

1 A connectome-based, corticothalamic model of state-
2 and stimulation-dependent modulation of rhythmic
3 neural activity and connectivity

4 John D Griffiths^{1,2,3,6}, Anthony Randal McIntosh^{4,5}, and Jeremie Lefebvre^{6,7}

5 ¹Krembil Centre for Neuroinformatics, Centre for Addiction and Mental
6 Health, Toronto, Canada

7 ²Department of Psychiatry, University of Toronto

8 ³Institute of Medical Science, University of Toronto

9 ⁴Rotman Research Institute at Baycrest, Toronto, Canada

10 ⁵Department of Psychology, University of Toronto

11 ⁶Krembil Research Institute, University Health Network, Toronto, Canada

12 ⁷Department of Mathematics, University of Toronto

13 Abstract

14 Rhythmic activity in the brain fluctuates with behaviour and cognitive state, through a
15 combination of coexisting and interacting frequencies. At large spatial scales such as those
16 studied in human M/EEG, measured oscillatory dynamics are believed to arise primarily
17 from a combination of cortical (intracolumnar) and corticothalamic rhythmogenic mecha-
18 nisms. Whilst considerable progress has been made in characterizing these two types of
19 neural circuit separately, relatively little work has been done that attempts to unify them
20 into a single consistent picture. This is the aim of the present paper. We present and examine
21 a whole-brain, connectome-based neural mass model with detailed long-range cortico-cortical
22 connectivity and strong, recurrent corticothalamic circuitry. This system reproduces a vari-
23 ety of known features of human M/EEG recordings, including a $1/f$ spectral profile, spectral
24 peaks at canonical frequencies, and functional connectivity structure that is shaped by the
25 underlying anatomical connectivity. Importantly, our model is able to capture state- (e.g.
26 idling/active) dependent fluctuations in oscillatory activity and the coexistence of multiple
27 oscillatory phenomena, as well as frequency-specific modulation of functional connectivity.
28 We find that increasing the level of sensory or neuromodulatory drive to the thalamus triggers
29 a suppression of the dominant low frequency rhythms generated by corticothalamic loops,
30 and subsequent disinhibition of higher frequency endogenous rhythmic behaviour of intra-
31 columnar microcircuits. These combine to yield simultaneous decreases in lower frequency
32 and increases in higher frequency components of the M/EEG power spectrum during states
33 of high sensory or cognitive drive. Building on this, we also explored the effect of pulsatile
34 brain stimulation on ongoing oscillatory activity, and evaluated the impact of coexistent fre-
35 quencies and state-dependent fluctuations on the response of cortical networks. Our results
36 provide new insight into the role played by cortical and corticothalamic circuits in shaping
37 intrinsic brain rhythms, and suggest new directions for brain stimulation therapies aimed at

38 state-and frequency-specific control of oscillatory brain activity.

39 **Author Summary**

40 One of the most distinctive features of brain activity is that it is highly rhythmic. Devel-
41 oping a better understanding of how these rhythms are generated, and how they can be
42 controlled in clinical applications, is a central goal of modern neuroscience. Here we have
43 developed a computational model that succinctly captures several key aspects of the rhyth-
44 mic brain activity most easily measurable in human subjects. In particular, it provides both
45 a conceptual and a concrete mathematical framework for understanding the well-established
46 experimental observation of antagonism between high- and low-frequency oscillations in hu-
47 man brain recordings. This dynamic has important implications for how we understand the
48 modulation of rhythmic activity in diverse cognitive states relating to arousal, attention, and
49 cognitive processing. As we demonstrate, our model also provides a tool for investigating
50 and improving the use of rhythmic brain stimulation in clinical applications.

51 **Introduction**

52 A key characteristic of the fluctuations in extracranial electrical and magnetic fields measured
53 by electroencephalography (EEG) and magnetoencephalography (MEG), resulting from the
54 collective activity of large numbers of (primarily) cortical neurons, is that they are highly
55 rhythmic. While the physiological origins and cognitive function of these rhythms remains
56 unclear, their features are clearly highly labile: spatial location, frequency, and oscillatory
57 power can vary considerably as a function of behavior, cognitive processes, and disease.
58 This suggests that not only the oscillations themselves, but also their fluctuations over time,
59 space, and cognitive state play a key role in brain function. Moreover, multiple frequencies

60 can coexist and interact, fluctuating in a highly correlated manner[1, 2]. Understanding the
61 mechanisms mediating the coexistence of these rhythms, as well as state-dependent changes
62 in their properties, would yield important insight about how collective neural activity and
63 synchronization phenomena, shaped by both sensory and recurrent inputs, mediate neural
64 communication[3]. ‘State’ here simply refers loosely to gross cognitive/perceptual/neural
65 activity regimes, as for example seen in the difference between low-frequency, high-amplitude
66 oscillations observed at rest, and the relatively higher-frequency activity elicited by focused
67 cognitive tasks. In the present paper we opt for the more neutral terms ‘idling’ and ‘active’
68 (as opposed to ‘rest’ and ‘task’) to indicate these two dynamical regimes. To date only
69 a few models in the literature have sought to explicitly capture transitions between these
70 oscillatory states, and the dependence of certain neural processes on the current state (e.g.
71 [4, 2]).

72 The majority of neural population models that have been developed to account for the
73 origins of large-scale brain rhythms can be grouped into two broad categories: i) cortical-
74 only and ii) corticothalamic. Cortical-only models typically propose that the oscillatory
75 activity visible in MEG/EEG has its mechanistic origin in interactions between excitatory
76 and inhibitory neurons within a cortical column (e.g. [61, 71, 58]). Corticothalamic models
77 (e.g. [39, 69, 55, 56]) are generally highly similar in overall structure, but differ critically
78 in placing the key excitatory-inhibitory interaction in the thalamus rather than the cortex.
79 These models thus attribute prominent spectral features such as low-frequency oscillations
80 to delayed inhibition in long-range recurrent corticothalamic loops. Given the substantial
81 bodies of empirical data from human and nonhuman physiological recordings supporting
82 each of these two mechanisms, it is highly likely that both play a role in the genesis of large-
83 scale rhythmic activity observed in local field potentials and extracranial electromagnetic
84 fields. Disambiguating the contribution of each to the different features of M/EEG signals,
85 and how they might interact, is a challenging problem, however. Addressing this disconnect

86 is one of the principal aims of the present study.

87 One of the major points of dispute between cortical-only and corticothalamic model
88 types is the alpha rhythm. Alpha frequency (8-12Hz) oscillations are a hallmark pattern of
89 encephalographic activity[5]. They have been linked to a wide variety of cognitive processes
90 such as perception and attention, and their dynamic features (such as power and frequency)
91 are also closely tied to changes in behaviour[6, 7]. Abnormal alpha activity is also involved
92 in many neurological disorders such as depression, Parkinson’s disease, and Alzheimer’s
93 disease[8, 9, 10]. A broad range of experimental data point to the corticothalamic system as
94 the most likely locus of the dominant alpha-frequency rhythmic activity seen in EEG and
95 MEG[11], as well as the phase relationship between alpha and other faster frequencies. In
96 contrast, gamma frequency oscillations have been robustly tied to intracolumnar excitatory-
97 inhibitory circuit mechanisms and active cortical information processing[12, 13]. It remains
98 an open question, however, how these two types of oscillatory activity (plus associated circuit
99 mechanisms) shape large-scale neural dynamics, functional connectivity, and information
100 integration in a state-dependent fashion.

101 A key experimental direction for investigating the dynamic properties and functional role
102 of neural oscillations is to study the relationship between endogenous activity and responses
103 to electromagnetic stimulation. This is not only critical for understanding the functional
104 role of brain oscillations in general, but also for improving the efficacy of clinical applica-
105 tions of noninvasive brain stimulation, such as in the treatment of depression[14]. Inter-
106 estingly, a confluence of experiments with both intra-cranial and non-invasive stimulation
107 have revealed frequency-specific responses, with low-frequency stimulation decreasing the
108 excitability of stimulated tissue[15], and conversely higher frequency stimulation having the
109 opposite effect[16]. Experiments in primates[17] and rodents[18] have indeed demonstrated
110 that thalamic stimulation can be used to either activate or inactivate cortical networks in
111 a frequency-dependent manner, opening new perspectives on the functional manipulation of

112 cortical dynamics by exogenous signals.

113 To better understand state-dependent changes in oscillatory dynamics, their involvement
114 in inter-area communication, and how they might be controlled by non-invasive stimula-
115 tion, we present in this paper a novel connectome-based neural mass model that combines
116 cortical and corticothalamic circuit mechanisms in a minimal and parsimonious fashion.
117 In the following sections, we first demonstrate that this model accurately reproduces sev-
118 eral key characteristics of measured power spectra and functional connectivity from resting
119 state MEG recordings. We then use the model to study the impact of sensory / neuro-
120 modulatory drive on brain rhythms, and how this serves to switch between low-frequency
121 corticothalamically-driven vs. high-frequency cortically-driven oscillatory regimes. Finally,
122 we show how the model predicts a number of empirical observations in humans and rodents
123 on the relationship between brain state, periodic brain stimulation, rhythmic entrainment of
124 neural activity.

125 Results

126 As detailed in the *Methods*, our full model consists of a network of 68 interconnected nodes,
127 representing brain regions derived from a commonly used parcellation covering most major
128 cortical structures in the human brain. The dynamics of each node is described by a novel
129 extension of the classic Wilson-Cowan (WC) equations[86], which we refer to as the ‘Cortico-
130 Thalamic Wilson-Cowan’ (CTWC) model. Our primary goal was to investigate how state-
131 dependent inputs mediate changes in brain oscillations within multiple frequency bands, and
132 how these spectral fluctuations shape functional connectivity. To do this, we first considered
133 the behaviour of a single isolated network node corresponding to a individual corticothalamic
134 motif. We then moved on to examining collective dynamics and interactions within the
135 whole-brain network.

136 **Alpha rhythms emerge from delayed recurrent cortico-thalamocortical** 137 **loops**

138 In examining the dynamics of our corticothalamic model, we first considered the idling state,
139 which we defined as being a state of minimal thalamic drive (see *Methods*) and thus reflecting
140 dynamics in the steady state. Consistent with previous work[4], this system produces a
141 robust alpha rhythm with a spectral peak at approximately 10Hz. In this idling regime,
142 the higher frequency peaks in the power spectrum at beta and gamma frequencies reflect
143 harmonics of the fundamental frequency (alpha), and the background trend in the power
144 spectrum follows a roughly 1/f trend, in line with previous reports[39]. As shown in Figure
145 1, this model gives a good fit to empirically measured, regionally-averaged MEG power
146 spectra, with all subjects tested showing $R^2 \geq 0.6$ or higher, and only minor variations in
147 fitted parameter values. Interestingly, we see in empirical MEG data that there are larger
148 differences in power spectra between subjects than between regions within a given subject
149 (data not shown). This observation supports the modelling strategy of choosing a single set
150 of parameters for each subject, and using those for all regions in the network; as opposed
151 to using regionally varying parameter values. We return to the question of spatially varying
152 spectral power below.

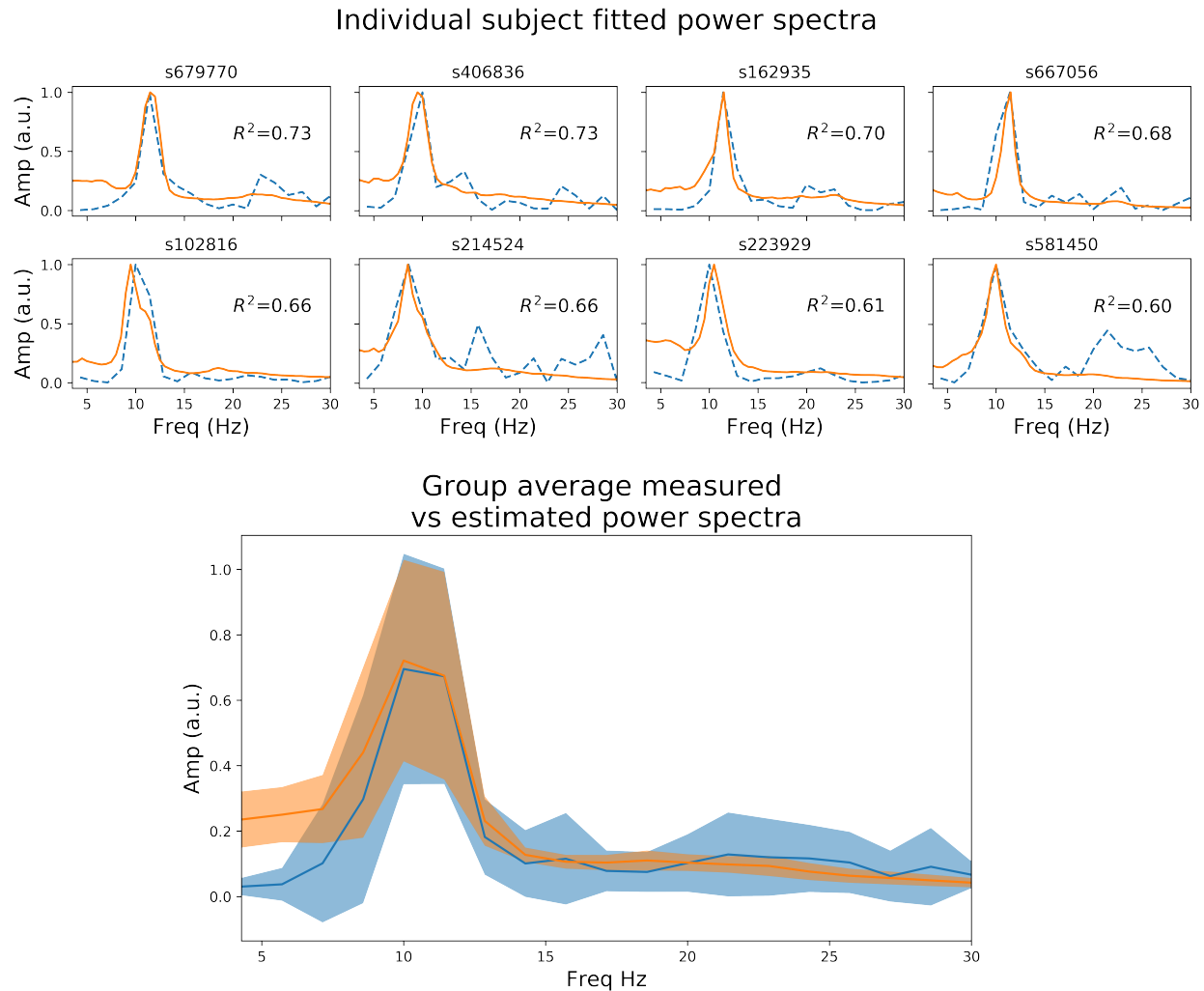


Figure 1: **Resting state power spectrum fit to MEG data.** *Upper panel:* Sensor-averaged power spectrum from eight example HCP subjects' resting state MEG data (orange line), and corresponding simulated power spectrum from the CTWC model (dotted blue line). The simulated activity shows excellent fit to the empirical power spectrum (R^2 between 0.6 and 0.8 in these examples), and accurately captures the alpha rhythm peak frequency in each subject. *Lower panel:* Mean ± 1 standard deviation of the empirical and fitted power spectra for all 10 HCP subjects.

153 **Phase transition from low-frequency idling to high-frequency active** 154 **state**

155 Having characterized the dynamics within the idling state and the prevalence of alpha ac-
156 tivity, we next asked how increasing the drive to the thalamic populations (either in one or
157 multiple nodes) would impact the spectral properties of cortical activity. To emulate a task
158 or 'active' state, we thus increased the drive to the thalamic populations (see *Methods*) and
159 observed the resulting behaviour.

160 We first studied this systematically for a single isolated node. Figure 2 shows trajectories
161 in the 3-dimensional phase space defined by the state variables u_e , u_i , and u_s (represent-
162 ing activity of excitatory cortical, inhibitory cortical, and thalamic specific relay nuclei,
163 respectively), along with time series and power spectra for u_e , which we take as a proxy
164 for M/EEG source activity[39, 58]. The top left panel of Figure 2 shows, the system in the
165 idling alpha-dominated regime, which (consistent with Figure 1) is characterized by a clean
166 and highly stereotyped 10Hz limit cycle. The bottom and top right panels of Figure 2 then
167 show how the system's dynamics and phase space are modified upon raising the static sen-
168 sory/neuromodulatory input or drive parameter I_o . We first observe (Figure 2, bottom row)
169 within increasing I_o a gradual destabilization of the resting alpha rhythm, and a transfer of
170 oscillatory power from alpha to higher frequencies. This destabilization is characterized in
171 the 3-dimensional phase space by an increase in the number and regularity of short, rapid
172 excursions ('twists') within the alpha limit cycle, which in the time series plots appear as
173 nested higher-frequency 'ripples' within the 10Hz base oscillation. Eventually, after a bi-
174 furcation point around $I_o=1.3$ is crossed, the system shifts completely to a noisier, low(er)
175 amplitude gamma-frequency limit cycle, with a clear peak in the power spectrum observed
176 at 30Hz. In line with a confluence of empirical studies[40], this high-frequency component
177 of the power spectrum reflects the fast-paced interplay between excitatory and inhibitory

178 neural populations, and is generated locally within the cortical compartments of each net-
179 work node. Due to the nature of the corticothalamic circuit motif we considered here, this
180 increased thalamic drive also represents an increased engagement of cortical excitatory and
181 inhibitory populations, that are now recruited for active processing of afferent inputs.

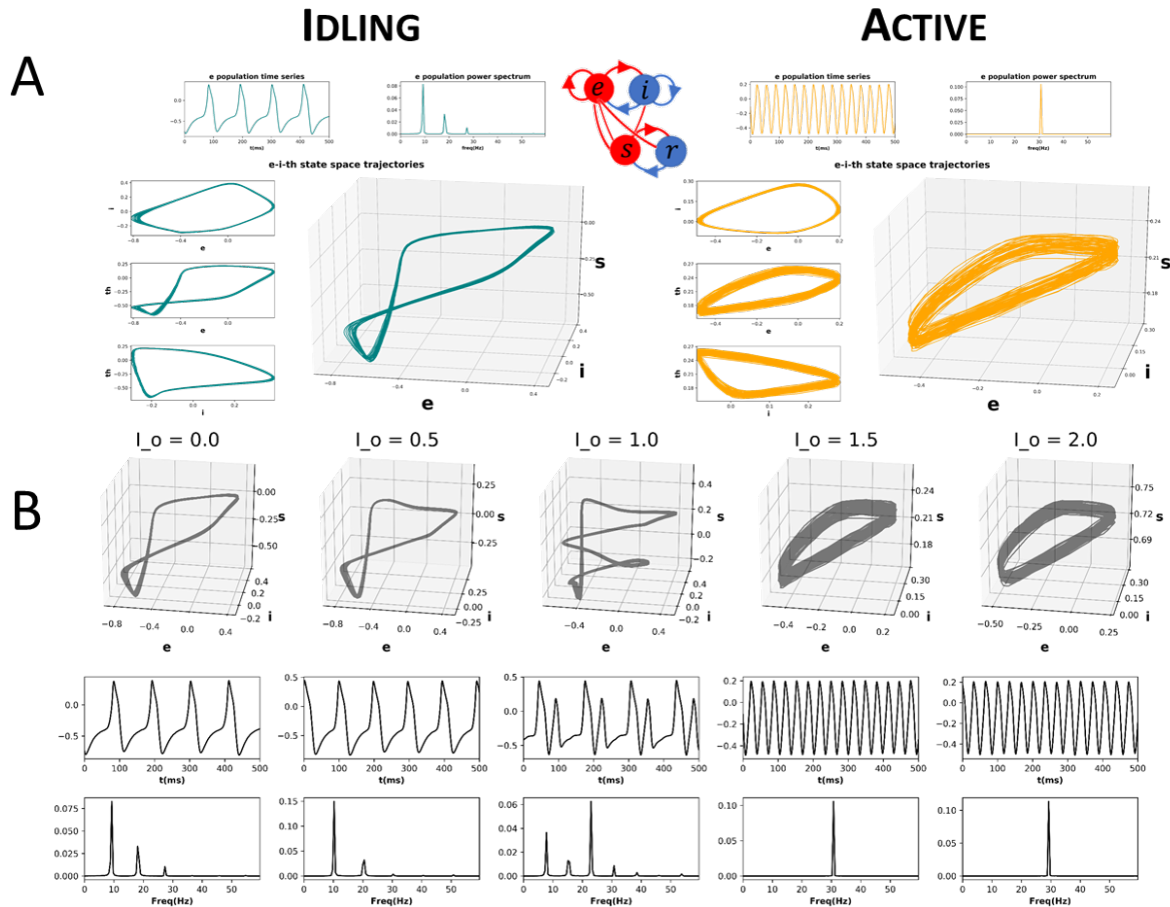


Figure 2: **CTWC model phase space trajectories.** A) Exemplary phase space trajectories for a single corticothalamic unit in the idling (left; teal) and active (right; orange) regimes. Central 3D plot in each panel shows trajectories in the 3-dimensional phase space defined by the cortical excitatory (e), cortical inhibitory (i), and thalamic specific relay (s) population state variables. Orthogonal 2-dimensional views for each pair of state variables are shown on the left hand side. Panels above the trajectory figures show corresponding time series and power spectra for the e variable. The idling state regime ($I_o=0$) is characterized by slow, nonlinear alpha-frequency (8-12Hz) oscillations. Increasing the static sensory/neuromodulatory thalamic drive (here by setting $I_o=1.5$) induces a phase transition into the active regime, where neural population activity is dominated by gamma-frequency (approximately 30Hz) limit cycle dynamics. B) Progression from idling to active regime. Sub panels show 3D phase plane trajectories, time series, and power spectra for incremental values of I_o between the idling and active states shown in panel A. As the system approaches the bifurcation point ($I_o \approx 1.4$), the gamma attractor begins to manifest as a ‘twist’ in the alpha limit cycle, which appears in the time series plot as embedded high-frequency ripples on the peak/trough of the oscillation. As I_o continues to be increase, eventually the low-frequency rhythm loses stability and the dynamics switches to a pure gamma oscillation.

182 **Influence of regionally focal sensory / neuromodulatory drive**

183 We now extend the observations and insights obtained from the single-node case considered
184 in the previous section to the case of whole-brain network behaviour. Figure 3 shows time
185 series, power spectra, and brain-wide plots of the change (Δ) in alpha and gamma power for
186 simulations where I_o is modulated focally for a single node (left V1) in the 68-node network.
187 The suppression of alpha power and enhancement of gamma power with increasing drive is
188 clearly evident in the surface plots and lower power spectrum figure in panel A.

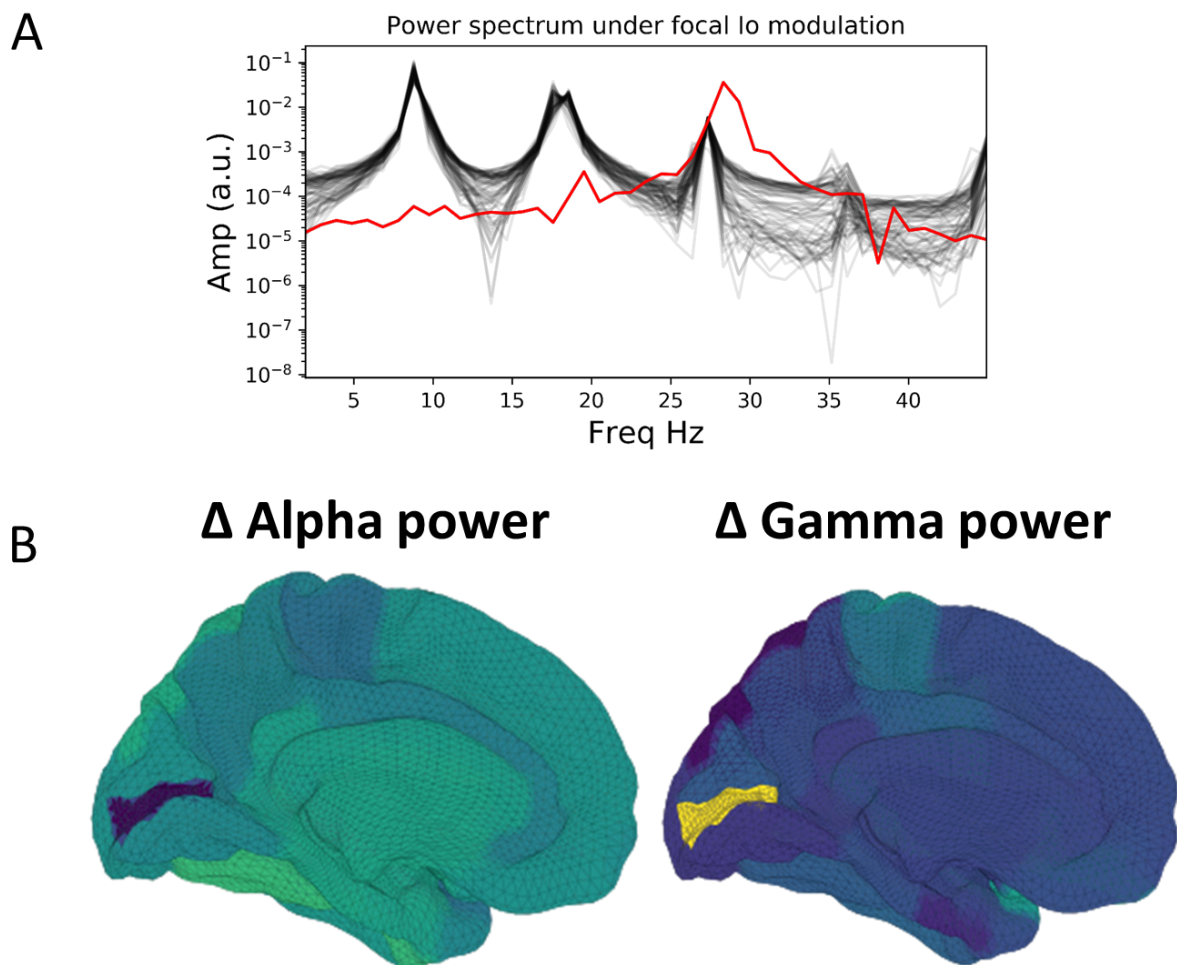


Figure 3: Influence of focal sensory/neuromodulatory drive in a whole brain network. A) Power spectra for baseline values of the tonic thalamic relay nucleus driving term ($I_o=0$), and for focal increase ($I_o=1.5$) in left visual cortex (IV1). Red lines show power spectra for the IV1 node; black lines for the other 67 nodes. Note the prominent increase in relative gamma power and decrease in relative alpha power in IV1 when that node's I_o value is increased. B) Surface renderings of the regional change (Δ) in alpha and gamma power from baseline to active state for all brain regions. Increased sensory/neuromodulatory drive in visual cortex results in suppression of alpha and enhancement of gamma band activity, reminiscent of the patterns routinely observed in M/EEG studies of visual-evoked gamma

189 **Functional Connectivity**

190 Given the salient differences in oscillatory dynamics observed in the idling and active states,
191 we investigated how these different oscillatory regimes shaped inter-area interactions in a
192 whole-brain network context. To do this, we compared functional connectivity, as measured
193 by amplitude-envelope correlations (AECs) of band-limited power time series, in model-
194 generated time series and empirically measured MEG data.

195 Heuristically, moving from an isolated node to a network of coupled nodes results in two
196 important changes in the ‘environment’ experienced by each node. First, the overall or time-
197 averaged activity level of a given brain region will be higher when there are inputs from other
198 regions than when there are no inputs. Second, depending on the behaviour of the incom-
199 ing signals from other regions, that node may experience periodic or otherwise temporally
200 structured driving inputs. This, in turn, may lead to the emergence of synchronization and
201 collective behaviour throughout the system due to processes of entrainment or resonance,
202 possibly also accompanied by bifurcations. As shown in Figure 4, we found idling and active
203 states in the model to be characterized by quite different functional connectivity profiles.
204 The idling state exhibits relatively weaker and spatially non-specific AEC patterns at both
205 alpha and gamma frequencies. In contrast, as the increased static drive I_o pushes the system
206 into the gamma-dominated active state, both alpha- and gamma-frequency AEC matrices
207 increasingly come to display the kind of spatial structure characteristic of empirically mea-
208 sured AEC (as well as by various other M/EEG, fMRI functional connectivity, and indeed
209 anatomical connectivity metrics). Specifically, the active state shows a stronger tendency
210 for spatially nearby regions to show high correlations (as indexed in the AEC matrices by a
211 the ‘halo’ of high connectivity values around the leading diagonal), and the classic two-block
212 hemispheric structure with stronger intra- than inter-hemispheric correlations. Interestingly,
213 although the two characteristic frequency regimes within the model are in the alpha- and
214 gamma- ranges, it also captures some properties of AEC outside of these ranges. Figure 5

215 shows empirical vs. simulated AEC for the full range of classic M/EEG frequencies: delta
216 (0.5-4Hz), theta (4-8Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (30-60Hz). As can
217 be seen, moving from low to high frequencies within the active regime is also accompanied
218 by sparser and more spatially structured correlation patterns. It is important to note here
219 that although our model does well at reproducing both resting-state power spectra (Figure
220 1) and MEG functional connectivity (Figures 4 and 5), the domains in which this success is
221 seen does not entirely overlap. For the power spectrum alone, best fits are achieved at or
222 near 'fully idling' parameter regime with $I_o = 0$. For AECs, however, best correspondence
223 with MEG data is achieved in the active regime, with I_o closer to 1.5. We return to this
224 point in the *Discussion*.

225 Our findings described thus far have shown that active and idling states are characterized
226 by different spectral signatures, and that functional connectivity is differentially expressed
227 in a frequency-specific way in these two states. Next, we examined the effects of periodic
228 stimulation on ongoing cortical activity. That is, we asked: can the temporal structure
229 neural activity be tuned by exogenous signals in a frequency-specific way?

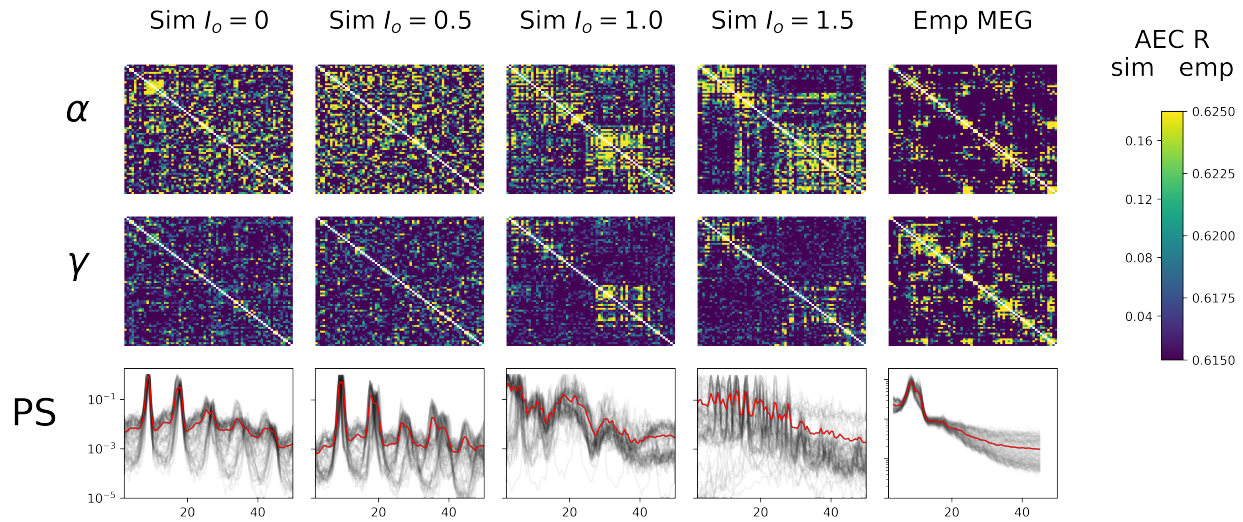


Figure 4: **AEC FC vs. I_o .** *Upper panel:* Gamma-frequency AEC matrices for 4 values of I_o ($I_o=0./0.5/1.0/1.5$), alongside the empirically-measured MEG gamma-frequency AEC matrix. *Lower panel:* Corresponding power spectra of whole-brain simulated data for these three simulation regimes, as well as for empirically measured MEG data (far right). Black lines show spectra for individual brain regions, thick red line is mean over all brain regions. The simulated power spectra transition from being alpha-dominated at $I_o=0$ to a noisier and higher-frequency regime at around $I_o=1.5$.

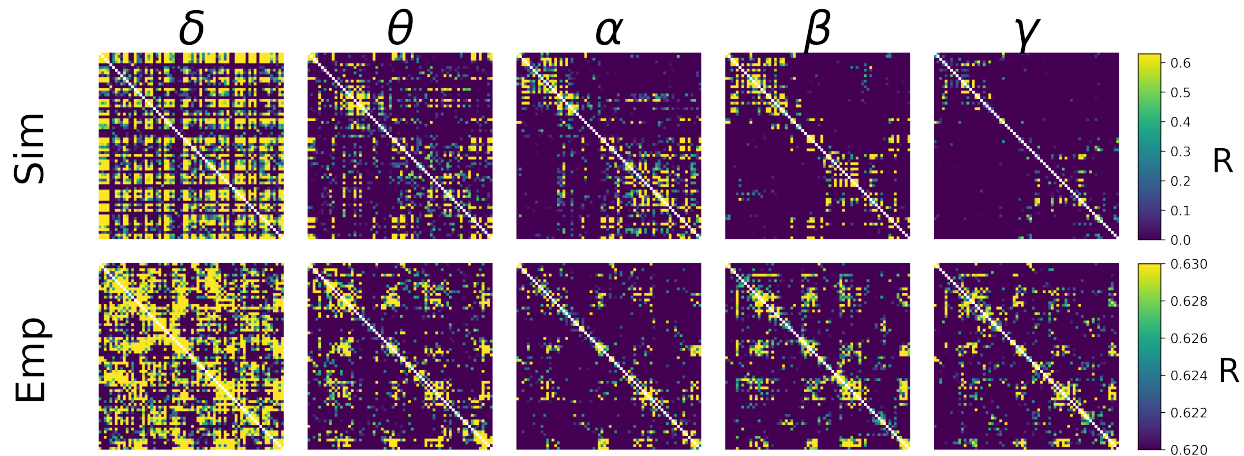


Figure 5: **AEC FC vs. Frequency.** Shown are AEC FC matrices at five different canonical frequency bands - δ (0.5-4Hz), θ (4-8Hz), α (8-12Hz), β (13-30Hz), and γ (30-45Hz) - from empirical MEG data (top row), and from simulations (bottom row). In both simulated and empirical data, lower frequencies (δ and θ) show less spatial specificity and more tendency towards random connectivity patterns. Note that the more compressed AEC range in empirical than simulated AEC data is due to the application of orthogonal leakage correction[89] in analyses of MEG data.

230 **Susceptibility to entrainment by exogenous stimulation is state-dependent**

231 Having characterized idling and active states, their dominant spectral features and how they
232 impact functional connectivity, we investigated how *exogenous* periodic stimulation shapes
233 the power spectrum of the system and engages ongoing oscillations. Numerous studies over
234 the last few decades have used stimulation paradigms of various kinds to access circuit
235 function and interfere with neural communication[42, 43, 44]. One of the most robust findings
236 is that entrainment of ongoing brain oscillation is state-dependent, and that susceptibility
237 to control is tuned by ongoing brain fluctuations - an effect that has also been reproduced
238 with modelling[45, 46] and shown to involve stochastic resonance[47]. Given the ability of
239 our model to switch between different states and express multiple frequencies, we subjected
240 cortical populations to exogenous periodic stimulation and monitored the spectral response.
241 Specifically, we again studied an isolated cortico-thalamo-cortical motif (i.e. a single network

node), and computed the peak power and frequency as a function of stimulation intensity and frequency. Through this process, we identified resonances and entrainment regimes (so-called *Arnold Tongues*) and thus measured the susceptibility of our model to entrainment. While oftentimes confused with one another, *resonance* refers to the enhancement of power when the stimulation frequency is in the vicinity of the system's natural frequency, while *entrainment*, refers to the phase locking of the system's response to the driving frequency[47]. As shown in Figure 6, idling and active states exhibited significant differences in their responses to stimulation and susceptibility to entrainment. Narrower Arnold Tongues were observed in the idling state compared to the active state, indicating that the suppression of alpha power in the active state facilitates phase locking of intrinsic dynamics with the stimulation signal. Specifically, only high intensity stimulation would provoke a shift in the peak frequency in the idling state. In the active state, the prominent gamma oscillations were easily suppressed and replaced by the frequency of the driving stimulus. This is in line with converging evidence indicating that intrinsic attractors limit the effect of perturbations, while irregular or high frequency content is more malleable[4].

Discussion

The aim of the present study was to investigate the mechanisms underlying state-dependent changes in oscillatory activity at the whole-brain scale, as well as the influence of fluctuations in spectral activity on functional connectivity. We have presented a novel connectome-based neural mass model that combines the two primary rhythmogenic mechanisms typically studied in large-scale brain network modelling: intracolumnar microcircuits and corticothalamic loops. This is an extension of previous work, that studied the behaviour of the basic corticothalamic motif in isolation[48]. Here we have embedded this corticothalamic unit into a whole-brain network, with anatomical connectivity derived from diffusion MRI tractography.

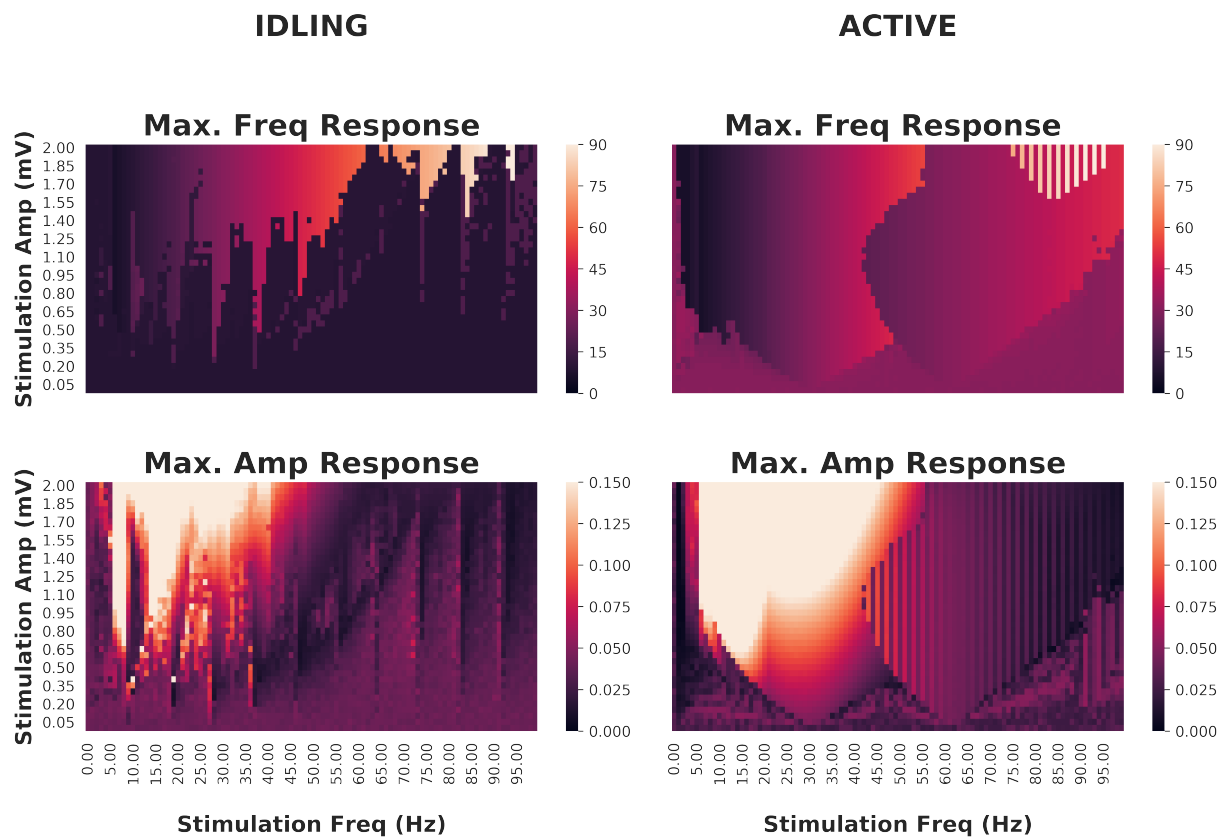


Figure 6: **Effects of periodic brain stimulation on corticothalamic loop dynamics**
Top row: Maximum frequencies displayed by the cortical excitatory population of an isolated cortico-thalamocortical loop (CTWC model, single node) in response to periodic (sine wave) stimulation of varying amplitudes (y axes) and frequencies (x axes). In the idling regime, an Arnold Tongue structure is clearly seen centred on the natural frequency (approximately 10 Hz): As the stimulation frequency moves away from the natural frequency, greater stimulation amplitude is required to achieve entrainment at the stimulation frequency. In the active regime, a broader and shallower Arnold Tongue structure is again seen, centred on the natural frequency (this time approximately 30Hz). Compared to the idling state, entrainment at the stimulation frequency is easier to achieve (requires lower amplitude stimulus) in the active than the idling regime. *Bottom row:* Maximum amplitudes displayed by cortical excitatory populations. Here again the amplitude response patterns match quite closely the Arnold Tongues seen in the maximum frequency responses.

266 Our model reproduces a variety of known features of human M/EEG recordings, including
267 a $1/f$ spectral profile, spectral peaks at canonical frequencies, and functional connectivity
268 structure that is shaped by the underlying anatomical connectivity. Using this model, we
269 have studied how thalamic drive mediates a shift in oscillatory regime, provoking a tran-
270 sition between alpha and gamma dominance in the power spectrum, and found that these
271 oscillations have a differential impact on functional connectivity patterns. We found that
272 spatially structured inter-area functional connectivity (as measured by band-limited power
273 amplitude envelope correlations), particularly at higher frequencies (gamma, beta, and alpha
274 to a lesser extent), are a hallmark of the active state. To better understand how these state-
275 and frequency-specific dynamics are impacted by exogenous stimulation, we applied cortical
276 periodic stimulation of various amplitudes and frequencies, eliciting endogenous resonances
277 both across the corticothalamic loop and within cortex. Our analysis confirms that, as com-
278 pared to the idling state, the active state is more susceptible to entrainment by exogenous
279 signals, as it shows wider and shallower Arnold Tongues. In contrast, the idling state's deep
280 and narrow Arnold Tongues indicate that the system has a strong preference for its natu-
281 ral frequency when in this regime, and will respond only to exogenous signals close to that
282 frequency or its harmonics.

283 **Relation to previous work**

284 The work presented here builds on previous work of several authors in a number of ways.
285 Most directly, the isolated CTWC neural mass model (without the whole-brain white matter
286 connectivity introduced here) was recently introduced in [48]. Previous to that we have also
287 studied resonance behaviour, response to stimulation, and state-dependence in corticothala-
288 mic circuits and generic feedback oscillators[45, 65, 64]. We emphasize however that the core
289 mathematical and conceptual component of the CTWC model presented in the present paper
290 and in our earlier work - namely the generation of slow M/EEG rhythms through a delayed

291 inhibitory cortico-thalamo-cortical recurrent circuit, has been used extensively by multiple
292 groups for several decades. One of the largest and most comprehensive bodies of work on this
293 is due to P. Robinson and colleagues, beginning with the introduction in [79] of a PDE wave
294 equation reformulation of the integro-differential cortical neural field model of [83], drawing
295 on earlier work of [11], [66], and others. This model was then augmented with thalamic retic-
296 ular and relay nuclei and their recurrent connections with the cortex[39], and the resultant
297 corticothalamic neural field model has been studied extensively over the past two decades -
298 both analytically and numerically, and in partial differential, ordinary differential, and lin-
299 earized equation forms, as well as being extended into the domains of epilepsy, Parkinson's,
300 sleep and arousal, plasticity, and brain stimulation (e.g. [39, 69, 67, 70, 84, 85, 82, 81, 68]).
301 Our approach in the present paper differs from this family of models in two key ways. First,
302 rather than the second-order equations of motion for the time-evolution of membrane volt-
303 age used by Robinson and many others[11, 61, 71], we began with the classic Wilson-Cowan
304 equations[86] to describe local interactions between excitatory and inhibitory neural popu-
305 lations in a cortical region. Second, rather than the using an integro- or partial-differential
306 equation formulation of a continuum neural field to represent spatio-temporal propagation
307 of activity across the cortex[79, 66, 51, 74, 72, 73], here we chose to follow the connectome-
308 based neural mass modelling methodology[75, 76, 77, 26, 63, 20, 54] of defining a discrete
309 network of point-process neural masses, interconnected via long-range white matter fibres
310 whose density was estimated from non-invasive diffusion MRI tractography. This combina-
311 tion of the cortico-thalamocortical circuit with the large-scale anatomical connectivity bears
312 some similarity to the work of some other authors (e.g. [25, 56, 55, 80]), but the present study
313 is the first to apply this directly to the key questions of state-dependence, alpha suppression,
314 functional connectivity, stimulation, and their relation to empirical M/EEG data. Notably,
315 this network-based approach allowed us to harmonize the analysis of functional connectivity
316 in simulated and empirical MEG data. In this we followed the approach of [36] and [87]

317 in our use of the bandpass-filtered amplitude envelope correlations[78, 37], and that line of
318 work is perhaps the closest of recent modelling studies to the present one. In [36], Abey-
319 suriya and colleagues studied the role of inhibitory synaptic plasticity in a connectome-based
320 network of Wilson-Cowan equations. As in the present study, these authors evaluated their
321 model in terms of its ability to accurately reproduce empirically measured MEG AEC ma-
322 trices (although they restricted their focus to only to alpha-frequency AECs). The relatively
323 simpler (as compared with our new CTWC) model used by these authors consisted of a
324 cortical Wilson-Cowan ensemble, tuned to have a natural frequency in the alpha range. This
325 stands somewhat in contrast to our new model, which features a *gamma* frequency-tuned
326 Wilson-Cowan ensemble, combined with an *alpha* frequency-tuned cortico-thalamocortical
327 motif. This additional two-component structure allows our model to exhibit more complex
328 behaviours, such as alpha-mediated inhibition and state-switching, as well as a rich reper-
329 toire of potential oscillation and frequency-specific synchronization patterns. The question
330 of whether and to what extent human M/EEG alpha activity is generated by corticothalamic
331 (as in e.g. the present study and much of the above-cited work by Robinson and colleagues),
332 or within intracortical microcircuits (as in e.g. [36], [58], [71]) remains a live and important
333 one however. Recent years has also seen growing interest in a third potential type of system-
334 level (low-frequency) rhythmogenic mechanism which can be broadly described as *network*
335 *eigenmodes*[51, 79, 72, 63, 62]. The proper evaluation and assessment of these hypotheses
336 around cortical rhythmogenesis shall most likely require a close interaction between novel
337 empirical work and hypothesis-generating computational models to properly settle. It is also
338 important to bear in mind here that there is no a priori reason (apart from explanatory
339 parsimony) to suppose a single mechanism for generation of rhythms[51]. Indeed, it may be
340 functionally advantageous for the brain to generate the same frequency through a variety
341 of mechanisms. If this were determined to be the case, then interaction across different
342 frequency-generating mechanisms would be a key question for future work.

343 **The alpha rhythm as a suppression mechanism**

344 The transition from idling to active state in our model is initiated by the gradual increase of
345 a tonic sensory/neuromodulatory drive term, I_o , that effectively hyperpolarizes the thalamic
346 relay nucleus, and thereby destroys the slow 10Hz alpha rhythm generated by the cortico-
347 thalamocortical loop. Once the alpha oscillation is removed in this way, the gamma rhythm
348 generated by intracortical excitatory-inhibitory interactions comes to the fore. One inter-
349 pretation of this phenomenon is that alpha resonance, mediated by corticothalamic loops,
350 plays an inhibitory role - through which slow oscillatory corticothalamic activity suppresses
351 and dominates higher frequency cortical activity. This alpha-as-suppression-mechanism the-
352 ory speaks to a major question in the field of M/EEG cognitive neuroscience: what is the
353 functional role of alpha? Specifically, the enhancement of alpha activity during disengage-
354 ment of the cortical network (such as during quiescence, sleep, anaesthesia, and withdrawal
355 of sensory stimulation) suggests that alpha oscillations implement a functionally inhibitory
356 signal, and represent a top-down shift towards internal encoding through suppressing the
357 activity of task-irrelevant areas[49]. In contrast, faster frequencies, such as those found in
358 the beta and gamma range, are found in states of arousal and sensory recruitment, sug-
359 gesting a positive, excitatory role of faster neural oscillatory states. In our model, the less
360 spatially-resolved structure of functional connectivity in the alpha vs. the gamma range -
361 at all I_o values, but particularly for $I_o \geq 1.4$ - does support this perspective. From this
362 point of view, a key feature of our model is its characterization of the relationship be-
363 tween corticothalamically-generated and cortically-generated rhythms. In particular, the
364 corticothalamic alpha dominates in the idling state, and can be understood as suppressing
365 the intrinsic rhythmic activity in the cortical ensemble, which can be ‘released’ with suffi-
366 cient sensory or neuromodulatory drive. This simple circuit mechanism therefore captures a
367 widely used theoretical concept in M/EEG cognitive neuroscience concerning the functional
368 role of alpha activity. On this account, alpha acts as a mechanism for selectively gating and

369 attentionally biasing sensory inputs. This phenomenon is also observed in EEG studies on
370 the effects of anesthesia, where low frequency activity becomes increasingly dominant with
371 higher doses of propofol[50]. This effect is observed concurrently with apparent attenuation
372 of sensory inputs, for example in reduced amplitude and increased latency of somatosensory
373 evoked potentials (SEPs). Recent work in mouse models has also shown that driving thala-
374 mic circuits with alpha-frequency activity causes widespread depression of cortical activity;
375 whereas stimulating at higher frequencies (e.g. gamma) causes widespread increase in both
376 baseline activity and the spatial spread of the stimulation influence[18].

377 Interestingly, in our analyses we observed that the active-state model AEC patterns ac-
378 tually showed closer resemblance to empirical resting-state MEG AEC patterns than the
379 idling-state AEC patterns. This is somewhat unexpected because resting-state MEG power
380 spectrum was unequivocally better fit by a CTWC model in the idling, alpha-dominated
381 regime. This result suggests that in the brain, during the rest or idling state, alpha power
382 is strong and AEC functional connectivity is largely random. In contrast, in the active
383 state, alpha power is relatively weaker, and AECs are more local and segregated. Func-
384 tional connectivity is thus facilitated in the high-drive state, when the alpha-generating loop
385 is inhibited, and dynamics are driven by cortico-cortical E-I interactions. In the state of
386 low-drive, the alpha rhythm is highly prominent and functional connectivity is largely asyn-
387 chronous. In the state of high drive, the alpha rhythm has been suppressed, and functional
388 connectivity is high. Together, these observations suggest that the alpha rhythm plays a
389 suppressing role in large-scale brain dynamics. We hypothesize that this may be a general
390 feature of alpha activity - this indicates that regional communication is facilitated by being
391 in the active state, and that there perhaps a constant interplay and balance between the
392 idling state and the active state.

393 Conclusions and future directions

394 To conclude: we have developed a novel whole-brain connectome-based neural mass model
395 that incorporates corticothalamic and intracortical rhythmogenic mechanisms. This model
396 reproduces qualitatively multiple features of MEG-measured neural activity. Importantly,
397 our model also lends some insight into the way that cortico-thalamically-generated alpha
398 rhythms could play a functional role in the organization of brain dynamics, by suppress-
399 ing high-frequency cortical activity associated with cognitive engagement and information
400 processing. Future work shall investigate further questions of subcortical parcellation and in-
401 tegration, model fitting, and compare alternative rhythmogenic mechanisms directly against
402 each other. Importantly, future work should also investigate the significance of intersub-
403 ject variability in anatomical connectivity on network dynamics. Although we demonstrated
404 here our model's ability to fit individual subjects' power spectra through small variations
405 in thalamic kinetic parameters, it was beyond the scope of the present study to incorpo-
406 rate individualized anatomical connectivities. One of the exciting and promising aspects
407 of connectome-based neural mass modelling is the possibility of constructing individual-
408 ized computational models using a subjects' own diffusion MRI tractography. However at
409 this point in time the extent to which this does actually deliver improvement in computa-
410 tional model accuracy remains an open question for the field (for recent work relevant to
411 this, see [36, 60]). Finally, we emphasize that neither our specific CTWC model, nor the
412 broader alpha-as-suppression-mechanism concept, constitute a universal account of all alpha-
413 frequency rhythms seen in the M/EEG or other recording modalities. Indeed we consider
414 the most likely scenario to be that multiple, dissociable mechanisms contribute indepen-
415 dently a proportion of the information and measured signal in that part of the frequency
416 spectrum[51]. Here we have, building on previous work, made we believe some progress in
417 characterizing the dynamic properties of one of these candidate mechanisms.

418 Methods

419 Our modelling approach follows the now-standard whole-brain connectome-based neural
420 mass modelling paradigm[75, 77, 19, 20], where dynamic units are placed at node locations
421 as defined by a grey matter parcellation, and coupled with an adjacency matrix (anatomical
422 connectome) defining the presence and associated strengths of long-range white matter
423 fibres interconnecting region pairs. The anatomical connectome used in the present study,
424 derived from group-average tractography streamline counts, was constructed from analyses
425 of the human connectome project (HCP) WU-Minn consortium diffusion-weighted MRI
426 (DWI) corpus[21, 22]. For details of this, see the below section *DWI data analyses* .

427 In the model, activity at each node is driven by background noise and/or exogenous
428 stimulation. Complete mathematical formulation and implementation details are given in
429 the section *Corticothalamic model*. Simulated nodal time series from the model can be
430 understood as approximations of regionally averaged source-space MEG signals. To assess
431 the performance of the model in reproducing key features of empirically measured human
432 brain dynamics, we additionally conducted new analyses of the HCP WU-Minn resting-state
433 MEG corpus[23]. These are described in the *MEG data analyses* section.

434 Corticothalamic model

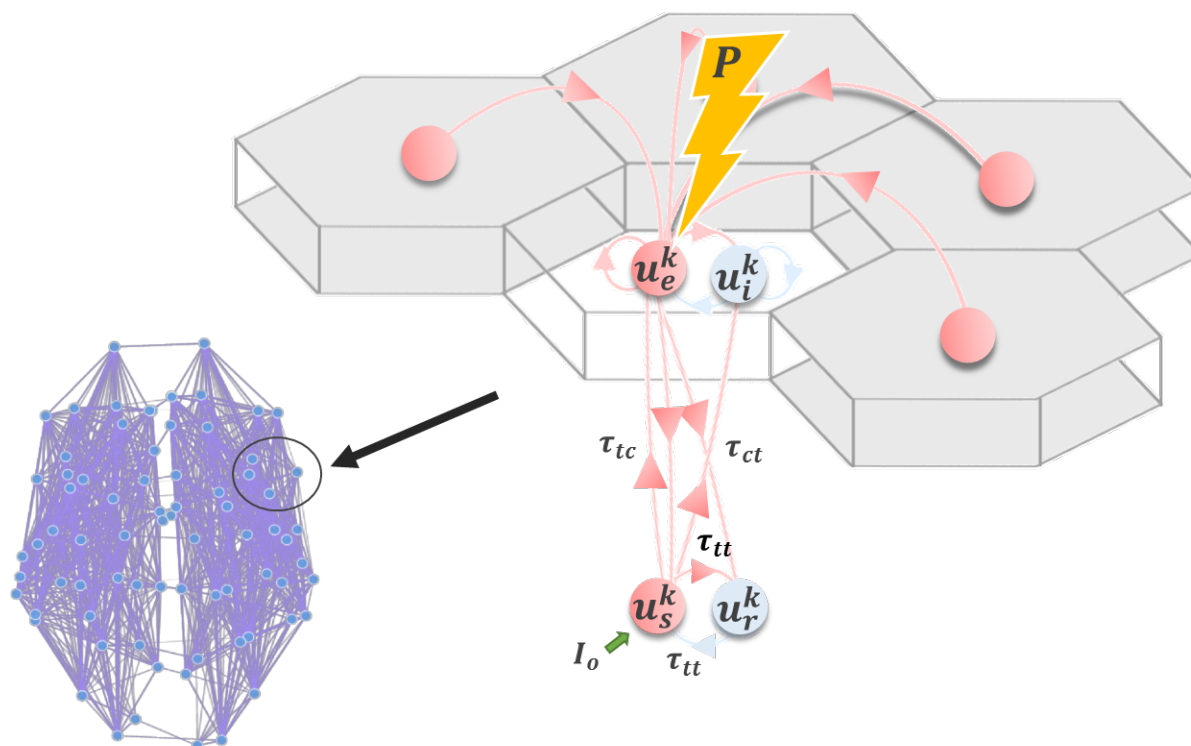


Figure 7: **Corticothalamic model**. Schematic of the corticothalamic model structure. Cortical (u_e , u_i) and thalamic (u_s , u_r) populations interact through a delayed feedback loop. Entrainment of the network activity through electromagnetic stimulation P applied to u_e depends on the amplitude and frequency of the stimulation pulse, as well as the network state, controlled by I_o .

435 Following other authors [39, 24, 25], we employ a model for neuronal dynamics at each node
 436 that incorporates both cortical and thalamic neural populations. The model describes a
 437 four-component cortico-thalamo-cortical motif, consisting of excitatory (\mathbf{u}_e) and inhibitory
 438 (\mathbf{u}_i) cortical neuronal populations, coupled to thalamic reticular (\mathbf{u}_r) and specific relay
 439 nuclei (Fig. 7). Both relay and reticular nuclei receive inputs from the cortical excitatory
 440 population, following a corticothalamic conduction delay τ_{ct} . However only the relay nucleus
 441 sends excitatory input back to the cortex; again received following a delay $\tau_{ct}=\tau_{tc}$. The

442 reticular nucleus, which is widely known to have an inhibitory influence of other thalamic
 443 regions[59], plays a similar role to the cortical inhibitory population, inhibiting the relay
 444 nucleus and thereby generating oscillatory dynamics.

445 As defined, our node-level model consists of a Wilson-Cowan oscillatory neural popu-
 446 lation, embedded in a delayed inhibitory feedback loop mediated by corticothalamic and
 447 thalamocortical connections. The full network-level model thus consists of a set of N such
 448 local units of this kind, coupled using the connectivity matrix \mathbf{W} (anatomical connectome).
 449 The system of stochastic delay-differential equations governing the time-evolution of neural
 450 activity within the network can be summarized as follows:

$$\mathcal{D}_p u_p^j = \underbrace{G[u_p^j]}_{\text{neural interactions}} + \underbrace{\mathbf{S}_p P^j + \mathbf{S}_i I_o^j}_{\text{static and time-varying stimulation}} + \underbrace{\sqrt{2D}\xi_p^j}_{\text{background noise}} \quad (1)$$

451 where the temporal differential operator $\mathcal{D}_p = (1 + \alpha_p^{-1} \frac{d}{dt})$ incorporates population time
 452 constants α_p , and u_p^j refers to the mean somatic membrane activity of the neural population
 453 $p \in \{e, i, r, s\}$ within one cortico-thalamic module j across the brain-scale network of $N=68$
 454 nodes. Irregular and independent fluctuations are also present in the network, modelled by
 455 the zero-mean Gaussian white noise processes ξ_p^j with standard deviation D . The neural
 456 interaction term $G[u_p^j]$ in Eq. 1 can be further broken down into

$$G[u_p^j(t)] = \mathbf{A}F[u_p^j(t)] + \mathbf{B}F[u_p^j(t - \tau_{ct})] + \mathbf{C}F[u_p^j(t - \tau_{tt})] + \mathbf{K}Q \quad (2)$$

457 where the matrices

$$\mathbf{A} = \begin{pmatrix} g_{ee} & g_{ei} & 0 & 0 \\ g_{ei} & g_{ie} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \mathbf{B} = \begin{pmatrix} 0 & 0 & 0 & g_{es} \\ 0 & 0 & 0 & g_{is} \\ g_{re} & 0 & 0 & 0 \\ g_{se} & 0 & 0 & 0 \end{pmatrix}, \mathbf{C} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & g_{rs} \\ 0 & 0 & g_{sr} & 0 \end{pmatrix} \quad (3)$$

458 respectively specify the gains (connection strengths) of intracortical, corticothalamic and
 459 intrathalamic interactions within a node. Intrathalamic and corticothalamic/thalamocortical
 460 connections are retarded by conduction delays $\tau_{ct}=20\text{ms}$ and $\tau_{tt}=5\text{ms}$, respectively. The
 461 matrix

$$\mathbf{K} = \begin{pmatrix} g_{cc} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (4)$$

462 specifies the global gain applied to all afferent activity Q arriving from other cortical
 463 neural populations. In the present model we assume for simplicity that afferent activity only
 464 impacts on the cortical excitatory population u_e ; and so only the upper left entry in \mathbf{K} is
 465 nonzero. The afferent activity in Q is a time-delayed summation of u_e at all other nodes in
 466 the network

$$Q^j = \sum_{k=1}^N \mathbf{W}^{jk} F[u_e^k(t - \mathbf{T}^{jk})] \quad (5)$$

467 where \mathbf{W} and \mathbf{T} are cortical white matter connectivity and conduction delay matrices,
 468 both of which are derived from empirical diffusion-MRI tractography reconstructions (see
 469 below). For the latter, the cortico-cortical conduction delay matrix $\mathbf{T} = \mathbf{L}/cv$ is calculated
 470 from a matrix of measured (average) fibre tract lengths \mathbf{L} , assuming a fixed conduction
 471 velocity $cv=4\text{m/s}$. The sigmoidal response function F in Eqs. 2 and 5 specifies the nonlinear
 472 response of a neural population to incoming inputs as follows

$$F[u] = (1 + \exp(-\beta(u - \sigma)))^{-1} \quad (6)$$

473 The matrices

$$\mathbf{S}_p = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}; \mathbf{S}_i = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad (7)$$

474 in Eq. 1 parametrize the impact on the four subpopulations e, i, r, s within a node of
 475 the time-varying exogenous input P (representing periodic brain stimulation such as rTMS
 476 or TACS) and static input I_o (representing here state-dependent sensory/neuromodulatory
 477 drive). Again, in the present study we only consider exogeneous inputs to impact the cortical
 478 excitatory populations, and so only the upper left entry in \mathbf{S}_p is nonzero. Similarly, I_o is
 479 for present purposes only considered to impact the thalamic relay nucleus, and so only the
 480 lower right entry of S_i is nonzero. The exogeneous periodic signal P here is given by the
 481 simple sinusoidal function

$$P^j = M^j \sin(2\pi\omega t) \quad (8)$$

482 with frequency ω and intensity M . The constant state-dependent drive I_o^j to thalamic
 483 relay populations serves as a control parameter indexing idling vs active states (see below).
 484 This static input current can be thought of as a tonic level of sensory (e.g. visual) drive,
 485 although it could also reflect a static influence of ascending (e.g. noradrenergic) neuromodu-
 486 latory drive, reflecting the level of engagement in a perceptual or cognitive task. Irrespective
 487 of its cause, the idling or rest-like state is defined as the dynamics resulting from setting
 488 $I_o^j=0$; i.e. in the absence of this constant thalamic input. The active state, in contrast, is
 489 defined by a greater engagement of thalamic nodes, and hence $I_o^j>0$ for active nodes. In
 490 both of these cases, nodes within the network may be differentially recruited by a given task,
 491 thus being activated while others remain inactivated. This represents an intermediate point

492 between the extreme cases where all nodes are either active or inactive.

493 With the described structure, and right choice of parameters, our system generates alpha
494 (8-12Hz) oscillations due to the presence of delayed inhibition, as well as gamma (30-120Hz)
495 oscillations resulting from the cortical activity and interactions, and also in a limited domain
496 of parameter space shows coexistence of both of these features. As has been demonstrated
497 previously [48], increasing the thalamic drive parameter past a critical point triggers sup-
498 pression of resting state alpha oscillations, and results in a greater susceptibility of cortical
499 neural populations to entrainment by exogenous inputs or noninvasive stimulation. In addi-
500 tion, this transition to the active state is accompanied by an increase in high-frequency (i.e.
501 gamma) activity. As such, the thalamic drive can be seen as a control parameter, controlling
502 the power of alpha and gamma oscillations, as well as tuning the response to exogenous
503 inputs.

504 Nominal parameter values and definitions from the above-specified system of equations
505 are summarized in Table 1. The system was numerically integrated using a stochastic Euler-
506 Maruyama scheme, implemented in Python. Simulations were carried out on an 8-core
507 Ubuntu 14.04 machine. Run time scaled approximately linearly: each 2-second simulation
508 ran in approximately 2 seconds real time. All code and processed data used in this study is
509 freely available at <https://github.com/GriffithsLab/ctwc-model>, along with additional notes
510 and comments. A version of the model has also been developed for direct use within The
511 Virtual Brain modelling and neuroinformatics platform (TVB; www.thevirtualbrain.org)[26,
512 27]). Our model produces regional time series for each network node, as specified by the
513 anatomical parcellation. These represent the collective activity of neural populations within
514 that region, and as such correspond to signals estimated from MEG source reconstruction.
515 Subsequent power spectrum and functional connectivity analyses of simulated activity time
516 series therefore proceeded identically to that for MEG data, and are described in the *MEG*
517 *data analyses* section below.

Name	Unit	Nominal Value	Description
a_e	ms	0.3	Cortical excitatory population time constant
a_i	ms	0.5	Cortical inhibitory population time constant
a_s	ms	0.2	Thalamic relay nucleus time constant
a_r	ms	0.2	Thalamic reticular nucleus time constant
i_e	mV	-0.35	Cortical excitatory population constant input
i_i	mV	-0.3	Cortical inhibitory population constant input
i_s	mV	0.5	Thalamic relay nucleus constant input
i_r	mV	-0.8	Thalamic reticular nucleus constant input
$\tau_{(ct/tc)}$	ms	20	Corticothalamic / Thalamocortical conduction delay
τ_{tt}	ms	5	Thalamo-thalamic conduction delay
I_o	mV	0.	Static sensory/neuromodulatory drive
dt	ms	0.1	Integration step size
w_{ee}		0.5	Excitatory-excitatory gain
w_{ei}		1	Excitatory-inhibitory gain
w_{ie}		-2.	Inhibitory-excitatory gain
w_{ii}		-0.5	Inhibitory-inhibitory gain
w_{er}		0.6	Excitatory-reticular gain
w_{es}		0.6	Excitatory-relay gain
w_{si}		0.2	Relay-inhibitory gain
w_{se}		1.65	Relay-excitatory gain
w_{rs}		-2.	Reticular-relay gain
w_{sr}		2.	Relay-reticular gain
$D_{(e,i,r,s)}$		0.0001	Noise standard deviation for all populations
g		0.9	Global connectivity scaling factor
β		20.	Activation function gain parameter
σ		0.	Activation function threshold parameter

Table 1: **Model parameters**

518 **DWI data analyses**

519 The anatomical connectivity matrices used in this paper were constructed using diffusion-
520 and T1-weighted MRI data from the HCP WU-Minn consortium[28, 21, 22]. For detailed
521 descriptions of the MR acquisition parameters and processing pipeline, see [21, 22]. The HCP
522 WU-Minn corpus consists of multimodal imaging and behavioural data from 1200 healthy,
523 young (ages 20-40) subjects. The tractography analysis described below was applied to a
524 700-subject subset of the full sample; and the connectivity matrix used for simulations in
525 the present paper was calculated from an average over these 700 subjects.

526 The HCP WU-Minn minimal diffusion pipeline[21] consists of gradient nonlinearity cor-
527 rection, eddy current correction, boundary-based registration and reorientation of diffusion
528 data to the T1 image, and gradient vector rotation. The outputs of this preprocessing
529 pipeline were the starting point for our diffusion data analyses. Using the minimally prepro-
530 cessed diffusion data, we performed whole brain deterministic tractography reconstructions
531 using the Dipy software library[29], following a methodology modelled closely on that of [30]
532 and [31]. ODFs were computed at each white matter voxel using a DSI tissue model. Stream-
533 lines were initiated from 60 regularly-spaced grid points within each voxel on the grey-white
534 matter interface (as determined from coregistered freesurfer surfaces), and propagated using
535 the EuDX algorithm[32]. Streamlines not terminating at the grey-white matter interface, or
536 having lengths greater than 250mm or less than 10mm, were discarded. Subjects' streamline
537 sets were segmented using the Lausanne scale-1 parcellation[30, 33], computed individually
538 for every subject from their freesurfer reconstructions using algorithms from the connectome
539 mapping toolkit[33]. All surface-based parcellations were then converted to image volumes
540 and resliced to diffusion space for streamline segmentations. For each parcellation, the in-
541 terconnecting streamlines for every ROI combination were determined using a logical AND
542 operation. Each segmented streamline set was counted and its average length computed, re-
543 sulting in streamline count and length matrices for each subject. The simulations described

544 in the present paper were computed using group-average tract length matrices (divided by
545 conduction velocity to convert to conduction delay), and group-average streamline count
546 matrices, with the latter first being log-transformed to adjust for the DWI tractography
547 over-estimation bias[36].

548 **MEG data analyses**

549 MEG analyses were performed using 10 randomly selected subjects from the HCP WU-
550 Minn corpus[23], using the MNE software library[35, 34]. The specific analyses done were
551 based on a modified version of the analysis pipeline developed by Engemann and colleagues
552 (<https://github.com/mne-tools/mne-hcp>), which implements a full source space analyses,
553 beginning with the HCP preprocessed sensor-space data. Key outcome variables from this
554 pipeline for the present study were whole-brain functional connectivity matrices and spectral
555 power maps, derived from regional source time series estimates. We opted to implement a
556 complete analysis here rather than use the high-level pipeline outputs provided with the
557 HCP WU-Minn corpus, as we needed complete control over the process. In particular, we
558 needed to a) use the same parcellation in the MEG as in the tractography analyses, and b)
559 ensure identical analyses were done on empirical and simulated MEG regional time series.
560 Regarding the first of these: as in the tractography analyses, the parcellation used for MEG
561 analyses was the Lausanne2008 scale 1 - but with 10 subcortical nodes (brainstem, basal
562 ganglia, thalamus) excluded. Note this is in fact identical to the freesurfer *aparc* parcellation
563 (but reordered and renamed).

564 Source time series were extracted for all vertices within a parcel using an L2 minimum-
565 norm inverse solution and averaged, yielding one representative time series per parcel. To
566 maximize robustness of these signals, this was operation was repeated five times, with 30-
567 second windows each[23]. Subsequent analysis of these regional time series proceeded iden-
568 tically for both the empirical and simulated MEG data. We first computed power spectra

569 for each region using Welch’s method. We then studied functional connectivity within the
570 system using the band-limited power Pearson correlation (BLPC) method[37, 38]. For this,
571 regional time series from each of the 5 windows were bandpass-filtered into six canonical fre-
572 quency bands: delta (0.5-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-30 Hz), low gamma
573 (30-50 Hz) and high gamma (60-80 Hz)[37]. Pearson correlations between the bandpass-
574 filtered time series were computed, and averaged over the 5 windows. Finally, these BLPC
575 matrices at each frequency band were averaged over subjects. Because our simulations used
576 a normative (rather than subject-specific) anatomical connectivity, these analyses were con-
577 ducted only once on the simulated MEG data, and this was compared to the group-averaged
578 MEG data to evaluate the performance of the model.

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