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From synapse to self: Spikes, synchrony, and attentive learning by laminar thalamocortical circuits

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ABSTRACT

How do our brains transform the "blooming buzzing confusion" of daily experience into a coherent sense of self that can learn and selectively attend to important information? How do local signals at multiple processing stages, none of which has a global view of brain dynamics or behavioral outcomes, trigger learning at multiple synaptic sites when appropriate, and prevent learning when inappropriate, to achieve useful behavioral goals in a continually changing world? How does the brain allow synaptic plasticity at a remarkably rapid rate, as anyone who has gone to an exciting movie is readily aware, yet also protect useful memories from catastrophic forgetting? A neural model provides a unified answer by explaining and quantitatively simulating data about single cell biophysics and neurophysiology, laminar neuroanatomy, aggregate cell recordings (current-source densities, local field potentials), large-scale oscillations (beta, gamma), and spike-timing dependent plasticity, and functionally linking them all to cognitive information processing requirements.
This article proposes how the brain coordinates multiple levels of thalamocortical and corticocortical processing to learn and pay attention to important information about the world. In order to discuss such a complex system clearly, a neural model is needed. Our model links attentive learning requirements to detailed brain circuits, notably the layered organization of cells in neocortical circuits and how they interact with primary and higher-order (i.e., the pulvinar nucleus, PULV\textsuperscript{1,2}) and nonspecific thalamic nuclei\textsuperscript{3} (Figure 1). In particular, it is known that corticothalamocortical pathways work in parallel with corticocortical routes\textsuperscript{4,5}. The model hereby predicts how fast learning occurs, without risking fast catastrophic forgetting, and proposes how spike synchronization enables spike-timing-dependent plasticity (STDP\textsuperscript{6}) to realize this goal. The model hereby embodies a solution of the fundamental stability-plasticity dilemma\textsuperscript{7,8}. Attentive matching between bottom-up sensory signals and top-down learned expectations play a key role in this solution: A good enough match generates synchronous attentive resonance and learning, whereas a mismatch causes reset and search for a new recognition category. To show how this happens, the model quantitatively simulates data about single cell biophysics and neurophysiology, laminar neuroanatomy, aggregate cell recordings (current-source densities, local field potentials), large-scale oscillations (beta, gamma), and functionally links them all to requirements about how to achieve fast stable attentive learning.

Many authors have turned to synchronous oscillations within and across brain regions as one way in which behaviorally significant brain states are organized\textsuperscript{9}. Aggregate and single-cell recordings from multiple thalamic and cortical levels of mammals have shown high and low-frequency rhythmic synchronous activity correlated with cognitive, perceptual and behavioral tasks. Large-scale neuronal population models have been proposed to model oscillatory dynamics\textsuperscript{10,11,12}. However, these models do not link brain spikes, oscillations, STDP, and the brain states that subserve cognitive information processing.

The present model fills this gap. It clarifies data about how bottom-up (BU) processing and learning is modulated by top-down (TD) learned expectations that embody predictions or hypotheses that focus attention on expected BU stimuli\textsuperscript{4,9,13-17}. These data support predictions of Adaptive Resonance Theory, or ART\textsuperscript{7,8,18}, that top-down expectations regulate predictive coding and matching and thereby help to focus attention, synchronize and gain-modulate attended feature representations, trigger fast new learning, and dynamically stabilize previously learned memories against catastrophic forgetting.

Our new SMART (Synchronous Matching ART) model significantly advances ART models by predicting how a BU/TD matches are regulated by spiking dynamics within laminar thalamic and cortical circuits. For example, corticothalamic signals from cortical layer 5 provide BU driving inputs to higher-order specific thalamic nuclei\textsuperscript{19}, where they are matched against modulatory cortical TD feedback from the corresponding higher-order cortical region (Figure 1). An analogous corticothalamic matching process takes place in the V1 to LGN primary thalamic nucleus loop\textsuperscript{7,20}. The model explains how such BU/TD matches control synchronization of spiking across multiple cortical and thalamocortical circuits, and how the ensuing synchronous resonance, in turn, selectively controls STDP. Simulations predict that a match between BU and TD information at the specific thalamus is accompanied by gamma oscillations (\(\gamma\), 20–70 Hz), whereas a mismatch initiated at the nonspecific thalamic nucleus causes lower-frequency beta oscillations (\(\beta\), 4–20 Hz). The model hereby explains how more superficial cortical layers (e.g., layer 2/3) may express more gamma oscillations, while deeper cortical layers (e.g., layers 6 and 4) may express more beta oscillations, as recent experiments have reported\textsuperscript{21}; see Results.
Figure 1 Model overview. A first-order and higher-order cortical area are linked by corticocortical and corticothalamocortical connections. The thalamus is subdivided into specific first-order, second-order, nonspecific, and thalamic reticular nucleus (TRN). The thalamic core (1 cell population) provides priming to layer 1, where layer 5 pyramidal cell apical dendrites terminate. The specific thalamus relays sensory information (first-order thalamus) or lower-order cortical information (second-order thalamus) to the respective cortical areas via plastic connections. The nonspecific thalamic nucleus receives convergent BU input and inhibition from the TRN, and projects to layer 1 of the laminar cortical circuit, where it regulates reset and search in the cortical circuit. Corticocortical feedback connections link layer 6I of the higher cortical area to layer 1 of the lower cortical area, whereas thalamocortical feedback originates in layer 6II and terminates in the specific thalamus after synapsing on the TRN. V1 receives two parallel BU thalamocortical pathways (LGN→V1 layer 4→2/3; LGN→V1 layer 6I→4) that can activate an intracortical loop (V1 layer 4→2/3→5→6I→4) and a corticothalamocortical loop (layer 4→2/3→5→6II→LGN→4). V1 also activates BU V1→V2 corticocortical pathways (V1 layer 2/3→V2 layers 6I and 4) and BU corticothalamocortical pathways (V1 layer 5→PULV→V2 layers 6I and 4).

Oscillation frequencies are, in turn, functionally linked to STDP<sup>6</sup>. STDP is maximal when pre- and post-synaptic cells fire within 10-20 ms of each other, and thus favors learning in match states whose synchronous fast oscillations fall within the temporal constraints of STDP<sup>22,23</sup>. The model hereby proposes a solution to the stability-plasticity dilemma in terms of matching, synchronous gamma oscillations and STDP learning.

Survival in the world requires that a human or animal learn to correctly discriminate and recognize important objects and events. How does the brain determine how specific (concrete) or general (abstract) a learned recognition category should be in a given situation? If matches trigger learning, then a flexible, situationally-sensitive, criterion of matching is needed to control specific vs. general learning. This criterion is called vigilance<sup>18</sup>, corresponding to the intuition that higher vigilance enables finer discriminations to be made. High vigilance triggers reset and search for a
new category when even small mismatches occur, thereby leading to concrete learning. Low vigilance allows even coarse matches to trigger resonance, and to thereby learn abstract categories that respond to many input variations. SMART predicts how neuromodulation by acetylcholine (ACh) may regulate the level of vigilance through time, as described below.

RESULTS

The SMART model (Figure 1) includes two hierarchically-organized thalamocortical loops: a first-order primary loop (analogous to the LGN-V1) and a higher-order loop (analogous to the PULV-V2). Each thalamocortical loop simulates a 1.2\text{mm} thick, 6-layered-cortical module with cortical excitatory and inhibitory neurons, a thalamic nucleus composed of core and matrix cells and local inhibitory interneurons, and a GABAergic thalamic reticular nucleus (TRN). The primary thalamocortical loop also includes a nonspecific thalamic nucleus. All cortical and subcortical layers are organized in 9x9 neural sheets, with the exception of the nonspecific thalamic nucleus and matrix thalamic cells that are simulated as single populations. Units are implemented as multi-compartment neurons obeying Hodgkin–Huxley-type dynamics and incorporate realistic anatomical and biophysical parameters (see Methods). The model implements online STDP learning, and the plastic synaptic weights, as well as each neuron’s compartmental currents, are recorded to allow off-line local-field potentials (LFP), current-source densities (CSD), and oscillation frequency/synchrony analysis. Stimuli are horizontally or vertically oriented bars that enable testing of model hypotheses about match/mismatch dynamics and learning.

SMART neocortical circuits functionally explain laminar circuit properties that have been reported in numerous experiments, and extend properties of previous laminar cortical models (see Supplementary Tabs. 1, 2 and 3 in appendix). In SMART, BU retinal input reaches the thalamus, and from here the cortex through two separate pathways, a specific pathway targeting middle cortical layers (LGN core cells to layers 4 and 6\text{I}), and a nonspecific pathway targeting superficial layers (LGN matrix cells and nonspecific thalamic nucleus to layer 1 of V1). These two pathways are treated separately due to their different functional roles. The SMART specific pathway is responsible for learning BU oriented filters, learning TD oriented modulatory expectations, matching BU and TD information in the specific thalamus, and learning in thalamocortical and corticocortical feedback connections. The nonspecific pathway regulates the excitability of the cortex, uses the match signal computed in the specific pathway to regulate reset and search for alternative recognition codes in layer 4 cells in the specific pathway, and regulates vigilance, and thereby the concreteness/abstractness of learned recognition categories. Supplementary Tab. 1 in appendix summarizes the detailed connectivity and functional properties of each model stage and pathway, along with their empirically determined physiological properties.

Specific pathway

Learning BU oriented filters. In both the brain and the model, LGN parvalbumin-rich “core” cells receive topographically highly ordered BU sensory input and project to layers 6\text{I} and 4 of cortical area V1 (Figure 1). Analogous to experimental findings, model layer 4 cells in primary visual cortex are sensitive to stimulus orientation. SMART simulates how adaptive synapses may become orientationally tuned in the pathways from LGN core relay cells to V1 layer 4 and layer 6\text{I} cortical neurons via post-synaptically gated STDP (Figure 2a, see Methods).

LGN excites both layer 4 and layer 6\text{I}, which together contrast-normalize layer 4 cell activities in response to BU input patterns via a modulatory on-center, off-surround network whose off-surround is mediated by layer 4 inhibitory interneurons. The on-center
Figure 2 (a) STDP curves obtained by varying the time interval between presynaptic and postsynaptic spike between [-30, 30]ms for five gating functions: grey (no gating), blue (dual OR gating), red (presynaptic gating), green (postsynaptic gating), yellow (dual AND gating), modified with permission from 50. (b) Presentation of a horizontal bar to a untrained thalamocortical circuit causes changes in the BU synaptic weights of LGN→layer 4 synapses (postsynaptic gating, 100ms episode). (c) At the same time, TD layer 6I→LGN weights change, adapting to the BU input shape (presynaptic gating). (d) TD synaptic weights in the connections from layer 6I→layer 1 dendrites of layer 5 cells change during learning when layer TD feedback is active (dual AND gating).

off-surround of the LGN→6I→4 pathway biases the emergence of orientation sensitivity in layer 4 cells that spike after the arrival of the LGN input within the STDP learning window. Figure 2b illustrates the development of orientation sensitivity in a layer 4 cell that wins the competition with its neighboring cells, or spikes within a few milliseconds after the arrival of the LGN input, while nearby cells are suppressed and their spiking delayed by the on-center off-surround layer 6I→4 network. This delay reduces or completely suppresses learning in cells other than the winning neurons. The orientation selectivity is expressed in terms of LGN→4 cell density of the simulated thalamic axonal synaptic weights (see Model) before and after a 1000ms exposure to a horizontally-oriented stimulus.

Orientationally selective cells in layer 4 of V1 excite layer 2/3 cells, which in turn project to layer 5 of V1. Layer 5 projects to layers 6I and 6II of the same area. Layer 6I closes the layer 2/3→6I→4→2/3 intracortical modulatory excitatory loop that helps select the most activated cells in layer 4, while strongly suppressing less active cells and noise. Layer 6II closes the thalamocortico-thalamic loop by projecting with TD modulatory connections to the specific and nonspecific thalamic nuclei, and with driving connections to the TRN.

**Learning TD oriented modulatory expectations.** Distal dendritic segments of thalamic relay cells receive modulatory, excitatory glutamatergic input from V1 cortical layer 6II cells. Although LGN neurons respond to unoriented stimulation, oriented spatial arrays of LGN neurons can respond to oriented contours in an image or scene, and corticothalamic feedback comes from oriented cortical cells. The model simulates how TD feedback signals from V1 layer 6II cortical...
neurons to LGN are matched (or mismatched) in the specific thalamic nucleus, and thereby help to stabilize learning in both BU adaptive filters and TD modulatory expectations. Learning leads to TD orientation sensitivity\textsuperscript{32} and to competitive selection, synchronization, and gain modulation of matched LGN cells\textsuperscript{33}. Figure 2c illustrates the simulation of learned oriented shaping of model corticothalamic synaptic weights (STDP rule with pre-synaptic gating, see Methods) before and after 1000\textit{ms} presentation of a horizontal bar.

\textbf{Matching in the specific thalamus.} The direct, on-center, excitatory, learnable TD projection to LGN core cells uses the TRN-mediated inhibitory off-surround to match BU and TD information in the specific thalamic pathway (Figure 3). A perfect match occurs when the same subset of LGN cells receives BU excitation and TD layer 6\textsuperscript{II} priming; e.g., they both represent the same horizontal bar. These matched LGN cells fire tonic action potentials which activate layers 4 and 6\textsuperscript{I} of the target cortical area (Figure 3a). Tonic firing mode preserves a linear input-output relationship in LGN cells, and relays information better than burst firing\textsuperscript{5}. A mismatch (e.g., TD horizontal bar expectation and a vertical bar BU input) hyperpolarizes LGN cells via layer 6\textsuperscript{II}→TRN→LGN feedback, with voltage-dependent T (transient) type Ca\textsuperscript{+} channels causing burst firing\textsuperscript{1} (Figure 3b).
Figure 4 (a) TD corticothalamic feedback exerts a subthreshold excitatory effect on membrane potential of thalamic relay cells. Data: whole-cell recording from a relay neuron in the somatosensory ventral posterior nucleus (VPN) of a mouse thalamocortical slice in vitro. A single weak electrical stimulus (arrow) applied to a corticothalamic fiber elicits a small monosynaptic EPSP (asterisk in enlarged inset) followed by a deep and long-lasting disynaptic IPSP resulting from collateral corticothalamic excitation of the TRN. Simulation: a complete cortico-thalamic module is used in the simulation. External stimulation via current injection is provided to a central layer 6II neuron which has previously learned a BU stimulus until a single spike is produced, and the somatic membrane potential of the topographically aligned thalamic relay cell is recorded in the absence of external stimulation. (b) TD stimulation of layer 5 apical dendrites via, for instance, layer 6II of V2 feedback, induces layer 4 priming via the 6I on-center/off surround network. (c) The nonspecific thalamic nucleus, but not the specific, is involved in novelty detection in an auditory MMN paradigm. Data: Extracellular recordings to standard (thin line) and deviant stimuli (thick line) obtained from the caudomedial portion of the nonspecific medial geniculate body (MGcm) in guinea pigs. Significant differences between the responses to standard (2300 Hz) and deviant (2450 Hz) stimuli are indicated by the box under the difference wave. Significant negative deflections (at 30-80ms and 135-170ms) were identified in the nonspecific thalamic nucleus (MGcm) but not in the specific (medial geniculate body, MGv). Simulation: a complete corticothalamic module is used in 300ms simulation epochs, and the potential of the nonspecific thalamic nucleus cell is recorded. Stimulation of a layer 6II cell that has previously learned a horizontal stimulus provides TD feedback to the thalamus, where it mismatches a vertically-oriented BU sensory stimulation. The mismatch corresponds to the MMN condition, in which a repetitive stimulus builds up TD expectations that are mismatched when the novel stimulus is presented. The first increase in the nonspecific nucleus firing rate is caused by the release from inhibition from the TRN due to the reduced firing of the primary thalamic nucleus, whereas the second increase in firing rate is caused by the thalamocortical layer 6II feedback, in turn caused by the synchronized layer 5 firing. (d) In a mismatch, all layer 5 cells fire synchronously in response to the increased nonspecific thalamic input. In these simulations the TD feedback (stimulation of a layer 6II cell with horizontal TD thalamocortical RF) is kept on for one second, during which the TD feedback mismatches the vertically oriented BU input.
**Learning in corticocortical feedback connections.** V1 excites V2 via the cortico-cortical pathway from V1 layer 2/3 to V2 layers 4 and 6I, and via the cortico-thalamo-cortical pathway mediated by V1 layer 5 projections to the PULV1,2. V2 repeats the laminar pattern of V1 circuitry, with the exception that feedforward, layer 2/3 output from V1 drives layers 4 and 6I of V2, and layer 5 provides the BU input to the PULV that is matched against the V2 TD corticothalamic expectation, as in the LGN-V1 loop.

The same STDP rule helps to learn the TD corticocortical attentive connection from V2 layer 6II cells to layer 1 apical dendrites of V1 layer 5 cortical cells during presentation of a BU input (Figure 2d). This learning correlates V2 TD layer 6II cell outputs with retrograde dendritic spikes from V1 layer 5 cells at their layer 1 dendrites. Such learning allows the V2 layer 6II cell to fire the associated V1 layer 5 cell, and from there the corresponding V1 layer 6I cell, which in turn primes V1 layer 4 via the modulatory on-center, off-surround layer 6I→4 network. Figure 4a shows neurophysiological data illustrating modulatory priming in the specific somatosensory thalamus, and simulated model thalamic cell modulation during TD layer 6II priming. Figure 4b shows simulated subthreshold activation of a V1 layer 4 cell after learned TD feedback from a V2 layer 6II cell.

**Nonspecific pathway**

**Thalamic regulation of cortical excitability.** LGN “matrix”, calbindin-rich cells have more ambiguous receptive fields than LGN core cells and receive more broadly distributed subcortical inputs from retinal ganglion cells and the tectum. These LGN cells then project nonspecifically to V1 superficial layers. A similar pattern is repeated in the nonspecific thalamic nucleus. SMART proposes that matrix cells in the nonspecific pathway subliminally excite layer 5 of a target cortical area, and thereby prime the specific pathway to process the BU input.

**Nonspecific thalamic nucleus and arousal regulation.** The nonspecific thalamic nucleus activity is regulated by the matching process in the specific pathway: a match decreases its firing rate, whereas a mismatch increases it (Figure 3). How does the nonspecific thalamus become sensitive to the degree of match in the specific thalamus? The total, convergent BU input to the nonspecific thalamic nucleus is unchanged by the matching process. When a match occurs, the TRN receives strong excitation via thalamocortical collaterals (Figure 3a), thereby causes strong, convergent inhibition to the nonspecific thalamic nucleus. When a mismatch occurs (Figure 3b), reduced specific thalamic spiking causes decreased TRN inhibition, and an increase in nonspecific thalamus firing rate, or arousal, that is proportional to the degree of mismatch (Figure 3c).

The human mismatch negativity (MMN) event-related potential supports this prediction. Physically deviant stimuli trigger a MMN roughly 200ms after stimulus onset. Kraus et al. demonstrated involvement of nonspecific, but not specific, thalamic nuclei (Figure 4c), with differences between novel and standard stimuli at 30-80ms and 135-170ms after stimulus onset. The late latency suggests a cortical contribution, which involves superficial cortical layers.

SMART explains and simulates these earlier thalamic and later cortical components: mismatch increases nonspecific thalamic nucleus firing at around 50 and 150ms after stimulus onset (Figure 4c), reaching layer 1 and causing synchronized firing in layer 5 (Figure 4d). Layer 5 then excites layer 6II (Figure 1), which in turn reactivates the nonspecific thalamic nucleus, thereby generating an additional burst of activation mediated by low threshold Ca++ spikes that are unmasked by TRN inhibition.

**Layer 5 regulation of cortical reset.** The nonspecific thalamic nucleus projects to layer 1 of cerebral cortex, where layer 5 pyramidal cell apical dendrites branch (Figure 5a). Larkum et al. found that these dendrites can produce action potentials that actively propagate to layer 5 cell
In the model, an increase in nonspecific thalamic firing rate during a mismatch is sensed at the apical dendrites of layer 5, where it can trigger dendritic spikes that can eventually cause somatic action potentials. (b) Input to the apical dendrite of layer 5 pyramidal neurons results in action potentials recorded at the soma. Data: recordings of a layer 5 pyramidal neuron (rats, in vitro) show apical (red), proximal (blue) dendritic and somatic (black) potentials during stimulation of the apical dendrite (modified from 38). Simulation: stimulation of the apical dendrites of a simulated layer 5 pyramidal cell via the nonspecific thalamic nucleus produces a stream of action potential at the soma. The arrow indicates the recording from the intermediate section of the dendrite of the simulated neuron, located at 400 μm from the soma, which is equivalent to the L4 recording electrode in the data. (c) Data: in vitro (rat) recordings of layer 5 pyramidal cells show that neuronal firing in response to extracellular synaptic excitation can consist of single spikes or burst firing (adapted from 39). Simulation: recordings from a layer 5 pyramidal neuron during a mismatch episode. Depending on the presence of a layer 2/3 input, the cell can either respond with a single spike (no layer 2/3 input) or a burst of spikes (layer 2/3 input). (dI) Layer 6l→4 on-center/off-surround networks normalize and primes layer 4 cells activations. Neurotransmitter depletion (green squares) does not bias the competition in layer 4 until a reset occurs. (dII) A reset, occurring in the form of a uniform layer 6l firing, temporally resets active layer 4 cells. (dIII) The reset unmasks previously inactive cells, favored by higher levels of neurotransmitters accumulated in non-depleted layer 6l→4 synapses. (e) Before a reset occurs, a “wrong” winning layer 4 cell spikes (1, light blue cell). Reset (red bar) favors the activation of previously inhibited cells (2, purple cell).

bodies and cause somatic action potentials (Figure 5b). Until now, there has been no functional explanation of these regenerative dendritic potentials. Spatially diffuse terminations of nonspecific thalamic afferents in layer 1 allow simultaneous activation of large populations of layer 5 pyramidal cells, which may in turn excite layer 6l and 6h cells. SMART layer 6l cells are predicted to respond to a thalamic mismatch with selective cortical reset and search for a more predictive cortical code in layers 4 and 2/3.
How does a spatially diffuse arousal burst from the nonspecific thalamic nucleus selectively reset the cortical codes that caused a mismatch? At the moment when a mismatch occurs, the brain does not know which cortical areas caused the predictive failure. Thus mismatch needs to be able to selectively reset active representations throughout the cortical hierarchy. SMART proposes, in accord with known anatomical and physiological data, that layer 5 pyramidal cell firing rate is jointly controlled by nonspecific thalamic inputs and specific layer 2/3 inputs, thus explaining how layer 5 cells exhibit two distinct firing modes. Layer 5 cells that receive layer 2/3 inputs and nonspecific thalamic inputs during a mismatch episode fire in bursts at high rates. Active 2/3 cells represent cortical codes that caused the mismatch. In contrast, single spikes are produced in layer 5 cells when only one of these sources is activated, either during a match, or during a mismatch when layer 2/3 cells are inactive. Figures 5b and 5c compare in vitro recordings of layer 5 pyramidal apical dendrites and soma, and model layer 5 cell simulations during match and mismatch episodes.

Layer 5 pyramidal cells send driving inputs directly to higher cortices through the thalamus (e.g., the PULV), indirectly control corticothalamic feedback at their own cortical level through layer 6, and also control corticocortical feedback to layer 4 at their own cortical level via layer 6. Layer 5 can hereby generate widespread bursts of synchronized activity throughout the neocortex, (including epileptogenic activity pathology), and selectively reset multiple cortical areas.

**Cortical search control by habituative synapses.** How does a mismatch-mediated layer 5 reset signal choose a new cortical representation that can lead to a better match, and thus a better prediction? How can reset do this without an external teacher? A proposed solution to this problem is herein realized using known laminar corticocortical and thalamocortical circuits. This solution predicts that the pathway which mediates reset utilizes habituative transmitter gates, also called depressing synapses. In particular, when a BU input activates a layer 6 cell, a fraction of its neurotransmitter is released to activate layer 4 target cells (see Methods, Supplementary Methods and Supplementary Fig. 2 in appendix). The transmitter recovery rate is slow relative to its release rate, and thus the net EPSP recorded at a post-synaptic site decreases through time. Despite this reduction, synaptic transmission remains unbiased and stronger inputs produce bigger steady-state EPSPs even as the corresponding transmitters habituate (Figure 5d(I)).

When a layer 5-mediated reset wave later hits layer 6 (Figure 5d(II)), this arousal burst changes the balance of total input to layer 4 cells. Simulations (Figure 5e) and mathematical proofs show how layer 4 cells reset based on their prior activation and the reset wave size, to favor previously inactive or weakly active layer 4 cells (Figure 5d(III)).

**Acetylcholine control of vigilance and learning.** In ART, resonance and learning occur when the degree of match between BU and TD representations is greater than a parameter, called vigilance, which can change due to internal factors, such as fatigue, or external factors, such as predictive mismatch or punishment. SMART traces vigilance control to factors that influence the firing threshold of layer 5 cells, notably acetylcholine (ACh) and its modulation of the after-hyperpolarization current of cortical neurons (see Supplementary Methods and Fig. 4 in appendix). ACh cortical release can be influenced by both the nonspecific thalamic nucleus and by cortical or homeostatic factors. Anatomical studies in monkeys, cats and rats have established that the nucleus basalis of Meynert (Fig. 4 in appendix), a cholinergic nucleus projecting to the neocortex, receives afferents from the nonspecific thalamic midline and central lateral nuclei, and is also influenced by noxious stimulation and cortical control. The nonspecific thalamic nucleus may hereby control the excitability of layer 5 cells by increasing ACh release in the cortex following mismatch. Since the nonspecific thalamic nucleus is sensitive to the degree of mismatch, the release of ACh may also be sensitive to the magnitude of predictive error. The mismatch-mediated, diffuse release of ACh increases layer 5 excitability to nonspecific thalamic input, therefore causing reset even in those
Figure 6 Power spectrums of the cumulative spike histogram of a laminar primary sensory cortical area during presentation of a stimulus (horizontal bar, 5 thalamic relay nuclei activated for 1000 msec) during match (a) and mismatch (b) conditions show a peak in the slow \( \gamma \) frequency band (20-70 Hz) in case of match, and lower frequencies in case of mismatch. The histograms were analyzed into three frequency bands (\( \delta \) and \( \theta \), 2–8 Hz; \( \alpha \) and \( \beta \), 8–20 Hz; \( \gamma \), 20–70 Hz) to highlight the separate contribution of different oscillation frequencies is a match (c) and mismatch (d). Notably, \( \gamma \) oscillations are drastically reduced in a mismatch in favor of lower-frequency oscillations.

Synchronous oscillations reflect match and mismatch.

Gamma (\( \gamma \), 20–70 Hz) and beta (\( \beta \), 12–30 Hz) oscillations are observed in visual cortex during various cognitive, perceptual and attentive states\(^8,9\). Beta oscillations often correlate with long-range synchronous activity of neocortical regions\(^{42}\), and gamma is restricted to sites within an area\(^43\) or between two areas with strong monosynaptic connections\(^{44}\).

In SMART, gamma and beta oscillation frequencies reflect match and mismatch dynamics, respectively. Gamma oscillations are amplified between cells of an input population and between cells of an input and a receiving population when a TD template matches its BU input\(^7,8\) (Figures 6a and 6c). During mismatch within lower cortical layers (Figure 5d), beta oscillations prevail (Figures 6b and 6d).

SMART also simulates data about short and long-range synchrony. Friedman-Hill et al.\(^{43}\) showed gamma synchronization between two adjacent macaque V1 cells with overlapping receptive fields in response to a preferred stimulus (Figure 7 top). Model V1 layer 4 cells during match of a learned stimulus (Figure 7 bottom) show a similar cross-correlation power spectrum.

areas where TD feedback may earlier have partially matched BU input. See Supplementary Figure 5 and Supplementary Methods in appendix for simulations of ACh modulation of layer 5 cell firing.
Figure 6 Power spectrums of the cumulative spike histogram of a laminar primary sensory cortical area during presentation of a stimulus (horizontal bar, 5 thalamic relay nuclei activated for 1000 msec) during match (a) and mismatch (b) conditions show a peak in the slow $\gamma$ frequency band (20–70 Hz) in case of match, and lower frequencies in case of mismatch. The histograms were analyzed into three frequency bands ($\delta$ and $\theta$, 2–8 Hz; $\alpha$ and $\beta$, 8–20 Hz; $\gamma$, 20–70 Hz) to highlight the separate contribution of different oscillation frequencies is a match (c) and mismatch (d). Notably, $\gamma$ oscillations are drastically reduced in a mismatch in favor of lower-frequency oscillations.

Figure 7 Example of short range (300 $\mu$m), single unit–single unit correlation of cells with overlapping receptive fields and similar orientation preference in V1; top, left: cross-correlation computed from the two spike trains during the response to the stimulus. top, right: power spectrum of the cross-correlation shown on the left, which shows a peak around 50 Hz. Bottom, left: cross-correlation computed from the spike trains of two nearby simulated layer 4 cells during stimulation of a learned stimulus (red lines show the 95% confidence limit). Bottom, right: power spectrum of the cross-correlogram shown on the left. Data adapted from13 (Figure 3).
Figure 8 Data: Cross-correlation functions of LFP from the middle layer of area 17 (lower-order visual area) and lower layers of area 7 (higher-order visual area) during presentation of a no-go stimulus in behaving cats. Simulation: The activity of two thalamocortical loops (synaptic delay between layer 2/3 of the first-order cortical area and layer 4 of the second-order cortical area is 10 ms) was simulated, and epochs of 1000 ms aligned to onset of a learned BU stimulus (presented for 1 s prior to the beginning of the recording) were analyzed. Analysis was performed on LFP recorded from two simulated 54-tip-electrodes from the two cortical areas, and data were separated into five different frequency ranges in accordance with classical electroencephalogram conventions: 2–4, 4–8, 8–12, 12–20, and 20–100 Hz. The data were Fourier transformed and multiplied with the complex conjugate, and the inverse transformation was performed for selected frequency bins (corresponding to one “band”) to obtain cross-correlation functions for separate frequency ranges. Cross-correlation functions at different frequency bands were performed between LFP produced in the lower 0.3 mm of the higher cortical area and the upper 0.3 mm of the lower cortical area (both areas are 1.2 mm thick).

Von Stein et al. showed (Figure 8, top) that synchronization between distant cortical areas (middle layers of area 17 and lower layers of area 7 in cats) is prevalent in the middle frequency range (theta, θ, 4-8 Hz), whereas local interactions (within areas 17 and 7) show gamma band dominance. The model simulates these properties (Figure 8, bottom), showing that synchrony between distant cortical areas is mediated mostly by slower frequency oscillations. These simulations support the hypothesis that monosynaptically connected cells, such as cells within an area or between nearby areas, can synchronize at gamma frequency bands, which is compatible with STDP. TD interactions between lower layers of higher-order and upper levels of lower-order cortical areas are mostly modulatory. Therefore, upper pyramidal layers of lower-order areas should not necessarily fire in response to a TD modulatory influence from higher cortical areas, and should not necessarily express gamma frequency synchronization, unless BU and TD signals match.

**DISCUSSION**

The SMART model proposes a solution to the stability-plasticity dilemma during laminar thalamocortical and corticocortical STDP learning. The model simulates how specific and nonspecific thalamic nuclei regulate learning via temporal cycles of match/resonance and mismatch/reset, wherein plasticity is enhanced in states of match and reduced in states of mismatch.
The involvement of the nonspecific thalamus in learning is consistent with lesion studies showing a role for the nonspecific intralaminar/midline thalamic nuclei in declarative memory\textsuperscript{45}. Simulation results (Figure 4a and 4b) also suggest how TD corticothalamic feedback causes both fast priming excitation and slower inhibitory effects, as confirmed by experimental data\textsuperscript{24}.

A novel role for the neurotransmitter acetylcholine is postulated, linking levels of cortical ACh release to layer 5 excitability and layer 4 reset. Strong ACh release, such as during repeated mismatches, or for instance as a consequence of an environmental stressor, can influence the sharpness of the neural code, or the degree of match required for BU and TD representation to prevent reset. Lower levels of ACh favors coarser codes, because higher levels of mismatch can be tolerated by the system, and more variable BU input patterns can be associated with the same active recognition category.

The model for the first time mechanistically links cognitive mechanisms with brain oscillations recorded from a variety of cortical and subcortical structures. Kopell et al.\textsuperscript{46} proposed that $\gamma$ and $\beta$ oscillations might subserve different functional roles. Their simulations showed that $\beta$ oscillations are more robust in synchronizing areas separated by larger transmission delays, whereas $\gamma$ oscillations tend to be dispersed when significant delays are interposed. Olufsen et al.\textsuperscript{47} have shown that $\beta$ oscillations allow a different separation between “leading” and “suppressed” cell assemblies than do $\gamma$ oscillations. Gamma oscillations promote a sharp dichotomy between active/inactive assemblies, a situation similar to a “choice”. SMART shows how $\beta$ oscillations become a signature of modulatory TD feedback and reset. TD processing, as shown by experimental and model results (Figure 6b), shows prevalence of lower frequency oscillations, consistent with their modulatory nature\textsuperscript{47} and their computational role of priming\textsuperscript{27}. SMART also explains how gamma oscillations emerge when modulatory TD expectations are matched by consistent BU input.

The SMART model also links the role of different oscillation frequencies with STDP. Learning episodes tend to be restricted to match conditions, when on average presynaptic and postsynaptic cells spike within 10-20ms, namely within the STDP learning window, consistently with recent experimental results\textsuperscript{23}. The model predicts that STDP further reinforces synchronous activation of related cortical and subcortical areas, and that the effect of spurious synchronizations on long-term memory weights in a fast learning regimen can be prevented or rapidly reversed by resonance (and synchrony) between TD representations and the consistent feature set. Gamma oscillations, amplified in case of a match, may favor propagation of spikes through the cortical hierarchy by packing pre-synaptic spikes within a narrow temporal window. This prediction is consistent with the observation that the efficacy of pairs of pre-synaptic LGN spikes to generate post-synaptic activation in the visual cortex falls off rapidly in time with the increase of the interspike interval\textsuperscript{48}.

\textbf{METHODS}

Excitatory (thalamic core, matrix, and nonspecific, cortical layers 4, 2/3, 5 and 6) and inhibitory (TRN and thalamic interneurons, cortical layers 4 and 2/3 interneurons) neurons, as well as their connections, were constructed according to known anatomical and biophysical data (primarily rats and cats). When unavailable, cell parameters were chosen in order to obtain the desired functional properties. See Supplementary Methods and Supplementary Figure 1 in appendix for a detailed description of the neurons. Each simulated thalamocortical loop consists of 732 multi-compartmental neurons and 2106 compartments. Supplementary Table 1 in appendix summarizes the main anatomical pathways simulated, their functional interpretation, and pertinent literature. Supplementary Figure 2 in appendix shows the spatial arrangement and cell sizes of the populations composing the simulated 1.2mm thick laminar cortical sheet.
Model cells obey Hodgkin–Huxley equations. The minimal numbers of compartments and currents needed to produce the desired network properties is used in each neuron’s unbranched cable sections (see Supplementary Fig. 1 in appendix). Compartmental membrane potential $V$ [mV] is described by the Equation:

$$C_M \frac{dV}{dt} = \sum I_i,$$

where $C_M$ [$\mu F \cdot cm^2$] is the membrane capacitance. Ionic or chemically-gated channels and intercompartmental currents are described by the current density $I_i$ [$\mu A/cm^2$] Equation:

$$I_i = g_{Ch}(V^{EQ} - V),$$

where the channel conductance $g_{Ch}$ and the equilibrium voltage $V^{EQ}$ [mV] change according to the nature of the current. Inter-compartmental currents from compartment $m$ to compartment $l$ are described by Equation 2, where $g_{Ch} = g_{ml}D_i^4L_i^2$ [$k\Omega cm$], $g_{ml}$ is the conductance between compartments $m$ and $l$, $D_i$ [mm] and $L_i$ [mm] are the diameter and length of membrane compartment $l$, respectively, and $V^{EQ} = V_m$ and $V = V_l$ are potentials of the neighboring compartments. See Supplementary Table 2 in appendix for dimensions, passive cable properties and non-synaptic channel parameters of all network compartments. Ionic channels, such as sodium ($Na^{++}$), potassium ($K^+$) and leakage channels obey Hodgkin–Huxley dynamics which are described in the Supplementary Methods in appendix, and their parameters are listed in Supplementary Table 2 in appendix. In chemically-gated channels (AMPA, GABA, etc.) between neurons $j$ and $k$, $V^{EQ} = E_i$[mV] is the reverse potential of the channel, and the conductance $g_{Ch} = w_{jk}g_{jk}g(t)$, where $w_{jk}$ is the synaptic weight connecting neurons $j$ and $k$, and $g_{jk}$ [pS] is the maximal conductance of the synaptic weight $w_{jk}$. Synaptic weight $w_{jk} = \frac{N_i}{2\pi DL} \left[ 10^6 \right]$ corresponds to the density of receptors (millions of channels per membrane $cm^2$). The conductance $g(t)$ is defined as a dual exponential factor describing the time course of the excitatory or inhibitory post-synaptic potentials (EPSP and IPSP, respectively) triggered by the pre-synaptic spike:

$$g(t) = \begin{cases} 
\frac{p}{\tau_f - \tau_r} \left( e^{\frac{t}{\tau_f}} - e^{\frac{-t}{\tau_r}} \right) & \text{if } \tau_f \neq \tau_r \\
\frac{t}{\tau_f} e^{\frac{t}{\tau_f}} & \text{if } \tau_f = \tau_r 
\end{cases},$$

where $t$ is the time since the onset of a pre-synaptic spike, $p$ is a normalizing coefficient that ensures:

$$\max\left( \frac{p}{\tau_f - \tau_r} \left( e^{\frac{t}{\tau_f}} - e^{\frac{-t}{\tau_r}} \right) \right) = 1,$$

and $\tau_r$ and $\tau_f$ are the EPSP/IPSP rise and fall time constants, respectively. See Supplementary Table 3 in appendix for parameters of chemically gated channels. Plasticity in the synaptic weight $w_{jk}$ modulates the post-synaptic conductance $g_{jk}g(t)$ by varying the density of post-synaptic channels, therefore influencing the impact of a spike on the magnitude of the current $I_i$. Learning in synaptic weights obeys:

$$\frac{dw_{jk}}{dt} = \lambda f_g(V_k, g_{jk})g_{jk}f_N(V_k)\left( \bar{w} - \bar{w} \right) + w_0 - w_{jk},$$

(5)
where \( \lambda \) is the learning rate, \( f_G(V_k, g_{jk}) \) is a gating signal that turns learning on and off, and

\[
f_N(V_k) = \begin{cases} 
D + 1 & \text{if } V_k \geq V_k^\theta \\
10(t-s) + D + 1 & \text{if } s < t < s - 0.1\,\text{ms} \\
-\frac{D}{25}(t-s+0.1\,\text{ms})+D & \text{if } s-0.1\,\text{ms} \leq t < s - 25.1\,\text{ms} \\
0 & \text{otherwise}
\end{cases}
\]  

(6)

In Equation 6, \( \bar{w}, \bar{w}, \text{and} w_0 \) (maximal, minimal, and baseline weights, respectively) scale the \( w_{jk} \) response, \( V_k^\theta \) is the spiking threshold potential, \( t \) is time, \( s \) is the moment of the postsynaptic spike, and \( D = (\bar{w} - w_0)/(\bar{w} - \bar{w}). \)

Two forms of gating are used: post-synaptic and dual-AND gating. Post-synaptic gating is implemented in specific thalamic projections terminating in layer 4 (BU-adaptive weights), where \( f_G(V_k, g_{jk}) = (V_k)^2 \). Dual-AND gating is implemented in layer 6\text{II} projections terminating in the specific thalamus and in layer 1 apical dendrites of layer 5 cells of a previous cortical stage (TD-adaptive weights, Figure 2), where \( f_G(V_k, g_{jk}) = g_{jk}(V_k)^2 \).

The neurotransmitter released by the pre-synaptic terminal can mediate, or scale, the EPSP or IPSP triggered at the postsynaptic site. The accumulation and depletion of neurotransmitter \( z_{jk} \) at a synapse between neurons \( j \) and \( k \) is described by:

\[
\frac{dz_{jk}}{dt} = \frac{(B - z_{jk}) - \varepsilon\delta(t)z_{jk}}{\tau},
\]

(7)

where \( B = 1 \) is the target level of neurotransmitter at rest, \( 0 < \varepsilon < 1 \) is the depletion coefficient that can scale the amount of neurotransmitter released at every spike, and \( 0.1 < \tau < 500 \) is the recovery rate (in ms) regulating the rate of neurotransmitter accumulation. A spike \( \delta(t) \) is defined as:

\[
\delta(t) = \begin{cases} 
1 & \text{if } V(t) < 0 \text{ and } V(t + \Delta t) > V^\theta \\
0 & \text{otherwise}
\end{cases}
\]

(8)

where \( V(t) \) is the soma membrane voltage at time \( t \), \( V^\theta \) is the voltage threshold that is invariably crossed during spikes (30 mV), \( V(t + \Delta t) \) is the soma membrane voltage at time \( t + \Delta t \) that precedes the soma voltage crossing 0mV. In Equation 6, the neurotransmitter \( z_{jk} \) accumulates towards \( B \) at a rate inversely proportional to the recovery rate \( \tau \), and habituates, or is depleted, by \( -\varepsilon\delta(t)z_{jk} \) every time a spike occurs. Neurotransmitter depletion allows EPSP/IPSP to be multiplicatively gated by the amount of neurotransmitter available, while still ensuring that \( 0 < g_{jk}z_{jk} < 1 \). Supplementary Figure 3 in appendix shows variation in neurotransmitter level with different values of \( \varepsilon \) and \( \tau \) and different pre-synaptic firing frequencies.

BU stimuli consist of static vertical or horizontal bars centered on the 9 x 9 receptor grid, and implemented via fixed intensity current injection to 5 vertically or horizontally aligned thalamic specific relay neurons until a stream of action potential is induced. When indicated, TD feedback is induced by injecting a stimulating current to the soma of a layer 6\text{II} cortical cell. A typical run of the model consists of 1000 ms epoch, with the membrane potentials of all neuronal compartments recorded along with the plastic synaptic weights configuration before and after the run.

The model is implemented in KInNeSS (KDE Integrated NeuroSimulation Software, www.kinness.net), a software package that allows the simulation of single neurons with an arbitrary
number of compartments as well as large networks of such elements. All off-line data analysis is implemented in Matlab (Mathworks Inc.). Simulations are run on 2.80 GHz Intel CPU, 1GB of RAM, under Linux operating system.

REFERENCES


APPENDIX

1 Compartmental ionic currents

Potassium ($K^+$) and Sodium ($Na^{+}$) currents $I_k$ and $I_{Na}$ are derived from Traub and Miles\(^1\), and are described as:

$$ I_k = \bar{g}_k n^4 (E_K - V), $$

where

$$ \frac{dn}{dt} = \alpha (1-n) - \beta n, $$

$$ \alpha = \frac{0.032 (15-V)}{e^{\frac{15-V}{4}} - 1}, $$

$$ \beta = 5 e^{\frac{10-V}{40}}, $$

and

$$ I_{Na} = m^3 h \bar{g}_{Na} (E_{Na} - V), $$

where

$$ \frac{dm}{dt} = \alpha (1-m) - \beta m, $$

$$ \alpha = \frac{0.032 (13-V)}{e^{\frac{13-V}{5}} - 1}, $$

$$ \beta = \frac{-0.28 (40-V)}{e^{\frac{40-V}{40}} - 1}, $$

$$ \frac{dh}{dt} = \alpha (1-h) - \beta h, $$

$$ \alpha = 0.128 e^{\frac{-27-V}{18}}, $$

$$ \beta = \frac{4}{e^{\frac{40-V}{5}} + 1}. $$

For all neurons, $E_K = -90 mV$ and $E_{Na} = 50 mV$. Leakage current $I_{leak}$ is defined as:

$$ I_{leak} = -\frac{g_{leak} N_{leak}}{\pi DL} V, $$

where $g_{leak}$ is the conductance of the leakage channel, $\frac{N_{leak}}{\pi DL}$ is the channel density, and $E_{leak} = 0$.

2 Cholinergic modulation and after-hyperpolarization currents (AHP)

Pharmacological and physiological studies have demonstrated that ACh has facilitatory effects on cortical pyramidal neurons\(^2\), and rat cortical layer 5 cells seem to be a preferential target for cholinergic innervation\(^3\). The known electrophysiological excitatory action is thought to be mediated by binding of ACh to muscarinic and/or nicotinic receptors on pyramidal neurons. This
causes a reduction of membrane $K^+$ conductance in cortical neurons, enhancing depolarization in response to glutamatergic input\cite{2} and reducing spike adaptation due to the after-hyperpolarization current (AHP\cite{4}) based on a slow and long-lasting increase in $K^+$ conductance (see Supplementary Fig. 4 online). Supplementary Figure 5a (top) online shows that a steady depolarization current causes rat pyramidal cell firing to rapidly habituate, whereas injection of the ACh agonist carbachol reduces the adaptation\cite{5}. Supplementary Figure 5a (bottom) shows the simulation results for an isolated layer 5 pyramidal cell which include AHP currents in its somatic compartment, before and after ACh stimulation. Data and simulations show that the release of ACh can modulate, through the reduction of AHP and the prevention of spike adaptation, the excitability of layer 5 pyramidal neurons, and consequently the amount of thalamic mismatch that can be tolerated by the cortical area. High levels of ACh may increase vigilance by reducing spiking adaptation, facilitating reset and therefore requiring a higher degree of match between BU and TD representations (Supplementary Fig. 5b online).

After-hyperpolarization current (AHP) and its modulation by acetylcholine are modeled by Equation 2 in the main paper, reproduced here for convenience:

$$I_i = g_{Ch}(V^{EQ} - V),$$

where the AHP current conductance $g_{Ch} = g^* \overline{g}_{AHP}(t)$ is modulated by the conductance $g^*$ controlled by the cholinergic presynaptic spike, and $\overline{g}_{AHP}$ [nS] is the maximal $K^+$ conductance of the AHP channel. The AHP conductance $g(t)$ is described by Equation 3 in the main paper, reproduced here for convenience:

$$g(t) = \begin{cases} 
\frac{p}{\tau_f - \tau_r} \left( e^{-\frac{t}{\tau_f}} - e^{-\frac{t}{\tau_r}} \right) \quad \text{if} \quad \tau_f \neq \tau_r \\
\frac{t}{\tau_f} \left(1 - e^{-\frac{t}{\tau_f}}\right) \quad \text{if} \quad \tau_f = \tau_r 
\end{cases},$$

where $t$ is time since the action potential of a modulatory cell; $p$ is the scaling coefficient described in Equation 4 in the main paper. For the AHP used in these simulations $\tau'$ and $\tau'$, namely the rise and fall time constants, respectively, are $\tau' = 80ms$ and $\tau' = 100ms$. The $K^+$ channels responsible for the AHP are opened by any cell's axonal output. If there is no spike, $t = \infty$, therefore $g = 0$. If there is a spike, $t = 0$, causing $g$ to rise. The cholinergic modulation conductance $g^*$ is described by

$$g^* = \begin{cases} 
1 - \frac{p}{\tau_f - \tau_r} \left( e^{-\frac{t}{\tau_f}} - e^{-\frac{t}{\tau_r}} \right) \quad \text{if} \quad \tau_f \neq \tau_r \\
1 - \frac{t}{\tau_f} e^{-\frac{t}{\tau_f}} \quad \text{if} \quad \tau_f = \tau_r 
\end{cases},$$

where $\tau' = 5ms$ and $\tau' = 6ms$, and $t$ is the time since the pre-synaptic cholinergic cell spikes (nucleus basalis of Maynert). These simulations investigate only the fast cholinergic dynamics, and do not address longer-lasting effect of ACh on target neural populations\cite{6}. The cholinergic input acts by closing the normally open gate $g^*$, therefore limiting the total AHP conductance when ACh modulation is active.

### 3 Network connectivity and parameters
Connections between and within cell populations link a presynaptic cell with a given postsynaptic cell compartment target of the axonal projection, and can be categorized as: 1-to-1, 1-to-many, or many-to-1 projections. Synaptic weights $w_{ij}$ can be defined between and within layers according to standard Gaussians:

$$w_{ij} = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

where $\mu$ is the mean and $\sigma$ is the standard deviation. Each axonal pathway can be considered as a “delay line”, which adds an additional component of delay between pre and post-synaptic spike, aside from the time required by EPSPs to trigger an action potential. Axonal delays were chosen to be consistent with both known transmission delays in cortical and subcortical areas, and with the spatial conformation of the model, and are summarized in Supplementary Table 3 online. In general, inhibitory to excitatory connections have small delays, intra-cortical feedforward connections have longer delays\(^7\), and feedback connections (both corticocortical and corticothalamic) have even longer delays\(^8\).\(^9\).

The model accounts for the driving vs. modulatory nature of synaptic connections by exploiting both the magnitude of the synaptic weight and the passive neuron cable properties. EPSPs occurring at the distal dendrite tend to be attenuated with respect to the one occurring at the proximal dendrite or the soma depending on compartmental length and diameter. Intercompartmental currents are described by Equation 2 in the main paper, where $g_{Ch} = g_{ml}D_l/\pi L_l^2 [k\Omega*cm]$. The longer and smaller the dendrite, the more attenuated the post-synaptic current will be at the soma. Differential dendritic termination and synaptic weight magnitudes can be used to simulate the proposed functional differentiation between driving, large, round (R-type) thalamic vesicles occurring at retinothalamic and thalamocortical synapses, and elongated, small vesicles that characterize many corticothalamic terminations\(^10\),\(^11\). Elongated and round-type synapses also widely occur at the level of corticocortical synapses\(^12\). Besides the different morphology of synaptic boutons, inputs to thalamic relay cells are not distributed evenly on their dendrites\(^13\),\(^14\),\(^15\). Retinal and parabrachial inputs are limited to proximal dendrites, while cortical inputs are located more distally. SMART captures these morphological and functional characteristics by concentrating driving connections in proximal dendrites, and modulatory connections with smaller synaptic weights in distal dendrites of the target cell. These characteristics are realized between neurons in the on-center/off-surround architecture implemented by inhibitory interneurons in cortical and thalamic areas.

### 4 Oscillations analysis

Power analysis of single or collective neural signals allows the extraction of information contained in different frequency ranges. Where indicated, analysis of 1000ms epochs is performed separately in three different frequency ranges: 2–8 (delta and theta, $\delta$ and $\theta$), 8–10 (alpha and beta, $\alpha$ and $\beta$) and 20–70 Hz (gamma, $\gamma$). The mean firing rate is subtracted from the data, and a Hamming window of 200ms is applied to smooth the resulting values. The results are then Fourier transformed and multiplied with the complex conjugate (cross- and auto-components), and the inverse transformation is performed for selected, continuous frequency bins (corresponding to one “band”). In this way, it is possible to reconstruct a time-averaged firing rate for selected frequency ranges. These values can then be used to compute cross- and auto-correlations at different frequency ranges\(^16\).

### 5 Local Field Potentials/Current Source Densities analysis

Cortical LFP are recorded via a simulated 54-tip-electrode. The distance of the electrode to the selected cell in the population is drawn from a uniform random distribution in the interval [10 - 200] $\mu$m, whereas the distance to all other cells in the layer is drawn from a uniform random distribution
in the interval \([10 - 1000] \mu m\). An extracellular inward current flow towards the interior of the cell creates a current \textit{sink}, while an outside flow creates a current \textit{source} in a particular membrane section. Assuming an extracellular fluid with constant conductance, the potential generated by such current dipole is\(^{17}\):

\[
V_e = \frac{1}{4\pi\sigma} \left( \frac{I^+}{r^+} + \frac{I^-}{r^-} \right),
\]

where \(I^\pm\)s and \(r^\pm\)s are currents and distances between the electrode and the point where the respective current flows through the membrane (approximated by the center of the compartment), respectively, + and – mark the attributes of source and sink, respectively, and \(\sigma = 15 \text{ [mS/cm]}\) is the extracellular conductivity. In the case of more complex cells with many possible sources and sinks, \(V_e\) becomes:

\[
V_e = \frac{1}{4\pi\sigma} \sum_i \frac{I_i}{r_i}.
\]

Compartmental trans-membrane currents \(I_i [\mu A]\) are expressed in terms of:

\[
I_i = J_i S_i = -\frac{g_i D_i}{4L_i^2} \left( V_i - V_{tie} \right) \left( \frac{2\pi D_i^2}{4} + \pi D_i L_i \right) = -\frac{g_i D_i}{4L_i^2} \left( V_i - V_{tie} \right) \left( \frac{D_i}{L_i} + L_i \right).
\]

Since CSD and LFP can be measured with multiple electrodes, for each electrode tip the distance \(r_i\) to the compartment center is different. CSD is calculated both in experimental studies and in KInNeSS by linear approximation of the second derivative of the voltage:

\[
\text{CSD} = \frac{V_{e_{i+1}} + V_{e_{i-1}} - 2V_e}{\Delta x},
\]

where \(\Delta x\) is the distance between neighboring electrode tips.\(^{18}\)

### 6 Simulation code

The network is described in Neuro Markup Language code (NeuroML, [http://www.neuroml.org/](http://www.neuroml.org/)). NeuroML is a variation of XML designed for modeling different aspects and levels of neural systems, from intracellular mechanisms and ion channel kinetics to the dynamics of networks of reconstructed neurons. The code is downloadable in the Research section at [http://www.kinness.net/](http://www.kinness.net/).

### 7 References