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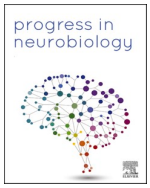

Neural selection in corticothalamocortical loops: Heterogeneity as a computational resource

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ABSTRACT

Neuroscience has long relied on (typically binary) categorisations to manage the complexity of brain organisation. Yet growing anatomical and physiological evidence reveals that these dichotomies artificially partition systems that are inherently continuous and heterogeneous. In the thalamus, neurons display mixed afferent-efferent motifs and graded physiological properties that defy rigid categorisation. In the cerebral cortex, laminar somatic labels obscure the contribution of multilayer active dendritic nonlinearities, such as burst spiking, which radically reshapes modes of neural communication. Here, we propose that heterogeneity is not taxonomic noise, rather it is a key functional resource. Specifically, we argue that corticothalamocortical loops implement a dynamical process algorithmically akin to natural selection. Cortical and thalamic heterogeneity provides variation across neural coalitions; inhibitory competition, particularly within the thalamic reticular nucleus, enacts selection among competing whole-brain signals; and neural amplification, paradigmatically via subcortical projecting bursting promotes inheritance by recruiting selected neural coalitions across time. This perspective emphasises the corticothalamocortical system as a dynamic substrate for neural selection, rather than a static circuit motif. By integrating anatomy, physiology, and dynamical systems theory, we outline a framework that leverages neural heterogeneity for flexible, adaptive behaviour.

1. Introduction

How can we understand how the brain works? Neuroscience has long relied on the power of anatomical categorisation – morphology, connectivity, physiology, genetics – to make sense of the brain's staggering complexity. Across corticothalamocortical (CTC) circuits, foundational classifications – core versus matrix cells, first-order versus higher-order nuclei, or layer 5 versus layer 2/3 pyramidal neurons – have shaped the questions we ask, the experiments we design, and the theories we construct. They hint at a hidden order amid the brain's complexity, with the implicit assumption that once we appreciate these discrete components in sufficient detail, explanations of brain function will naturally emerge from their composition.

Despite progress on this front, many anatomical classifications are beginning to show inherent limitations. As experimental methods become more precise and context-sensitive (ranging from dense single-cell transcriptomics, high-resolution connectivity, *in vivo* cellular imaging) via powerful new tools (such as optogenetics and dynamic molecular sensors), the sharp rules that once anchored these classifications are now breaking (seemingly as often as they are observed), revealing

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overlaps and continuities that blur categorical boundaries. In the thalamus, cells once labelled anatomically as 'core' or 'matrix' exhibit hybrid or intermediate axonal projections that contain aspects of each class (Clascá et al., 2012a; Sherman and Usrey, 2024). In the cerebral cortex, neurons are often categorised by their somatic position or projection targets, even though their functional roles may be shaped more by their dendritic integration sites located in differing layers (Larkum et al., 2018). These are just two examples of the abundant heterogeneity and variation across cellular features in the mammalian thalamocortical system that erode the conceptual clarity of distinct functional classes.

A growing recognition of this heterogeneity has led to a renewed interest in dynamical systems approaches and biophysical modelling that distil complex mechanisms into simplified, interpretable functions. These dynamical models abstract away idiosyncratic detail to reveal potential organising principles – e.g., how oscillations emerge from conduction delays and interactions between excitatory and inhibitory cell populations (Tahvili and Destexhe, 2024; Buzsáki and Wang, 2012; Robinson et al., 2003a), how dynamical attractors shape decision-making (Gain neuromodulation mediates task-relevant perceptual switches: (n.d.); Wong and Wang, 2006), or how networks balance flexibility and stability (Munn et al., 2023a, 2024). These models typically embrace neural diversity in two ways: by initialising model instances with parameters drawn from random distributions, and by simulating multiple instances drawn from sweeps across parameter spaces. When ideally applied, this approach enables predictions that extend beyond the scope of any one experiment (Munn et al., 2023a; Müller et al., 2020a; Shine et al., 2018). A key lesson from computational modelling studies is that distinct anatomical motifs can give rise to equivalent neural dynamics (degeneracy (Edelman and Gally, 2001); Tononi et al., 1999), emphasising that many multiscale structural routes can implement the same adaptive function. Nevertheless, such model abstractions may be somewhat unsatisfactory to anatomists, in that they may overgeneralise specific features and underutilise systematic variation, leading to theories that describe a system that is not brain-like at all.

Here, we unify cellular, circuit, and dynamical findings, adopting a broader view of neural activity as a multiscale dynamical system, to propose that CTC circuits implement a form of *neural selection (*Munn et al., 2024; Müller et al., 2025). We first review how heterogeneity across thalamus, TRN, and cortex establishes a high-dimensional substrate of possible affordances. We then examine inhibitory and competitive motifs that enable suppression and gating within and across CTC loops. Next, we consider the dynamical mechanisms, including burst firing and recurrent amplification, that determine how selected activity patterns are stabilised or propagated. It should be noted these features are identified across studies from multiple species such as humans, nonhuman primates, and rodents, with the goal of identifying a universal pathway across species, which is underdeveloped in modern neuroscience. Finally, we integrate these elements into a framework that can unify and integrate these distinct mechanisms. This framework, inspired in part by the analogous roles played by variation and selection in evolutionary theory, is the algorithmic equivalent of complex, adaptive behaviour. Charles Darwin used these concepts to revolutionise biology by showing that trait variation was not simply an undesirable failure to conform to a Platonic template, but the basis for adaptability

Box 1
Testable predictions of the Neural Selection framework.

1. Dimensionality compression. Cortical populations exhibit high-dimensional, sparse activity, whereas the many-to-few architecture of corticothalamic projections should drive thalamic populations toward lower-dimensional representations of behaviorally relevant signals. This compression is predicted to occur during the selection epoch – approximately 200–400 msec post-stimulus onset, prior to response commitment (Gold and Shadlen, 2007) – rather than continuously. Unselected dimensions should show suppressed but non-zero variance, remaining recoverable by sub-threshold perturbation. *Prediction:* simultaneous cortical and thalamic population recordings will show transient, trial-locked reductions in thalamic dimensionality during decision epochs, with the identity of the compressed thalamic ensemble predictive of cortical coalition membership on that trial. A pattern that dissociates from standard normalization accounts, which predict single-neuron gain changes rather than coordinated population-level compression.
2. TRN as action selector. Actions are selected through the interaction of TRN-mediated inhibition and $L6_{CT}$ feedback, with the TRN resolving competition among coalitions spanning the sensorimotor interface: neither purely sensory nor purely motor, but integrating signals across both. *Prediction:* optogenetic suppression of TRN during decision epochs should increase effective cortical ensemble dimensionality within the selection window, manifest as greater trial-to-trial variability in ensemble identity and reduced behavioral choice precision – a graded impairment in the accuracy and consistency of action selection rather than a categorical disruption of behavior.
3. Variation of burst-mediated inheritance. Contiguous patterns of $L5_{ET}$ bursting propagate variation provided coalitions across trials via transthalamic loops, providing a mechanism of sequential coalition inheritance that is distinct from local cortical recurrence. *Prediction:* suppression of $L5_{ET}$ bursting via selectively decoupling the apical and basal compartments should selectively abolish cross-trial autocorrelation across spatially separated cortical ensemble identity – reducing the tendency of the same coalition to dominate across successive trials – and impair sequential behavioral consistency, while leaving within-trial persistent activity largely intact. Homogenisation of $L5_{ET}$ burst thresholds and thalamic projection classes should degrade selection performance in a graded, dose-dependent way, and the degradation should track the variance of the parameter rather than its mean. This dissociation from the effects of disrupting local cortical recurrence (e.g., AMPA, and NMDA blockade within a single area) is the key signature distinguishing burst-mediated inheritance from attractor-based stabilization.
4. Cross-Species Algorithmic Degeneracy. While thalamic/cortical architecture exhibit species-specific circuit variations (e.g., primates possess thalamic interneurons), the fundamental CTC motif is conserved. If neural selection is an algorithmic principle implemented by these circuits, then the behavioural signature of selection should be preserved across species even when the underlying microcircuit details differ. *Prediction:* During action selection tasks, population activity in cortex and thalamus across rodents, non-human primates, and humans should exhibit convergent dynamical signatures of selection, including dimensionality reduction, loop-specific gain modulation, and recurrent stabilisation, even though the cellular circuits implementing these computations differ.
5. Multiscale TRN Control of Loop Segregation. TRN contains local lateral connectivity capable of shaping the spatial distribution of thalamic inhibition. If these connections coordinate competition across CTC loops, then manipulating TRN connectivity (e.g., via Cx36 deletion) should alter the spatial segregation of thalamocortical activity patterns. *Prediction:* Increasing TRN lateral connectivity should enhance the segregation of parallel CTC loops, producing more spatially distinct activity patterns across thalamic nuclei. Conversely, reducing TRN effective coupling should broaden inhibitory fields and produce more diffuse CTC activation patterns.

(Darwin, 1859). Here, we adopt the same conceptual inversion (Dennett, 2013): neural heterogeneity is the richness from which adaptive computation emerges. In this way variation, competition, and inheritance across CTC coalitions privileges computations compatible with current goals and contextual demands to shape attention, cognition, and action, and we outline five experimentally testable predictions that follow from this view (see Box 1).

2. The Thalamus – the alluring seduction of anatomical dichotomies

Although often described as a single entity, the thalamus is better conceptualised as a collection of discrete sub-nuclei, each of which contains complex, heterogeneous circuits and cell-types that exhibit substantial heterogeneity (Shine, 2021a; Petty and Bruno, 2024). Two influential neuronal dichotomies – core/matrix (Jones, 1998; Whyte et al., 2024) and first-order/higher-order (Theyel et al., 2010; Rovo et al., 2012; Halassa and Sherman, 2019) – have structured both experimental work and theoretical understanding. In the core/matrix dichotomy – historically guided by an immunocytochemical division of thalamocortical cells into calbindin-positive (matrix) and parvalbumin-positive (core) subtypes – core cells primarily target layer 4 with dense, bushy axons, whereas matrix cells project to layers 1 and 5 of the cortex, where their more diffuse axons often bifurcate (Jones, 1998, 2001). In parallel, the first-order/higher-order dichotomy – arising from the driver/modulator framework based on the strength and kinetics of glutamate synapses on thalamocortical cells (Sherman, 2007) – defines first-order cells as receiving driving input from ascending subcortical pathways, whereas higher-order cells receive driving input from cortex (via layer 5). However, many thalamic cells exhibit mixed properties, violating the assumptions of mutual exclusivity, indicating that a binary classification is insufficient to capture thalamic function.

Recent work has further complicated these schemas, expanding core/matrix to explicitly incorporate varied bifurcating projection types (Clascá et al., 2012a, 2016; Sherman and Usrey, 2024; Suzuki and Larkum, 2020; Shepherd and Yamawaki, 2021), and identifying non-canonical tectothalamic input that deliver driver-like signals via modulator-like anatomical routes (Smith et al., 2007; Masterson et al., 2010; Bickford, 2016). Other findings show basal ganglia input to ventral anterior nuclei (Phillips et al., 2025a) and cerebellar projections to the mediodorsal nucleus in primates (Prevosto and Sommer, 2013; Shine, 2022), even though the latter are typically-labelled as higher-order. Together, these results make it clear that dichotomous descriptions of thalamic cells are inadequate and may even obscure (rather than clarify) latent functional principles.

At a broader, region-level perspective (Fig. 1), the same difficulties arise. For instance, resting state fMRI studies show no single optimal functional parcellation of the thalamus; instead, multiple partitions into finer or coarser subdivisions can each broadly align with areal boundaries at different spatial resolutions (Tian et al., 2020). Like all clustering approaches, it can be difficult to clearly determine whether any one perspective is better than any other, particularly as different choices of clustering criteria are appropriate for different research questions (von Luxburg et al., 2012). Importantly, the functional allegiance of thalamic populations is often state-dependent, reorganising with cognitive demand (McCormick et al., 2015). These examples highlight a crucial point: thalamic categorisations are useful heuristics, but they require continual updating as new data emerge (Sherman and Usrey, 2024; Bickford, 2016). We worry that any single-feature perspective, whether anatomical, biophysical, or dynamical, risks presupposing distinct functions and thereby constraining scientific insight (Jones, 1998; Halassa and Sherman, 2019; Sherman and Guillery, 2013). A promising example comes from transcriptional profiling, which revealed a relatively continuous spectrum of thalamic cellular variation (Phillips et al., 2019a). Thus, we argue for a pluralistic, functionally-driven perspective that embraces the heterogeneity of the thalamus.

If we dissolve rigid dichotomies and instead view the thalamus as a multidimensional continuum, multiple new avenues of investigation emerge. Features can be emphasised depending on the scientific problem at hand (Fig. 1). For instance, to interrogate how thalamic cells are driven by glutamatergic inputs, or how dendritic arbors shape behaviour, it may be useful to categorise nuclei into first-order (predominantly subcortical input, then layer 6 cortex) versus higher-order (predominantly cortical layer 5 input, then subcortical input). In contrast, when attempting to understand thalamocortical output, core (granular layer targets) versus matrix (diffuse projections predominantly to layer 1) classifications may be more informative. While many of these maps show overlap (indeed this was, to our understanding, a key insight of the investigations by Jones (Jones, 1998)), the point we wish to emphasise is that there isn't a clear right or wrong dichotomy in which to view the

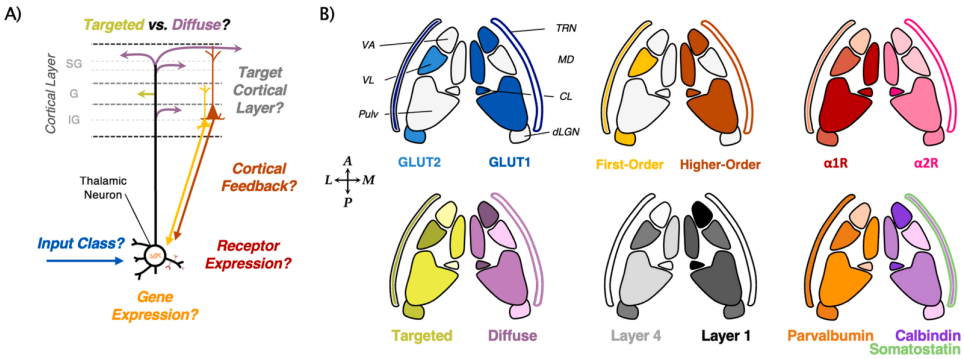

Fig. 1. Various Categorisations of the Thalamus. Left: cartoon of six different ways to characterise thalamic cell diversity. Right: approximate location and intensity of the different approaches and how they relate to the traditional thalamic nuclear compartments: Blue: GLUT1 — vesicular glutamate transporter 1, cortical (L5 and L6) terminals vs. GLUT2 — vesicular glutamate transporter 2, indicative of subcortical driver origin (Rovo et al., 2012); Orange: First-order (driver input from subcortex) vs. Higher-order (driver input from cerebral cortex; Sherman and Guillery, 2002); Red/Pink: expression of adrenergic neuromodulatory receptors (Pérez-Santos et al., 2021); Green/Purple: targeted vs. diffuse projections (Clascá et al., 2012a); Grey: thalamic targets innervating layer 4 vs. layer 1 & 5 (Jones, 2001); Orange/Purple/Green: expression of calcium-binding proteins, parvalbumin and calbindin distinguishing core/matrix thalamic ratios (Münkle et al., 2000), along with neuropeptide somatostatin expression in shell TRN (Martinez-Garcia et al., 2020). Note that these visualisations are not intended to be accurate but rather to demonstrate the diversity of different perspectives. Key: α1R – alpha−1 adrenoreceptor; α2R – alpha−2 adrenoreceptor; CL - central lateral, dLGN - dorsal lateral geniculate nucleus, G – granular; GLUT1 – glutamate 1 transporter; GLUT2 – glutamate 2 transporter (indicative of subcortical origin); IG – infragranular; MD - mediodorsal, Pulv - pulvinar, TRN - thalamic reticular nucleus, SG – supragranular; VA - ventral anterior, and VL - ventral lateral nucleus. Figures adapted from Whyte et al., 2024.

thalamus, but rather a diversity of perspectives that each permits different kinds of questions and insights whose usefulness can be calibrated by the question at hand. Acknowledging this continuum reframes thalamic heterogeneity, not as a taxonomic inconvenience, but as a functional clue that the thalamus is able to influence the cerebral cortex in diverse ways, providing a range of rich, flexible information streams.

The diversity of cell types within the thalamus is not constrained to the excitatory relay nuclei. Organised as a sheet-like inhibitory shell surrounding the thalamus, the exclusively GABAergic (i.e., inhibitory) thalamic reticular nucleus (TRN) is anatomically interposed between corticothalamic and thalamocortical streams, integrating signals from both and redistributing inhibition back onto thalamic relay nuclei (Halassa and Acsády, 2016). While originally conceptualised as a homogeneous inhibitory sheet (Halassa and Acsády, 2016), recent single-cell transcriptomic and circuit-level studies have overturned the classical view by demonstrating that there are distinct subpopulations that are located in the central core (Spp1 +/CB+) and bordering shell (Ecel1 +/SST+) of the TRN (Crabtree, 2018; Li, 2020; Martinez-Garcia, 2020). There are features that are conserved across the two groups – they both receive cortical collateral (from infragranular layers) and send open-loop projections to many thalamic neurons (Martinez-Garcia et al., 2020), but there are also key differences that align with other observed thalamic diversity. Anatomically, core and shell TRN cells receive distinct (but recurrent) projections from First-order and higher-order thalamic nuclei, respectively (Li et al., 2020); and shell TRN neurons also receive more widespread input from both thalamus and cortex along with $L5_{ET}$ projections (mirroring their HO thalamic counterparts). Physiologically, core TRN cells readily display strong arousal dependent hyperpolarised-induced low-threshold Ca^{2+} mediated bursting (via T-type currents) and contribute to spindles and delta power during slow-wave-sleep, whereas shell TRN cells rarely burst, diminish sleep spindles, and show comparatively reduced sensitivity to global arousal (Li et al., 2020). These differences imply variation in the connectivity, temporal precision, and duration of inhibitory control that are organised at the level of populations of thalamocortical loops.

3. The cortical spectrum – systematic variation of structural and dynamical properties

Much like the thalamus, there is identifiable variability at every scale of cortical organisation. The idea that every cortical area has a canonical six-layered structure is a widespread oversimplification, particularly among theoreticians and modellers, to distinguish the phylogenetically-new 'neocortex' from more highly-conserved three-layered cortex. Anatomists have long recognised that laminar structure varies across the neocortex (Bailey and Bonin, 1951; Sanides, 1962; Barbas, 1986; Barbas and Rempel-Clower, 1997; Beul et al., 2017; John et al., 2022) (Fig. 2A). This variation is not random: the cortical mantle is not a patchwork quilt of disparate areas, as the Brodmann map might suggest; instead, the cerebral cortex shows graded variations (Palomero-Gallagher and Zilles, 2019) in features such as the thickness of granular layer, the relative density of supragranular versus infragranular layers, and the density and distribution of inhibitory interneuron subtypes. The variations in these different cytoarchitectonic factors are not independent of each other: they reveal a "cortical spectrum" that ranges from eulaminate, well-laminated areas, which include primary sensory cortices, through to agranular 'limbic' and motor areas that have a poorly defined (dysgranular) or absent (agranular) layer 4 (John et al., 2022). This continuum, initially defined by classical cytoarchitecture, has been corroborated by modern methods: structural MRI indices of myelination (T1w/T2w ratio) (Glasser et al., 2016; Zhang et al., 2020) correlate with the principal axis of the cortical spectrum (John et al., 2022), as do gene expression patterns (Goulas et al., 2019; Sancha-Velasco et al., 2023), and of neurotransmitter receptor distributions (Goulas et al., 2021). Thus, cortical heterogeneity is directly linked to functional specialisation and information processing (Murray et al., 2014).

Across these cortical dimensions, there are prototypical extremes, but most of the cerebral cortex exists as a blend of these axes. The anatomical features mentioned above tend to vary monotonically along the eulaminate-to-limbic spectrum (John et al., 2022) and can be summarised as reflecting changes in the *"degree of lamination"*, an overarching structural pattern that anatomists were able to recognise even without modern quantitative analyses. This spectrum also appears to correlate with physiological properties, including intrinsic and task-related timescales (Song et al., 2024). The cortical spectrum has been shown to predict cortico-cortical connectivity: if a pair of cortical areas are known to be connected, then their relative difference in degree of lamination predicts the layer-specific connection patterns between them (Barbas and Rempel-Clower, 1997; Beul et al., 2017) (Fig. 2B). Interpreting how these patterns of connectivity influence local processing requires understanding the nature of columnar computation.

4. The cerebral cortex – soma ≠ site of integration

Peering into the cerebral cortex is like looking into a dense forest. The aphorism that we *"can't see the forest for the trees"* reads like a premonition for 21st-century cortical neuroscience. Much like a forest, the cortex is dominated by towering, branching structures: vertically oriented pyramidal neurons with basal dendrites like root systems anchored across multiple layers and a dense canopy of apical dendrites fanning out like branches along the cortical surface. Yet, a problem emerges when observing this cortical forest: we tend to label the trees by

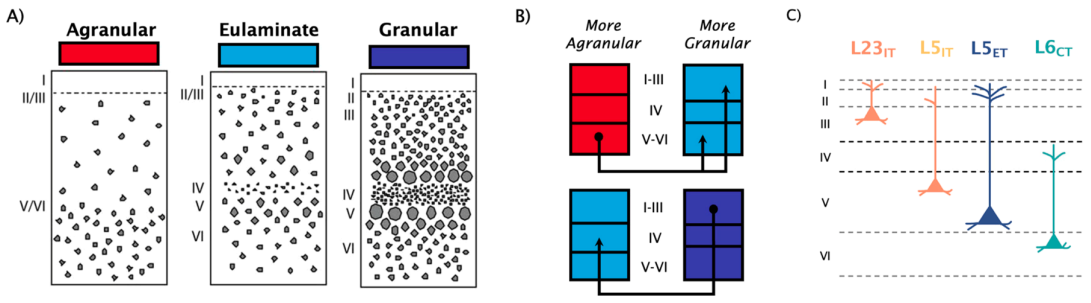

Fig. 2. The Diversity of the Cerebral Cortex. A) The relative granularity and laminar differentiation changes across the cerebral cortex, with agranular cortical areas (left) prevalent in limbic and motor regions, granular cortical areas (right) prevalent in primary sensory regions, and eulaminate regions covering the regions between the two extremes. B) The Structural Model proposes that the relative laminar differentiation of two cortical areas determines the laminar pattern of their interconnections:agranular regions send projections from infragranular areas (layers V-VI) that terminate in the supragranular (I-III) and infragranular layers of more granular cortex, whereas granular areas send projections originating in supragranular layers that terminate in the middle-to-deep layers of more agranular cortex. C) Different classes of pyramidal neurons have cell bodies in distinct layers, with distinct biophysical properties and connectivity profiles (not shown) that are used together to classify the cells from one another. Panel A is partially adapted from (Joyce and Barbas, 2018).

where their trunks begin, not where (or how) the trunks branch. That is, pyramidal neurons are typically classified by the location of their soma (e.g. L2/3 or 6) and further classified by their axonal targets (e.g., cortico-cortical vs corticothalamic; Fig. 2C). While this taxonomic approach has been foundational (Harris and Shepherd, 2015), it overlooks a crucial fact: computation doesn't exclusively happen at the soma (Larkum et al., 2018), it emerges from the integration of inputs across dendrites – this framework is similarly integral for thalamic input (Sampathkumar et al., 2021). Thus, how well do the categories we use to identify pyramidal neurons consistently map to their function?

This somatic bias obscures the role of active dendritic processing (Larkum et al., 2018; Hausser et al., 2000; Stuart et al., 2016). Of all cortical cells, the physiology of L5 pyramidal neurons paradigmatically exemplify this complexity. Their apical dendrites contain voltage-gated calcium channels, enabling nonlinear events such as calcium spikes (Larkum et al., 2022, 1999). In these cells, a somatic action potential can back-propagate into the dendrites and, if it is paired with distal input at the apical tuft (from top-down feedback, thalamic priming, or modulatory sources), it triggers a dendritic calcium spike that propagates down the apical trunk and switches the cell's somatic output from regular spiking to intrinsic bursting. That is, basal input alone yields regular spiking behavior, whereas coincident basal and apical input can induce bursting. In this way, we can see how the somatic terminology can obfuscate function, as bursting in this extra-telencephalic Layer 5 ($L5_{ET;}$ also referred to as thick-tufted, pyramidal tract) cells can be controlled by dendritic dynamics in Layer 1. Even this unique emergent feature is heterogeneous and influenced by cortical geometry, where visual cortex $L5_{ET}$ cells with a short apical trunk (~310μm) are rarely capable of back-propagating initiated bursting, unlike larger (~410μm) visual $L5_{ET}$ cells (Fletcher and Williams, 2019; Galloni et al., 2020). This region- and species-dependent variation in burst capacity suggests that the inheritance mechanism may operate with varying gain across cortical areas, and in ways that may also differ across species.

Other pyramidal cells show similar complexity. Intratelencephalic L2/3 cells integrate across distinct information streams, higher-cortical feedback into the apical dendrites (like layer 5 cells) and lower-cortical feedforward signals (such as sensory signals from first-order thalamocortical cells). Even here, there is variability, albeit across species, where in humans the elongated pyramidal size permits complex dendritic integration (e.g., XOR calculations) which is not present in rodent L2/3 pyramidal cells (Gidon et al., 2020a).

The variability discussed so far is within a cortical cell's integrative capacity; there is similar richness in their corticothalamic projections, particularly between $L5_{ET}$ and $L6_{CT}$ cells (Shine, 2021; Shine et al., 2023). As branches of longer axons that descend into the brainstem and spinal cord, $L5_{ET}$ corticothalamic cells send driver inputs predominantly to higher-order thalamic nuclei (Sherman and Usrey, 2024; Shepherd and Yamawaki, 2021), which are well poised to forward the output of cortical computations across areas via the thalamus (Mo et al., 2024; Mo and Sherman, 2019). This feature is likely enhanced by both $L5_{ET}$ neurons' capacity to burst and their diffuse thalamic projections (Kakei et al., 2001). That is, their outputs are carefully gated signals that reflect the cortical coincidence of categorically different information arriving at different compartments within these cells (Larkum et al., 2022, 1999). This information can then be sent via trans-thalamic relays throughout the brain, whereas layer 6 corticothalamic neurons send feedback projections to both first-order and higher-order nuclei. These projections are diffuse, small-bouton, and modulatory in nature (Sherman and Guillery, 2013; Usrey and Sherman, 2019). Their role is not to drive thalamic activity, but to adjust it, fine-tuning the gain and contextual sensitivity of thalamic relays. There is also heterogeneity in L6 where deep $L6_B$ cells have axon projections that resemble the matrix thalamus(Zolnik et al., 2024), albeit within a local cortical region.

Ultimately, just as in the case of the thalamus, cortical dynamics resist reduction using any single anatomical lens. Framing research around these classifications risks overlooking key features of adaptive computation (Larkum et al., 2018; John et al., 2022; Acsády, 2022).

4.1. Corticothalamic loops of amplification and suppression

What makes CTC circuits particularly suited to implement selection is their integrated, recurrent architecture: cortical output shapes thalamic gating, which in turn determines what cortical activity is amplified or suppressed (Steriade, 2000; Robinson et al., 2005). The partially-closed loop that is formed through these interactions provides an emergent object that can form the basis of a selection process, which itself is a fundamental requirement for complex, adaptive behavior. Sensory systems must attend to certain stimuli over others; motor systems must select actions; and cognitive systems must stabilize affordances while suppressing alternatives (Shine, 2021a; Pezzulo and Cisek, 2016). Although many of these processes are attributed primarily to cortical or basal ganglia inhibition, the TRN is ideally positioned to integrate collaterals from both and implement contextual selection via cross-nuclear and cross-loop divisive normalisation (a winner-take-all effect) (Wimmer et al., 2015). These circuits are further shaped by local cortical interneurons, thalamic interneuron subtypes, and basal ganglia input.

The loops that are amplified at any given moment depend not just on synaptic connectivity but on intrinsic firing modes, behavioral state, and the temporal structure of recurrent excitation and inhibition. Amplified loops elevate their local gain (Munn et al., 2023a), increasing the probability that the same loop will dominate in subsequent competitive interactions – $L5_{ET}$ burst-mediated corticothalamic drive, for instance, transiently increases the responsiveness of higher-order thalamic nuclei (Theyel et al., 2010), thereby shifting the immediate competitive landscape (Munn et al., 2023a; Shine, 2021a). These dynamics extend beyond local circuits via intra-telencephalic projections, higher-order trans-thalamic pathways, and diffuse thalamic and TRN projections, sustaining coherent thalamocortical subnetwork activity for hundreds of milliseconds to seconds during working memory and sensorimotor planning. In dynamical systems terms, these distinct patterns of coordinated activity correspond to transient attractors: stable fixed points, limit-cycle oscillations, and spatially structured modes (Khona and Fiete, 2022).

Selection among these configurations is implemented through inhibitory competition at multiple anatomical sites. Within cortex, heterogeneous interneuron populations shape local excitability through feedforward, feedback, and lateral inhibition; beyond the cortex, the TRN and basal ganglia output nuclei – particularly the globus pallidus internus and pars reticulata (Halassa and Acsády, 2016) – provide powerful external inhibition modulating motor, prefrontal, and limbic thalamocortical circuits. From these interactions emerge competitive dynamics (formalised as divisive normalisation), in which the gain of a neuronal population is scaled by the weighted activity of competing populations. This neural competition spans a continuum from weak interactions to near-winner-take-all, depending on the inhibitory regime (John et al., 2018). Critically, these processes operate on behavioral timescales rather than across learning: learning will refine the recurrent architectures within which selection operates, but the mechanism described here concerns moment-to-moment competition within already-established circuits.

Together, excitatory-inhibitory competition provides the selection operation of the CTC framework, dynamically amplifying contextually relevant coalitions while suppressing competing configurations. Cortical interneurons and TRN inhibition are therefore not redundant but complementary: the former shapes which coalitions are plausible candidates within an area, the latter determines which coalition prevails across areas.

4.2. Using computational modelling for understanding brain function – inferring function from abstraction

A parallel approach to understanding the brain is through *in silico* experimentation (i.e., biophysical modelling). While this approach is potentially more inclusive of heterogeneity than standard anatomical investigations, in that model parameters can (in principle) be drawn from continuous empirical distributions rather than discrete categorical labels, it has historically only been superficially incorporated. This reflects a central aim of computational modelling: to reproduce biophysical and behavioural features of neural systems in a way that balances neurobiological realism with analytical tractability. The goal is to answer specific hypotheses using the minimal necessary complexity – models that are *"as simple as possible, but no simpler"* – preserving the interpretability that makes modelling scientifically useful (Munn et al., 2023a; Müller et al., 2020a; Wilson and Cowan, 1972; Wang and Buzsáki, 1996; Whittington et al., 2020). Nevertheless, advances in computational power, empirical neuroscience, and modelling techniques have enabled the development of anatomically-inspired biophysical models that generate genuine functional insights.

At the cortical scale, simulations of (thick-tufted) L5 pyramidal neurons have revealed how dendritic bursting can support multiplexed neural codes (Munn et al., 2023a; Naud and Sprekeler, 2018), implement burst-dependent credit assignment rules (Payeur et al., 2021), enhance orientation tuning (Shai et al., 2015), and when embedded in thalamocortical loops can explain behavioural responses and reproduce psychophysical laws (Whyte et al., 2025). Similarly, modelling of thalamocortical interactions along a core-matrix gradient has uncovered sharp transitions between functionally distinct cortical regimes (Müller et al., 2020b, 2023). These shifts have strong links to neuronal transitions between different states of consciousness and arousal, grounded in a rich literature concerned with critical transitions in cognition and naturalistic behaviour (Munn et al., 2023a, 2023a; Müller et al., 2020a, 2023). At the cellular scale, increasing input from diffuse matrix-type thalamic cells can trigger nonlinear shifts in coordinated information capacity – such as integrated information, a proxy measure for consciousness (Tononi et al., 2016). At the macroscale, neural mass models demonstrate a similar principle: increasing diffuse thalamic drive pushes the cortex into a quasi-critical state, altering its information-processing capabilities (Müller et al., 2020a, 2023).

Across these examples, a consistent finding emerges: distinct anatomical configurations can converge on similar functional output (termed degeneracy (Edelman and Gally, 2001); Tononi et al., 1999). Multistable perception (Whyte et al., 2025; Mueller, 1990), cortical oscillations (Robinson et al., 2003; Volo et al., 2019; Ritter et al., 2013), and gain modulation (Müller et al., 2020a; Shine et al., 2018) have all been reproduced in distinct modelling architectures. Similarly, many of these models contain similarities as features of anatomy can appear similar at coarse-grained resolutions (e.g., whole-brain diffuse neuromodulatory projections can resemble regionally diffuse thalamic projections) (Munn et al., 2023a, 2023a; Whyte et al., 2025; Müller et al., 2023). This functional convergence can appear at odds with the goals of neuroanatomy, which often seeks to discriminate functional classes based on increasingly fine-grained structural detail.

Rather than a limitation, this degeneracy of structure-function mappings may be a core principle of brain organisation. This suggests that, across scales and recurrent networks, neural heterogeneity may utilise a process akin to selection, where useful patterns of neural activity are reinforced and stabilised ('selected') rather than relying on fixed anatomically constrained motifs. Such a multiscale selective process may aid the brain to be robust (Edelman and Gally, 2001) by mapping functions onto multiple realisations, permitting the system to easily adapt across perturbations, deviations in anatomy, and a dynamic environment (Munn and Gong, 2018).

In practice, however, most published biophysical models still employ discrete, representative cell-type parameters rather than drawing from empirical distributions of heterogeneous properties. This is a crucial gap between modelling aspiration and execution that the field has yet to close. Closing it would require at least three things: first, initialising model instances directly from transcriptomic or connectomic atlas data rather than canonical cell-class values (Müller et al., 2023; Froudist-Walsh et al., 2021); second, running simulations across parameter sweeps that explicitly span the ranges of heterogeneity documented anatomically – for instance, varying $L5_{ET}$ burst threshold as a function of apical trunk length across species; and third, using degeneracy analyses to identify which axes of heterogeneity are functionally critical and which are interchangeable, thereby generating specific predictions that anatomical studies could test.

The computational modelling perspective, grounded in the integration of anatomy and modelling, reframes robust information processing as an emergent property of flexible, interacting systems. That is, the brain is designed not around rigid blueprints, but around variation, a feature that is reused across scales.

4.3. A Dynamical systems perspective on the corticothalamic microcircuit – toward an algorithmic framework of natural selection across neural coalitions

How should we interpret the variable and complex interactions between thalamus and cortex? A key implication is that brain function is not coordinated by a homunculus or controller in a "Cartesian theatre"; rather, it emerges from the dynamic interactions of recurrently connected neuronal circuits. We suggest that, viewed as a coherent entity, the extended corticothalamic microcircuit implements a process algorithmically analogous to natural selection, comprising three subprocesses, variation, selection, and inheritance – that unfold across behaviourally relevant timescales (Edelman, 1993a; Dennett, 1996; Watson and Szathmáry, 2016). We would like to emphasise that we have used the terminology of natural selection, not to imply a one-to-one mapping with genetic evolution, but instead as a heuristic framework to highlight the functional roles of heterogeneity, inhibitory competition, and in recurrent bursting activity in shaping adaptive function; roles that are often obscured when cortical and thalamic circuits are viewed solely through anatomical taxonomies. Having reviewed the anatomical and physiological evidence for heterogeneity within thalamus and cerebral cortex, we now turn to a computational interpretation of this heterogeneity as a selection process, before closing with falsifiable predictions that distinguish this interpretation from existing accounts (Box 1).

Thalamic and cortical biophysical heterogeneity provides a natural substrate for *Variation* (Fig. 3D). The variability we emphasise here occurs across populations, representing the set of possible coalitions that could become active in a given context, rather than the number of neurons that contribute on a trial; which itself is a complex byproduct of development, context complexity, and stimulus exposure history. The dense, interconnected web of dendritic integration sites, synaptic inputs, and projection motifs in corticothalamic and corticocortical systems ensures that many distinct responses are possible to the same environmental state, analogous to phenotypic variability across individuals in a species. For example, cortical intratelencephalic (IT) neurons (Fig. 3D, orange) display sparse and variable activity to repeated stimuli (Shadlen and Newsome, 1998), are densely interconnected both locally and across cortical regions (Harris and Shepherd, 2015; Hage et al., 2022) (Fig. 3D), show high context- and outcome-dependent plasticity, especially at their apical dendrites (Williams and Holtmaat, 2019), and they have been linked to motor planning (Li et al., 2019) and decision-making (Musall et al., 2023) , via their heterogenous dendritic architectures (Gidon et al., 2020) that variably influences other pyramidal cells and interneurons, modulating excitation:inhibition balance, both locally and across cortical areas. Together, this example demonstrates how one facet of cellular heterogeneity (amongst the many described) acts as major contributors to the pool of variable neural

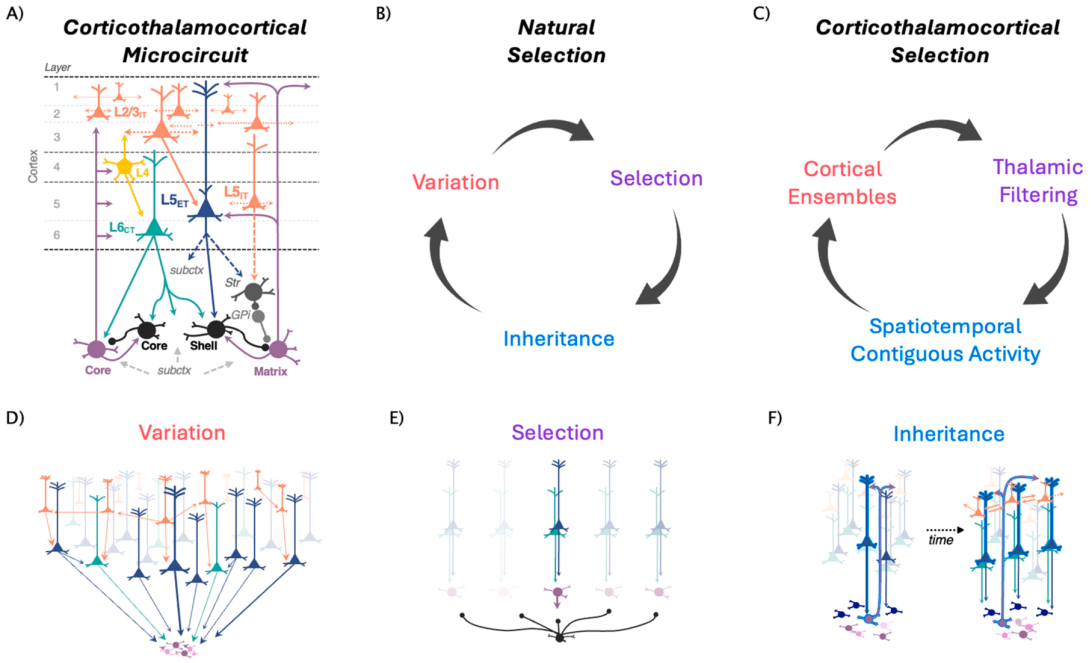

Fig. 3. Mapping corticothalamocortical dynamics to the algorithm of natural selection. A) summary diagram of the discussed cell types in the cerebral cortex (top) and thalamus (bottom), and the connections between the cell types that determine their putative role in the natural selection process. Key: $L2/3_{IT}$ – layer 2–3 intratelencephalic cells (orange); L4 – layer 4 stellate cells (lemon); $L5_{IT}$ – layer 5 intratelencephalic cells (orange); $L6_{CT}$ – layer 6 CT-cells (teal); $L5_{ET}$ – layer 5 extratelencephalic cells (dark blue); TRN –thalamic reticular nucleus Core/Shell (black); Str – striatum (dark grey); GPi – globus pallidus internus (light grey); Core/Matrix – thalamic neurons (purple); thick lines represent connections between elements of the circuit, whereas dotted lines represent connections to targets outside the circuit. B) The process of evolution by natural selection can be summarised as passing through three distinct stages: Variation – differences in traits amongst the population , Selection – environmental pressures favour particular traits , and Inheritance – advantageous traits are passed on, becoming more common. C) The proposed mapping between elements of the corticothalamocortical microcircuit and the natural selection process: cortical ensembles – promote variation (among potential circuits that could be activated); thalamic filtering – thalamic and TRN cells promote selection toward certain corticothalamocortical circuits over others; and spatiotemporal contiguous activity – support inheritance by amplifying neural coalitions activation across time. D-F) We propose that the key features of neural selection are distributed across the circuit, such as: (D) Variation – arising from the large number of different possibly active cortical and thalamic cells. (E) Selection – a natural byproduct of a mutual-inhibitory mechanisms that arises from activity-dependent recruitment of the inhibitory thalamic reticular nucleus (black), we also anticipate this is locally enhanced via intra-columnar cortical, thalamic, and basal ganglia inhibition. (F) Inheritance – wherein the combination of recurrent bursting $L5_{ET}$ cells (light blue highlighted) and matrix thalamus CTC loops creates a 'Matthew' effect on cellular populations recruiting successive CTC loops that are connected to currently dominant CTC ensemble. The colours of cells in Panel D-F were chosen to match those in panel A.

coalitions across the brain.

Selection (Fig. 3E) is enacted via inhibitory-competition, primarily within the thalamus, which integrates diverse cortical and subcortical inputs and refines them via recurrent and reticular inhibition. First, the thalamus compresses many-to-few convergent inputs from deep cortical layers into lower-dimensional patterns (Halassa and Sherman, 2019; Shine et al., 2023; Suzuki et al., 2023) via inhibitory-competition (e.g., divisive normalisation) from thalamic interneurons, reticular, and basal ganglia input (John et al., 2018; Reynolds and Heeger, 2009; Schmitz and Duncan, 2018; Halassa et al., 2014). The mediodorsal nucleus (MD) exemplifies this most clearly. Recent findings show that abstract rule information emerges first in ventral anterior (VA) thalamus – the main hub between basal ganglia and PFC – before appearing in MD, which then persists to maintain activation of relevant PFC ensembles and is the first structure to represent behavioural outcomes (Phillips et al., 2025a; Bolkan et al., 2017; Parnaudeau et al., 2013; Rikhye et al., 2018). This suggests a two-stage thalamic selection process: BG-informed VA selects the relevant rule, MD sustains the winning PFC coalition – a division of labour that maps naturally onto the Selection and Inheritance components of our framework. Computational lesioning of these nuclei disrupts PFC rule representations (Phillips et al., 2025), and MD lesions selectively impair working memory and cognitive flexibility without abolishing sensory processing (Bolkan et al., 2017; Parnaudeau et al., 2013) – precisely the profile expected if MD implements selection among prefrontal coalitions rather than relaying sensory content. Similarly, descending axons from deep layer 6 corticothalamic cells ($L6_{CT}$; Fig. 3E, teal) innervate the TRN, establishing activity-dependent inhibitory competition that functionally mimics selection (Shine, 2021a; Crick, 1984; Harris and Shepherd, 2015; Halassa et al., 2014; Kirchgessner et al., 2020). Early work concluded that $L6_{CT}$ cells conferred a relative inhibition on thalamic targets (Olsen et al., 2012), but *in vivo* experiments and modelling studies indicate they also generate a ~10 Hz resonance, supporting rhythmic selection windows (Robinson et al., 2003a).

Inheritance is ubiquitous in recurrent networks: any event (be it a spike or silence), shapes and constrains subsequent neural events, reinforced by the shallow architecture of whole-brain connectivity (Suzuki et al., 2023). Here, inheritance does not refer to genetic transmission but to the persistence and recurrence of selected activity patterns, such that prior coalitions bias the probability of subsequent ones. This form of inheritance resembles the transmission of acquired characteristics, where activity patterns directly shape future "generations" of coalitions, without sharp separation between variation and inheritance. Nonetheless, the principle is algorithmically equivalent: spatiotemporally contiguous neural activity allows selected behaviours to accumulate.

Not all inherited activity is created equal. Recurrence in neural circuits takes many forms, including local persistent activity, attractor dynamics, and NMDA-dependent reverberation in prefrontal networks, each capable of stabilising a coalition within a cortical area across time

(Buzsáki and Wang, 2012; Izhikevich et al., 2003). Burst-mediated inheritance provides a distinct mechanism for propagating a selected coalition (Izhikevich et al., 2003) across anatomically distal areas via the trans-thalamic pathway, a function that purely corticocortical recurrence cannot fulfil. Physiologically, the trigger is coincidence of basal and apical dendritic input in $L5_{ET}$ cells: feedforward sensory and motor drive arrives at basal dendrites, while top-down contextual signals and matrix-type thalamic priming arrive at the apical tuft, with coincidence most likely at moments of contextual integration such as attention shifts, action selection, and behavioural transitions, when both streams are simultaneously active (Larkum, 2013). This coincidence induces a burst that drives higher-order thalamic nuclei via $L5_{ET}$ collaterals, which in turn broadcast via matrix projections back to layer 1 of distal cortical areas, priming the next competitive cycle across the full CTC circuit.

In this way, bursting coalitions function like Dennett's notion of 'fame in the brain' (Dennett, 2001), where the currently dominant coalition is most likely to guide the next generation of coalitions. Individual burst events unfold over ~5–50 msec (Larkum et al., 1999; Beierlein et al., 2002), and the downstream bias on corticocortical dynamics persists for multiple thalamocortical resonance cycles (~300 msec), sustained across cycles if the coalition continues to win selection. Crucially, the mechanism is self-limiting: because ongoing basal-apical coincidence is required to sustain inheritance, a coalition loses its advantage as soon as the contextual trigger resolves, unlike fixed-point attractor dynamics that can persist indefinitely without external perturbation (Shine, 2021a; Suzuki and Larkum, 2020; Whyte et al., 2025; Takahashi et al., 2016, 2020; Aru et al., 2020; Whyte et al., 2024b). Activity-dependent adaptation in $L5_{ET}$ cells and TRN-mediated termination of selection windows provide additional reset mechanisms, ensuring no single coalition maintains dominance at the cost of neural variability. Notably, because $L5_{ET}$ thalamic projections are collaterals of longer descending axons targeting brainstem and spinal cord (Shepherd and Yamawaki, 2021), a winning coalition's burst simultaneously propagates inheritance via the trans-thalamic pathway and issues a descending motor or modulatory command – a dual broadcast reminiscent of efference copy, in which the sensorimotor system is updated to anticipate the consequences of the action being initiated (Shine, 2021a). Together, these factors suggest that the mesoscopic scale of circuits that integrate thalamic and cortical territories will be the most effective scale at which to identify the signatures of the neural selection process.

To illustrate this concept of 'neural selection', consider an individual navigating a busy street. Variation arises from diverse cortical ensembles, whose dendritic trees enable the representation of diverse environmental inputs, such as the colour of traffic lights, the movement of vehicles, and auditory cues like honking horns (Shin et al., 2021) (Fig. 3D). Selection occurs in thalamus, where convergent cortical and subcortical inputs, shaped by TRN and locally refined by interneurons and globus pallidus (Smith et al., 2022) (Fig. 3E), filter relevant signals (e.g., timing of the light) while suppressing noise (e.g., a distant conversation). Inheritance is implemented via bursting in Layer 5_{ET} cells, whose outputs both drive immediate motor commands and bias future actions through modulating trans-thalamic loops. Together, this cycle of variation, selection, and inheritance enables adaptive, goal-directed behaviour in real time.

Extending the analogy, we can consider the 'ecosystem' in which different corticothalamocortical coalitions evolve. For example, the Structural model (Barbas and Rempel-Clower, 1997; Beul et al., 2017) (Fig. 2) will bias which ensembles compete (rather than cooperate) – for instance, granular cortical areas are known to contain different proportions and levels of distinct classes of GABAergic interneurons, which could plausibly alter interactions between ensembles. Within this framing, we can also consider the way in which the thalamocortical system dynamically interacts with other highly-conserved features of the vertebrate brain, such as the cerebellum, basal ganglia, and the neuromodulatory arousal system (Shine et al., 2019). In each case, the unique topography of each system defines its putative role in the selection process: the cerebellum contributes to error correction and facilitates temporal precision, informing the inheritance process through feedback loops that refine motor and cognitive outputs (Shine, 2021a; Koziol et al., 2013); the basal ganglia facilitates action selection, complementing the selection role of the thalamic reticular nucleus by integrating reward-based information (Shine, 2021a; Redgrave et al., 1999); and neuromodulatory ligands further modulate the balance of excitation and inhibition across corticothalamic circuits, tuning their responsiveness to environmental demands and internal goals (Brown et al., 2011; Shine et al., 2021). Together, these interactions create a multiscale hierarchy in which variation is constantly present, selection is refined, and inheritance sustains adaptive, patterns across time.

5. Concluding remarks: toward a framework of function through heterogeneity

The famous adage that *"all models are wrong, but some are useful"* applies as much to anatomical categorisations as it does to biophysical models. Rather than seeing anatomical and computational perspectives as competing, we argue that a dynamical systems approach can foster deeper collaboration between theoretical and empirical domains and lead to faster understanding of how the brain processes information. This dynamical lens embraces the heterogeneity within the thalamus (e.g., input integration) and cerebral cortex (e.g., cell types) as a key feature (Acsády, 2022). In particular, we suggest CTC loops may implement a dynamic integrative filter, akin to a process of natural selection operating on competing neural ensembles (see Box 1).

Considering the inconsistencies and limitations inherent in rigid anatomical taxonomies, we advocate for a different strategy: a functional approach, embracing the heterogeneity of thalamic and cortical features into a high-dimensional, continuous representational space that reflects both structural and dynamic complexity (Sherman and Usrey, 2024; Larkum et al., 2018; Clascá et al., 2016, 2012; Bickford, 2016; John et al., 2022; Phillips et al., 2019; Munn et al., 2020). Concretely, this representational space can be thought of as the joint embedding of anatomical, physiological, and molecular properties that co-vary continuously across thalamic and cortical populations (Müller et al., 2025) – properties that single-cell transcriptomic atlases, dense connectomic reconstructions, and in vivo electrophysiology are now beginning to sample at sufficient resolution to make tractable. Dimensionality reduction of such multimodal datasets already reveals continuous gradients that cut across classical nuclear and laminar boundaries (Halassa and Sherman, 2019; Phillips et al., 2019); generative models trained on these representations could go further, generating explicit predictions about how circuit function should vary along those axes and identifying where discrete-category descriptions are adequate approximations versus where they materially mislead. For instance, continuous biophysical features can lead to spatial and dynamical phase transitions. By moving away from coarse-grained labels for thalamic nuclei and cortical layers, we avoid oversimplifications that can obscure important functional insights. This dynamical backbone rides atop relatively static synaptic connections between neurons that are refined by experience-dependent plasticity.

Like so many simple ideas in science, the concepts espoused here are not without precedent. For instance, the hierarchical cortical models highlighted by Barbas and colleagues (John et al., 2022) denote how laminar-specific connectivity underpins adaptive computations, similar to the variability functional utility that we map to cortical heterogeneity. Similarly, Mountcastle's discovery of the columnar organisation (Mountcastle, 1997) provides the structural basis for the iterative processes of selection and inheritance. Edelman's Neural Darwinism explicitly links neural circuits to selectionist principles, paralleling the corticothalamic system's emergent properties (Edelman, 1993), and these ideas have been further expanded to make contact with the

mechanisms that give rise to the properties of phenomenal consciousness (Seth and Baars, 2005). Our framework extends this selectionist logic to behaviourally relevant timescales: where the theory of neuronal group selection invokes re-entrant signalling to select among stable, developmentally defined neuronal groups, corticothalamocortical selection operates via inhibitory competition (particularly TRN-mediated) among transient coalitions – a faster, synapse-independent process that may be nested within, rather than opposed to, the longer-term plasticity dynamics Edelman described. Llinás' work on the central role of oscillations in thalamocortical interactions (Llinás, 1988) further underscores the system's evolutionary-like mechanism, where rhythmic activity plays a pivotal role in filtering and sustaining functional coalitions of neurons. We anticipate that further refinement of these ideas, combined with explicit implementation in computational models, will further improve our understanding of the complex, adaptive system that comprises the mammalian brain.

The selection framework also positions naturally relative to existing computational accounts of thalamic function. Burst-dependent credit assignment (Larkum, 2013; Payeur et al., 2021) is directly implemented within the inheritance mechanism – $L5_{ET}$ bursts propagate coalition success via trans-thalamic loops, giving this account an explicit circuit identity. Similarly, thalamic prediction error accounts (Mumford, 1991) are complementary rather than competing: in our framework, prediction errors constitute the signals that drive TRN-mediated selection, such that the coalition best predicting the current context is the one selected. Kalman-style state estimation and coalition-level selection may operate in parallel across timescales: the key advantage of the selection framework is not that it replaces these accounts but that it provides a single algorithmic description integrating heterogeneity, inhibitory competition, and recurrent bursting across the full CTC circuit, rather than isolating one computational feature in turn. Of note, the analogy between corticothalamic dynamics and natural selection may be better aligned with Lamarckian or Waddingtonian selection than Darwinian mechanisms, which may be more naturally aligned with the impact of plasticity on thalamocortical dynamics across an animal's lifespan – we look forward to refining these concepts with constraints imposed by empirical recordings across species and behavioural contexts.

In this work, we have advocated for a pluralistic perspective that seeks to bridge multiscale anatomical features with dynamical abstraction. While challenging, the potential benefits are substantial. For one, modellers can (hopefully) provide tractable theories for anatomists and physiologists to test, which in turn will necessitate the refinement and augmentation of future model iterations. Secondly, if successful in providing accurate predictions, neurobiologically-informed models can be extrapolated, such that predictions from one brain region (Abbott et al., 2017) and species (e.g., perception in barrel cortex in a mouse or states of arousal in macaque ECoG) can be used to constrain predictions in a different system (e.g., visual cortex binocular rivalry and anaesthesia in humans) (Munn et al., 2024, 2023; Whyte et al., 2025). This cross-species predictive power is currently sorely lacking in modern neuroscience, and it is necessary if we are ever going to create a robust translational pathway from animal models to human neurological and psychiatric patients.

We anticipate that this perspective will yield several benefits for neuroscience: it invites new, testable predictions; enhances cross-species and multimodal data integration; and supports a dialogue between systems neuroscientists and anatomists with detailed cellular knowledge (Shine et al., 2023; Finn et al., 2023). Ultimately, embracing diversity across anatomical substrates may help us move closer to general principles of brain organisation.

CRediT authorship contribution statement

Matthew E. Larkum: Writing – review & editing. **Yuri B. Saalmann:** Writing – review & editing. **Mototaka Suzuki:** Writing – review & editing. **Jaan Aru:** Writing – review & editing. **Yohan John:** Writing – review & editing. **Toon Brouwer:** Writing – review & editing. **Christopher J. Whyte:** Writing – review & editing. **Eli J. Müller:** Writing – review & editing. **Munn Brandon:** Writing – review & editing, Writing – original draft, Conceptualization. **James M. Shine:** Writing – review & editing, Writing – original draft, Conceptualization.

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