Thalamic bursts modulate cortical synchrony locally to switch between states of global functional connectivity in a cognitive task

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This PDF file includes:

abstract,
author summary,
introduction,
results (with figures),
discussion,
methods,
acknowledgments,
author contributions,
declaration of interests,
supplemental information,
references

24 **Abstract**

25 Performing a cognitive task requires going through a sequence of functionally diverse
 26 stages. Although it is typically assumed that these stages are characterized by distinct
 27 states of cortical synchrony that are triggered by sub-cortical events, little reported
 28 evidence supports this hypothesis. To test this hypothesis, we first identified cognitive
 29 stages in single-trial MEG data of an associative recognition task, showing with a novel
 30 method that each stage begins with local modulations of synchrony followed by a state of
 31 directed functional connectivity. Second, we developed the first whole-brain model that can
 32 simulate cortical synchrony throughout a task. The model suggests that the observed
 33 synchrony is caused by thalamocortical bursts at the onset of each stage, targeted at
 34 cortical synapses and interacting with the structural anatomical connectivity. These
 35 findings confirm that cognitive stages are defined by distinct states of cortical synchrony
 36 and explains the network-level mechanisms necessary for reaching stage-dependent
 37 synchrony states.

39 **Author summary**

40 A novel machine-learning method was applied to unveil the dynamics of local and cortex-wide
 41 neural coordination underlying the fundamental cognitive processes involved in a memory task. To
 42 explain how neural activity – and ultimately behavior – was coordinated throughout the task, we
 43 developed a whole-brain model that incorporates cognitive mechanisms, anatomy, and neural
 44 biophysics. Similar models are used with resting state data, however, simulating a cognitive task
 45 remained elusive. The model showed that sub-cortical pulses at the onset of cognitive processes – as
 46 hypothesized by cognitive and neurophysiological theories – were sufficient to switch between the
 47 states of neural coordination observed. These findings have implications to understand goal-directed
 48 cognitive processing and the mechanisms to reach states of neural coordination.

49

50 **Key words**

51 cognitive stages, cognitive processes, associative memory, MEG, functional connectivity,
52 synchronization, hidden Markov model, brain network, biophysical model, whole-brain model,
53 Kuramoto model

54

55 **Introduction**

56 Already in the 19th century, Donders hypothesized that information processing in the brain proceeds
57 through a sequence of fundamental cognitive stages with different functions such as visual
58 encoding, memory retrieval, and decision making [1]. Initially, cognitive stages were investigated
59 with behavioral metrics like reaction time (e.g., [2]). Over the past decade, neuroimaging analyses
60 have begun to uncover the neural correlates of these cognitive stages (e.g., [3]).

61

62 The dominant view is that cognitive stages require specific patterns of neural coordination across
63 the cortex [3–5]. The transition from one cognitive stage to the next is thought to be driven by the
64 basal-ganglia-thalamus (BGT) system which sets new states of cortical coordination [6–8]. The
65 striatum monitors the current state of the cortex, and based on a comparison to predefined states,
66 selects and triggers the next cognitive stage. The role of the BGT system modulating cortical
67 coordination is supported by animal studies, intracranial recordings, and neural models [9–14].
68 However, the network-level mechanisms required to reach a new state of cortical coordination from
69 subcortical inputs are poorly understood.

70

71

72 To give a detailed account of these mechanisms, one first needs to characterize the different states
73 of neural coordination within the sequence of cognitive stages. We measured neural activity with

74 cortically projected magnetoencephalographic (MEG) recordings as these have a sufficiently fine
 75 temporal resolution to measure cognitive stages, as well as adequate spatial resolution. However,
 76 cognitive stages have high temporal variability – that is, stages typically have a different duration
 77 on each trial of an experimental task – which makes it difficult to measure neural coordination. To
 78 overcome this problem, we used a machine learning method that identifies the onsets of cognitive
 79 stages on a trial-by-trial basis [15]. Afterwards, the identified stage onsets were used to time-lock
 80 the measures of neural coordination within regions (local synchrony) and between regions
 81 (functional connectivity, FC), as there are concurrent changes at both spatial scales [16,17].

82
 83 The machine learning method used to identify cognitive stages combines multivariate pattern
 84 analysis with a Hidden semi-Markov Model (HSMM-MVPA). The HSMM-MVPA method searches
 85 in each trial for a sequence of short-lived modulations of MEG amplitude (hereafter called *bumps*,
 86 following the original paper [15]) that have a consistent topology across trials. These bumps signify
 87 the onset of cognitive stages, and are thought to be triggered by the BGT system. Previously this
 88 method has been used successfully to, for example, identify the cognitive stages that are affected by
 89 task manipulations such as difficulty, stage insertion, and evidence accumulation for decisions
 90 [4,5,15,18].

91
 92 To understand how events from the BGT system can cause switches between states of neural
 93 coordination – and thus between cognitive stages – we build upon generative whole-brain
 94 biophysical models of large-scale activity (GWBM) that have been used to explain the dynamics of
 95 neural coordination at rest [19]. GWBMs reduce the whole-brain network of neurons and synapses
 96 to a smaller network that still incorporates the most relevant principles of neural dynamics. The
 97 nodes of such a network describe the macroscopic activity within a region, while the links reflect
 98 the neural fibers that connect these regions (i.e. structural connectivity).

99

100 GWBMs of resting state indicate that time-resolved patterns of neural coordination are related to the
 101 anatomical structure of the brain and that these patterns evolve without requiring any input (a
 102 phenomenon referred to as *metastable coordination*; [17,19]. Such coordination dynamics are
 103 thought to provide an optimal mechanism for simultaneously integrating and segregating
 104 information that allows the system to adapt quickly or alternatively, to persist in a given state [20].
 105 While this is sufficient to explain resting-state data, cognitive tasks require specific, controlled
 106 sequences of coordination states.

107
 108 Here, we explored a GWBM in which inputs from the BGT system modulated local connectivity
 109 strength briefly at the onset of cognitive stages, as suggested by cognitive theories and
 110 electrophysiology measurements [6–14]. In other complex networks with similar dynamics as the
 111 brain, such local perturbations can, in turn, produce controlled switches between global states [21].
 112 Similarly, even though the inputs from the BGT system only triggered direct changes in local
 113 connectivity strength, we observed transient modulations of local synchrony and switches to the
 114 targeted states of directed functional connectivity that lasted until the next input. When there were
 115 no further inputs from the BGT system, neural coordination returned to resting-state patterns after
 116 tens of seconds. These results matched the observed neural coordination throughout the cognitive
 117 stages in the empirical data. Finally, we used the GWBM to determine the importance of each brain
 118 region in facilitating the switches between states of coordination.

119

120 **Results**

121 **Five cognitive stages in an associative memory task.**

122 We re-analyzed MEG data from an associative memory recognition task with 18 participants [3].
 123 We chose this task because associative recognition memory involves a rich variety in cognitive

124 stages that have also been widely studied [3,5,15,22,23]. The task consisted of a self-directed
 125 learning phase during which participants memorized 32 word pairs and a test phase. In the test
 126 phase – which we analyzed here – participants were again presented with word pairs. These could
 127 be *target* pairs from the learning phase or *re-paired foil* pairs, which consisted of the same words
 128 paired differently (e.g., if the participants learned apple-tree and month-house, a foil pair could be
 129 apple-house). Participants were asked to indicate as quickly and accurately as possible with a key
 130 press if it was a learned pair or a re-paired foil. Only correct responses were included in our
 131 analysis. We were interested in the evolution of neural coordination along with the cognitive stages
 132 involved in performing the task, and in particular in how the brain switches between these
 133 consecutive states of functional neural coordination.

134

135 As the goal is to develop a cortical model, the MEG signals were projected onto 5,124 cortical
 136 sources using the structural MRI of each participant with minimum-norm estimation [3]. The
 137 resulting cortical activity was parcellated and averaged into time-series for 68 cortical regions
 138 following the Desikan-Killiany atlas [24]. Next, HSMM-MVPA was used to estimate the timing of
 139 bumps that indicate the onset of cognitive stages in each trial. All trials were assumed to go through
 140 the same sequence of stages as in previous studies [3,4,15]. Thus, bumps were assumed to have the
 141 same spatial topology across trials, but trial-to-trial variable temporal location. Nevertheless, the
 142 HSMM-MVPA can cope relatively well with extra bumps in some trials [15]. The intervals between
 143 stimulus-onset-to-bump, bump-to-bump, and bump-to-response constitute the cognitive stages. A
 144 leave-one-subject-out cross validation method showed that the MEG data were best explained by a
 145 HSMM-MVPA model with four bumps, which corresponds to five cognitive stages (Figure 1A).

146

147 Following previous work on associative recognition [3,5,15], we interpreted the five cognitive
 148 stages as follows: pre-encoding, encoding of visual information, memory retrieval, decision
 149 making, and motor response. We did not analyze the pre-encoding stage as it is mostly driven by the

task stimulus and not by events from the BGT system that produce the transitions between cognitive stages. The retrieval and motor stages were longer and had larger across-trial variability than the encoding and decision stages (Figure 1A and E).

Figure 1. Theta-band MEG local synchrony and directed functional connectivity by cognitive

stages. (A) Cognitive stages derived with the HSMM-MVPA along with their median durations.

(B) Significant directed functional connectivity throughout the stage (*within-stage dpFC*). Links go from phase-ahead to phase-behind regions. The nodes represent the nodal degree (size) and the difference between phase-ahead and phase-behind links (color). (C) Directed functional connectivity time-locked at the onset of the stages (*across-trials dpFC*). Colored (dark gray) line: average across links with (without) significant across-trial dpFC at the current stage; Shading: standard error of the mean across subjects. Black horizontal lines are the onset of the stages. The

white background spans the median stage duration. Retrieval and response insets: Directed functional connectivity time-locked to the onsets of the decision stage and to the end-of-trial response, respectively (D) Across-trials averaged local synchrony (z-scored envelope of amplitudes) time-locked at the onset of the stages. Y-axis represents cortical regions – blue: temporal, orange: occipital, red: parietal, and green: frontal. Magenta lines: time windows to measure the relative change in local coordination at the onset of the stages. (E) Histogram of stage durations derived with the HSMM-MVPA.

154

155 **Different local synchrony and directed functional connectivity states between** 156 **stages.**

157 Next, we measured neural coordination in the discovered stages. We focused on coordination of
158 theta band oscillations (4-8 Hz), for several reasons: we previously found synchrony patterns in this
159 frequency band to vary across task stages [4]; theta oscillations have been related to cognitive
160 processes such as attention, memory, control, and decision making [25–28]; the phase of theta
161 oscillations is known to modulate the activity in higher frequency bands [26,29]; local modulations
162 of theta-band activity are hypothesized to mediate changes in long-range functional connectivity
163 [30]; and thalamic activity modulates cortical theta band activity [31].

164

165 Directed FC in the theta band was operationalized by means of the directed phase-lag index [32]
166 (dpFC). A significant dpFC indicates that the phase in one region is consistently ahead or behind
167 another region. The significance of dpFC was obtained using 200 surrogate data sets with random
168 circular shifts of the original phases. We measured first *within-stage dpFC* to capture directed FC
169 states that are constant from the start to the end of a cognitive stage. Figure 1B shows the links with
170 significant within-stage dpFC, as well as the local difference between phase-ahead and phase-
171 behind links (node color) and the total number of links regardless of their direction (node size).

172 Next, we measured *across-trial dpFC* of the significant links in a stage to reveal the temporal
 173 evolution of directed FC during the stage (Figure 1C). Across-trial dpFC was calculated sample-by-
 174 sample with the trials time-locked to the onset of each stage.

175

176 Across-trial dpFC revealed that functional states of directed FC switch at the transition between
 177 cognitive stages. These switches are visible because across-trial dpFC takes into account the trial-
 178 to-trial temporal variability of the cognitive stages as revealed by the HSMM-MVPA analysis. For
 179 example, for the memory retrieval stage, across-trial dpFC seems to fade halfway through.

180 However, when across-trial dpFC is time-locked to the onset of the next stage – the decision stage –
 181 dpFC for memory retrieval materializes until shortly before the decision stage (see the insets in
 182 Figure 1). This illustrates why the HSMM-MVPA analysis is crucial: otherwise dpFC would appear
 183 to fade quickly after stimulus onset, while that is not the case when first isolating cognitive stages.

184

185 Local synchrony was operationalized as the envelope of the theta band analytic signals in each
 186 region, which indicates the degree of synchronous neural activity within a region. The envelopes
 187 were z-scored over time and then averaged across trials and participants. Across-trial averages were
 188 time-locked to the onset of cognitive stages which gave a time course of local synchrony for each
 189 stage (Figure 1D). This showed that the local modulations of synchrony occurred only briefly at the
 190 start of each stage, and involved different regions depending on the cognitive operations involved in
 191 that stage.

192

193 As expected, each stage had a different neural coordination pattern. In the visual encoding stage,
 194 occipital and left-temporal regions showed local synchrony and dpFC which might facilitate the
 195 transfer of visual information to the medial temporal lobe and the hippocampus to start a retrieval
 196 process [23]. The encoding of information is controlled by a large fronto-posterior, fronto-lateral
 197 network [25,26]. During the memory retrieval stage, local synchrony at occipital and temporal

198 regions is reduced. dpFC now happens mostly between left-medial-temporal and frontal regions,
 199 whose coordination is required for memory tasks [23,33]. At the onset of decision making the
 200 frontal regions begin to synchronize locally. The decision process is mediated by fronto-parietal
 201 dpFC [27], and dpFC between temporal and parietal regions dpFC to reinsert the memory retrieved
 202 into the left-parietal cortex [23]. Finally, at the motor stage a large dpFC network appears between
 203 motor, temporal, left-parietal, and pre-frontal regions. This complex network has previously been
 204 associated with motor preparation, action reevaluation, decision, and cognitive control [27,28,34],
 205 in line with the idea that the action is reevaluated during the motor response [35].

206
 207 Together, these analyses unveiled that right at the onset of a cognitive stage there is a reorganization
 208 of neural coordination in the cortex. Whereas the change in local synchrony was only brief, dpFC
 209 lasted throughout the cognitive stage, indicating that short modulations of local synchrony can have
 210 persistent global effects. Next, we used a GWBM to investigate the mechanism underlying this.

211 **Generative large-scale whole-brain model (GWBM)**

212 In order to integrate cognitive stages and neural coordination into one framework along with neural
 213 anatomy and neural dynamics, we used a parsimonious GWBM that describes within- and between-
 214 region modulations of synchrony. Previously, we have used this model to demonstrate that
 215 modulations of local synchrony are related to time-resolved FC during resting state [17].

216
 217 This GWBM is a low-dimensional reduction of a network-of-networks of Kuramoto oscillators
 218 [36]. Kuramoto oscillators describe the dynamics of synchrony in biological systems including
 219 neural networks [19,37,38]. Each sub-network represents a cortical region. All units in a region are
 220 assumed to be fully and instantly connected, while connections between regions are weighted and
 221 delayed by the density and length of the neural fibers in MRI-derived structural connectivity

222 networks. The regions in the GWBM were defined with the same parcellation atlas as the MEG data
223 that we sought to model.

224

225 First, we set default values for local connectivity strength (L in Eq. 2, identical for all regions), and
226 global scaling (G in Eq. 2 and Eq. 3) of the structural connectivity such that the model simulated
227 resting-state coordination dynamics in the theta-band [19,39]. Resting-state dynamics are
228 characterized by fluctuations over time of the local and global synchrony as well as time-resolved
229 FC patterns (i.e. local and global metastability) [17,19,39]. These dynamical properties of resting
230 state neural coordination were identified with GWBMs simulated over a grid of L and G values. The
231 identified L and G values displayed the most similar dynamics to local and global metastability in
232 the grid search.(see Supplementary Figure 1A).

233

234 Next, we simulated the switching between cognitive states by adding short inputs (30 milliseconds)
235 from the BGT system at the onset of cognitive stages. The rationale for using this mechanism
236 derives from theories of cognition and data derived from electrophysiology. Specifically, cognitive
237 theories state that the BGT system modulates cortical synchrony at the onset of cognitive stages via
238 thalamocortical signals [6,22]. Electrophysiology has shown that thalamocortical neurons can
239 indeed drive cortical activity [10,13] and establish FC [40,41]. These thalamocortical neurons tend
240 to produce short burst of activity [42], which target pools of either excitatory or inhibitory cortical
241 neurons specifically [12,43]. Therefore, our model simulated thalamocortical inputs as short pulses
242 of increased or decreased local connectivity strength (L in Eq. 2) that represent transient
243 modulations of excitatory or inhibitory synaptic activity [38].

244

245 To simulate the sequence of neural coordination states found in the MEG data, we estimated the
246 required activity pulses simultaneously in all regions, stage-by-stage. The optimization scheme

maximized concurrently the fitness of local synchrony and within-stage dpFC, while minimizing the total magnitude of the pulses. The optimization was accomplished with the generalized island model for distributed evolutionary optimization which in relatively short time explores and exploits different areas of the parameter space simultaneously [44].

Changes in local connectivity cause switches between global states of cognitive coordination

To assess how well the model simulated local synchrony, we measured the relative change in theta envelope before and after stage onset (magenta lines in Figure 1D). All model results were computed from 1000 models randomly selected from the top one percentile of models after the optimization. Relative changes in simulated and MEG envelopes were correlated significantly across different cortical regions (Spearman's ρ – encoding: 0.552 ± 0.00158 SEM; retrieval: 0.702 ± 0.000434 SEM; decision: 0.743 ± 0.000683 SEM; motor 0.477 ± 0.00151 SEM; all p-values < 0.05).

Figure 2. Simulated directed functional connectivity. (A) Blue histograms show the fitness between 20,000 randomly generated *within-stage dpFCs* and the MEG *within-stage dpFC*. The red line indicates the *within-stage dpFCs* fitness of the model with the lowest fitness index within the top 1 percentile of the optimized models. (B) Fitness of simulated-to-MEG *within-stage dpFC* is shown in cyan-purple grading over MEG links with significant *within-stage dpFC* (same as Figure 1B). The nodes indicate the relevance of a region for reaching a state of within-stage dpFC (size), and the pulse of local connectivity strength at the onset of the stage due to sub-cortical inputs (colors). These results show the averages of 1000 random picks from top ~1% of the optimizations. (C) Temporal evolution of simulated-to-MEG fitness of *within-stage dpFC* for the current stages (solid lines) compared to other stages (dashed). The white background spans the median stage duration. The color of the lines represent the different stages and follows Figure 1C.

262

263 Figure 2A compares the within-stage dpFC fitness of the *worst* model in the top one percentile to a
 264 distribution of the same fitness metric obtained with 20,000 random within-stage dpFCs, and shows
 265 that the model performs much better than chance. Figure 2B shows the fitness of within-stage dpFC
 266 at individual links. The fitness was quantified as the proportion of links with the same phase-lag
 267 direction as in the MEG data (encoding: 0.697 ± 0.00014 SEM; retrieval: 0.837 ± 0.0016 SEM;
 268 decision: 0.749 ± 0.00092 SEM; motor: 0.758 ± 0.001 SEM). Figure 2C compares the across-trial
 269 dpFC of the model to the MEG data over time. Each state of dpFC begins after the pulse that
 270 modulates local connectivity strength at the onset of the stage, and vanishes with the next onset
 271 (Figure 2C). The last state of dpFC – the motor response – vanishes slowly (in ~10 seconds), and
 272 the GWBM returns to resting-state coordination dynamics (Supplementary Figure 2).

273

274 Taken together, the GWBM showed that a short pulse of local connectivity strength at the onset of a
 275 cognitive stage can first cause a modulation of local synchrony and then a new state of dpFC that

276 lasts until the onset of the next stage (Figure 2C). If there is no subsequent cognitive stage, the
277 GWBM returns to the coordination dynamics that are characteristic of the resting state.

278

279 **Relevance of regions to switch between functional states of coordination**

280 Not all regions in the GWBM are equally important for switching between states of dpFC. The
281 relevance of a region increases with the size of the pulses and the strength of structural connectivity
282 with other regions. The size of the nodes in Figure 2B indicates the relevance of a region for
283 switching between states of dpFC. The absolute size of the pulses from the BGT predicts 22.52 %
284 (± 0.096 SEM) of the variance in the relevance of the nodes, while the interaction between the
285 absolute size of these BGT pulses and the log-scaled strength of structural connectivity predicts
286 25.98 % (± 0.12 SEM) of the same variance.

287 This analysis shows that there are regions such as the left superior frontal region in the last stage
288 that do not show dpFC, but that are still highly relevant for entering a state of high dpFC between
289 other regions. This supports the mechanistic role of the superior frontal regions in exerting
290 cognitive control [25,27] and highlights the complexity of interactions required for implementing
291 changes in FC patterns.

292

293 **Discussion**

294 In this paper, we first analyzed the evolution of macroscopic neural coordination states across the
295 cortex during an associative recognition memory task. Our analysis of MEG data showed that at the
296 onset of fundamental cognitive stages there are transient modulations of local synchrony, which are
297 directly followed by a new state of dpFC that persists until the next cognitive stage. Next, we used a
298 generative model of whole brain activity (GWBM) with inputs from the basal-ganglia-thalamus
299 system to explain these findings. The GWBM showed that short pulses that strengthen or weaken

300 local connectivity strength at the onset of cognitive stages were sufficient to cause the switch
301 between states of neural coordination consistent with empirical data. In addition, the GWBM
302 indicated which individual regions were most relevant for causing these switches.

303

304 **GWBM and the Basal Ganglia-Thalamus Circuit**

305 The GWBM that we developed in this paper has shown that inputs from the basal-ganglia-thalamus
306 system at the onset of cognitive stages are sufficient to cause switches between cognitive stages.
307 This role of the BGT system had been hypothesized by cognitive theories [6,22]. Direct evidence
308 for thalamic modulations of cortical activity is limited to some cortical regions due to
309 methodological constraints, such as the fact that it is challenging to record simultaneously from
310 many sub-cortical and cortical areas with high temporal resolution [10,12,13,40]. Nevertheless, a
311 recent meta-analysis has shown that the thalamus plays a critical role as a central hub that connects
312 neighboring and distant regions to allow for cognitive functions [9], which is in line with the
313 hypothesis that local thalamocortical inputs can mediate FC [14]. In addition, there is evidence for
314 neural fibers connecting the thalamus with most cortical regions [45]. Our model provides
315 additional support for both hypotheses: the BGT systems can trigger a switch between fundamental
316 stages of cognition [6,22] and thalamic input modulates coordination of cortical activity according
317 to cognitive demands [14].

318

319 Given our limited understanding of how the thalamus modulates cortical activity, we opted for a
320 very simple representation of thalamocortical input. These inputs were short [40–42], targeted
321 excitatory or inhibitory local connections [12,43], and came at the onset of cognitive stages [6,22].
322 Such inputs drove the GWBM throughout the sequence of empirical local synchrony and dpFC
323 states. Afterwards, the GWBM returned to resting state dynamics. In other words, a short

324 modulation of local excitation/inhibition modified the local synchrony and the phase of the local
 325 mean-field oscillation. This change in local mean-field phase set a new phase-lag relationship with
 326 other regions that vanished over time due to structural cortical interactions. This response to local
 327 perturbations suggests that cortical dynamics are metastable as many states of coordination can be
 328 reached, and the brain does not remain into a particular state in the absence of perturbations.
 329 Metastable dynamics are thought to allow for integrating and segregating information
 330 simultaneously, as well as for the flexibility of cognitive functions and behaviors [20].

331

332 Importantly, dpFC was not driven by thalamocortical inputs exclusively. Instead, the macroscopic
 333 connectivity structure of the brain also played an important role. The relevance of the structural
 334 connectivity was highlighted by the presence of regions with very low dpFC that turn out to be very
 335 important for coordinating other pairs of regions. One example of such regions is the left superior
 336 frontal region during the motor response stage, a region that has been related to cognitive control,
 337 attention, and decision making [25,27,28]. The role of structural connectivity for generating specific
 338 coordination patterns was first brought to light by GWBMs of resting-state dynamics [19]. In a
 339 previous study we have shown analytically that the strength of structural connectivity plays an
 340 important role in selectively coordinating regions by means of modulations of local connectivity
 341 strength [46]. Additionally, structural symmetries and time-delays might have influenced dpFC in
 342 our simulations [19,47,48].

343

344 There are other biological aspects that might be relevant for coordination of cortical activity that
 345 were not included here, including the delay over thalamocortical neurons [49], the dynamics of the
 346 synapses targeted by thalamocortical inputs [12], tonic activity in the thalamus [42], noise, or the
 347 state of cortical oscillations at the time of a thalamic input. Moreover, our measurement of directed
 348 FC has neglected zero-phase-lag coordination which can emerge from thalamocortical and cortico-

349 cortical loops [49]. However, while including these additional aspects might improve the fit of the
350 model, the current model could already account for the data surprisingly well. Additionally, we have
351 assumed that perturbations of cortical dynamics at the onset of cognitive stages come exclusively
352 from the thalamus. However, there might be other regions such as the hypothalamus that modulate
353 cortical activity in the same or another way that is not included in our model.

354

355 **Neural coordination across the cortex along a sequence of cognitive stages**

356 Our stage-by-stage analyses of neural coordination corroborates the hypothesis that the local
357 modulations of phase synchrony in the theta-band mark a change in long-range functional
358 connectivity and enable a new cognitive function [30]. Moreover, our results confirm the hypothesis
359 that a new state of neural coordination is established at the onset of cognitive stages [6,22]. Our
360 previous research has shown that alpha band FC also varies across cognitive stages [4], but cortical
361 alpha has been found to lead thalamic activity rather than being caused by it [50], as is the case with
362 theta [13].

363

364 To uncover neural coordination stage-by-stage it was crucial to account for the temporal variability
365 of cognitive stages across trials using the HsMM-MVPA analysis. Only after correcting for this
366 variability, our analyses showed that dpFC lasts throughout a cognitive stage and differs across
367 stages. The corresponding states of dpFC had different length, strength, and topology. This diversity
368 of properties might have biased some traditional metrics of neural coordination. For example, if one
369 were interested in the FC at the interval between 250 and 600 milliseconds after stimulus onset –
370 roughly the period of memory retrieval, this interval would contain elements of the encoding or
371 decision stages. The first reason for this is the trial-by-trial variability in stage durations: in one trial
372 encoding might last till 400 ms, while in another trial memory retrieval might already have finished

by 400 ms. Secondly, the retrieval stage has fewer and weaker connections than the encoding and decision stages in our study, which mean that these connections might have been missed altogether. These effects are worse the further one moves away from fixed time points (trial onset/response), which is one of the reasons that M/EEG studies have had severely limited trial lengths traditionally.

Furthermore, our stage-by-stage analysis might contribute to disentangling competing theories. For example, our results suggest that the decision is made and evaluated in the last two stages. We interpreted the penultimate stage as a decision process in which memories are transferred to parietal areas by coordinating left-temporal regions with parietal regions, mediated by local frontal and fronto-parietal coordination [15,23,25,27]. The last stage has been traditionally related with a pure motor response. However, our results indicate that the motor stage has elements associated with motor preparation, action reevaluation, decision, and cognitive control [26,28,34]. This functional network in the last stage suggests that during the motor stage the decision is reevaluated, and it supports the line of thought in which responding is a process that is not independent from decision making (e.g., [28,35]).

Conclusion

To the best of our knowledge we have developed the first generative large-scale brain model that simulates the dynamics of the states of neural coordination along the fundamental cognitive stages in a task. In this model we have integrated structural connectivity, macroscopic neural dynamics, sub-cortical inputs, and the cognitive theories of associative recognition memory. The model has multiple simplifying assumptions which made it feasible to simulate and optimize the model while taking into account the macroscopic properties of neural anatomy and dynamics. This work opens

up the way for considering other tasks in similarly integrated and multidimensional manners to better understand how the brain implements cognition through cortical coordination.

Methods

Experimental paradigm

We re-analyzed MEG data from an associative memory task [3]. We combined the trials with correct responses from all experimental conditions, as we were interested in the transition between fundamental cognitive stages and not in the differences between conditions (which did all proceed through the same stages; [15]). All 18 participants were right handed (6 males and 12 females with a mean age of 23.6 years).

First, participants studied 32 pairs of words until they knew them well [3]. This was followed by a test session in which MEG was recorded. In the test session participants were presented with pairs of words which were either the same as in the study session (*targets*) or paired differently (*re-paired foils*). The pairs of words remained on the screen until the participant responded, and were followed by 1-sec feedback and a brief inter-trial interval. A full description of the task and the recording procedure can be found in [3].

MEG data preprocessing

MEG data was preprocessed and source-reconstructed following the analysis pipeline of the original manuscript [3]. After artifact rejection there were 6,708 trials left. The MEG data of each participant was combined with their own structural MRI to obtain the cortical sources of MEG data. MEG sources consisted of 5,024 dipoles estimated with cortically constrained minimum norm estimates

[3,51]. Source estimates were then morphed onto the standard MNI brain and parcellated into 68 cortical regions with the Desikan-Killiany atlas [24,52]. Each parcel contained the average activity of all dipoles within the region with a 100 Hz sampling rate.

Identification of cognitive stages

To find the onset of cognitive stages the data were bandpass filtered (1-30 Hz, which are default values in Field Trip [53]) and epoched from trial onset to response. Single trials were baseline corrected (-0.4 to 0 seconds), and transformed to one covariance matrix per subject. The average covariance matrix across subjects was used to reduce the dimensionality of the data to 33 principal components (which together accounted for 90 % of variance). These principal components were z-scored and fed into the HSMM-MVPA. The HSMM-MVPA first applies a half-sine window function to increase the signal-to-noise ratio of the *bumps*, the cortical response to sub-cortical input. The bumps are assumed to be 50-millisecond modulations of amplitude at the onset of cognitive stages with the same topology across trials. The signals from the end of a bump to the next bump are assumed to have zero-mean amplitude, a *flat*. The duration of a given stage (bump + flat) is assumed to come from a gamma distribution with shape parameter equal to two. Consequently, a stage is modeled as a bump of a certain amplitude followed by a zero-mean amplitude flat and a duration given by a gamma-2 distribution. There is one exception and this is the first stage (pre-visual encoding here) which does not start with a bump. With this stage model and a predefined number of stages, the Baum-Welch algorithm for HSMMs searches the amplitude and location of bumps that explain the z-scored principal components best [54]. The bump amplitudes (for the 33 PCA components) are the same for all trials and vary across stages. The temporal location of the bumps also varies across trials, but the resulting stage durations are constrained to gamma-2 distributions with one scale parameter per stage.

444 We explored models with 3 to 7 cognitive stages as previous studies have shown that this memory
 445 task consists of 5 to 6 stages [4,5,15]. For each model we ran the HSMM-MVPA 200 times with
 446 random initial parameters to avoid converging in local maxima. We used a leave-one-subject-out
 447 cross-validation to assess whether a model with $N+1$ stages could explain the data significantly
 448 better (using a sign-test) than a model with N stages [15]. The final model was the simplest one that
 449 generalized across subjects – a five-stage model. Then, we allowed one stage to have different
 450 gamma-scale parameters across experimental conditions, and we used leave-one-subject-out cross-
 451 validation to decide on the best model. As in previous studies [4,15], a model with different gamma
 452 distributions in the retrieval stage explained the MEG data best.

453

454 **Measurements of neural coordination**

455 To measure neural coordination – local synchrony and directed functional connectivity – we used
 456 the analytic signal of theta band oscillations. The parcellated MEG data were band pass filtered
 457 (cut-off frequencies: 3.8, and 8.5 Hz; forward-backward IIR Butterworth filter of order 4) and
 458 epoched from -0.4 seconds before stimulus onset to 0.4 seconds after the response. Epochs were
 459 Hilbert transformed to the analytic signal using a symmetric padding of 0.4 seconds to avoid edge
 460 artifacts.

461

462 Directed functional connectivity between regions i and j was measured with the directed phase-lag
 463 index (dpFC) [32] as follows:

464

$$465 \quad dpFC^{ij} = \frac{1}{N} \sum_{n=1}^N \frac{1}{T} \sum_{t=s+1}^{s+T_n} \text{sgn}(\text{Im}(S_{nt}^{ij})) \quad \text{Eq. 1}$$

466

In Eq. 1, $Im(S^{ij})$ is the imaginary part of the cross-spectral density, and sgn is the sign function. To compute within-stage dpFC, $s+1$ was the first sample 0.05 seconds after the onset of the stage, Tn was the length of the stage in trial n , and N is the number of trials. Across-trials dpFC was computed sample-by-sample with $Tn = 1$ and time-locked to stage onset. Both within-stage and across-trial dpFC were later averaged across subjects. A detailed explanation can be found in the SI.

Generative whole-brain model

The generative whole-brain model (GWBM) was derived with the Ott-Antonsen ansatz [55] from a network-of-networks of Kuramoto oscillators [36]. See [17] for a step-by-step derivation. The dynamics of synchrony in a region are given by the Kuramoto order parameter (KOP) which describes the dynamics of synchrony in biological systems as well as a pool of neurons [56]. The KOP is a complex number ($KOP = r e^{i\psi}$) with the modulus bound by zero (asynchrony) and one (full synchrony). Here, the KOP simulated the analytic signal of the MEG data. Beforehand we set the natural frequencies of the oscillators to a Lorentzian distribution centered in the theta band (center, Ω : 6 Hz, spread, Δ : 1), and the spike-propagation velocity along the structural fibers to 5 m/s. The equations of the KOP in on region, i , of the GWBM are as follows:

$$\dot{r}_i = -\Delta_i r_i + \frac{L_i}{2}(1 - r_i^2)r_i + \frac{G}{2R}(1 - r_i^2) \sum_{j=1, j \neq i}^R A_{ij} r_j(t - \tau_{ij}) \cos(\psi_j(t - \tau_{ij}) - \psi_i) \quad \text{Eq. 2}$$

$$\dot{\psi}_i = \Omega_i + \frac{G}{2R}(r_i + \frac{1}{r_i}) \sum_{j=1, j \neq i}^R A_{ij} r_j(t - \tau_{ij}) \sin(\psi_j(t - \tau_{ij}) - \psi_i) \quad \text{Eq. 3}$$

The time dependency has been removed in variables without time delays; τ are the time delays between regions (fiber length x spike-propagation velocity); A is the coupling strength between

regions (density of structural fibers); and R is the number of regions. To simulate resting state dynamics we explored parameters G (global scaling of structural connectivity) and L (local connectivity strength, same in all regions) with 25 randomly initialized models. The results of this exploration are shown in SI Figure 1. With G and L set to correctly reproducing the resting state, the thalamocortical inputs were simulated as 0.03 second increases/decreases of L at each region and stage onset independently. Simulated dpFC was measured with Eq. 1, but here N represented 25 models with different initial conditions and T_n was the median duration of the MEG stages. The initial conditions for the first stage were the MEG phases and amplitudes at the pre-encoding stage plus random noise. More details of the simulations are reported in the SI.

498

499 **Generative whole-brain model: Resting-state**

To identify a GWBM that simulated resting-state dynamics we performed a grid-search over the global and local coupling parameter space. The local couplings were assumed to be identical for all regions. Resting-state dynamics are characterized by temporal fluctuations of global and local synchrony, and time-resolved patterns of functional connectivity (i.e. metastable dynamics). Metastability was measured as the standard deviation of the modulus of the KOP over time at local and global levels [57,58]. At the local level, the metastabilities were averaged across regions. To obtain the global KOP over time we averaged the phases of the local KOPs across regions (ψ in Equation 3 of the main text). To assess the temporal structure of the global metastability we computed the mean of the absolute values of its autocorrelation function. To avoid the influence of the initial conditions on the simulations we ran twenty-five GWBMs with random initial conditions for each combination of parameters. The simulations were run for 1000 seconds, but the initial 200 seconds were removed to discard initial transients. All simulations were performed with a time-delayed first-order Euler method and an integration step of 1 millisecond. We ended up with a global coupling of 0.15 and a local coupling of 0.7, which had the best trade-off between high

514 metastability and low autocorrelation of global KOP, and therefore were chosen as the default
515 values for the following GWBMs. Supplementary Figure 1 shows the grid search results of resting-
516 state dynamics.

517

518 **Generative whole-brain model: cognitive task**

519 To simulate the sequence of cognitive stages and their associated neural coordination patterns, we
520 initialized 25 models informed by the theta-band phases and envelope amplitudes observed at the
521 pre-encoding stage. The MEG envelopes were measured 0.1 and 0.05 seconds before the onset of
522 the encoding stage. Then, the initial history of the KOP modulus was a straight line that joined the
523 mean of these amplitudes across trials plus Gaussian noise ($\sigma=0.01$). To choose the initial history of
524 phases we measured inter-trial phase consistency, and within-stage dpFC at the pre-encoding stage.
525 There were 10 regions (mostly occipital and parietal) that showed significant inter-trial phase
526 consistency. The initial history of phases at these regions were set to the average MEG phases
527 across trials at 0.05 seconds before the onset of the first stage plus Gaussian noise ($\sigma=0.01$). The
528 phases of these regions were used as a referent point for the remaining regions. The initial phases of
529 the remaining regions were set by an optimization algorithm (CMAES [59]) which tried to establish
530 a phase-lag relationship between regions as in the empirical within-stage dpFC. The dpFC of the
531 initial history of phases had an average similarity to empirical within-stage dpFC of 78%. The 25
532 GWBMs of the later stages were initialized with the last simulated samples of the previous stage in
533 the best individual of the optimization process (see section *Optimization of thalamocortical inputs*).

534

535 The model with the best fitting sequence of parameters was left to run 400 seconds after the last
536 stage. Supplementary Figure 2 shows that the model neither remained trapped into the functional
537 connectivity state of the last stage, nor did it return to any of the previous states (SI Fig. 2, bottom).

538 Instead, the model returned to resting state patterns of global and local synchrony for which the
539 functional connectivity fluctuated over time (i.e. metastable dynamics; SI Fig. 2, top & middle).

540

541 **Optimization of thalamocortical inputs**

542 To find the optimal thalamocortical inputs for reproducing the observed connectivity patterns, we
543 used the generalized island model for evolutionary optimization [44] – algorithm DE1220 as
544 implemented in the pagmo toolbox [60]. The generalized island model optimized in parallel ten
545 islands connected in a ring. Each island consisted of 50 individuals and had a particular
546 parametrization of a differential evolution algorithm (see *Supplementary Table 1*). The islands
547 occasionally exchanged their best-fitted individuals. This configuration allowed for simultaneously
548 exploring and exploiting multiple areas of the parameter space. Their fitness function had three
549 objectives that were combined into one index of fitness. The dominant objective was to maximize
550 the similarity of simulated and empirical within-stage dpFC, f_1 :

551

$$552 \quad f_1 = \sum_{i=1}^E x_i \cdot y_i \left(\sum_{i=1}^E |x_i| \right)^{-1} \quad \text{Eq. 4}$$

553

554 The links, E , in the empirical dpFC, x , were either 0 (not significant), 1 (lag-ahead) or -1 (lag-
555 behind). Simulated dpFC links, y , were either -1 or 1. The objective f_1 gave discrete values which
556 interval was used by the other two objectives. The second objective, f_2 , maximized the topological
557 similarity of the relative change in envelope amplitude at the onset of each stage. This similarity
558 was measured with the Spearman rank-correlation between MEG and simulated relative amplitudes.
559 The third objective, f_3 , minimized the absolute size of the thalamic pulses as

560

$$f_3 = \frac{1}{L_{max}} \sum_{j=1}^R |L_j| \left(\sum_{i=1}^E |x_i| \right)^{-1} \quad \text{Eq. 5}$$

562

563 where L_i are the local connectivities, and L_{max} is the largest absolute pulse allowed to the optimizers.

564 The combined fitness index was $f = f_1 - (1-f_2)f_3$. The best individual had the minimal $(1-f_2)f_3$ among

565 the 5000 individuals with the highest f in order to avoid a GWBM with low f_2 and f_3 . The last

566 simulated samples of this individual were used to initialize the simulations of the next stage (see

567 section *Generative whole-brain model: Cognitive task*).

568

569 Supplementary Figure 3 shows the parameters of the individuals and their fitness along the

570 evolution in one island as example. This figure shows how the cost function could simultaneously

571 maximize the fitness of within-stage dpFC and relative local synchrony at the onset (Spearman

572 correlation), while the change in local coupling was minimized. The optimization of the four stages

573 took approximately 4 days using 10 CPUs, one for each island.

574

575 **Relevance of individual regions for switches**

576 To assess the relevance of a region for switching between states of dpFC, a GWBM was lesioned by

577 setting the thalamocortical pulse in this region to zero while the remaining regions were left

578 untouched. Then, the fitness of the lesioned GWBM (Eq. 4) was compared to the fitness achieved

579 by the original GWBM. The relevance of a region was measured as the number of within-stage

580 dpFC links in the lesioned model that were not matching MEG data relative to the number of links

581 matching MEG data in the full model. This process for measuring relevance was repeated for the 68

582 regions in the GWBM and the four transitions between stages. To obtain a measure of relevance that

583 was not dependent on a single GWBM, relevance was evaluated in 1,000 GWBMs randomly picked

584 from among the models in the top one percentile after optimization. Next, we used linear regions

models with one independent variable to explain the relevance of regions. Each linear model included as dependent variable the relevance of the 68 regions and four stages in a lesioned GWBM. A linear model was fitted for each of the 1,000 lesioned models independently.

Structural connectivity, MRI acquisition and processing

We used 45 subjects from the test-retest dataset of the Human Connectome Project (HCP) 3T. This data set consisted of T1-weighted and multi-shell diffusion MRI data. T1-weighted data were acquired with 0.7 mm isotropic voxel size, TE = 2.14 ms, and TR = 2400 ms. Diffusion MRI data were acquired with a 1.25-mm isotropic voxel size, TE = 89.5 ms, and TR 5520 ms, with three shells with $b = 1000, 2000, \text{ and } 3000 \text{ s/mm}^2$, each shell with 90 diffusion weighted volumes and 6 non-weighted images [61]. The diffusion MRI data was already preprocessed as described in [62]. In short, diffusion MRI data were corrected for head motion and geometrical distortions arising from eddy currents and susceptibility artifacts [63]. Finally, the diffusion MRI images were aligned to the structural T1 image. The T1w image was parcellated using the Desikan–Killany parcellation [24], resulting in 68 cortical ROIs. Using the T1w image, the probability maps of the different tissues were obtained to create the five tissue-type files [64,65].

Tractography was carried out with constrained spherical deconvolution [66,67]. A multi-tissue response function was calculated [68] and the average response functions were calculated. The multi-tissue fiber orientation distribution was calculated [69] with the average response function ($L_{max} = 8$). The fiber orientation distribution images had a joint bias field correction and a multi-tissue informed log-domain intensity normalization [70]. Then, tractography was performed with the iFOD2 algorithm [71] using anatomically constrained tractography [72]; generating 10 million streamlines (cutoff at 0.05, default); and using backtracking [72] and a dynamic seeding [73]. The length of the

fibers was set to a minimum of 20 mm and a maximum of 250 mm [72]. To be able to quantitatively assess the connectivity, SIFT2 was applied to the resulting tractograms [73].

The connectivity matrix was built with a robust approach. In particular a 2-mm radial search at the end of the streamline was performed to allow the tracts to reach the gray matter parcellation [74]. Each connectivity matrix was multiplied by its μ coefficient obtained from the SIFT2 process, as the sum of the streamline weights needs to be proportional to the units of fiber density for each subject [75]. Connectivity matrices were averaged across subjects, and the 10% of links with the highest coefficient of variation across subjects were set to zero[76]. Finally, the averaged and thresholded structural connectivity matrix was normalized to have an average value of one.

Supplementary Information

Supplementary Table 1. *Parameters of DE1220 algorithm on each island.*

Island IDs	Mutation variants allowed	Adaptation scheme for parameters F and C
1	best/1/exp; rand-to-best/1/exp; best/1/bin; rand-to-best/1/bin	jDE
2	rand-to-current/2/exp; rand-to-current/2/bin	jDE
3	rand-to-current/2/exp; rand-to-current/2/bin	iDE
4	best/1/exp; rand-to-best/1/exp; best/1/bin; rand-to-best/1/bin	iDE
5	rand/1/exp; rand/1/bin	jDE
6	rand-to-current/2/exp; rand-to-current/2/bin	jDE
7	rand-to-current/2/exp; rand-to-current/2/bin	iDE
8	best/1/exp; rand-to-best/1/exp; best/1/bin; rand-to-best/1/bin	jDE
9	best/1/exp; rand-to-best/1/exp; best/1/bin; rand-to-best/1/bin	iDE
10	rand/1/exp; rand/1/bin	jDE

Supplementary Figures

626

627

Figure S1, Resting state neural coordination dynamics. The green dot indicates the parametrization of the model. The location of the green dot was based on the idea that resting state dynamics should have simultaneously the lightest color in the three panels and the weakest coupling parameters.

Figure S2. Return to resting-state after cognitive stages. (top) Modulus of the global KOP.

(middle) Modulus of the local Kuramoto order parameter (KOP) for the cortical 68 ROIs. (bottom)

Temporal evolution of simulated-to-MEG fitness of *within-stage dpFC* for the four cognitive stages.

This is similar to Figure 2B but for a much longer period of time. The MEG *within-stage dpFC* of each stage (Figure 1B) were compared (Eq. 4) with the simulated *dpFC* sample-by-sample (Eq. 1).

Figure S3. Individuals and their fitness along the optimization in one island. (A) fitness index f . (B) Spearman correlation, objective f . (C) Sum of the absolute change in local coupling at the onset of the stage. Blue dots are the A, B and C values in the order that they were evaluated along the optimization process. Orange dots are the same values but sorted by the Fit Index (A). (D) Change in local coupling (thalamic input) at the onset that produces the blue dots in A, B, C. (E) Same as (D) but sorted by their Fit Index.

632 **Acknowledgments**

633 The work of Cao was supported in part by the European Research Council (ERC-CoG-771687).
 634 HCP datasets were provided by the Human Connectome Project, WU-Minn Consortium (Principal
 635 Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH
 636 Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the
 637 McDonnell Center for Systems Neuroscience at Washington University. We thank Lionel Newman
 638 from the University of Groningen for proofreading the manuscript.

639

640 **Author contributions**

Oscar Portoles: Designed research, Performed research, Analysed data, Wrote the paper

Manuel Blesa: Analysed and wrote structural data processing

Marieke van Vugt: Contributed in writing

Ming Cao: Contributed in writing

Jelmer P. Borst: Designed research, Wrote the paper

641 **Competing Interests**

The authors declare no conflict of interest

642

643 **References**

1. Donders FC. On the speed of mental processes. *Acta Psychol (Ams)*. 1969;30: 412–431. doi:10.1016/0001-6918(69)90065-1
2. Sternberg S. The discovery of processing stages: Extensions of Donders' method. *Acta Psychologica*. 1969;30: 276–315. doi:10.1016/0001-6918(69)90055-9
3. Borst JP, Ghuman AS, Anderson JR. Tracking cognitive processing stages with MEG: A spatio-temporal model of associative recognition in the brain. *NeuroImage*. 2016;141: 416–430. doi:10.1016/j.neuroimage.2016.08.002

4. Portoles O, Borst JP, van Vugt MK. Characterizing synchrony patterns across cognitive task stages of associative recognition memory. *Eur J Neurosci.* 2018;48: 2759–2769. doi:10.1111/ejn.13817
5. Anderson JR, Borst JP, Fincham JM, Ghuman AS, Tenison C, Zhang Q. The Common Time Course of Memory Processes Revealed. *Psychol Sci.* 2018;29: 1463–1474. doi:10.1177/0956797618774526
6. Stocco A, Lebiere C, Anderson JR. Conditional routing of information to the cortex: A model of the basal ganglia's role in cognitive coordination. *Psychol Rev.* 2010;117: 541–574. doi:10.1037/a0019077
7. O'Reilly RC, Frank MJ. Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia. *Neural Comput.* 2006;18: 283–328. doi:10.1162/089976606775093909
8. Redgrave P, Prescott TJ, Gurney K. The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience.* 1999;89: 1009–1023. doi:10.1016/s0306-4522(98)00319-4
9. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The Human Thalamus Is an Integrative Hub for Functional Brain Networks. *J Neurosci.* 2017;37: 5594–5607. doi:10.1523/JNEUROSCI.0067-17.2017
10. Bruno RM, Sakmann B. Cortex Is Driven by Weak but Synchronously Active Thalamocortical Synapses. *Science.* 2006;312: 1622–1627. doi:10.1126/science.1124593
11. Rektor I, Bareš M, Brázdil M, Kaňovský P, Rektorová I, Sochůrková D, et al. Cognitive- and movement-related potentials recorded in the human basal ganglia. *Mov Disord.* 2005;20: 562–568. doi:https://doi.org/10.1002/mds.20368
12. Cruikshank SJ, Lewis TJ, Connors BW. Synaptic basis for intense thalamocortical activation of feedforward inhibitory cells in neocortex. *Nat Neurosci.* 2007;10: 462–468. doi:10.1038/nn1861
13. Malekmohammadi M, Elias WJ, Pouratian N. Human thalamus regulates cortical activity via spatially specific and structurally constrained phase-amplitude coupling. *Cereb Cortex.* 2015;25: 1618–1628. doi:10.1093/cercor/bht358
14. Saalmann YB. Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition. *Front Syst Neurosci.* 2014;8. doi:10.3389/fnsys.2014.00083
15. Anderson JR, Zhang Q, Borst JP, Walsh MM. The discovery of processing stages: Extension of Sternberg's method. *Psychol Rev.* 2016;123: 481–509. doi:10.1037/rev0000030
16. Tewarie P, Hunt BAE, O'Neill GC, Byrne A, Aquino K, Bauer M, et al. Relationships Between Neuronal Oscillatory Amplitude and Dynamic Functional Connectivity. *Cerebral Cortex.* 2019;29: 2668–2681. doi:10.1093/cercor/bhy136
17. Portoles O, Qin Y, Hadida J, Woolrich M, Cao M, Vugt M van. Modulations of local synchrony over time lead to resting-state functional connectivity in a parsimonious large-scale brain model. *bioRxiv.* 2021; 2021.01.20.427443. doi:10.1101/2021.01.20.427443

18. Zhang Q, Walsh MM, Anderson JR. The Impact of Inserting an Additional Mental Process. *Comput Brain Behav.* 2018;1: 22–35. doi:10.1007/s42113-018-0002-8
19. Cabral J, Kringelbach ML, Deco G. Functional connectivity dynamically evolves on multiple time-scales over a static structural connectome: Models and mechanisms. *NeuroImage.* 2017;160: 84–96. doi:10.1016/j.neuroimage.2017.03.045
20. Tognoli E, Kelso JAS. The Metastable Brain. *Neuron.* 2014;81: 35–48. doi:10.1016/j.neuron.2013.12.022
21. Wang L-Z, Su R-Q, Huang Z-G, Wang X, Wang W-X, Grebogi C, et al. A geometrical approach to control and controllability of nonlinear dynamical networks. *Nat Commun.* 2016;7: 11323. doi:10.1038/ncomms11323
22. Anderson JR. How can the human mind occur in the physical universe? Oxford ; New York: Oxford University Press; 2007.
23. Staresina BP, Wimber M. A Neural Chronometry of Memory Recall. *Trends Cogn Sci.* 2019;23: 1071–1085. doi:10.1016/j.tics.2019.09.011
24. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage.* 2006;31: 968–980. doi:10.1016/j.neuroimage.2006.01.021
25. Cavanagh JF, Frank MJ. Frontal theta as a mechanism for cognitive control. *Trends Cogn Sci.* 2014;18: 414–421. doi:10.1016/j.tics.2014.04.012
26. Sauseng P, Griesmayr B, Freunberger R, Klimesch W. Control mechanisms in working memory: a possible function of EEG theta oscillations. *Neurosci Biobehav Rev.* 2010;34: 1015–1022. doi:10.1016/j.neubiorev.2009.12.006
27. Rajan A, Siegel SN, Liu Y, Bengson J, Mangun GR, Ding M. Theta Oscillations Index Frontal Decision-Making and Mediate Reciprocal Frontal–Parietal Interactions in Willed Attention. *Cereb Cortex.* 2019;29: 2832. doi:10.1093/cercor/bhy149
28. Pellegrino G, Tomasevic L, Herz DM, Larsen KM, Siebner HR. Theta Activity in the Left Dorsal Premotor Cortex During Action Re-Evaluation and Motor Reprogramming. *Front Hum Neurosci.* 2018;12. doi:10.3389/fnhum.2018.00364
29. Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, et al. High Gamma Power Is Phase-Locked to Theta Oscillations in Human Neocortex. *Science.* 2006;313: 1626–1628. doi:10.1126/science.1128115
30. Voloh B, Womelsdorf T. A Role of Phase-Resetting in Coordinating Large Scale Neural Networks During Attention and Goal-Directed Behavior. *Front Syst Neurosci.* 2016;10. doi:10.3389/fnsys.2016.00018
31. Ketz NA, Jensen O, O'Reilly RC. Thalamic pathways underlying prefrontal cortex-medial temporal lobe oscillatory interactions. *Trends Neurosci.* 2015;38: 3–12. doi:10.1016/j.tins.2014.09.007
32. Stam CJ, van Straaten ECW. Go with the flow: Use of a directed phase lag index (dPLI) to

- characterize patterns of phase relations in a large-scale model of brain dynamics. *NeuroImage*. 2012;62: 1415–1428. doi:10.1016/j.neuroimage.2012.05.050
33. Reinhart RMG. Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nat Neurosci.* : 16.
34. Hartwigsen G, Siebner HR. Joint Contribution of Left Dorsal Premotor Cortex and Supramarginal Gyrus to Rapid Action Reprogramming. *Brain Stimul.* 2015;8: 945–952. doi:10.1016/j.brs.2015.04.011
35. Gallivan JP, Chapman CS, Wolpert DM, Flanagan JR. Decision-making in sensorimotor control. *Nat Rev Neurosci.* 2018;19: 519–534. doi:10.1038/s41583-018-0045-9
36. Skardal PS, Restrepo JG. Hierarchical synchrony of phase oscillators in modular networks. *Phys Rev E.* 2012;85: 016208. doi:10.1103/PhysRevE.85.016208
37. Breakspear M, Heitmann S, Daffertshofer A. Generative Models of Cortical Oscillations: Neurobiological Implications of the Kuramoto Model. *Front Hum Neurosci.* 2010;4. doi:10.3389/fnhum.2010.00190
38. Maistrenko YL, Lysyansky B, Hauptmann C, Burylko O, Tass PA. Multistability in the Kuramoto model with synaptic plasticity. *Phys Rev E.* 2007;75: 066207. doi:10.1103/PhysRevE.75.066207
39. Deco G, Cabral J, Woolrich MW, Stevner ABA, van Hartevelt TJ, Kringelbach ML. Single or multiple frequency generators in on-going brain activity: A mechanistic whole-brain model of empirical MEG data. *NeuroImage.* 2017;152: 538–550. doi:10.1016/j.neuroimage.2017.03.023
40. Saalmann YB, Pinsk MA, Wang L, Li X, Kastner S. The Pulvinar Regulates Information Transmission Between Cortical Areas Based on Attention Demands. *Science.* 2012;337: 753–756. doi:10.1126/science.1223082
41. Sherman SM. The thalamus is more than just a relay. *Curr Opin Neurobiol.* 2007;17: 417–422. doi:10.1016/j.conb.2007.07.003
42. Ramcharan EJ, Gnadt JW, Sherman SM. Higher-order thalamic relays burst more than first-order relays. *Proc Natl Acad Sci USA.* 2005;102: 12236–12241. doi:10.1073/pnas.0502843102
43. Kloc M, Maffei A. Target-Specific Properties of Thalamocortical Synapses onto Layer 4 of Mouse Primary Visual Cortex. *J Neurosci.* 2014;34: 15455–15465. doi:10.1523/JNEUROSCI.2595-14.2014
44. Izzo D, Ruciński M, Biscani F. The Generalized Island Model. *Parallel Architectures and Bioinspired Algorithms.* 2012; 151–169. doi:10.1007/978-3-642-28789-3_7
45. Behrens TEJ, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott C a. M, Boulby PA, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci.* 2003;6: 750–757. doi:10.1038/nn1075
46. Qin Y, Kawano Y, Portoles O, Cao M. Partial Phase Cohesiveness in Networks of Networks of Kuramoto Oscillators. *IEEE Trans Automat Contr.* 2021; 1–1. doi:10.1109/TAC.2021.3062005

47. Nicosia V, Valencia M, Chavez M, Díaz-Guilera A, Latora V. Remote Synchronization Reveals Network Symmetries and Functional Modules. *Phys Rev Lett*. 2013;110: 174102. doi:10.1103/PhysRevLett.110.174102
48. Petkoski S, Spiegler A, Proix T, Aram P, Temprado J-J, Jirsa VK. Heterogeneity of time delays determines synchronization of coupled oscillators. *Phys Rev E*. 2016;94: 012209. doi:10.1103/PhysRevE.94.012209
49. Vicente R, Gollo LL, Mirasso CR, Fischer I, Pipa G. Dynamical relaying can yield zero time lag neuronal synchrony despite long conduction delays. *Proc Natl Acad Sci USA*. 2008;105: 17157–17162. doi:10.1073/pnas.0809353105
50. Halgren M, Ulbert I, Bastuji H, Fabó D, Eróss L, Rey M, et al. The generation and propagation of the human alpha rhythm. *Proc Natl Acad Sci USA*. 2019;116: 23772–23782. doi:10.1073/pnas.1913092116
51. Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, et al. MNE software for processing MEG and EEG data. *NeuroImage*. 2014;86: 446–460. doi:10.1016/j.neuroimage.2013.10.027
52. Fischl B. FreeSurfer. *NeuroImage*. 2012;62: 774–781. doi:10.1016/j.neuroimage.2012.01.021
53. Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. In: *Computational Intelligence and Neuroscience* [Internet]. Hindawi; 23 Dec 2010 [cited 10 Feb 2021] p. e156869. doi:https://doi.org/10.1155/2011/156869
54. Yu S-Z. Hidden semi-Markov models. *Artificial Intelligence*. 2010; 29.
55. Ott E, Antonsen TM. Low dimensional behavior of large systems of globally coupled oscillators. *Chaos*. 2008;18: 037113. doi:10.1063/1.2930766
56. Montbrió E, Pazó D, Roxin A. Macroscopic Description for Networks of Spiking Neurons. *Phys Rev X*. 2015;5: 021028. doi:10.1103/PhysRevX.5.021028
57. Wildie M, Shanahan M. Metastability and chimera states in modular delay and pulse-coupled oscillator networks. *Chaos*. 2012;22: 043131. doi:10.1063/1.4766592
58. Cabral J, Luckhoo H, Woolrich M, Joensson M, Mohseni H, Baker A, et al. Exploring mechanisms of spontaneous functional connectivity in MEG: how delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. *Neuroimage*. 2014;90: 423–435. doi:10.1016/j.neuroimage.2013.11.047
59. Hansen N. The CMA Evolution Strategy: A Comparing Review. : 28.
60. Biscani F, Izzo D. A parallel global multiobjective framework for optimization: pagmo. *Journal of Open Source Software*. 2020;5: 2338. doi:10.21105/joss.02338
61. Van Essen DC, Ugurbil K, Auerbach E, Barch D, Behrens TEJ, Bucholz R, et al. The Human Connectome Project: a data acquisition perspective. *Neuroimage*. 2012;62: 2222–2231. doi:10.1016/j.neuroimage.2012.02.018

62. Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage*. 2013;80: 105–124. doi:10.1016/j.neuroimage.2013.04.127
63. Sotiropoulos SN, Jbabdi S, Xu J, Andersson JL, Moeller S, Auerbach EJ, et al. Advances in diffusion MRI acquisition and processing in the Human Connectome Project. *Neuroimage*. 2013;80: 125–143. doi:10.1016/j.neuroimage.2013.05.057
64. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001;20: 45–57. doi:10.1109/42.906424
65. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. 2011;56: 907–922. doi:10.1016/j.neuroimage.2011.02.046
66. Tournier J-D, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *NeuroImage*. 2007;35: 1459–1472. doi:10.1016/j.neuroimage.2007.02.016
67. Tournier J-D, Smith R, Raffelt D, Tabbara R, Dhollander T, Pietsch M, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *Neuroimage*. 2019;202: 116137. doi:10.1016/j.neuroimage.2019.116137
68. Dhollander T, Raffelt D, Connelly A. Unsupervised 3-tissue response function estimation from single-shell or multi-shell diffusion MR data without a co-registered T1 image. 2016.
69. Jeurissen B, Tournier J-D, Dhollander T, Connelly A, Sijbers J. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *Neuroimage*. 2014;103: 411–426. doi:10.1016/j.neuroimage.2014.07.061
70. Raffelt D, Dhollander T, Tournier J-D, Tabbara R, Smith R, Pierre E, et al. Bias Field Correction and Intensity Normalisation for Quantitative Analysis of Apparent Fibre Density. 2017.
71. Tournier J-D, Calamante F, Connelly A. Improved probabilistic streamlines tractography by 2nd order integration over fibre orientation distributions. 2009 [cited 10 Feb 2021]. Available: /paper/Improved-probabilistic-streamlines-tractography-by-Tournier-Calamante/b4ffcb9ec889a8a68bffc46387a96b78a50ef94a
72. Smith RE, Tournier J-D, Calamante F, Connelly A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. *Neuroimage*. 2012;62: 1924–1938. doi:10.1016/j.neuroimage.2012.06.005
73. Smith RE, Tournier J-D, Calamante F, Connelly A. SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. *Neuroimage*. 2015;119: 338–351. doi:10.1016/j.neuroimage.2015.06.092
74. Smith RE, Tournier J-D, Calamante F, Connelly A. The effects of SIFT on the reproducibility and biological accuracy of the structural connectome. *Neuroimage*. 2015;104: 253–265. doi:10.1016/j.neuroimage.2014.10.004

75. Smith R, Raffelt D, Tournier J-D, Connelly A. Quantitative streamlines tractography: methods and inter-subject normalisation. OSF Preprints; 2020. doi:10.31219/osf.io/c67kn
76. Roberts JA, Perry A, Roberts G, Mitchell PB, Breakspear M. Consistency-based thresholding of the human connectome. NeuroImage. 2017;145: 118–129. doi:10.1016/j.neuroimage.2016.09.053

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