A theory of subcortical control of cortical dynamics during movement planning

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Abstract

Planning, a prospective form of short-term memory, is a cognitive function that has been predominantly attributed to the cortex. Recent experiments, however, have concluded that the thalamus and other subcortical structures participate in this function. A comprehensive computational framework to link neural dynamics and cognition in the context of large-scale subcortical-cortical circuits is lacking. In this computational study, we elucidated the dynamical mechanisms by which the cortex, thalamus and other subcortical structures jointly contribute to planning. We propose the following multi-regional mechanism: first, recurrent circuitry in the cortex generates stimulus-selective activity patterns, which are maintained by reciprocal corticothalamic projections across a memory epoch. Next, subcortical signals are routed through the thalamus to selectively modify these patterns to enable successful completion of a behavioral task. We refer to this dynamical process as subcortex control of dynamical modes, as the cortical activity patterns ('dynamical modes') are low-dimensional in comparison to the number of neurons that are modulated by the task. We evaluated the implications of subcortex control by simulating networks of interconnected thalamic and cortical 'rate' units in the context of a motor planning task. In tight link with electrophysiological data from mice, we identified subcortical excitatory and inhibitory contributions to the planning computations across distinct epochs of this task. Our model predicts that the distinct computational roles of the pars reticulata (SNr) and thalamic reticular nucleus (TRN) during planning are a result of their specific selectivity-dependent connectivity patterns with the thalamus. Moreover, a 'switch' from movement planning to execution is instantiated by a midbrain-mediated thalamic burst, which uncovers a latent motor instruction that is stored in deep cortical layers during the memory epoch. Overall, we propose a novel framework to analyze planning computations in terms of cortical dynamical modes, which are shaped by subcortical structures via the thalamus based on task demands.

Introduction

Systems neuroscience research is witnessing an unprecedented expansion of our data acquisition capabilities. Given the advances in recording technology (e.g., Stringer et al. [2019]), it is now possible to relate processing at the level of microcircuits to the level of interacting brain areas. The activity of simultaneously recorded cells for a given stimulus or task condition constitutes a paradigm for neural coding at the network or population level [Cunningham and Yu, 2014]. For a given brain area, such population activity may represent task and stimulus parameters, as well as behaviorally-relevant computations that can be decoded downstream. In many tasks, it has been observed that population activity patterns are low-dimensional in comparison to the number of neurons modulated by the task. Such redundancy in neural coding is also reflected in mixed-selective responses [Rigotti et al., 2013], whereby two or more task or stimulus parameters are embedded in the response of single cells. Effectively, only a few 'modes' of activity are sufficient to effectively reproduce the complex circuit dynamics for a given task (but see Stringer et al. [2019]). Several methods based on population-level statistical analysis exist to reduce the dimensionality of simultaneously recorded neurons (reviewed in Cunningham and Yu [2014]). Commonly used methods, including principal component analysis (PCA), can effectively reduce the number of dimensions by finding linear combinations of the original features that account for most of the statistical variance. However, principal components are not as interpretable as the original features. Critically, the biophysical interactions within neural assemblies, including intrinsic and synaptic mechanisms, that generate these behaviorally-relevant neural activity patterns remain obscure.

Population activity patterns in animal models are typically recorded via calcium imaging or multi-electrode recordings. Recently, many studies have shown the participation of multiple cortical areas in cognitive functions, such as decision making and working memory [Siegel et al., 2015]. However, subcortical contributions to these functions have been relatively understudied. For example, the contribution of thalamic circuits to these and other cognitive functions have only been relatively recently investigated in rodents [Schmitt et al., 2017, Bolkan et al., 2017]. The thalamus is now known to play a role in cognitive processes beyond the sensory domain. Similarly, subcortical structures such as the basal ganglia and cerebellum were thought to be uniquely motor, but are now known to participate in functions typically attributed to the cortex alone. Indeed, anatomical data strongly suggests that both cerebellum and basal ganglia through cerebello-thalamic and nigro-thalamic pathways might modulate the cortex for cognition [Middleton and Strick, 2000]. Earlier computational studies have proposed roles for the thalamus, basal ganglia, and cerebellum in controlling cortical dynamics [Wei and Wang, 2016, Logiaco et al., 2019]. However, the precise mechanism by which thalamus and subcortical structures modulate dynamics underlying the slow dynamical activity that characterizes decision making and working memory computations is not known.

A paradigm to study cognitive function is the two alternative forced choice (2AFC) task, in particular those variants with a delay period that allow for the investigation of short-term memory. Motor preparation is a prospective form of short-term memory [Svoboda and Li, 2018] whereby an external stimulus such as pole location or tone is to be maintained in memory for the future acquision of a reward. Combined behavioral and electrophysiological analysis has revealed that the secondary motor cortex (ALM: anterolateral motor cortex) is necessary for motor preparation and execution for this task [Li et al., 2016]. Similarly, the thalamus is needed for maintenance of activity and selectivity during the delay period, while the cerebellum is causally involved in the multi-regional loop

behind motor preparation [Gao et al., 2018]. Although both thalamus and cortex seem to be essential for movement planning[Guo et al., 2017], the degree to which thalamus and cortex differentially contribute to persistent activity and motor preparation remains unclear.

In the same motor preparation task, it was shown that ramping activity during the delay period reflects the stimulus held in memory and anticipates the motor action. A 'coding' direction in the neural activity space that maximally discriminates the two possible motor choices [Li et al., 2016, Inagaki et al., 2018], exhibits ramping as many single neurons do. Neural dynamics were found to be low-dimensional in the sense that a significant fraction of neural variance is captured by the coding direction. The origin of the coding direction, from the perspective of interacting neural assemblies has not been elucidated. Moreover, the sequence of neural computations that link sample-period activity to delay-period maintenance to motor execution remain unclear.

To address these questions, we propose the 'dynamical modes' framework: a novel paradigm to study multi-regional dynamics and distributed computation in the brain. The dynamical mode framework connects behaviorally relevant dynamical activity patterns in the cortex to the subcortical inputs that control them. The role of the thalamus in this framework is to route subcortical signals to control the modes that were specified in the cortex. Thus, the thalamus via thalamo-cortical projections can selectively modify these functional modes.

Results

Dynamical modes: a computational framework

We introduce a firing-rate based framework to model two alternative forced choice tasks (2AFC), in which an action must be made in response to sensory stimuli. Importantly, we characterize choice-related computations in 2AFC via behaviorally-relevant and controllable population activity patterns in the cortex, referred to as 'dynamical modes'. Dynamical modes are patterns of activity at the population level in the cortex that subserve behavioral computations, e.g., persistent activity for working memory, ramping activity for evidence accumulation, phasic activity for transition from memory to movement, etc (Figure 1). Thus, the behavioral computations underlying a given task (e.g. motor

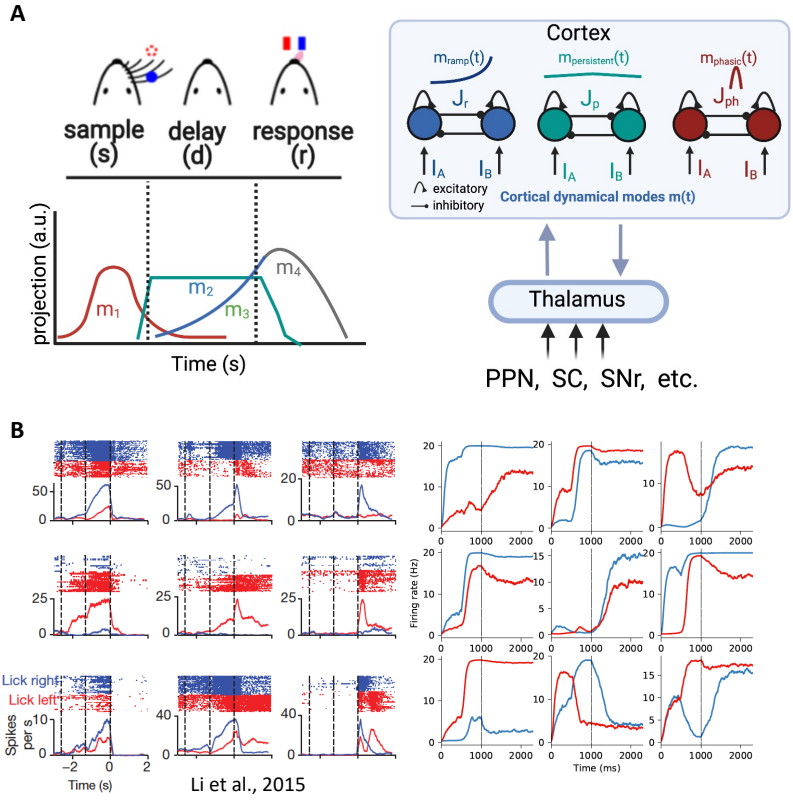

Figure 1: Subcortical control of cortical dynamical modes through the thalamus. A) Left, a memory-guided response task (Svoboda and Li, 2018) can be conceptualized as a sequence of dynamical modes : population activity patterns that subserve behaviorally-relevant computations. Right, dynamical modes arise from excitatory and inhibitory interactions between selective neural pools in the cortex. Three modes are shown. Modes can be controlled (e.g., amplified, suppressed, etc.) by subcortical inputs onto the thalamus. B) Firing rate activity of single units is a linear combination of modes.

planning) correspond to a sequence of dynamical modes (Figure 1 A). The function of the thalamus in this framework is twofold: first, it contributes to the maintenance of selective activity in the cortex and second, it routes subcortical signals through specific thalamocortical pathways to modulate dynamical modes as a function of task demands. Subcortical modulation of dynamical modes can take different forms, including: amplification, suppression, switching from one mode to another, and de novo generation. In our framework, distinct modes are generated by distinct pairs of neural pools. Single neurons, however, may form part of more than one pool and contribute to more than one mode, which provides a basis for heterogeneous neural activity across time and neurons (Figure 1 B). Based

on this framework, we studied the involvement of thalamic nuclei and other subcortical structures during motor planning.

The thalamus helps sustain persistent activity in the cortex

Parts of the thalamus are necessary for the maintenance of information across a delay period, as demonstrated by optogenetic inhibition (Schmitt, et al., 2017; Guo et al., 2017; Bolkan et al., 2017). However, it is not clear how thalamocortical projections interact with cortical circuits to produce

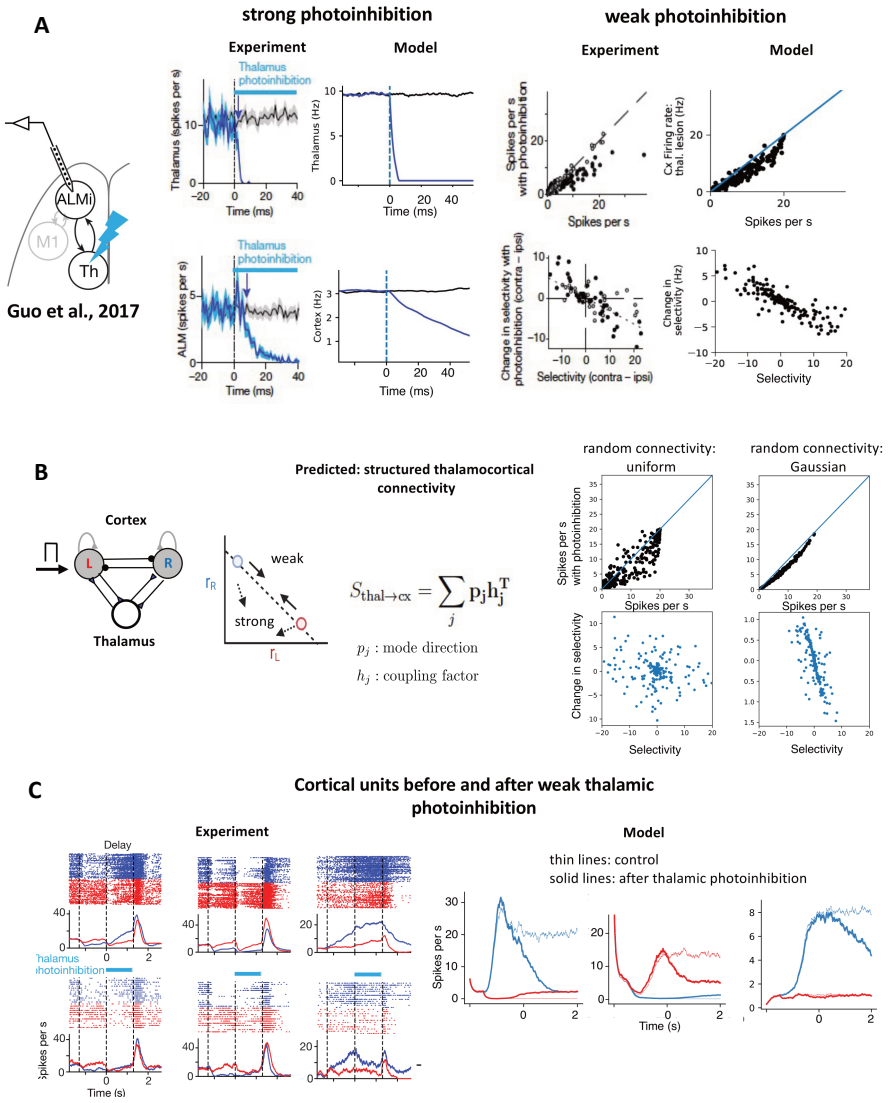

Figure 2: Model of photoinhibition of the thalamus reveals connectivity patterns of thalamocortical circuits. A) Thalamic photoinhibition experiment and concurrent recording in the cortex. Cortical activity strongly depends on thalamic input as shown by strong photoinhibition. During weak photoinhibition, selectivity is strongly affected while the average firing rate is only midly affected B) Schematic of the model and phase plane, depicting the trajectories of the population firing rate after weak and strong perturbations.Non-structured connectivity patterns are not able to reproduce the patterns observed in A C) Cortical units before and after weak thalamic photoinhibition

reverberatory activity. Guo et al., 2017 inhibited the thalamus during the delay period of a memory-guided response task (Figure 2). They found that the firing rate strongly and quickly decreases, suggesting that the thalamus provides monosynaptic excitation. After repeating the experiment with low-amplitude photoinhibition, they found that selectivity was greatly diminished. Our model can repro-

duce these findings by assuming that thalamocortical connectivity is designed to selectively target cortical dynamical modes (Figure 2). In particular, we propose a structured thalamocortical connectivity that favors stimulus-selective pools in the cortex (Figure 2 B). After weak perturbation, firing rate activities decrease along a direction in neural activity space that miniminally affects average firing rate. For example, right lick-selective pool will decrease its firing rate during right-lick trials, but increase its activity during left-lick trials. In this case, selectivity decreases, but average firing rate remains approximately the same. The framework can explain the effects of photoinhibition at the single cell level (Figure 2 C).

Inhibitory control and regulation of thalamocortical dynamics

As shown by the experiments by Guo et al. [2017], optogenetic inhibition of the thalamus greatly reduces trial selectivity in the cortex. Under physiological conditions, the thalamus receives inhibitory input from the pars reticulata (SNr), involved in action selection and the thalamic reticular nucleus (TRN). It is not clear what the role of these inhibitory structures are in the context of motor planning, and whether they modulate thalamocortical dynamics in the same manner. Wang et al., 2021 activated and inactivated SNr and TRN projections onto the thalamus in one hemisphere and studied the effects on cortical dynamics during motor planning (Figure 3 A). The SNr manipulation differentially affected contra and ipsi trials w.r.t. the affected hemisphere. In stark contrast, the TRN manipulation

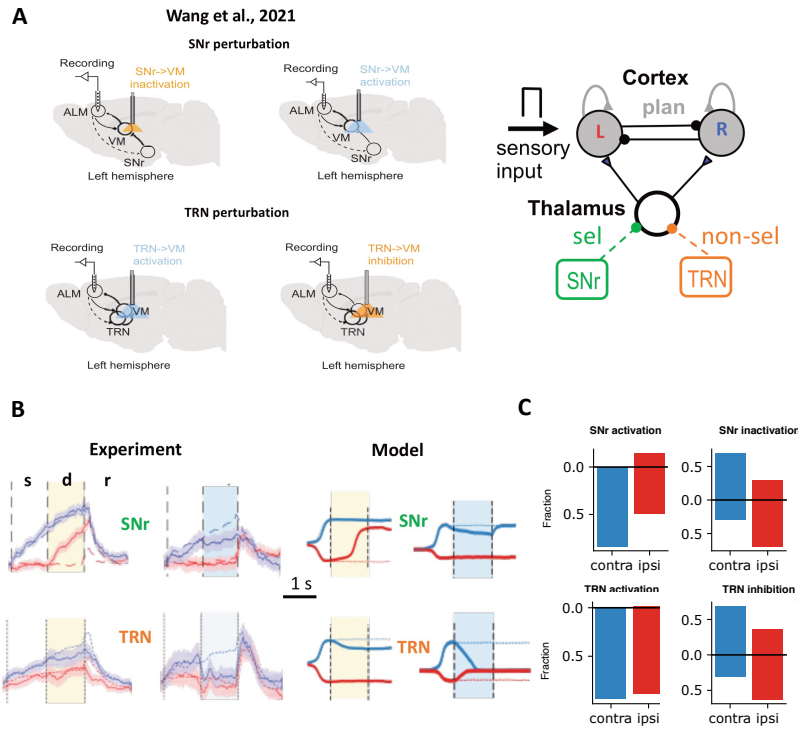

Figure 3: Differential effects in the cortex after perturbation of thalamic reticular nucleus (TRN) and pars reticulata (SNr) A) Left, schematic of the photoinhibition task used by Wang et al., 2021. Right, schematic of the computational model, where SNr and TRN are hypothesized to target selective and non-selective cortical dynamical modes, respectively. B) Under the assumption that the two inhibitory structures target different modes, the model reproduces the perturbation effects on the cortical coding direction (yellow and blue shades denote inhibition and activation, respectively). C) Activation and inhibition of SNr and TRN predicts a differential modulation of ipsi- and contra-preferring cells.

was more uniform across contra and ipsi trials (Figure 3 B). We modelled thalamocortical dynamics

under the assumption that SNr and TRN inputs targeted selective and non-selective modes, respectively (Figure 3 A). The model could reproduce the dynamics during the delay period as exemplified by population-projections on the coding direction, defined as the direction in neural activity space that maximally discriminates between trial types (Li et al., 2016). The model predicts that thalamic neurons receive uniform input from TRN, selective input from SNr, and that they form closed thalamocortical loops. Moreover, contra- and ipsi-preferring neurons are predicted to be differentially modulated by the type of perturbation (Figure 3 C). We suggest that the SNr suppresses incorrect choices depending on context (e.g., suppress a 'lick-left' action in a 'lick-right' trial), while the TRN regulates delay activity to prevent runaway excitation from excitatory thalamocortical loops. Thus, the SNr and TRN manipulate information throughout a stimulus-absent delay period: cognitive roles that argue against a generic subcortical inhibition uniquely ascribed to motor execution.

Subcortical origin of ramping dynamics

Ramping in single unit and population activity is observed in multiple regions of the large-scale circuit involved in movement planning[Svoboda and Li, 2018]. Ramping may be related to different computations, including evidence accumulation, urgency, or timing. The biophysical origin of ramping dynamics is not yet clear. Perturbation experiments point to a potential subcortical origin, as ramping dynamics quickly and consistently recover after intracortical perturbations. Here we consider the possibility that a cortico-basal ganglia loop, composed of the cortex, striatum, SNr and thalamus may contribute to the generation of ramping in this circuit. To this end, we modeled dynamics in the basal ganglia direct pathway during the memory-guided response task (Figure 4). Briefly, thalamocorti-

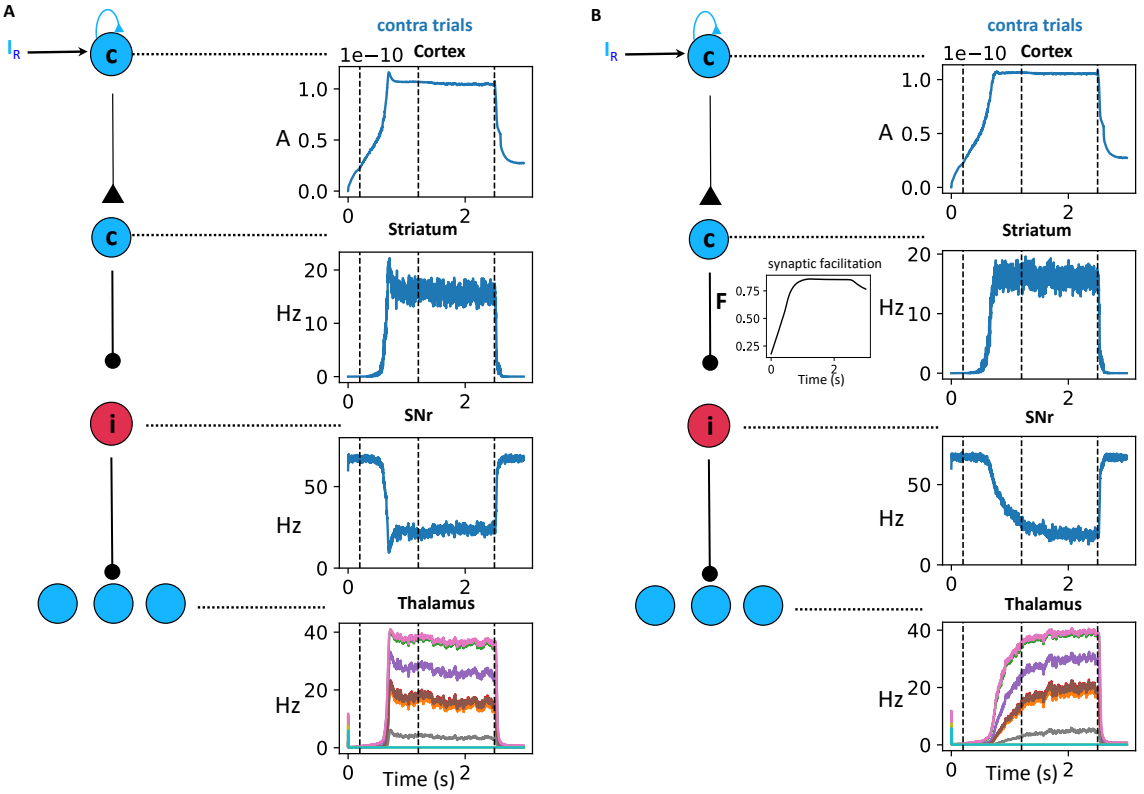

Figure 4: Ramping generation in a cortico-basal ganglia-thalamic circuit A) Schematic and dynamics of the direct pathway. Only contra trials are shown B) Same as A) but with synaptic facilitation at the striato-nigral synapses.

cal activity produces persistent activity which is fed onto the striatum (basal ganglia input), which subsequently inhibits the SNr (basal ganglia output). Reductions in firing in the SNr leads to the disinhibition of thalamic activity (Figure 4 A). Thalamic activity does not show ramping activity in this scenario. On the other hand, if we include short-term synaptic facilitation at striato-nigral synapses, the thalamus exhibits ramping activity which may then be propagated to the cortex (Figure 4 B). Critically, synaptic facilitation caused a ramping-down of activity in the SNr, which is reminiscent of the ramping-down observed in the saccade circuit just before a saccade will occur. We suggest that facilitation may contribute to ramping generation in the thalamocortical circuit.

A 'behavioral switch': from movement planning to execution

In many cognitive tasks, a sensory cue (i.e., a GO cue) signals the subject to make a choice after a preparatory period. The mechanisms underlying the relationship of the cue to motor planning and execution are not well understood. Inagaki et al. [2020] found that the GO cue is processed subcortically and is subsequently relayed to the thalamus and frontal cortex to generate cue-related and movement dynamics. We investigated the possible circuit-level mechanism behind the planning- to-movement transition (Figure 5). We hypothesized that the movement mode is negligibly small until amplified

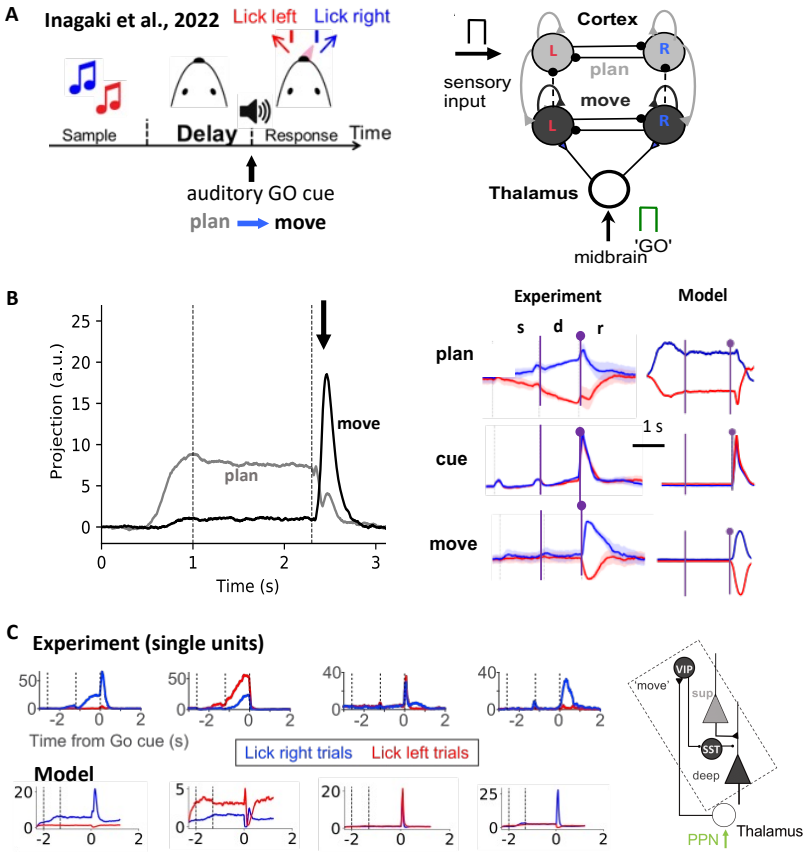

Figure 5: The thalamus causes a switch and network reorganization in the cortex A) Schematic of the behavioral task, highlighting the GO cue. Right, model schematic where plan neural assemblies project to move assemblies. B) Left, planning-related activity (gray) is transformed into movement activity (black) only after thalamic input(black arrow). Right, the model can reproduce three experimentally defined modes: plan, cue, move (Inagaki et al., 2022). C) The formalism allows to reproduce dynamics at the single neuron level, and predicts a a disinhibitory motif to accomplish the switch.

and deployed by the GO cue through the thalamus. To explicitly show this, we considered two pairs

of neural pools, responsible for generating persistent and movement modes, respectively (Figure 5 A). Neurons with persistent activity project to the movement neural pool during the delay period, but their activity remains low because they are less excitable (e.g. low baseline currents). Our model suggests that the GO input arriving from the thalamus generates selective activity in the cortex during the response epoch, thus enabling movement (Figure 5 B). Moreover, the GO input shuts down delay period activity by thalamocortical engagement of intracortical inhibition. The model predicts the existence of neurons in deep layers with low firing during the delay that switch to high firing at the GO cue. Moreover, the switch could be achieved via a disinhibitory circuit that releases deep layer cortical neurons from inhibition during the response period (Figure 5) C. Thus, the thalamus implements a 'behavioral switch' by amplifying latent movement dynamics in the cortex.

Discussion

We designed and implemented a multiregional circuit model composed of the cortex, thalamus, and subcortical inputs to interpret recent physiological and behavioral experiments in the mouse during motor planning. The model was constrained by electrophysiological data from rodents during motor planning and encourages new experiments based on anatomical and physiological model predictions. We propose that the thalamus controls behaviorally- relevant cortical dynamics across task epochs, based on differential contributions of excitatory and inhibitory subcortical projections.

A central component of the framework and the modeling results is the thalamus. The thalamus is involved in a myriad of functions essential to an animal's survival, including linking the sensory world to the cortex and regulating sleep, alertness, and wakefulness [Ward, 2013]. The study of thalamocortical interactions in particular has elucidated multiple, though not necessarily exclusive, thalamic functions: the thalamus changes cortical state [Poulet et al., 2012, Zhou et al., 2016] maintains excitatory-inhibitory balance [Ferguson and Gao, 2017], enhances sensory responses [Mease et al., 2016, Purushothaman et al., 2012], signals context [Halassa and Kastner, 2017, El-Boustani et al., 2020], and may be even fundamental for cortico-cortical communication [Sherman and Guillery, 2013, Theyel et al., 2010]. Most of the knowledge accumulated with respect to thalamic function concerns sensory thalamic nuclei, which directly receive input from the periphery via sense organs. Interestingly, recent studies have demonstrated contributions from non-sensory thalamic nuclei to cognitive and sensorimotor computations such as attention, working memory, decision making, and movement planning that had been exclusively ascribed to the cortex [Saalmann and Kastner, 2009, Saalmann et al., 2012, Roth et al., 2015, Schmitt et al., 2017, Bolkan et al., 2017, McAlonan et al., 2008, Komura et al., 2013, Alcaraz et al., 2018, Chakraborty et al., 2016]. To explain the role of the thalamus in these computations, experimental and computational studies [Jaramillo et al., 2019], have suggested that the activation of higher-order thalamic nuclei may change the dynamical regime of the cortex, for example by enhancing local recurrent connectivity within [Schmitt et al., 2017, Halassa and Kastner, 2017, Logiaco et al., 2019] and across [Saalmann et al., 2012, Theyel et al., 2010] cortical areas. The motor thalamus, as well as other higher-order thalamic nuclei are known to form extensive thalamocortical loops. The details underlying these connectivity patterns may be informative of the ensuing computations. For example, the motor thalamus VM forms closed excitatory loops with the secondary motor cortex (ALM) [Guo et al., 2018]. Corticothalamic cells from Layer V project to VM neurons which reciprocally project to the same neurons. Such organization is not observed in Layer VI neurons, the classic source of corticothalamic projections. According to the driver-modulator classification [Sherman and Guillery, 2013], layer V synapses onto single thalamic cells are fast and effective, exhibiting paired pulse depression. The speed and reliability of these connections are suggestive of the role of the thalamus in sustaining reverberatory activity during the stimulus-absent delay period of movement planning tasks [Guo et al., 2017].

It is interesting to note that the number of neurons in the cortex is higher than that of a typical thalamic nucleus. Also referred to as fan-out, the thalamus may control many more cortical cells than the number of available thalamic neurons. Thus, thalamocortical connectivity is suggestive of low-rank perturbations to the cortex [Mastrogiuseppe and Ostojic, 2018]. Beyond merely providing depolarizing input to cortical cells the thalamus may effectively modify circuits in the cortex [Jaramillo et al., 2019, Halassa and Kastner, 2017, Logiaco et al., 2019], perhaps as a function of task demand.

We found that inhibitory inputs from two subcortical structures, TRN and SNr, exert different

effects on cortical dynamics as a function of trial type and selectivity. The effects in the cortex are then reflected in the motor centers to eventually affect movement. Neurons in the basal ganglia output nuclei GPi and SNr directly inhibit the brainstem motor centers to regulate locomotion, licking and eye movements, whereas the pathway to the thalamus, which in turn projects to the cortex, requires more synaptic steps to reach motor neurons to control specific muscle activity. For example, the superior colliculus also receives input from the SNr. It is thus possible that the cortex and SNr compete for control of the final motor output, e.g., the medulla in case of the licking circuit. Thus, we suggest the basal ganglia plays a dual role in controlling movements: a direct pathway that inhibits colliculus and an indirect pathway through the thalamus that modulates the cortex.

The ascending pathway through the motor thalamus is important in triggering an externally cued action. Motor thalamus shows urgency/timing signals to predict upcoming saccades or lickings [Catanese and Jaeger, 2021, Cisek et al., 2009]. The form of the urgency signal is a ramp that is observed throughout the multiregional circuit. There are multiple mechanisms that can account for ramping, including evidence integration [Roitman and Shadlen, 2002, Wang, 2002] urgency[Cisek, 2007], expectation of reward [Schultz et al., 1997], etc. Our model suggests that ramping may be a product of a cortico-BG-thalamic loop. In terms of the movement planning task, we propose that a cortico-thalamic loop subserves decision making during the sample period, while the BG is recruited to produce ramping which may be shaped by plasticity mechanisms as to account for different task contingencies [Inagaki et al., 2019].

One of our modeling results refers to Inagaki et al. [2020], who investigated what happens when an auditory go cue signals the switch from planning to movement. They recorded from neurons in the ALM (cortex) and recorded from the VM thalamus, some portions of which overlap with VIM thalamus, a DBS target for tremor. The authors found that the latency in the the thalamus was shorter than in the cortex, interesting being that this is a motor section of the thalamus. We used this fact to propose a very specific function for the thalamus in this task, namely to provide the necessary input for cortical cells to produce movement-related activity. We predict that movement-related cells are PT cells that are under inhibitory control during the delay period. This raises the possibility of two distinct yet complementary mechanisms of avoiding premature licks: PT cells may be inhibited and/or may be active yet do not propagate their information as they are in the null space of their (subcortical) motor target [Kaufman et al., 2014].

Our framework can be augmented to include diverse physiological features not considered that may be important, such as dendritic and axonal compartments as well as cell types with specific dynamics. Importantly, the framework we propose is sufficiently general to address other cognitive computations and the role of other subcortical structures in dynamical interplay with the cortex.

Methods

Overview

The dynamical modes framework has two major components. For the first component, we construct a dynamical system that represents the activity of neurons in the cortex with a priori specified low-dimensional dynamics (or 'dynamical modes'). That is, we describe a *generative* procedure to embed a set of cortical modes, time-dependent neural activity patterns, onto a neural network. In this self-consistent description, the neural network dynamics, when projected onto a predefined set of directions (equal to the number of modes), gives rise precisely to the cortical modes. Moreover, through this procedure we obtain a synaptic connectivity matrix in the cortex, which could represent both intracortical and interareal connections. The second component of the framework refers to thalamocortical interactions. The thalamus, which sends and receives projections from the cortex, routes control signals from subcortical structures to modulate cortical modes. For example, subcortical structures can selectively amplify a mode, or it could modify the stability of a particular mode.

Dynamical modes: distinct population activity patterns in the cortex

Here we introduce formally the concept of *dynamical mode* in terms of neural activity and the (synaptic) network underlying this activity. We proceed to describe a *generative* procedure to embed a set of cortical modes onto a neural network. In this self-consistent description, the neural network dynamics, when projected onto a predefined set of directions (equal to the number of modes), gives rise precisely to the cortical modes. Finally, we describe the framework by which the thalamus exerts control on the cortical modes for dynamic computations.

We consider a population of N excitatory neurons in the cortex. Such neurons could describe a particular cortical area or more generally, a set of interconnected areas. The N neurons are assumed to be coupled via a synaptic connectivity matrix J_{NxN}. Neurons can inhibit each other through feed-forward inhibition mediated by interneurons. This implies that J will generally have positive and negative entries. We denote the time dependent firing rate of each neuron $i = 1, 2, ...N$ as $r_i(t)$. The firing rate population vector $\mathbf{r(t)} = \{\mathbf{r_i(t)}\} \in \mathbf{R^N}$ evolves as:

$$\tau_J \frac{\mathrm{d}\mathbf{r(t)}}{\mathrm{dt}} = -\mathbf{r(t)} + \mathbf{\Phi}(\mathbf{Jr(t)} + \mathbf{I}) \tag{1}$$

where τ_J is the time constant of the population, Φ is a non-linear function whose argument is the total current containing synaptic currents $\mathbf{J} \cdot \mathbf{r}$ from within the population and currents $\mathbf{I}$ that represent external inputs to the cortical network (e.g., sensory stimulation or thalamocortical input that will be specified below). The goal of the framework is to calculate the synaptic connectivity matrix J based on the following properties. First, the population activity $\mathbf{r(t)}$ can be decomposed onto distinct activity patterns, dynamical modes, that are specified *a priori*. Second, the modes result from the dynamical interaction between two populations of neurons selective to two stimuli, denoted A and B. Finally, any given neuron may generally participate in multiple modes. Here we describe these conditions in detail.

Relationship between modes and the population firing rate

The population firing rate (also referred to as the full neural network dynamics) **r(t)** can be decomposed onto distinct activity patterns that are specified *a priori*. Thus, a mode is a linear combination of the firing rates of units belonging to the network. From the point of view of read out populations, a mode can be interpreted as a synaptic current (Figure 1A). Each individual synaptic current represents the projection of $\mathbf{r(t)}$ onto a vector $\mathbf{p_j} \in \mathbf{R^N}$, with $j = 1, 2, ...M \ll N$. Each synaptic current $I_{m_j}(t)$ is given by

$$I_{m_j}(t) = \mathbf{r(t)} \cdot \mathbf{p_j} + \mathbf{i_j}, \tag{2}$$

where i_j is a current that contains baseline and other currents external to the network. The synaptic current $I_{m_j}(t)$, is referred to as a *dynamical mode*, while the vector $\mathbf{p_j}$ is referred to as the direction in neural space along which mode $I_{m_j}(t)$ lies. Each dynamical mode is thus a scalar function of time. To rewrite this equation in vector form, we define the vector of modes (i.e., synaptic currents) $\mathbf{I_m} = \{\mathbf{I_{m_j}}\}$ as $\mathbf{I_m} = \mathbf{Pr} + \mathbf{i}$, where each row of the matrix $\mathbf{P}$ corresponds to each direction $\mathbf{p_j}$: $\mathbf{P} = [\mathbf{p_j}]$. If $\mathbf{P}$ is non-singular, we can write $\mathbf{r} = \mathbf{P^{-1}}(\mathbf{I_m} - \mathbf{i})$.

Dynamical modes result from the dynamical interaction between two populations

We now specify the dynamics of individual modes I_{m_j}. We assume that each mode I_{m_j} arises from the interaction between neural populations referred to as 'readout populations' (Figure 1B). We focus on modes that are relevant and/or arise from the study of two alternative forced choice (2AFC) tasks. To model two-alternative forced choice tasks, we consider two pools of excitatory neurons that are selective to two different stimuli,e,g. objects, features, or spatial locations. Within each pool there are recurrent connections and the pools inhibit each other through a common pool of interneurons. respectively. We write the following pair of equations, for *reduced* neural populations j and $j+1$

$$\tau_J \frac{\mathrm{dI_{m_j}(t)}}{\mathrm{dt}} = -I_{m_j}(t) + J_{E_j}\phi(I_{m_j}) + J_{I_j}\phi(I_{m_{j+1}}) + i_j \tag{3}$$

$$\tau_J \frac{\mathrm{dI_{m_{j+1}}(t)}}{\mathrm{dt}} = -I_{m_{j+1}}(t) + J_{E_{j+1}}\phi(I_{m_{j+1}}) + J_{I_{j+1}}\phi(I_{m_j}) + i_{j+1} \tag{4}$$

We will typically consider the case where modes are coupled pairwise and independent from other pairwise couplings: a mode m_j is exclusively coupled to mode $I_{m_{j+1}}$ (via equations 3-4) and no other mode. This means that I_{m_1} is coupled (exclusively) to I_{m_2}, I_{m_3} is coupled (exclusively) to I_{m_4}, etc., although below we will consider a case where a mode I_{m_j} is coupled to both $I_{m_{j-1}}$ and $I_{m_{j+1}}$. In the scheme described by Eqs.3-4, a mode $I_{m_j(t)}$ will be completely specified by the input current i_j and by the recurrent excitatory and inhibitory weights J_{Ej} and J_{Ij}. We can rewrite equations 3-4 in vector form as

$$\tau_J \frac{\mathrm{d}\mathbf{I_m(t)}}{\mathrm{dt}} = -\mathbf{I_m(t)} + \mathbf{J_m}\mathbf{\Phi}(\mathbf{I_m(t)}) + \mathbf{i}, \tag{5}$$

where $\mathbf{I_m} = \{I_j\},\ j = 1, 2, ...N$ and J_m is the connectivity matrix with the following block diagonal form:

$$\mathbf{J_m} = \begin{pmatrix} J_{E1} & J_{I1} & 0 & 0 & \cdots \\ J_{I2} & J_{E2} & 0 & 0 & \cdots \\ 0 & 0 & J_{E3} & J_{I3} & \cdots \\ 0 & 0 & J_{I4} & J_{E4} & \cdots \\ \vdots & \vdots & 0 & \ddots & 0 \\ 0 & 0 & \cdots & \cdots & 0 \end{pmatrix}$$

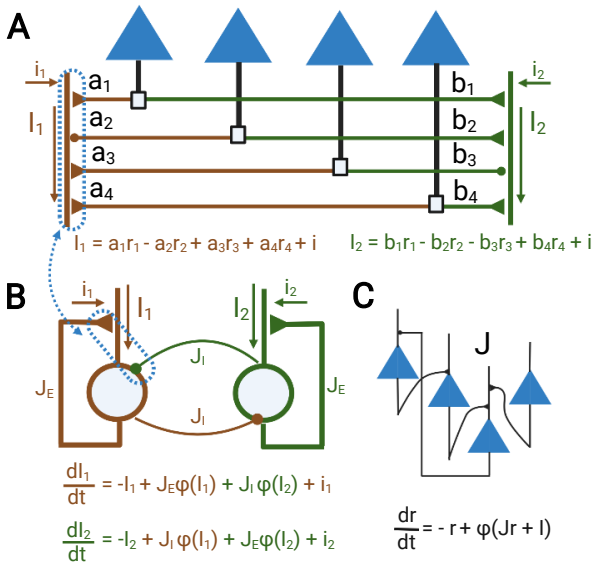

Figure 6: Derivation of dynamical modes equations: explicit calculation of two modes that result from the interaction between four neurons. **A**. A dynamical mode can be viewed as a readout from a population of neurons (blue triangles). The same population may have different readouts, depending on the readout synaptic weights (e.g., a_i, b_i, $i = 1, 2, 3, 4$). These four neurons give rise to two distinct synaptic currents I_{m_1} and I_{m_2}. **B**. The synaptic currents in **A** are *matched* to the input currents to two readout assemblies, whose dynamics we specify a priori. The assemblies are characterized by recurrent excitatory connections J_E and interact through inhibitory connections J_I. **C**. By comparing Eq. 8 with Eq. 1, we can extract a network with synaptic matrix $\mathbf{J}$ that encodes the synaptic currents as latent variables. Thus, these two descriptions, reduced assembly and full network level, are equivalent.

where each block specifies the pairwise interaction between modes. Moreover, each block is symmetric: $J_{E1} = J_{E2},\ J_{E1} = J_{I2}, J_{E3} = J_{E4},\ J_{I3} = J_{I4}$, etc.

Dynamical modes as projections from the full neural network dynamics

The full neural network dynamics is given by $\mathbf{r(t)}$, which are solutions to Equation 1. To obtain an expression for the modes I_{m_j} in terms of the full neural network dynamics, we insert the expression for I_m in terms of $r(t)$ (Eq. 2) in Eq. 5:

$$\tau_J \frac{\mathrm{d}\mathbf{I_m(t)}}{\mathrm{dt}} = -\mathbf{I_m(t)} + \mathbf{J_m \Phi(I_m(t))} + \mathbf{i} \tag{6}$$

$$\tau_J \frac{\mathrm{d}(\mathbf{Pr} + \mathbf{i})}{\mathrm{dt}} = -(\mathbf{Pr} + \mathbf{i}) + \mathbf{J_m \Phi(Pr} + \mathbf{i}) + \mathbf{i} \tag{7}$$

$$\tau_J \frac{\mathrm{d}(\mathbf{r})}{\mathrm{dt}} = -\mathbf{r} + \mathbf{P^{-1} J_m \Phi(Pr} + \mathbf{i}), \tag{8}$$

As the modes I_{m_j} are designed *a priori*, we assume that the reduced connectivity matrix $\mathbf{J_m}$, the current vector $\mathbf{i}$, and matrix of projection directions $\mathbf{P}$ are known. With this we can, in principle, find the recurrent connectivity $\mathbf{J}$ and current $\mathbf{I}$ by comparing Eq. 8 with Eq. 1. Figure 1C shows the relationship between the two population readout model and the full network dynamics. The scheme above only leads to a unique solution if the projection matrix $\mathbf{P}$ is specified. Below we specify some constraints for the matrix of projection directions $\mathbf{P}$.

Constraints on projection directions $\mathbf{p_j}$: space multiplexing through dynamical modes

Here we consider the computational paradigm of space multiplexing: any given neuron may form part of multiple assemblies and participate in the generation of multiple modes. In one extreme, every neuron participates in all modes. In another, a neuron is associated to only cortical mode such that the ensemble of units associated to the modes are segregated anatomically. Space multiplexing across neurons (or lack thereof) sets an important constraint on the directions $\mathbf{p_j}$. Recall that each mode I_{m_j} lies along a projection $\mathbf{p_j}$ as $I_{m_j(t)} = \mathbf{r(t)} \cdot \mathbf{p_j}$. We write this explictly as

$$I_{m_j} = \mathbf{p_j} \cdot \mathbf{r} \tag{9}$$

$$= p_{j1}r_1 + p_{j2}r_2 + p_{j3}r_3 + ... \tag{10}$$

We define the degree of participation of neuron i to mode j as $|p_{ji}|$. Thus, if $\mathbf{p_j}$ is a sparse vector, then only few neurons participate in the generation of mode I_{m_j}. Along these lines, the condition for anatomical segregation of modes is that, if neuron i with firing rate r_i participates in a mode I_{m_j}, then it should not participate in any other mode $k \neq j$. Thus, two modes I_{m_j} and I_{m_k} are anatomically segregated if the contribution of neuron i to mode I_{m_j} is a number different from zero ($p_{ji} \neq 0$), then the contribution of the same neuron to mode I_{m_k} is zero ($p_{ki} \neq 0$). Equivalently, two modes are anatomically segregated when row vectors $\mathbf{p_j}$ and $\mathbf{p_k}$ are *trivially orthogonal*, i.e., when an entry in one vector is non-zero, then it is zero in the other vector. A related notion is that of *mixed selectivity*, which we here define as the degree to which a given neuron represents or encodes more than one mode. To this end, we now expand the firing rates r_i of neuron i in terms of the rows of $\mathbf{P^{-1}}$ (which we refer to as p_k^*) and modes I_m,

$$r_i = \Sigma_k p_{ik}^* I_{m_k} \tag{11}$$

If p_k^* is not sparse, then the neuron i will be a mixture of different modes and thus will exhibit mixed selectivity and heterogeneity across time.

Subcortical control of cortical modes through thalamo-cortical projections

Given the generative procedure above to embed cortical modes onto a neural network, we now consider the issue of control. By control, we mean the mechanism by which cortical modes are modified based on some desired computational principle. For example, for a given computation it might be desirable to amplify a particular mode or change its stability. The cortex is reciprocally connected to the thalamus so the thalamus is a source of such control input. We first define and calculate thalamo-cortical inputs that can selectively target a mode. From that analysis, we proceed to define a thalamus model such that an extra-thalamic input from subcortical structures (e.g., superior colliculus, basal ganglia, cerebellum, etc.) results in a modification of the cortical modes.

A model of the thalamus and thalamo-cortical projections

We consider a population of $N_{\text{thal}} < N$ excitatory neurons in the thalamus. Notably, recurrent excitatory collaterals are absent in the thalamus. We denote the firing rate of each neuron $i = 1, 2, ...N_{\text{thal}}$ as $r_{thal_i}(t)$. The thalamic firing rate vector $\mathbf{r_{thal}} \in \mathbf{R}^{\mathbf{N}_{\text{thal}}}$ evolves as:

$$\tau_{\text{thal}} \frac{d\mathbf{r_{thal}}}{dt} = -\mathbf{r_{thal}} + \mathbf{\Phi}_{\text{thal}}(\mathbf{I}_{\text{thal}}) \tag{12}$$

where τ_{thal} is the time constant of the thalamic population, Φ_{thal} is a non-linear function, and $\mathbf{I}_{\text{thal}}$ is a current that contains contributions from extra-thalamic sources (e.g., cortical and subcortical sources).

$$\mathbf{I}_{\text{thal}} = \mathbf{J}_{\text{cx}\rightarrow\text{thal}}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sub}} \tag{13}$$

where $J_{\text{cx}\rightarrow\text{thal}}$ is the cortico-thalamic connectivity matrix and $\mathbf{r}$ is the cortical firin rate. We write the external current $\mathbf{I}$ arriving to the cortex in Eq. 1 as as a sum of sensory, thalamic, and baseline contributions:

$$\mathbf{I} = \mathbf{I}_{\text{sensory}} + \mathbf{I}_{\text{thal}\rightarrow\text{cx}} + \mathbf{I_b} \tag{14}$$

where $I_{\text{thal}\rightarrow\text{cx}} = J_{\text{thal}\rightarrow\text{cx}}\mathbf{r_{thal}}(\mathbf{t})$

General structure of the thalamo-cortical current

For the thalamocortical current $\mathbf{I}_{\text{thal}\rightarrow\text{cx}}$ to have an impact on cortical dynamics along a particular direction $\mathbf{p_j}$, the current should be parallel to this direction. Thus, a current $\mathbf{I}_{\text{thal}\rightarrow\text{cx}} = \alpha\mathbf{p_j}$ will have an amplifying (reducing) effect on mode I_{m_j} if $\alpha > 0$ ($\alpha < 0$). We now sketch the form of the thalamo-cortical projections such that an extra-thalamic input results in a modification of a given cortical mode I_{m_j}. We assume that there are thalamo-cortical projections, i.e., a thalamo-cortical matrix $J_{\text{thal}\rightarrow\text{cx}}$) such that such mode can be targeted. We recall that the direction (vector) associated with the mode I_{m_j} is $\mathbf{p_j}$. We proceed to construct a thalamo-cortical matrix of the form $J_{\text{thal}\rightarrow\text{cx}} = \mathbf{p_j}\mathbf{h_j^T}$ where $\mathbf{h_j} \in \mathbf{R}^{\mathbf{N}_{\text{thal}}}$ is a vector of weights that couple the thalamic output to a mode I_{m_j}. Along these lines, a thalamo-cortical current would have the form $\mathbf{p_j}\mathbf{h_j^T}\mathbf{r_{thal}}(\mathbf{t})$ where $\mathbf{r_{thal}}(\mathbf{t})$ is the firing rate of the thalamic population. Given a set of mode directions $\mathbf{p_j}$, the expression for the thalamo-cortical matrix is thus:

$$J_{\text{thal}\rightarrow\text{cx}} = \sum_j \mathbf{p_j}\mathbf{h_j^T} \tag{15}$$

We note that components of $\mathbf{r}_{\text{thal}}$ parallel to h_j will contribute to the thalamo-cortical current, while components orthogonal to h_j will not. In other words, the thalamocortical matrix is such that it effectively 'filters out' directions orthogonal to h_j. This formulation suggests the design of extra-thalamic currents that can serve as control inputs to control dynamical modes. The extra-thalamic control currents that target a particular mode I_{m_j} have the form

$$I_{\text{cont}_j} = \alpha_{\text{thal}} h_j.$$

Assuming that $h_j,\ j = 1, 2, ..., N$ form an orthonormal set, a current $I_{\text{cont}_j} = \alpha_{\text{thal}} h_j$ applied to the thalamus will produce an effective thalamo-cortical contribution $I_{\text{thal}\rightarrow\text{cx}}$ proportional to $\alpha\alpha_{\text{thal}}\mathbf{p_j}$. In addition to supra-threshold mode-specific control, it is also possible to control the cortical output by controlling the baseline thalamic current I_b, i.e., I_b sets the operation point of the thalamus.

Steady-state solutions and effective cortical connectivity

We calculate the steady state firing rate of the thalamic population $r_{thal_{ss}}$ by setting the left-hand side of Eq. 12 to zero:

$$\mathbf{r_{thal}}_{\text{ss}} = \mathbf{\Phi}_{\text{thal}}(\mathbf{I}_{\text{thal}}). \tag{16}$$

We assume that the thalamic population reaches a steady state firing rate more quickly than the cortical population. This is reasonable given that there are no recurrent excitatory collaterals in thalamic cells

and further requiring that $\tau_{\text{thal}} << \tau_{\text{cx}}$. This allows us to insert $\mathbf{r_{thal}} \approx \mathbf{r_{thal_{ss}}}$ in the equation for the cortical dynamics, Eq. 1 to obtain

$$\tau_J \frac{\mathrm{d}\mathbf{r}(\mathbf{t})}{\mathrm{dt}} = -\mathbf{r}(\mathbf{t}) + \mathbf{\Phi}(\mathbf{J}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sensory}} + \mathbf{I}_{\text{thal}\to\text{cx}}) \tag{17}$$

$$= -\mathbf{r}(\mathbf{t}) + \mathbf{\Phi}(\mathbf{J}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sensory}} + \mathbf{J}_{\text{thal}\to\text{cx}}\mathbf{r_{thal_{ss}}}) \tag{18}$$

$$= -\mathbf{r}(\mathbf{t}) + \mathbf{\Phi}(\mathbf{J}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sensory}} + \mathbf{J}_{\text{thal}\to\text{cx}}\mathbf{\Phi}_{\text{thal}}(\mathbf{I}_{\text{thal}})) \tag{19}$$

$$= -\mathbf{r}(\mathbf{t}) + \mathbf{\Phi}(\mathbf{J}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sensory}} + \mathbf{J}_{\text{thal}\to\text{cx}}\mathbf{\Phi}_{\text{thal}}(\mathbf{J}_{\text{cx}\to\text{thal}}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sub}})) \tag{20}$$

where we used the expression for $\mathbf{I}_{\text{thal}}$ in Eq. 13.

We now focus on the argument of the cortical transfer function Φ, i.e., the current I_{total} which corresponds to the second term of the right hand side of Eq. 20. We assume linear dynamics for the function Φ_{thal} so that the argument I_{total} is

$$I_{\text{total}} = \mathbf{J}\mathbf{r}(\mathbf{t}) + \mathbf{J}_{\text{thal}\to\text{cx}}\alpha_{\text{thal}}(\mathbf{J}_{\text{cx}\to\text{thal}}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{sub}}) + \mathbf{I}_{\text{sen}} \tag{21}$$

$$= [\mathbf{J} + \alpha_{\text{thal}}\mathbf{J}_{\text{thal}\to\text{cx}}\mathbf{J}_{\text{cx}\to\text{thal}}]\mathbf{r}(\mathbf{t}) + \alpha_{\text{thal}}(\mathbf{J}_{\text{thal}\to\text{cx}}\mathbf{I}_{\text{sub}}) + \mathbf{I}_{\text{sensory}} \tag{22}$$

$$= \mathbf{J}_{\text{eff}}\mathbf{r}(\mathbf{t}) + \mathbf{I}_{\text{eff}} + \mathbf{I}_{\text{sensory}} \tag{23}$$

where $\mathbf{J}_{\text{eff}} = \mathbf{J} + \alpha_{\text{thal}}\mathbf{J}_{\text{thal}\to\text{cx}}\mathbf{J}_{\text{cx}\to\text{thal}}$ is the effective cortical connectivity matrix and I_{eff} is the effective (non-thalamic) subcortical current. The overlap between the matrices $\alpha_{\text{thal}}J_{\text{thal}\to\text{cx}}$ and $J_{\text{cx}\to\text{thal}}$ determine the recurrent loops between the thalamus and cortex, the de novo generation of modes through thalmo-cortical connections, and the degree to which thalamic control is open or closed-loop, as well as the ge. Similarly, the degree of overlap between between the current I_{sub} and the matrix $J_{\text{thal}\to\text{cx}}$ dictates the contribution from (non-thalamic) subcortical inputs.

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