStochastic dt = 0.05 ms D = 0.001
Monitors: <i>SubSample</i> (of neural signal) sampling period	3.90625ms (= 256Hz)	3.90625ms (= 256Hz)
BOLD HRF Kernel sampling period	MixtureOfGammas 500ms (=2Hz)	MixtureOfGammas 500ms (=2Hz)
Duration of simulated time series	180s	300s

228

Table 2: Local parameters in delta and alpha set simulations.

Parameter	r	a	b	c	d	s
Delta set	0,006	1.0	3.0	1.0	5.0	4.0
Alpha set	0,006	1.0	3.0	1.0	5.0	4.0
Parameter	xo	K11	K12	K21	σ	μ
Delta set	-1.6	0.5	0.1	0.15	0.3	2.2
Alpha set	-1.6	4.0	1.6	0.15	0.4	2.2

229 We coupled local nodes via long-range connections in the model. The anatomical connectome served as the structural
 230 backbone of these connections. In both sets, we varied two free parameters in order to examine the spatiotemporal
 231 dynamics: the global coupling which scales the input to a node from others and the conduction speed (mm/ms) which
 232 represented delays in the propagation of the signal. The global coupling scaling factor is named “a” in the TVB
 233 interface. In this article, we will refer to it as just global coupling or “G”. The goal was to achieve a good approximate
 234 fit between the simulated and empirical FCs. Due to changes of local parameters, we also changed the noise distribution
 235 and integration step size in the second set of simulations. BOLD time-series were generated by convolving the neural
 236 signal with a mixture of gamma kernel of 20s length (54).

237 **Local Stefanescu-Jirsa 3D Model**

238 We used a local Stefanescu-Jirsa 3D Hindmarsh-Rose (SJHMR3D) mean-field model (19) in TVB to simulate nodal
 239 neural behaviour. The SJHMR3D is a biologically realistic model based on a network of heterogeneous excitatory and
 240 inhibitory coupled Hindmarsh-Rose neurons (55) that exhibit a complex repertoire of neural behaviour - such as
 241 synchronization and random firing, multiclustering, bursting, transient oscillations and oscillation death. Coupled
 242 neurons of the detailed network showed reorganizing behaviour into clusters with similar dynamics. Using mode
 243 decomposition techniques the authors were able to capture cluster dynamics from the detailed network in a low
 244 dimensional representation of only 3 modes. The set of equations **Eq.2** describe local dynamics at a node i , with each
 245 state variable being a vector of length 3 to represent the different modes. SJHMR3D aims to describe the average
 246 membrane potential of a population of neurons that are electrically coupled. The model is comprised of six differential
 247 equations representing interconnected neural populations of excitatory (x, y, z), and inhibitory (w, v, u) populations as
 248 such:

$$\begin{aligned}\dot{x}_i &= y_i - ax_i^3 + bx_i^2 - z_i + [K_{11}(X_1 - x_i) - K_{12}(X_2 - x_i)] + IE_i \\ \dot{y}_i &= c_i - dx_i^2 - y_i \\ \dot{z}_i &= rsx_i - rz_i - m_i \\ \dot{w}_i &= v_i - aw_i^3 + bw_i^2 - u_i + K_{21}(X_1 - w_i) + II_i \\ \dot{v}_i &= h_i - p_i w_i^2 - v_i \\ \dot{u}_i &= rsw_i - ru_i - n_i\end{aligned}$$

2

249 **Eq. 2.** Local dynamics of the SJHMR3D model.

250 **Legend:** x, y, z, v, w, u – state variables; a, b, c, d – constants representing fast ion channels; r – constant representing
251 slow ion channels; s – bursting strength; IE, II – excitatory and inhibitory input current; K_{11} – excito-excitatory
252 coupling; K_{12} – inhibito-excitatory coupling; K_{21} – excitato-inhibitory coupling; X_1, X_2 – mean field potential of
253 inhibitory and excitatory subpopulation; m, n, p, h – constant parameters.

254 Here, $x(t)$ and $w(t)$ represents the membrane potential, $y(t)$ and $v(t)$ represents the recovery variable via fast ion
255 channels, and $z(t)$ and $u(t)$ the inward current via slow channels in the membrane. From each simulation the state
256 variables x and w have been recorded. Their three modes were averaged to generate the mean field potential of
257 excitatory and inhibitory neurons. The local parameters that we used for the simulations are described in Table 2.

258 Our goal was to create resting state activity that shows the electrophysiological alpha band frequency oscillation that is
259 present in empirical EEG data. In order to achieve faster oscillations in the alpha set we had to not only change the
260 global but also the local parameters. Therefore, we conducted an exploration of the local model and its parameters
261 which is described in detail in the supplementary materials S1 Text. Shortly summarized we simulated 2250 different
262 combinations of parameters in an uncoupled network (i.e. connections weights = 0) to observe the effect of parameter
263 changes on the local model. From there we selected those combinations which peaked around 8-12 Hz in the spectral
264 density.

265 **Data Analysis**

All data preprocessing and analysis has been performed with Python and the statistical computing language R (56). Figs
have been generated with the Python library Seaborn. In order to allow the neural signal to stabilize, and to account for
random initial conditions in our simulation, we deleted the first 2 s of each simulated time series. The BOLD signal was
simulated using a mixture of gammas kernel as a hemodynamic response function (HRF). To account for the 20 s
length of the kernel, we removed the first 20s of the BOLD signal. For better comparison of simulated to empirical data,
we down-sampled the simulated BOLD signal to a 2Hz sampling frequency. Simulated FC was derived by Pearson-
correlating all brain regions' pairs of simulated BOLD signals. Correlation was also used to quantify similarities
between the simulated and the empirical FC:

266 *Bimodality: Hartigan's Dip Test*

267 For every neural signal, we calculated a time-frequency analysis using Scipy's spectrogram function(57). The frequency
268 with the highest power values in the spectrogram was then used to test for bimodality. We used Hartigan's Dip test (as
269 implemented in R) on the distribution of power coefficients of the selected frequency to assess whether power is uni-
270 modally or bi-modally distributed. With $p < 0.05$, we can reject our null-hypothesis that the distribution is unimodal and
271 therefore it must at least be bimodal. Bimodality of the mean simulated neural signal was assessed, whereby mean
272 neural signal was taken as the average of all regional time series. We also conducted this analysis on a regional level to
273 account for potential regional differences in bimodality. For an example of unimodal and bimodal power distribution
274 see Fig 1.

275 **Fig 1. Example of a unimodal and a bimodal power distribution of the simulated neural signal of an individual**
276 **subject.** Time series in A and B were simulated using parameters as in the alpha set with different global coupling
277 strength. $G = 0.03$ and $G = 0.0328$ for A and B respectively. Each panel depicts the neural signal, a time-frequency
278 analysis and on the right the distribution of power coefficients at the highest power frequency for a unimodal (bimodal)
279 signal. In B the time series and spectrogram show a switching between high and low amplitude oscillations. Hartigan's
280 Dip Test p-values are 1 and <0.001 for the unimodal and bimodal distribution.

281 As the frequency of the oscillations varies across simulations, we are not assessing the same frequency for every
282 simulation. Rather, we test the frequency that is most dominant in the signal, i.e. the frequency that has the highest
283 power in spectrogram. Therefore subsequent figures which assess bimodality for a certain parameter range will have
284 corresponding figures showing the dominant frequencies which were tested.

285 *Functional Connectivity Dynamics (FCD)*

286 It is known that FC is not static over time. It rather changes and switches between different modes during rest (58) but
287 also during tasks(59), learning(60), sleep(61), sedation (62)and aging(63). Resting state FCD is also affected by
288 diseases such as schizophrenia (64) or Alzheimer's (65)

289 The non-stationarity of functional connections has been modeled before already(66). Hansen et al. modeled a large-
290 scale brain network model with three different local models. They show that only a mean field model with enhanced
291 non-linearity was able to create switching between states in the FCD. Since our local model is highly non-linear we

292 expect to see dynamical changes in functional connections as well.

293 In order to characterize FCD, we required a longer simulation to be able to divide the time series into meaningful time

294 windows. To this end, we conducted 22 minutes simulations for four sample subjects. We used local parameters and

295 global coupling values from alpha set. Conduction speed was set to the subject specific optimum derived from the

296 previous analysis of the alpha set simulations. For each simulated BOLD signal, we created an FCD matrix. Time

297 windows of size 60s with an overlap of 40s were used for all FCDs. The fit between empirical and simulated FCD was

298 assessed with Kolmogorov-Smirnoff Distance(34).

299 *Subject Specificity*

300 An important feature of TVB is to provide subject specific simulations. Since we know that structure shapes function

301 (67–70) in the brain one could assume that by providing a subject specific input the output fits best to its own empirical

302 data, i.e. by using individual SCs as a structural backbone of a simulation we generate data that is closer to its own

303 empirical counterpart than to that when using SCs of other subjects. So far, we compared simulated to empirical FCs of

304 the same subject to optimize our parameters. To test for subject specificity of our TVB model predictions, we compared

305 all simulated FCs of a subject to the empirical FCs of all other subjects to determine whether the best fit is achieved

306 with the subjects own FC or the FC of another subject.

307 Results

308 We conducted two sets of simulations and examined the effect of global parameters such as global coupling and
 309 conduction speed on the generated signal and the comparison to empirical data. In one set our chosen parameters
 310 produced delta-frequency activity (hence delta set), and in the other we modelled oscillations in the more prevalent
 311 alpha band frequency (hence alpha set), which is common in human EEG signal. Bimodality in this frequency range has
 312 been previously reported as a biological tenet of the signal (37,38,42). Because we were interested in the bimodality
 313 mechanisms in the alpha, we conducted more extensive exploration of the alpha set. Afterwards, we present the
 314 mechanism that generates bimodality in our model, and finally we focus on the subject specificity of our models.

315 *Overview of the simulation sets.*

316 In both simulation set the parameter conduction speed and global coupling were varied. In the first simulation set
 317 conduction speed was explored in a range from 20 mm/ms to 100 mm/ms in steps of 20 mm/ms and global coupling
 318 from 0.05 to 0.25 in steps of 0.01. This gave rise to 5250 simulations (50 subjects * 105 parameter combinations). For
 319 the second set, achieving bimodality in the alpha frequency oscillations, we varied conduction speed from 10 mm/ms to
 320 100 mm/ms in steps of 10 mm/ms and global coupling from 0.025 to 0.04 in steps of 0.0001, for a total of 75500
 321 simulations (50 subjects * 1510 parameter combination). Aside from different ranges for the global parameters, also the
 322 local parameters have changed (**Table 2**). All simulations were evaluated by their goodness of fit to their corresponding
 323 empirical FC by correlation. This produced one 3D matrix with the dimensions [subjects, conduction speed values,
 324 global coupling values] for each simulation set. The elements of the matrix are correlation coefficients. Similarly, a 3D
 325 matrix was calculated for bimodality and frequency analysis of the mean neural signal. To visualize our results we
 326 averaged over the [subjects] dimension of each 3D matrix. The result is a 2D matrix with dimensions [conduction speed
 327 and global coupling]. The elements are the averaged metrics. (**Fig 2**).

328 **Fig 2. Overview of the parameter exploration generating oscillations in the alpha and delta rhythm range.** Both
 329 sets varied the parameters conduction speed and global coupling, but across different ranges. 1st row shows prediction
 330 quality (comparison of simulated and empirical data) of all simulations averaged across all subjects. 2nd row
 331 bimodality assessed on the mean neural signal using Hartigan's dip test. 3rd row Frequency of the oscillating mean
 332 neural signal. For both simulation sets there is an overlap between best empirical-simulated FC fit and bimodality of
 333 the neural signal at distinct global coupling. 4th row Distribution of optimal parameter points for all subjects derived by
 334 correlation to empirical FC. Density plot is smoothed with a Gaussian kernel. Best fits can be seen across a wide range

of speed, but only few coupling values. The scatter plot showing a linear relation between optimal global coupling and average degree. (delta: $r = -0.68$, $p < 0.0001$, alpha $r = -0.88$, $p < 0.1 \cdot 10^{-15}$). Average degree was defined as the mean of row sums in each SC.

We demonstrate that best predictions of empirical signal features (FC, oscillations and bimodality of the neural signal) arise as a function of particular ranges of neural parameters, which we term the optimized parameters. Empirical features were optimally reproduced through our models at a wide range of conduction speeds, but only in a narrow range of global coupling values. For the delta (alpha) set these were around $G = 0.1 - 0.14$ ($0.0280 - 0.031$).

The mean best correlation to empirical data for individual subjects was 0.45 (0.514) with $STD = 0.094$ (0.088) and highest correlation = 0.66 (0.68) in the delta (alpha) set. The distribution of best correlations to empirical FCs are shown in **Fig 6 (D)**, red density estimate). We compared the alpha and delta sets, and found that correlation fits were in the same range (Wilcoxon signed-rank test on the distribution of best correlations of the two sets was non-significant). Bimodality can be seen at global coupling values between 0.11 and 0.14 ($0.0286 - 0.031$) and was more likely to appear at higher conduction speeds. (The fastest average oscillation was observed at lower couplings than the peaks of the two other metrics. As we increased global coupling from low absolute values, an increase in frequency was observed in the delta set. This continued until a critical point at which the oscillation speed began to decrease again. In the alpha set the frequency is continuously decreasing as a function of global coupling. However, if we explore the parameter space more to the left of the x-axis the same phenomenon, increasing frequency, should be visible. We will explain this mechanism later, when we explore bimodality.

Because averaging over subjects may obscure individual features of the signal, we also extracted an optimal parameter set for each subject. Optimal was defined as the best fit to empirical FC. The 50 resulting parameter combinations were plotted in a 2D density plot (**Fig 2 4th row**).

Again, we observed that best fits to empirical data were distributed across many conduction speed values but in a narrow range of global coupling. Interestingly, in the delta set there were two modes of highest fit along the conduction speed axis, suggesting a large degree of between-subject variability in this metric. Some subjects had best fits at conduction speeds around 40 mm/ms whereas others had best fits around 100 mm/ms. Within the alpha set the optimal parameters were distributed around one single mode. Distribution parameters of individual optimal points can be seen in

Table 3: Parameters of optimal working point distributions.

	Delta set		Alpha set	
	Global coupling	Conduction speed [mm/ms]	Global coupling	Conduction speed [mm/ms]
Median	0.14	80	0.03	50
Mean	0.1398	70.8	0.0304	50
Standard Dev.	0.0113	26.56	0.0021	25.0713

361 We found that the optimal global coupling is correlated to the average degree of the SC used for the simulation. In both
362 simulation sets optimal coupling decreased with increasing average degree, $r = -0.68$, $p < 0.0001$ for delta and $r = -0.88$,
363 $p < 0.1 \cdot 10^{-15}$ for alpha set.

364 This is because the output of a node is multiplied by weights of the SC and then scaled by the global coupling factor
365 (**Equation 1**). Therefore, strongly connected SCs require lower couplings than weak connected ones. We examined
366 whether a similar relation exists between optimal conduction speed and features of the SC. We checked for the relation
367 to numerous graph theoretical measure like degree, characteristic path length or average clustering of SC (weights and
368 tract lengths) and FC, but found no significant correlation.

369 We were interested in the variability of our findings across the connectome. To this end, we analysed bimodality and the
370 frequency of the neural signal of each region individually. Results are visualized in **Fig 3**, with data averaged across
371 subjects.

372 **Fig 3. Regional behaviour of neural signal for delta and alpha set simulations.** 1st and 3rd row depicts the effect of
373 global coupling on regional bimodality and frequency. Bimodality and fast oscillations only occur at a critical range of
374 global coupling. (The peak in bimodality occurs at coupling values slightly higher than for the maximum frequency. 2nd
375 and 4th row depicts the effect of conduction speed on regional bimodality and frequency. The oscillations get faster with
376 higher speed, but bimodality is observed only for speed greater than 20 [mm/ms].

377 Similarly, to what we found for the global signal, regional signals at critical values of conduction speed and global
378 coupling also shaped oscillations and bimodality. Optimal values of conduction speed occurring at the higher end of the
379 range. Note that the averaging across the subjects and global coupling dimensions when generating **Fig 3** renders the p-
380 values of the Hartigan's dip test of bimodality non-significant, therefore we show the percentage of subjects with
381 bimodality (i.e. $p > 0.05$) on the colorbar. The trend of more subjects with bimodality around $G = 0.14$ (0.0295) and at
382 conduction speeds of 60-100 mm/ms (> 20 mm/ms) in the delta (alpha) set, is indicative of the optimal parameter space
383 that shows significant bimodality within individual subjects. At the same positions in oscillations in the respective
384 frequency band were generated.

385 Within the delta set we found an interesting distribution of features across regions, with only some showing bimodal
386 power distribution and faster oscillations. In order to understand the basis of these inter-regional differences, we

387 examined the relationship between degree and bimodality: We took the regional Hartigan's Dip Test p-value at optimal
388 parameter points and plotted against the mean degree of each region. We showed that regions that have a bimodal power
389 distribution were also strongly connected within the network, **Fig. 4 C**. Regional bimodality in anatomical space was
390 shown in **Fig. 4 B**. Here, the nodes connected by the thickest edges (i.e. high degree) were coloured blue (i.e.
391 bimodality). Bimodality was observed primarily along the parietal and temporal cortex ($p < 0.05$ for most of these
392 regions). However, not all subjects at their optimal parameter combinations showed bimodality within these regions
393 (these are the outliers in the **Fig 4 A**). At their optimal parameter point, 80% (92%) of subjects in the delta (alpha) set
394 showed bimodal power distribution for their mean neural signal.

395 **Fig 4. Anatomical distribution of bimodality in the delta set.** A: At the optimal parameter point of each subject we
396 assessed bimodality for all regions on the left (lh_...) and right (rh_...) hemisphere. Distribution of Hartigan's Dip Test
397 p-values per region are shown in a boxplot. Regions are sorted from top to bottom by decreasing degree. B: 3D graph of
398 our brain network model. To display edges, we used the mean SC across subjects, thresholded to a sparsity of 17% (i.e.
399 showing only 17% strongest connections). Edge thickness represents the connection weight. Node colors represent the
400 mean p-value at optimal parameter points, with blue colors indicating bimodality. C: 2D histogram showing relation
401 between regional bimodality and mean degree. At the optimal parameter combination we assessed bimodality in each
402 region. All graphs indicate how strongly connected brain regions observe bimodality at the optimal parameter point.

403 For the alpha set the regional analysis did not reveal as much of the inter-regional variation. At the optimal parameter
404 point, nearly all regions demonstrated bimodal power distribution. Regions with number 4 and 38 are the entorhinal
405 cortices of both hemispheres showing no bimodality. With a degree of 7.5 and 6.4 for left and right hemisphere
406 respectively, they share the lowest degree of the whole connectome. Their activity seems to be mostly uncoupled from
407 the rest of the system.

408 **Mechanisms underlying alpha bimodality**

409 Bimodality can be described as the switching of the neural signal between two modes:
410 One mode with high and another with low amplitude to no oscillation. Bimodality was observed in both simulation sets.
411 The high amplitude signal oscillated with 10-14 Hz and 2-4 Hz in the alpha and delta set respectively. The low
412 amplitude mode showed no neural oscillations. We were interested in understanding the mechanisms underlying
413 bimodality. To this aim, we conducted further simulations where we decreased global couplings gradually in five steps
414 to 0 (**Fig 5 and S1 Video**). At $G = 0$, there are no influences between nodes in the network, as we set the inter-regional

connections to 0 (the local activity at the nodes was multiplied by 0). Thus, the mean field potential was the time series generated solely by the local SJHMR3D model, without the influences of the network within which the node resides.

Fig 5. Bimodal behaviour of neural dynamics in the brain network model. Time series represent simulated neural activity in the left inferior temporal cortex of an exemplary subject. Local parameters were chosen as in the alpha set with conduction speed set to 100. Plots from top to bottom with increasing global coupling 0, 0.01, 0.025, 0.032 and 0.04. Blue time series depict the mean field potential (i.e. neural signal). Green is the global input to the inferior parietal cortex from all other nodes, scaled by connectivity weights and global coupling. On the right, the excitatory phase space is depicted with excitatory state variables x , y and z . For $G = 0$ it shows the switching between a limit cycle and a fixed point, creating a burst like behaviour. With increasing G the system gets more and more shifted towards the fixed point. It reaches oscillation death at $G = 0.04$. For $G = 0.032$ we have can observe a bimodal state between oscillation death (i.e. residing in the fixed point) and oscillations (i.e. limit cycling).

With the present local parameters (**Table 2**) and no global coupling, we observed a bursting behaviour in the neural signal that has been documented by the authors of the model. The burst is sometimes called square wave bursting, due to the burst shape. A fold/homoclinic bifurcation is characteristic for this type of burst, where the trajectory follows a limit cycle in the 3D phase space and generates spikes. Meanwhile the slow variable (z) increases and moves an unstable fixed point towards the limit cycle, generating a saddle homoclinic bifurcation, i.e. the unstable fixed point touches the cycle and breaks it up. The trajectory then switches towards a stable fixed point, which corresponds to the resting period. During “rest”, the slow variable decreases and moves the unstable system back towards the stable fixed point creating a fold bifurcation - a transition from rest back to spiking. This bifurcation type has been described for the single Hindmarsh-Rose neuron(71), which is the foundation of the SJHMR3D.

As we increased global coupling (to $G = 0.01$), we began to see the impact of other regions on the local model. At a global coupling of 0.01, regions were unsynchronized, and the global input consisted of noisy fluctuations. Note that the global input range was negative (y -axis of **Fig 5**). This is because the SJHMR3D model’s excitatory state variable x has a negative baseline (and positive values during spikes). When state variable x -reflecting the membrane potential of the excitatory population- was coupled with a linear scaling function to other regions of the network, it results in an inhibiting effect during baseline activity (when its values were negative) and an excitatory effect during spikes (when its values were positive). In other words, in SJHMR3d it can happen that an excitatory population *decreases or increases* the membrane potential of another neural population, depending of the current membrane potential (i.e. whether it is negative or positive).

444 For even higher couplings ($G = 0.025$), we observed a synchronization of local dynamics with global input. The
445 regional neural signal displayed single spikes or bursts with few spikes rather than the bursting behaviour we had
446 observed at $G = 0$. In the phase space there were only a few turns on the limit cycle before the homoclinic bifurcation
447 occurs. The global input became even more negative (ie -4) than at $G = 0.01$. We show that the spiking in the regional
448 neural signal actually coincided with the times at which the global input reached 0. This can be interpreted as a
449 temporary reduction in global inhibition that leads to spikes in the local model.

450 For very high global coupling ($G = 0.04$), oscillation death occurred. The spikes and bursts were no longer present and
451 very slow noisy fluctuations in the neural signal were observed. The neural signal and the global input had negative
452 amplitudes and fluctuated very little. The trajectory remained at a stable fixed point.

453 The state of bimodality occurred in between the synchronized and the oscillation death state ($G = 0.032$). Namely, we
454 observed a switching between oscillation death and spikes that occur in synchrony with a reduction in global inhibition.
455 We show this behaviour in **S1 Video**.

456 Note, that the observation we made in the delta set – that there were regional differences in bimodality due to variations
457 of regional degree, was not found in the alpha set. This may be due to differences in local parameters such as K_{11} , K_{12}
458 or σ between the two sets. It can be shown that only by changing K_{12} , global dynamics change between
459 unsynchronized and total synchronization, and regional differences in frequency arise (**Fig S7**).

460 **Subject specificity**

461 We were interested in the subject specificity of a subject's simulations, and the degree to which parameters are driven
462 by empirical SC and FC. To determine the subject specificity of simulations, we first assessed how a subject's set of
463 simulated FCs fits to empirical FC of other subjects (Methods). If simulations are subject specific, we would expect
464 simulated FC to fit best to a subject's own empirical FC than to that of others. We therefore correlated the set of 105
465 (1510) simulated FCs in the delta (alpha) set of each subject to all subject's 50 acquired empirical FCs. This procedure
466 yields one highest possible correlation for each pair of: subject's set of simulations, and empirical FCs. Generating a 2D
467 matrix of size 50×50 with dimensions: being empirical FC x a subject's set of simulated FCs. The diagonal of that
468 matrix represents the individual subject comparison, (a subject's simulated FC compared to their own empirical FC). If
469 simulations were subject specific, we would see the highest correlation values on this diagonal.

470 Note that the simulated FC that fits best to the same subject's empirical FC may not necessarily be the same simulated
471 FC that fits best to other subjects, (i.e. optimal parameter points may vary if we compare a set of simulations of one
472 subject to empirical FCs of other subjects). We therefore extracted 50 optimal parameter points for each subject and
473 visualized these (**Fig 6 and 7**).

Fig. 6. Cross subject comparison of simulations results. A (B): Delta set (alpha set): Left: We correlate all 105 (1510) simulations of one subject to all 50 empirical FC's. For each empirical FC we correlate to, there will be one best (i.e. highest) correlation. In other words comparing all simulations from one subject to all FC's, generates 50 highest possible correlations. Resulting in a 50*50 matrix when comparing for all 50 subjects. Along the diagonal of the matrix we find the highest possible correlation for the individual subject prediction. (i.e. predicting a subject's empirical FC by using the same subject's SC for simulation). Horizontal red and blue stripes already indicate that some empirical FC's can be predicted better than others, regardless of the SC used for the simulation. Middle: The same as the left matrix but now comparing simulations to SC, instead of empirical FC's. We test the possible prediction SC's from the simulation. A vague red diagonal indicates a best individual fit. Pointing to the fact that the simulated FC contains typical features of the used SC. Right: To test for subject specificity we now take the diagonal values (i.e. subject's individual prediction) and test their distribution against the values above and below the diagonal (i.e. all-to-all prediction). Comparing simulations to empirical FC shows no significant better individual prediction. Individual SC's can be predicted significantly better than all-to-all (two-sample Kolmogorov-Smirnoff test $d = 0.4963$ ($d = 0.5492$) and $p < 0.1 \cdot 10^{-9}$ ($p < 0.1 \cdot 10^{-12}$) for delta (alpha)). This indicates how strong the SC shapes the simulated FC. C: Left matrix shows correlation between all 50 empirical FCs. There e.g. the FC of subject #27 is very different to the rest FC, see the blue horizontal and vertical line. Right matrix is the same for SCs. The SC's seem to be much more homogeneous. Compare the high correlation coefficients on the colorbar. Middle matrix shows how similar FCs are to SC's Already without simulation some FC's can be predicted better by many SC's. E.g. see the red horizontal line for subject #29 and #35 D: Left: Scatterplot from comparison of the SC to empirical FC and empirical FC to set of simulated FCs. The better an empirical FC correlates to any given SC, the better we can predict it by simulating on that SC. Correlation $r = 0.73$ ($r = 0.8$) with $p = 0$ ($p = 0$) for delta (alpha) set. Right: Best possible individual prediction of empirical FC by SC and simulated FC, as well as SC by simulated FC. (top delta set, bottom alpha set). Simulations correlate higher to empirical FC (red) than to SC (blue). Also the prediction of the empirical FC is better with simulation rather than using the SC alone (red > green). Though we are not able to reproduce subject specific FC features, our simulations in general still compare better to functional rather than structural data.

There was no individual subject fit of simulated to empirical FCs. Individual fits (where simulated FC and empirical FC are from the same subject) are no higher than all-to-all fits (where simulated FC and empirical FC come from different subjects). Some empirical FCs correlate highly with all simulated FCs, as can be observed by the horizontal striping in the empirical FC-simulated FC plot (**Fig 6A and B left side**). That is, the goodness-of-fit is more determined by

503 variations in the empirical FC connectome than the simulated FC (and the underlying SC).

504 However, there was an individual subject fit of the SC to the simulated FC (see the stronger correlations on the diagonal
505 of **Fig 6 A and B middle**). This is shown also on the density distributions where individual fits (where SC and
506 simulated FC come from the same subjects) outweigh all-to-all fits (where SC and simulated FC come from different
507 subjects).

508 In order to understand the lack of subject specificity in the empirical-simulated FC fit, we examined variations between
509 subjects' empirical FCs and also the variations between subjects' SCs (as SCs are the input to our simulations). In our
510 SC-SC correlation and empirical FC-empirical FC correlation plots (See Fig 8C right and left), we show that empirical
511 FCs are less homogeneous than the SCs. Thus, when we then look at the fit between individual SC and empirical FC,
512 there was no subject-specific fit, as the fits were driven by the comparatively large variability in the empirical FC, such
513 that there were particular empirical FCs that fit best to all SCs. Whether this is due to lower sensitivity of diffusion
514 techniques to individual differences, or to a real lack of individual differences in SC remains to be investigated. On the
515 other hand different success in fMRI artefact removal and processing steps could be the reason for different FC quality.

516 There is a linear relation between the fit of empirical FC to SC and the fit of simulated to empirical FC (**Fig 6D left**).
517 Correlations between empirical SC and FC, empirical SC with simulated FC and simulated and empirical FC are shown
518 in **Fig 6D right**. For both sets, we see the correlation between individual SC and empirical FC (green) is lower than that
519 of simulated to empirical FCs (red). In other words, by using the SC only we cannot predict the empirical FC as good as
520 by using the SC in a simulation. That is the value added by TVB. Although simulated FC fit specific to their underlying
521 SC they still fit better to their empirical counterpart (blue < red). Meaning the combination of SC and our model is more
522 like a FC than an SC.

523 Another interesting aspect of this inter subject comparison is the variance of the optimal parameters (**Fig 7**). Here we
524 ask the question, what are the optimal parameters for a set of simulations (i.e. the underlying SC). Does the optimal
525 point change when correlating to different empirical FCs? Are optimal parameters determined by the underlying SC or
526 the empirical FC we compare to? The variation of optimal global coupling within a set of simulation is small compared
527 to the variation between sets (**Fig 7A**). As we've shown earlier the global coupling relies on the weights supplied by the
528 SC. In combination with the mechanism of bimodality it makes sense that regardless of the FC we compare to, the
529 optimal global coupling has to stay in a close range because otherwise the local dynamics will generate unphysiological/
530 a non-meaningful signal. In other words, the explained variation of global coupling by the underlying SC is great.
531 Whereas for conduction speed the inter and intra subject variation is high.

Fig 7. Optimal parameter combinations of cross subject comparison. A. Comparing all simulations of one subject to its own empirical FC yields one optimal parameter combination. However, this parameter combination doesn't have to be optimal in terms of goodness of fit if we compare the same set of simulations to the empirical FC of other subjects. In other words when we correlate the simulations of one subject to all 50 empirical FC's we will get 50 optimal parameter combinations – one for each subject's empirical reference FC. Doing this for all 50 subjects yields 50×50 optimal parameter combinations and highest correlations. The matrices of correlation are displayed in Fig 8. B. Next, we analyse how these optimal parameter distributions change in-between subjects. The parameters are influenced by the set of simulations (i.e. underlying SC) if the distribution means vary strongly in-between them. This can be seen for optimal global coupling in the upper boxplot. The variance within one set of simulation is small compared to the variance between them. If we transpose the 50×50 optimal parameter matrix we can analyse the influence of the empirical FC on the distributions. Empirical FC doesn't influence the parameter distribution strongly. This Fig indicates the high importance of the SC on optimal coupling determination regardless of the empirical FC we are trying to fit. Optimal conduction speed (not shown here) however doesn't seem to be determined by SC or FC, as the variance between subjects in A and B is small.

To assess if optimal parameters are more determined by the set of simulations (in other words underlying SC) or by the empirical FC we have to ask the reverse questions: How do optimal parameters vary across empirical FCs and is this variation greater or smaller than the one before. To do that, we transpose the boxplot with the x-axis now being empirical FCs. We see the within one empirical FC variation of coupling and speed is large and the between variation small. In other words, the explained variance of parameters by empirical FC is small. The plots in **Fig 7** can be shown for the delta set too, with similar but smaller trends.

Now we want to quantify if the underlying SC or the empirical FC determines optimal parameters. Therefore, we use the eta squared effect size which is computed as the ratio of sum of squares between groups and sum of squares total using the boxplot in **Fig 7**. This metric will have values between 0 (no variance explained by the variable) and 1 (variance completely explained) (**Table 4**).

Table 4: Eta squared. Explained variance of optimal parameters by empirical FC and the simulations underlying SC for both set.

	Delta set		Alpha set	
Explained variance	by underlying SC	by empirical FC	by underlying SC	by empirical FC
for global coupling	0.4629	0.2826	0.7968	0.0175
for conduction speed	0.0735	0.0913	0.0989	0.0809

Optimal coupling is mostly determined by the underlying SC. The effect is more visible in the alpha set with an eta

squared of 0.7968 for coupling explained by SC compared to 0.0175 by empirical FC. Also, delta set shows same characteristics with small differences in effect sizes.

Our question could be asked in a different way: Are there specific features in an empirical FC that can only be reproduced by a certain set of parameter combinations? The answer would be no for global coupling. The parameter is more or less bound to the underlying SC to generate meaningful simulations. However, conduction speed is neither determined by the SC nor by empirical FC. At this point we cannot give an explanation why optimal conduction speed differs between subjects. However the change in simulation result is very small for different conduction speed. So that a variety of transmission speeds can be seen as optimal.

FCD

In order to investigate FCDs in our model we conducted simulations of 22 min lengths. Due to long computation times we limited the exploration to four exemplary subjects (gender/age: f/30, f/47, m/20, m/73). Parameters were chosen from the alpha set with conduction speed set to the individual optimal value (derived from analysis in alpha set section).

In **Fig 8** an empirical and a simulated FCD are shown. It is visible that there are recurrent patterns in the recorded BOLD signal creating time shifted but highly correlated FCs. The same can be observed in our simulation. Though highest correlations are lower than in the empirical data. Interestingly FCD fit, bimodality and static FC fit are highly correlated. They all show their optimum in the same range of global coupling. Meaning that only when our local model is in a bistable situation we are able to generate switching of modes in our global network. In our supplementary material **S2 Video** we show simulated and empirical FCDs and FCs for subject #2 while sliding across the range of global coupling values.

Fig. 8. Functional connectivity dynamics aligns with bimodal behaviour of neural dynamics A: Shows example empirical and simulated FCD of Subject #2. B: Metrics of 22 minutes simulations for four sample subjects. In blue the Kolmogorov-Smirnoff distance between the simulated and empirical FCD. Best FCD fit occurs at the same range of global coupling as bimodality of the global signal (green) and best fit between FC's (red).

580 Discussion

581 In the current study, we conducted a large parameter space exploration with TVB, simulating BOLD fMRI and
582 electrophysiological neural signals for 50 individual human brains. TVB has previously been used to study how neural
583 networks behave in healthy and diseased states (8,10,13,18,21,26). Here, we assert that goodness-of-fit of simulated to
584 empirical data converge at a particular parameter set across multiple tenets of the EEG and fMRI signal, and that there
585 are reliable inter-individual differences in biophysical parameters that lead to optimal functioning. In order to
586 understand the behaviour of the system at multiple time scales, we conducted two sets of simulations, one that shows
587 neural behaviour in the delta frequency range, and a second that shows alpha oscillations.

588 It has been shown that the space-time formation of the dynamic repertoire of the neural system arises from a
589 combination of the structural connectome, and the time delays determined by conduction speed with which the signal
590 propagates across the anatomical skeleton(26,72–75). The global coupling and the conduction speed capture the
591 influence of the structural backbone and the time delays, respectively, and were the two free parameters of interest in
592 the current study.

593 The global coupling is responsible for the balance between local (nodal behaviour described by the SJHMR3D model)
594 and global (network-level) dynamics of the system, by scaling the SC connection weights. The conduction speed
595 defines the speed of signal propagation across the structural connectome.

596 Importantly, minute variations in these parameters were shown to give rise to fluctuations in 1) the correlation between
597 empirical and simulated BOLD FC, 2) frequency of the mean neural signal, as well as 3) bimodality in the frequency
598 power in the alpha band, a feature that has been observed in empirical (37,38), and model (42) EEG data. 4) fit of FCD
599 (characterized as KS distance between simulated and empirical FCD). These features converge at a particular parameter
600 point unique to each subject. Typically, a single metric (typically a correlation between empirical and simulated FC) is
601 used to assess model fit. Yet, it is important to validate that optimal models converge across multiple metrics and
602 modalities.

603 *Biological interpretation of SJHMR3D based BNMs*

604 SJHMR3d primarily aims to describe the average membrane potential of a population of neurons that are electrically
605 coupled via gap junction (19). On a local scale, this is achieved via difference coupling: the input that an excitatory
606 (respectively inhibitory) neuron receives is the difference between the neuron's membrane potential and the mean field
607 of the excitatory (respectively inhibitory) subpopulation. That is, inputs are based on the difference between a neuron's
608 state and the average state of all presynaptic neurons, instead of being based on the sum of presynaptic neurons' states.

609 This leads to a situation where an excitatory population can decrease the membrane potential of a postsynaptic neuron
 610 and an inhibitory neuron can increase the membrane potential of a postsynaptic neuron, which simulates the behaviour
 611 of electrical coupling via gap junctions, but not coupling via chemical synapses with neurotransmitters like NMDA,
 612 AMPA and GABA, which are either only excitatory or only inhibitory. For a demonstration see our **S1 Video**, where
 613 excitatory large-scale coupling leads to inhibitory inputs to individual brain regions over the majority of time in all
 614 simulations. In (76) an example is shown of how chemical synapses can be implemented in a Hindmarsh-Rose neuron
 615 in a way that biological plausibility is maintained. There, in Equation 14 a sigmoidal function is used for chemical
 616 coupling, which is set up, such that coupled values are always positive. This ensures that excitatory neurons always
 617 excite and inhibitory neurons always inhibit. In the present study, the SJHMR3D model was used on the local scale, and
 618 regions were coupled using a linear scaling function on the global scale. For such a scenario, due to the reasons
 619 discussed above, claims made about the SJHMR3D regarding GABAergic or NMDAergic neurotransmission are not
 620 justified. Conclusions about NMDA and GABA neurotransmission and about local disinhibition etc. cannot be drawn
 621 from a model like SJHMR3d that represents electrical coupling between neurons. This needs to be kept in mind when
 622 running TVB simulations with SJHMR3d.

623 ***Biological meaning of biophysical model parameters***

624 **Conduction speed:** Our range of conduction velocities (10-100m/s) was comparable to that found in the adult primate
 625 brain (5-94m/s), where neural axons were heavily biased towards those with large diameters and high conduction
 626 speeds(77). Similarly, we found that features of our empirical signal were best reproduced at conduction velocities
 627 higher than 20 mm/ms. **Global coupling:** Optimal global coupling is largely dependent on the underlying SC (78),
 628 which varies across studies that have used this connectivity scaling factor(22,25,73,74,79). For instance, our global
 629 coupling factor was quite low, and comparable to studies with dense SCs due to coarse parcellation schemes (Results:
 630 delta set ~ 0.13 , alpha set ~ 0.03). Previous results for global coupling ~ 0.007 (22), ~ 0.016 (73), ~ 0.3 - 0.9 (69).

631 ***Role of biophysical parameters for model fit***

632 We found that the ability of the model to approximate the empirical neural signal (in correlation, mean frequency, and
 633 bimodality of the frequency power spectrum at the alpha band) was determined predominantly by the global coupling,
 634 and less by the conduction velocity; such that, for example, the highest correlation between the FCs occurred at a small
 635 range of couplings, but across a wide range of conduction speeds. Previous resting-state models have all emphasized the
 636 critical role of the inter-nodal coupling in determining spatial structure(22,72–74,79,80); whereby the effects of delays
 637 are determined by local dynamics. Spiking models (30) such as the Deco Wong Wang, in contrast with simple
 638 oscillators (22,74,80), may not necessitate time delays, as synchronization is decreased through system heterogeneity,

639 noise, and greater time between individual spikes(30). Oscillatory dynamics (75), but not slow asynchronous dynamics
640 (81) are influenced by time delays. Moreover, delays have a greater influence on dynamics in directed (asymmetric)
641 graphs, than undirected symmetric networks (78) such as our diffusion SCs. This is because real symmetric matrices
642 will have real eigenvalues, thus the connectivity will affect the system's equilibrium, however not its dynamic
643 oscillatory behaviour (78). The Hindmarsh-Rose local neural model is similar to the FitzHugh-Nagumo, where time
644 delays were not critical in shaping network dynamics. Critical behaviours are independent of very high conduction
645 velocities that correspond to time delays approaching zero, which is the case in the present study.

646 Coupling, on the other hand, is important in determining the coordinated behaviour of the system. With low coupling
647 values, nodal models are largely disconnected, their behaviour independent of one another, resulting in low signal
648 correlations and little synchronization throughout the system. As coupling increases, inter-regional influences are taken
649 into account in the network dynamics. Increasing the coupling beyond a certain critical threshold point was found to
650 drastically change the system behaviour, where too much synchrony results in waning bimodality, for example. Thus, an
651 intermediate coupling may best represent the realistic influence of inter-nodal inputs.

652 Importantly, we found that optimal coupling decreased with increasing average SC weights. We explain these results as
653 follows: In order to realistically model local dynamics within one node, a certain amount of input from other nodes is
654 needed. Therefore, if the SC weights are low, a sufficient high global coupling value is necessary to scale up the input
655 from other nodes. A link between coupling and global efficiency in the SC has previously been reported (8), yet the
656 association to mean SC has not yet been clearly emphasized. This is important, as using SJHMR3D and similar models
657 to make interpretations about clinical populations rest on the comparison of SCs that vary greatly across individuals.

658 The realistic properties of the simulated neural signal that we found, do not arise linearly with global coupling, but
659 rather slowly emerge or strengthen, sharply peak, and drop off afterwards. Interestingly, a number of other resting-state
660 neural network properties, such as system multistability (25), changes in the attractor landscape (the entropy and
661 number of attractors)(32,81), cluster synchronization(22,74), emergence of resting state networks (72,74), instability of
662 the equilibrium state(73,78), system efficiency(8), or network entropy (82), have similarly been shown to develop and
663 transition as a function of this inter-regional coupling, conduction velocity, or a combination of the two (22,73,74,78).
664 Similarly to what we noticed in our study, these behaviours actually emerge at the point where global coupling produces
665 the highest correlation between empirical and simulated FC. Taken together, these findings point to the significance of a
666 critical point at which the system performs/operates/functions optimally. Note that noise, among other parameters, may

667 additionally influence the emergence of these features (22), however, may not be necessary for resting-state
668 fluctuations(74).

669 *Role of biophysical parameters for functional connectivity dynamics*

670 Recently, it has been shown that functional connectivity fluctuates across time, and that functional connectivity
671 dynamics emphasize important features of the signal that cannot be captured by the static FC(66,83). Static FC is the FC
672 from a single time series, while dynamic FC is characterized as changing patterns in the FC captured by correlating
673 numerous FCs from sub-windows of the time series. We verified that non-static FCD is observed at the bimodal state.
674 In particular, we showed that the region of parameter space that gives rises to the best fit between simulated and
675 empirical static FC, and bimodality, also gives rise to the best model of FCD. This is important, as we are able to show
676 that our simulations can reproduce time-varying features of the signal which are relevant to capturing individual
677 differences (63), and other resting-state phenomena(34). Our findings are in line with previous findings showing the
678 meta-stable state as a function of a bifurcation parameter called “a” along with global coupling, and importantly, that
679 best FCD fit is achieved at this meta-stable state(34).

680 *Role of biophysical parameters for frequency and alpha bimodality*

681 In a second set of simulations, we explored a narrower range of global coupling and reproduced alpha frequency (8-15
682 Hz) oscillations in the neural signal, a characteristic feature of human empirical EEG (37,38), which has previously
683 been modelled as a function of global coupling in MEG (30). Here, it was shown that transmission delays and global
684 cortical coupling affect the mean power in an MEG model, and the best model fit was found in the alpha band power.
685 However, this work is limited to the traditional mean power metric, without taking into account the bistable switching
686 between two distinct alpha modes that occurs in empirical neural signal. We found that global coupling that exceeded a
687 certain threshold led to a sharp reduction in oscillation frequency to a predominantly delta frequency range with low
688 amplitude.

689 Because the mean power metric that is commonly reported in frequency analyses lacks information about fluctuations
690 around the mean, we also examined the distribution of the frequency power. We were able to reproduce bistable
691 switching between two distinct alpha modes, a feature of empirical EEG (37,38). The two modes (a low power mode
692 and a high-power mode) represent the switching, or bursting, between two distinct dynamic behaviours within a cortical
693 region. The non-Gaussian, multistable nature of these neural processes should be taken into account in any realistic
694 neural model, however, has largely been overlooked. We show that this bimodality, which has previously been modelled

as a function of noise (42), arises also as a function of optimal global coupling. It is reasonable that the long-range inter-nodal global connections shape the bimodality particularly of the mean global neural signal. This can be contrasted with previous studies (42), where bimodality was modelled on the neural signal of a single node, thus global parameters would likely not play a large role in determining the behaviour. Further, note that the optimal working point where bimodality emerges is the same one that gives rise to high correlations between simulated and empirical FC, as well as FCD, suggesting that realistic modelling of empirical data can be attained in a particular parameter space.

Mechanisms underlying alpha bimodality

We sought to elucidate the mechanisms behind the emergence of bimodality in our model. Bimodality was shown as a function of the global coupling parameter. For low values of global coupling, (i.e. $G = 0$), we observed bursting behavior at the local model (local dynamics dominate, as the coupling from other regions is 0). Such square-wave bursting behavior, as well as single spikes and chaotic behaviour, have been observed in the SJHMR3D and the single Hindmarsh-Rose model (19,71). As we then increase global coupling, a synchronized state is achieved, such that many regions show synchronized spiking behavior. Increasing global coupling yet further results in the bimodality we observe, and finally, oscillation death.

These changes can be understood by looking at our global coupling function. The current SJHMR3D model uses the linear coupling function of the form: " $x_i = a * x_j + b$ ", where " x_i " is the value that gets integrated in the local model and " x_j " is the activity at other regions with some time delay. " a " is the global coupling factor that scales the activity of the other regions and " b " = 0 in our case. In our SJHMR3D model, the state variable " x " (activity of excitatory neurons) gets transmitted in the global network. This corresponds to a biological global excitatory coupling in the brain.

The baseline of this variable is around -2 [a.u.] corresponding to a neuron at rest, while spikes peak at +2 [a.u.]. At rest, this negative value is the " x_j " of a region that gets transmitted throughout our network. Thereby we create global inhibition. Thus, at low values of global coupling, bursts/spikes still occur at a node as global inhibition is not strong enough to suppress this activity. However, as we increase global coupling, we increase global inhibition up to a point where inhibition is strong enough to cancel out all activity. In between, there is a narrow range of coupling values where a switching between periods of spiking behaviour and periods of oscillation death can be observed, giving rise to a bimodal power distribution. Taking into account that different nodes have different degrees, we can explain that some nodes reach bimodality and oscillation death earlier than others. Thus, inter-regional input plays an important role in

723 driving oscillatory activity, as seen previously in the alpha band (30).

724 In follow-up studies, we will seek to understand the impact of a different global coupling function, a
725 sigmoidal/hyperbolic tangent function, to avoid global inhibition and oscillation death.

726 *Inter-individual differences.*

727 We show that there are inter-individual differences in the optimal long-range global coupling that result in the best fit
728 between the empirical and simulated functional connectome, in predominating alpha frequencies of the neural signal,
729 and bimodality in the frequency power spectrum at the alpha range. The critical value at which these behaviours
730 emerge and the simulated-empirical FC correlation is the highest is consistent across behaviours, and varies reliably
731 across subjects. This suggests that the optimal point of functioning is highly dependent on the individual's anatomical
732 architecture in combination with the spatio-temporal dynamics from the model. Our findings indicate the importance of
733 conducting parameter space explorations at the individual level, as more standard group-level analyses (32,74) may
734 obscure important and reliable variability. Moreover, we show that individual variability in the connectomes was driven
735 primarily by the simulated FC, and the underlying SC, and to a lesser extent by the empirical FC. This is important if
736 one starts to simulate or explore parameters for a subject. Typically, we have empirical data such as fMRI FC and DTI
737 derived SC but we do not know what parameter values to choose. The best orientation for optimal global coupling can
738 be drawn from the SC rather than the empirical FC. The same cannot be said for conduction velocity. There may be
739 other parameters we didn't explore which may be determined more by the empirical FC rather than the SC.

740 The simulated-empirical FC correlations (*delta set*: mean $r = 0.45$; max $r = 0.66$; *alpha set*: mean $r = 0.51$, max $r =$
741 0.68) that we achieve are in the range of those obtained in parameter explorations with similar models (74,82) ($r =$
742 0.427); (32)($r = 0.42$); (25)($r = \sim 0.4$). It is important to note that the ability of our model to reproduce the empirical data
743 is limited by the quality of current diffusion techniques. Existing links that are not captured by the SC may conceal how
744 real structural connections influence FC. However, in light of these inherent limitations, our model has captured a
745 number of important properties of the neural and BOLD signal.

746 In sum, we have demonstrated that as global coupling and conduction speed approach an optimal working point, the
747 behaviour of the neural system maximally reproduces the resting-state BOLD static and dynamic FC, as well as the
748 neural signal.

749 Taken together, The Virtual Brain is a neuroinformatics platform that allows reproducible computational brain
750 modelling. With the present work, we aim to provide guidance for personalized brain network modelling using
751 SJHMR3D nodes. Example data sets, code and didactic video tutorials for published TVB studies are being made
752 available as didactic use cases (84). A systematic exploration of other population models and comparisons of their
753 respective parameter landscapes will help to further put to test and to validate the biological interpretability of
754 parameters and variables of those models (85).

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957 **Supporting information captions**

958 **S1 Text. Supporting information.**

959 **S1 Table. Region labels.** Labels for the 68 regions, using the same order as in the connectome. lh_* and rh_* are
960 specifying left and right hemisphere respectively.

961 **S2 Table. SJHMR3D parameter exploration.** Parameter values used for exploring the dynamics of the SJHMR3D
962 mean-field model.

963 **S1 Fig. Exploration of excitation/inhibition balance, noise dispersion, mean and standard deviation of population**
964 **membrane excitability.** Each row of scatter plots shows a different noise level. Each column depicts a different value
965 of n (=K12/K11). In each scatter plot X, Y and Z axis are μ , K11 and σ respectively. One can see that alpha band
966 frequency (red) is mostly likely to occur at low noise levels, $\sigma = 0.4$, and for many values of μ , K11 and n. Dark colours
967 correspond to alpha band activity.

968 **S2 Fig. Exploration of standard deviation of membrane excitability (σ).** Each row of plots shows the timeseries of
969 the mean field potential (MFP); On the right, the power spectral density (PSD). For $\sigma = 0.4$, the power in the alpha band
970 is highest. Parameters from the exploration not mentioned here are the ones used in the alpha set.

971 **S3 Fig. Exploration of excitatory to excitatory coupling (K11).** Each row of plots shows the time series of the MFP.
972 On the right, the PSD. For K11 = 4, the power in the alpha band was highest.

973 **S4 Fig. Exploration of the mean of membrane excitability (μ).** Each row of plots shows the time series of the MFP.
974 On the right, the PSD. For $\mu = 2.2$, the power in the alpha band was highest.

975 **S5 Fig. Alpha band frequency can be seen for nearly all μ , and high K11 values.** However, the power (indicated by
976 color) is highest for a low μ . Lines are drawn for better identification of points.

977 **S6 Fig. Power spectral density (PSD) estimate for different values of n.** The desired alpha frequency is observed
978 only for n = 0.4. All coupled simulations are performed with global coupling = 0.03.

979 **S7 Fig. Impact of inhibitory to excitatory coupling strength (K12) on the coupled network.** Regions were sorted by
980 their degree in ascending order. Frequency was log-scaled to better visualize regional differences in the slow frequency
981 band. All other parameters were set to the alpha set parameters defined in Table 1 and 2, with global coupling set to
982 0.032 and conduction speed to 100. For increasing coupling the global network observes different states of
983 synchronized and unsynchronized oscillations. In the range of K12 = 4 to 6 oscillation frequency increases with degree.

984 **S8 Fig. No significant relation between the optimal parameters and age.** For the alpha (A) and delta (B) set the plots

985 show age against the optimal parameter of each subject. The relation of age and optimal global coupling in the alpha set
986 was close to significant with $r = 0.2659$ p-value: 0.062. The other p-values were > 0.6 for all comparisons.

987 **S9 Fig. PLS analysis to reveal the relation between age and simulated FC.** From the PLS analysis only the first
988 latent variable (LV) was found to be significant and is reported here. It uncovers inverse relation between the SC,
989 simFC, and SC-FC metric with age. All three measures decrease with increasing age. A PLS bootstrap ratios are shown
990 for the LV loadings. Regions above the threshold ($= 2$) have reliable age-related reductions in SC, FC, and SC-FC
991 coupling. B Bar graph showing the correlation between SC and age, simFC and age, and SC-FC coupling and age,
992 confidence intervals on each of these correlations are shown. There is a reliable relationship between each of these and
993 age. C Scatterplots visualizing the correlations between SC brain scores and age, simFC brain scores and age, and SC-
994 FC brain scores and age.

995 **S1 Video. Mechanisms of bimodality in the alpha range.** Each row shows signals of a single simulation with one
996 global coupling value G. Global coupling G was varied from top to the bottom row with values of [0, 0.025, 0.0328,
997 0.04]. Conduction speed was set to 100 and the other parameters were as in the alpha set. Note: In the video
998 “xi”, “eta”, “tau” and “alpha” correspond to state variables x, y, z and w of our local model.

999 **S2 Video. Functional connectivity and functional connectivity dynamics in dependence of global coupling.** For
1000 subject #2 we show empirical FCD and FC in the left column. The right column animates how simulated FCD and FC
1001 change in relation to global coupling. The shift of global coupling is highlighted by the black vertical line in the lowest
1002 plot. In the range of ~ 0.029 the simulation achieves a good fit according to all three metrics, i.e. bimodality, FCD and
1003 FC comparison.

A

B

Figure 1

Delta set

Alpha set

Correlation between sim and emp FC

Bimodality

Frequency

Optimal parameters

Figure 2

Figure 3

Figure 4

Excitatory phase space

Figure 5

Figure 7

Figure 6

Figure 8