From Active Affordance to Active Inference: Vertical Integration of Cognition in the Cerebral Cortex Through Dual Subcortical Control Systems

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Abstract
In previous papers, we proposed that the dorsal attention system's top-down control is regulated by the dorsal division of the limbic system, providing a feedforward or impulsive form of control generating expectancies during active inference. In contrast, we proposed that the ventral attention system is regulated by the ventral limbic division, regulating feedback constraints and error-correction for active inference within the neocortical hierarchy. Here, we propose that these forms of cognitive control reflect vertical integration of subcortical arousal systems that evolved for specific forms of behavior control. The feedforward impetus to action is regulated by phasic arousal, mediated by lemnothalamic projections from the reticular activating system of the lower brainstem, and then elaborated by the hippocampus and dorsal limbic division. In contrast, feedback constraint—based on environmental requirements—is regulated by the tonic activation furnished by collothalamic projections form the midbrain arousal control centers, and then sustained and elaborated by the amygdala, basal ganglia, and ventral limbic division. In an evolutionary-developmental analysis, understanding these differing forms of *active affordance*—for arousal and motor control within the subcortical vertebrate neuraxis—may help explain the evolution of *active inference* regulating the cognition of expectancy and error-correction within the mammalian 6-layered neocortex.

Overview

The organization of the laminar architecture of the primate neocortex can be described by the Structural Model of increasing laminar differentiation of the neocortex as it has evolved from the limbic base (Barbas & Rempel-Clower, 1997; J. O. Berger, 2013; García-Cabezas, Zikopoulos, & Barbas, 2019; Lisman, 2012; Parr & Friston, 2017). The process of concept-formation—within this architecture of the neocortex—can be described formally in terms of *predictive coding* (see **Box 1**) and ensuing *active inference* (see **Box 2**), in which predictions generated in the limbifugal direction (from expectations about the world) are revised by prediction errors from sensory input in the limbipetal direction (i.e., sensory evidence from the world) (Karl Friston, 2010; Lisman, 2012; D. M. Tucker & Luu, 2021).

The present emphasis on control of the neocortical hierarchy by limbic networks at the "top" of the hierarchy (Tucker & Luu, 2021) is shared with the theoretical analysis of Chanes and Barrett (Chanes & Barrett, 2016). A difference in our terminology is that we abandon the conventional neuroscience term of *feedforward pathway* for the input (sensory-to-association-to-limbic) direction of information, describing it as *limbipetal* instead. This is because a functional analysis, under active inference, clearly shows this is a *feedback control* pathway, when the neural interactions are considered in relation to the cybernetics, or control, of activity (Tucker & Luu, 2021). Similarly, we drop the conventional term *feedback pathway* for the output or limbifugal direction of top down (higher association area to lower area) control, because this is clearly a *feedforward* form of information processing, generating predictions for active sensing and perception (Tucker & Luu, 2021). What were arbitrary terms initially used (reasonably enough) to describe different directions of processing in the visual system (Felleman & Van Essen, 1991) are a misdirection (sic), in relation to the control functions of limbifugal and limbipetal directions of processing.

We have recently proposed that active inference in both sensory and motor pathways in the cerebral cortex is guided by unique regulatory influences from dual limbic divisions: the dorsal (mediodorsal) limbic (archicortical, Papez circuit) generation of urges and expectations is balanced by the ventral (ventrolateral) limbic (paleocortical, Yakovlev circuit) regulation of vigilance for errors in matching the facts of the environment (Don M. Tucker & Luu, 2023). Certainly, both the dorsal and the ventral divisions of neocortex have both limbipetal as well as limbifugal directions of connection, as described in the Structural Model (Barbas & Rempel-Clower, 1997). However, we emphasize there is a *relative* balance between dorsal and ventral neocortical divisions, with a relative feedforward (excitatory) bias for the dorsal division operating strongly in the limbifugal direction, compared with a relative elaboration of the

Level of Neuraxis	Functional Divisions	
Neocortical	Dorsal Neocortex; Dorsal Attention (intention/endogenous?) Network	Ventral Neocortex; Ventral Attention (exogenous?) Network
Limbic	Dorsal Limbic; Archicortical; Hippocampus; Papez Circuit	Ventral Limbic; Paleocortical; Extended Amygdala & Insula; Yakovlev Circuit
Basal Forebrain	Hippocampal-Septal-Mammillary Body Network	Basal-Ganglia and Amygdala-Striatal Circuits
Thalamic	Lemnothalamus; Inputs not relayed through the tectum. Of the non-sensory nuclei, the anterior nucleus is an example.	Collothalamus; Inputs relayed from the tectum. Of the non-sensory nuclei, the mediodorsal nucleus is an example.
Brainstem/Midbrain	Lower brainstem; Reticular Activating System; Rhombencephalon	Midbrain; Colliculi and Ventral Tegmental Area; Mesencephalon

Table 1. Hierarchic organization of the human nervous system, aligned in dorsal and ventral functional divisions.

feedback (inhibitory) bias for the ventral division actualized in the limbipetal direction (Tucker & Luu, 2023). These relative control biases are consistent with the classical cytoarchitectural differences observed in both humans and monkeys (Eidelberg & Galaburda, 1984; Galaburda, 1984) in which dorsal neocortex shows a greater dominance of pyramidal (excitatory) neurons, where ventral neocortex shows a more prominent granular (inhibitory) layer.

In the present paper, we emphasize that these differential limbic controls—on memory and cognition—must be supported by *vertical integration*: namely, the coordinated function of the evolved hierarchy of the subcortical neuraxis, including basal forebrain, hypothalamic, thalamic, midbrain, and brainstem control systems (**Table 1**; **Figure 1**). In the present review, we first summarize the evidence for unique modes of feedforward and feedback regulation of behavior within the neocortex, aligned with dorsal (hippocampal) and ventral (olfactory) limbic-cortical organization, respectively. Then we show how the archicortical and paleocortical primitive pallial fields have been elaborated in the evolution of the neocortex, in broad dorsal and ventral corticolimbic evolutionary-developmental trends that created the specific layered organization of the 6-layered mammalian neocortex. This frames the challenge for explaining how such organization and corticolimbic networks of action control are derived from—and supported by—the evolved anatomy of vertical integration across not only telencephalic, but diencephalic, mesencephalic, and rhombencephalic levels.

In this functional anatomy, we propose that the regulatory control by the brainstem (rhombencephalic) reticular activating system is mediated through *lemnothalamic* pathways to the forebrain. In parallel, the regulatory control from the midbrain (mesencephalic) control system is mediated through *collothalamic* pathways to the forebrain. We use these terms to describe vertically integrated control systems, and not just the anatomical pathways with their differential thalamic targets described by Butler (A. B. Butler, 1994). We consider the collothalamic system to include forebrain projections from the midbrain generally, including the tectum and substantia nigra as well as the colliculus). Although our goal is to differentiate these as separate control systems, we recognize the considerable overlap at several points.

Conceptually, we build our model from Puelles's key insight into the fundamental pattern of the telencephalon seen in amphibians and reptiles, of pallial excitatory (pyramidal, glutamatergic) neuronal control, contrasted with subpallial inhibitory (interneuron, GABAergic) control (Luis Puelles, 2001). In fact, for amphibians and reptiles, the organization of vertical integration of the neuraxis is clear, as these pallial and subpallial forms of control reflect the differential actions of lemnothalamic (excitatory, glutamatergic, pallial sensory integration) and collothalamic (inhibitory, GABAergic, subpallial, basal ganglia motor control) pathways in the regulation of excitatory-inhibitory balance of the forebrain, consistent with Puelles's (2001) general characterization.

This fundamental architecture describes motivated generation of adaptive behavior that we describe as *active affordance*. In this basic vertebrate plan, the creation of feedforward impulses (adaptive expectancies) by the lemnothalamic pathway guides feedforward behavior control through active exploration for adaptive goals. The collothalamic pathway then constrains this exploration in relation to ongoing environmental exploitation (Cisek, 2022; Parr & Friston, 2019), with efficient motor sequences and habit patterns regulated by the subpallial basal ganglia under midbrain (collothalamic) control.

The further evolution of active affordance, and the extended memory capacities of the 6-layered mammalian neocortex, eventually allowed elaboration of active inference as a cognitive process for planned perception and action. The mammalian neocortex appears to have been formed through the ontogenetic mutation of components of both the pallial and subpallial architectures to form the 6-layered mammalian neocortical architecture of the Structural Model. Although interpreting this evolution of the mammalian neocortex has been famously controversial, we propose that it can be understood in light of the full vertical hierarchy of behavior control. In this vertical hierarchy, norepinephrine (NE) projections from the locus coeruleus (LC) of the reticular activating system and the lemnothalamically aligned septum and mammillary body regulate the dorsal limbic system and dorsal division of the 6-layered neocortex primarily. In a complementary manner, the midbrain ventral tegmental area (VTA) and substantia nigra compacta (SNc) form the mesencephalic component for arousal control, and together with the colliculus/tectum, regulate the ventral limbic system, basal ganglia, amygdala, and the ventral neocortical division.

We argue that, together, these elementary and complementary forms of feedforward, open-loop control (lemnothalamic) and feedback, closed-loop control (collothalamic) that evolved to support active affordance came to underwrite — and are underwritten by — the evolution of the dorsal and ventral divisions of the 6-layered neocortex. The effect of this mammalian mutation of the interdigitated neocortex was to generate more complex representational cognition (progressing from reflexive homeostasis to anticipatory allostasis) through the mammalian cognitive process of *active inference* (Friston, 2010). We speculate that an important aspect of this process has been ventral limbic (and collothalamic) regulation of the feedback layers (2, 3, 4), in contrast to the dorsal limbic (and lemnothalamic) regulation of the infragranular (5, 6) feedforward layers, as general biases for regulating active inference in the 6-layered mammalian neocortex.

Within this theoretical framework we reconsider classical models for how the primitives of locomotor/arousal control systems (Pribram & McGuinness, 1975) can give rise to general systems for multilevel control of cognition (Goldman-Rakic, 1988). We will suggest that at the level of the reticular activating system of the lower brainstem the NE projections appear to be the primary regulator of the lemnothalamic pathway that provided a form of *phasic arousal* for control of the primitive pallium. This form of control remains integral to the *generative impulses* of the dorsal, archicortical division of the mammalian limbic system and neocortex (D. M. Tucker & Luu, 2012; D. M. Tucker & Williamson, 1984).

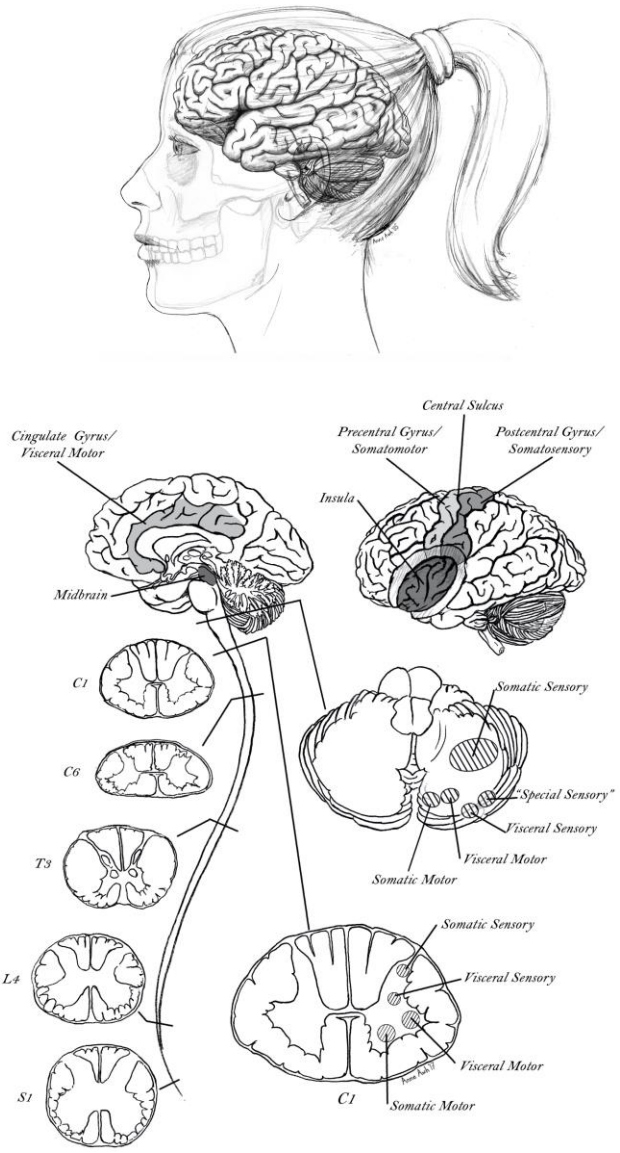
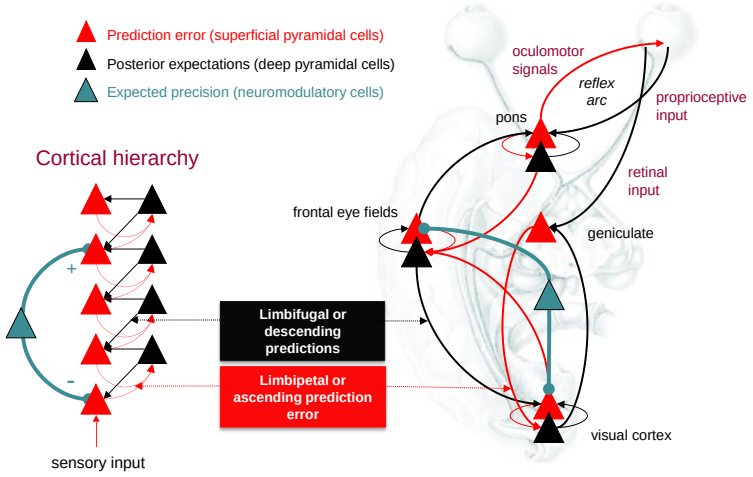


Figure 1. Levels of the Human Neuraxis. The generic vertebrate neural body plan is seen in the organization of the spinal cord, with sensory control dorsally and motor control ventrally, such as at C1 (bottom). From Tucker & Luu (2012).

In parallel, at the level of the midbrain, the dopamine (DA) projections from the SNc and VTA provide a form of *tonic activation* that has been key for control of the subpallial basal ganglia in evolution. This mode now remains integral to the operation of *constraint* as the dominant cybernetic bias within ventral, paleocortical division of the mammalian limbic system and neocortex (D. M. Tucker & Luu, 2012; D. M. Tucker & Williamson, 1984). The midbrain DA controls are mesencephalic and thus superordinate over the lower rhombencephalic brainstem (with its lemnothalamic projections to the forebrain) as illustrated in in Figures 1, 7, and 10.

We thus propose that dual regulatory systems continually organize the arousal, activation, and thus vertical integration of the neuraxis. In a final section, we examine the organization of motor control as reflecting the hierarchic arrangement of motor reflexes and their subordination to successively higher levels of representation and control, providing the cybernetic framework for understanding the organization of action — and function generally — in the cerebral cortex. We start this theoretical analysis in the next section, with the evidence that behavior control reflects dual neural control systems, one biased toward impulsive, feedforward control and the other biased toward constrained, feedback control.

Box 1. Predictive coding and precision



This schematic summarizes hierarchical message passing in predictive coding formulations of message passing in the brain. Predictive coding is a scheme for inverting generative models based upon continuous states. In these schemes, neuronal activity is assumed to encode expectations about the causes of sensory input that are continually updated to minimize prediction error. Prediction error is the difference between (ascending, limbipetal) sensory input and (descending, limbifugal) predictions of that input. This minimization rests upon recurrent neuronal interactions among different levels of a cortical hierarchy. Here, superficial pyramidal cells (red triangles) compare the expectations (at each hierarchical level) with limbifugal predictions from deep pyramidal cells (black triangles) of higher levels: see (Bastos et al., 2012) for a review.

Left panel: this schematic shows a simple cortical hierarchy that includes neuromodulatory gating or gain control (teal) of superficial pyramidal cells, which determines their influence on deep pyramidal cells encoding expectations. Precision is the reliability associated with prediction errors, where the relative precision of different prediction errors can have a profound effect on expectations and ensuing predictions. Physiologically, precision can be equated with postsynaptic gain, established via neuromodulatory mechanisms.

Right panel: this provides a schematic example in the visual system: it shows the putative cells of origin of ascending connections that convey prediction errors (red arrows) and descending connections (black arrows) that furnish predictions. Prediction errors are weighted by their expected precision, which have been associated with projections from classical modulatory neurotransmitter systems. In this example, the frontal eye fields send predictions to primary visual cortex, which projects to the lateral geniculate body. However, the frontal eye fields also send proprioceptive predictions to pontine nuclei, which are passed to the oculomotor system to induce movement, through classical oculomotor reflexes. This means that saccadic eye movements, for example, realise proprioceptive predictions that are deeply informed by hierarchical processing of data from all sensory modalities.

Similar schemes can be elaborated for discrete state space generative models, responsible for planning and motor control—or allostasis and autonomic function: see (Parr and Friston, 2018) for equivalent schematics and (Friston et al., 2017) for mixtures of continuous and discrete models. Active inference in this setting is more elaborate and rests upon planning and the evaluation of affordances. See **Box 2**.

Box 2. Active inference and affordance

Active inference formulations of sentient behavior rest upon equipping predictive processing schemes with reflexes, such that predicted behaviors are enacted (Friston, Mattout et al. 2011). However, in hierarchical schemes based upon discrete representations, these predictions inherit from a process known as planning as inference (Attias 2003, Botvinick and Toussaint 2012, Kaplan and Friston 2018). In other words, deep adaptive behavior rest upon the selection among plausible plans that are scored in terms of their likelihood. This likelihood is, technically, evaluated in terms of the *expected free energy* that would follow from committing to a particular course of action (Parr and Friston 2017, Da Costa, Parr et al. 2021).

Expected free energy can be decomposed into two kinds of affordance; namely, epistemic affordance that drives exploratory (information-seeking) behavior and instrumental affordance that drives exploitative (preference-seeking) behavior (Da Costa, Parr et al. 2021). These two components reflect the dual aspects of Bayes optimality; namely, making Bayes optimal decisions and complying with the principles of optimal Bayesian design (Lindley 1956).

Crucially, the balance between epistemic and instrumental affordance depends upon the precision afforded prior preferences, of the kind that engender reward seeking or avoidance behavior (Schwartenbeck, FitzGerald et al. 2015, Schwartenbeck, Passecker et al. 2019). Again, we see a key role for neuromodulatory regulation of precision; in this instance, in terms of balancing the epistemic and instrumental imperatives for action; and, on some readings, the balance between an immediate homeostatic, reflexive response and a more prospective allostatic response (Corcoran, Pezzulo et al. 2020).

The functional anatomy that mediates this balance is the focus of this paper. Of particular relevance is the balance of exploratory versus exploitative behavior that may rest sensitively on the precision afforded representations of prior preferences and goals – and the neuromodulatory mechanisms this affordance implicates.

Feedforward and Feedback Forms of Motor Control in the Dorsal and Ventral Cortices

In the seminal model of cortical visual processing (Ungerleider & Mishkin, 1982), visual processing in V1 diverges into a ventral lateral extrastriate stream involved in *object* identification and a dorsal (inferior parietal lobe) stream conveying *spatial* information. Even early on, it was noted that the dorsal stream may not be best characterized as processing spatial information but rather in motor control processing (Goodale & Milner, 1992; D. M. Tucker & Luu, 2012). With the recognition that the dorsal stream is involved in motor control, the concept has been further elaborated, such that the dorsal stream is now forked into two streams centered around the inferior and superior aspects of the parietal lobe. The inferior parietal cortex is involved in object related grasping actions (as seen in disorders such as apraxia following inferior parietal damage) — a form of motor control in which an object provides direct guidance to the action (closed-loop control) (Rizzolatti & Matelli, 2003). In contrast, the superior parietal

cortex is involved in reaching, with strong somatosensory guidance (Luppino & Rizzolatti, 2000), towards visual inputs from the periphery (as seen in optic ataxia following damage to the superior parietal cortex). Reaching actions are aligned with feedforward control, in which an action is launched with minimal feedback guidance (open-loop control).

These concepts of feedback (closed-loop: ventral, paleocortical derivation) versus feedforward (open-loop: dorsal, archicortical derivation) kinds of action (Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; D. M. Tucker & Luu, 2012) may help in interpreting the interactions among sensorimotor networks of the primate neocortices. **Table 2** summarizes the modes of control that can be aligned with the dorsal and ventral limbic divisions, and that appear to reflect the extension of elemental brainstem and midbrain arousal/motivation control systems into the modes of limbic regulation. The alignment of limbifugal ("descending" or top-down endogenous) control with the dorsal limbic division, and limbipetal ("ascending" or bottom-up exogenous) control with the ventral limbic division, is an obvious over-generalization, because both these directions of control are manifested by the neocortical architecture, in both dorsal and ventral corticolimbic pathways. However, we argue that there is a *relative* specialization that has become integral to the feedforward expectancies that dominate in the dorsal corticolimbic networks, and the feedback specification and error correction that dominate in the ventral corticolimbic networks, as we explain below.

Control Mode	Dorsal Limbic	Ventral Limbic
Dominant Cortical Connectivity Control	Limbifugal: Direction of connections starting with allocortex leading outward to isocortex.	Limbipetal: Direction of connections starting with isocortex leading inward to allocortex.
Attentional Bias (Tucker & Williamson, 1984)	Phasic Arousal	Tonic Activation
Cybernetic (Goldberg, 1985)	Feedforward (open-loop): Projections of internally generated intentions and urges.	Feedback (closed-loop): Feedback control of actions constrained by environmental stimuli.
Active Inference (Schwartenbeck et al., 2019)	Epistemic	Instrumental
Behavioral Control (Cisek, 2022)	Exploration	Exploitation
Embryologic Control	Hem	Antihem

Table 2. Forms of control aligned with dorsal and ventral divisions of the limbic system.

The cytoarchitectonic differences between dorsal and ventral divisions of the neocortex may be relevant to these functional biases or specializations. Greater predominance of pyramidal neurons in the dorsal division, compared with elaboration of the granular layer in the ventral division, was observed in monkey studies by Pandya and Seltzer, and also confirmed in human brains in the Yakovlev collection (Eidelberg & Galaburda, 1984; Galaburda, 1984). This cytoarchitectonic difference may be relevant to the greater feedforward, limbifugal control in the dorsal division, given that this control is exerted in the Structural Model by infragranular to supragranular projections. Similarly, the elaboration of the granular layer in the ventral division may support greater limbipetal constraint and feedback control, given that this inhibitory control (controlling the error-correction implicit in active inference) is mediated in large part by the inhibitory interneurons in granular layers 2-3 and 4 (Tucker & Luu, 2012).

Figure 2 shows cortical inputs to motor and premotor cortices of the frontal lobe. The first thing to notice in Figure 2 is that aside from PMv (which is of paleocortical lineage), the remaining premotor areas are of archicortical lineage (Pandya & Yeterian, 1996). Second, the archicortical lineage is strongly connected with the primary somatosensory areas and the superior parietal cortex. Third, dorsal PMd does not receive projections from the inferior parietal cortex. Fourth, PMv does not receive inputs from the cingulate cortex, which is a structure of archicortical lineage. Finally, the PMv has inputs from the insula (which carries gustatory and olfactory information associated with ventral limbic networks).

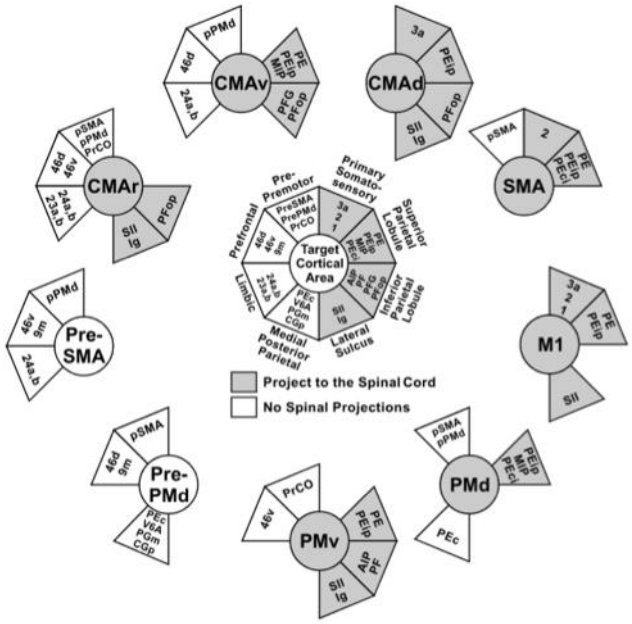


Figure 2. Connections of motor and premotor areas. Gray areas = premotor areas, white areas = pre-premotor. From Dum and Strick (2005). CMAd, dorsal cingulate motor area; CMAr, rostral cingulate motor area; CMAv, ventral cingulate motor area; M1, primary motor cortex; PMd, dorsal premotor area; PMv, ventral premotor area; SMA, supplementary motor area.

To Dum and Strick (Dum & Strick, 2004), the presence of these multiple premotor areas suggests that they provide different aspects of motor control. While not accounting for all of the premotor areas, following Goldberg's integrative review (Goldberg, 1985) we have proposed a higher-level organization of motor control: a feedforward projection (dorsal limbic) and a sensory constrained feedback (ventral limbic) form of control rooted in adaptive (visceral) salience (D. M. Tucker & Luu, 2012; Don M. Tucker & Luu, 2023).

The importance of visual feedback for PMv is shown through evidence, from primates, that visual feedback provides fine tuning of object grasping, as evinced by neuronal correlates in the PMv (Murata, Fadiga, Fogassi, Gallese, Raos, & Rizzolatti, 1997; Umilta, Brochier, Spinks, & Lemon, 2007). For example, in an object grasping task, PMv neurons show preferences for particular grasped objects. Clinically, damage to the inferior parietal lobe produces ideomotor apraxia, which is characterized as an inability to form gestures, such as grasping an object, based on internal representation of the object. The visceral homologue of this form of motor control arises from integration of visceral responses with sensory information, as seen in the insula and

amygdala. In this sense, (closed-loop) feedback control is rooted in what Neafsy considers viscerosensory cortex (i.e., insula), implying the adaptive visceral basis of feedback control (Neafsey, 1990).

Another notable aspect of the connectivity of the premotor areas is the lack of limbic cingulate cortex connectivity with PMv; only the ventral and rostral cingulate motor areas (CMAv and CMAr, respectively) are directly connected to the cingulate division of limbic cortex. The role of the cingulate cortex in visceral and autonomic responses is now well recognized and has been argued to be the basis of visceromotor control (Neafsey, 1990). The feedforward (open-loop) nature of this form of motor control can be seen in both animal studies and clinical observations. In CMAs, movement planning is not associated with perceptual guidance, but rather with general contextual information, such as tracking reward level, and movement initiation (Shima & Tanji, 1998), suggesting that the CMA is involved in the selection of action based on reward expectancy. In a different study it was found that cells in the supplementary motor area (SMA) were not responsive to visual cues to initiate a movement, but rather they appeared to be active in the preparatory phase of movement to code a series of actions (Tanji & Shima, 1994). Thus, a common theme across these studies is the internal representation of the intention to act based on internal representations of contingencies (either reward or ordering of movement).

In humans, the role of the anterior cingulate cortex (ACC) in movement initiation has long been appreciated. In severe cases — where large portions of the ACC is lesioned bilaterally — akinesia and akinetic mutism are the prominent symptoms (Barris & Schuman, 1953). In human studies, the intention to act is reflected in the readiness potential (from EEG recordings) localized over the medial frontal areas, apparently arising from the SMA (Libet, 1985). In a clinical case study, it was reported that when the CMA was stimulated in a patient, an "irresistible urge to grasp" was reported, even when there was not an obvious target to grasp or when the patient's eyes were closed (Kremer, Chassagnon, Hoffmann, Benabid, & Kahane, 2001). This may be an example of how a strong urge may appear in conscious experience, without a clear target in the world, exemplifying the feedforward motive control of action.

Dual Pallial Roots of Cortical Evolution and Function

Understanding the unique regulatory biases that we propose for the dorsal and ventral divisions of corticolimbic organization of motor control may require a theoretical model of how these divisions evolved their complementary control properties. Although our goal in this paper is to trace the subcortical foundations for these dorsal and ventral limbic-cortical divisions, the evolution of the 6-layered neocortex from the primordial telencephalon described by Puelles (2001) suggests to us that the dorsal neocortex retains as its dominant feature the primordial pallial (glutamatergic, pyramidal, excitatory) architecture, whereas the dominant granular feature of the ventral neocortex (Eidelberg & Galaburda, 1984; Galaburda, 1984) reflects the particularly strong incorporation of subpallial (GABAergic, interneuron, inhibitory) neural elements into the neocortical architecture.

Sanides (Sanides, 1964) proposed that cortical evolution is rooted in the elaboration of two primitive cortical moieties: the primitive olfactory (ventral division) and hippocampal (medial division) cortices. A schematic overview is given by **Figure 3** from Giaccio's integrative review paper (Giaccio, 2006). At a broad level, the proposal is that (from the perspective of primate cortex) the hippocampus gave rise to the dorsal cortices, including ACC, medial prefrontal and

premotor areas, lateral prefrontal cortex to the level of the principal sulcus, PMd and motor areas of trunk and limbs.

Although the hippocampus ends up on the ventromedial surface of the temporal lobe in primates including humans, this simply reflects the displacement given the enlargement of the neocortex; the hippocampus retains its connectivity with the Papez circuit and dorsal neocortical division (as shown in Figure 12 below). In post-Rolandic regions, the mediodorsal cortices include the posterior cingulate cortex, ventromedial temporal and occipital areas, medial parietal lobe, lateral aspects of the parietal lobe to the level of the intraparietal sulcus and primary somatosensory areas related to trunk and limb representations.

In a complementary way, the ventral cortices are rooted in the olfactory cortex, which gave rise to the insula, temporal pole, orbitofrontal cortex, ventral prefrontal cortex up to the level of the principal sulcus laterally, the PMv and motor regions up the level of neck, face and head representation. Posterior to the Rolandic sulcus, the ventral cortices include the secondary somatosensory area, auditory areas, secondary visual areas of the lateral surface of the occipital lobe (Pandya & Yeterian, 1996).

Modern studies have identified the pallial sectors corresponding to the two architectonic moieties; the ventral pallium is equivalent to the olfactory cortex and the medial pallium is equivalent to the hippocampus. Two additional pallial fields, dorsal and lateral Puelles et al., (L. Puelles, 2017) are observed in amniotes (but see (L. Medina, Abellan, & Desfilis, 2022), who argue for additional fields). These primordial pallial fields are essentially tri-layered. The dorsal pallium is now accepted to be the ancestral origin of the neocortex. The ventral aspects of the mesocortex, a cortical type with laminar structure that is intermediate between allocortex and isocortex, arise from the lateral pallium (L. Puelles, 2017). There is

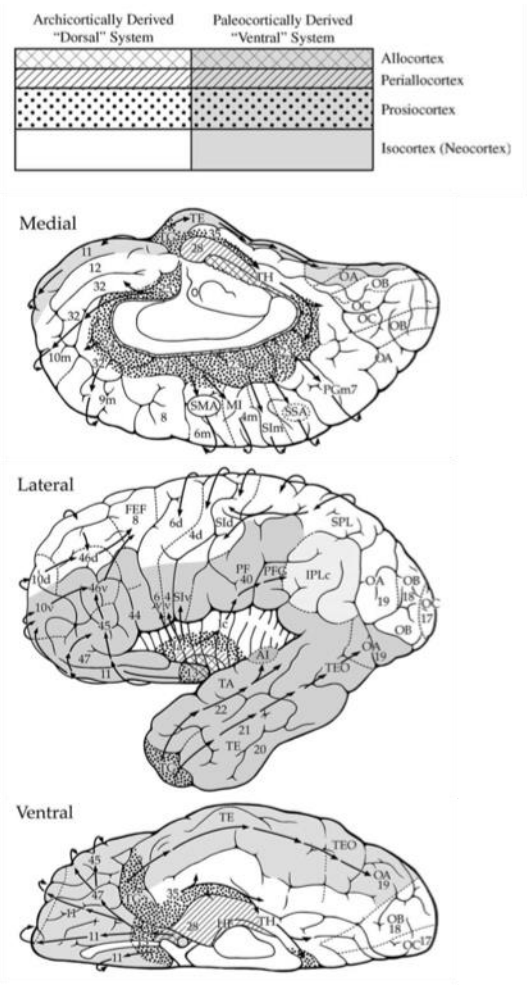


Figure 3. From Giaccio (2006): The Dual Origins of the Cerebral Cortex. "Cortical areas arising from the amygdala and adjacent olfactory cortex form the *ventral* (paleocortical) system and are shaded gray. Cortical areas derived from the hippocampal-induseal moeity form the *dorsal* (archicortical) system, and are unshaded. The caudal Inferior Parietal Lobule (IPLc), lying at the abutment of both protogradations, appears to be a transitional area (Eidelberg and Galaburda, 1984), and is shaded intermediately. Arrows indicate (multiple) lines of cortical development arising by outgrowth from each of these primordial moieties. Each line constitutes a "functional unit" within the cerebral cortex, and shows progressive laminar differentiation as one moves away from the central "limbic core." Each line also represents a chain of bidirectional short cortico-cortical connections linking successive architectonic stages within each line, thus providing inbound and outbound pathways for information flow to/from the limbic core. Abbreviations: AI, primary Auditory cortex; FEF, Frontal Eye Field; I, Insula; IPL, Inferior Parietal Lobule; SI, primary Somatosensory cortex; SMA, Supplementary Motor Area; SPL, Superior Parietal Lobule; SSA, Supplementary Somatosensory Area; a, anterior; c, caudal; d, dorsal; m, medial; v, ventral. Otherwise, numerical designations for cytoarchitectonic fields are from Brodmann (1909), letter designations after von Economo (1925)."

a suspected, but yet to be identified, field that would make up the dorsal mesocortex (García-Cabezas, Hacker, & Zikopoulos, 2022).

The framework of these pallial fields provides a basis for understanding the evolution of the cortex. Specifically — as noted by Garcia-Cabezas et al. (and consistent with Sanides) — the laminar elaboration of cortical types (i.e., from allocortex to mesocortex to neocortex) begins in the two allocortical pallial fields that are rooted in embryonic patterning centers: the hem adjacent to the medial pallium and antihem of the ventral pallium (**Figure 4**). The medial and ventral pallia take on the fate specified by the transcription factors that define these centers. The antihem is specified by the Pax-6 transcription factor, and Pax-6 is expressed in a rostroventrolateral (high) to caudodorsomedial (low) gradient. Wnt and Emx2 specify the hem patterning (Subramanian, Remedios, Shetty, & Tole, 2009) and Emx2 is expressed in an exact complimentary gradient to Pax-6.

Early on, when examining the cytoarchitecture of the cortex, Sanides (1964) noted that the 6-layered neocortex appears as an island, surrounded by rings of cortices with fewer layers. He posited that cortical evolution reflects increasing laminar differentiation that starts from the two primitive cortical fields, ending with the highly laminated primary sensory cortices. Recent evidence is in support of this ring architecture (García-Cabezas, Hacker, & Zikopoulos, 2022; Luis Puelles, Alonso, García-Calero, & Martínez-de-la-Torre, 2019), which can be placed within the modern evidence of hem and antihem patterning zones.

Because cortical evolution is marked by the notable expansion of the neocortex, accounting for how this occurred is marked by controversy (Luis Puelles, 2022a). A core issue is what events can reasonably account for this expansion. The controversies illustrate nuanced differences (particularly when comparing cortical evolution from different amniote lineages such as reptiles, birds and mammals) about homology of pallial structures. However, a common theme has emerged, even between researchers with very different views of homology (Karten, 1997)(L. Puelles, 2017). This common theme is rooted in the proposal that neocortical evolution has been directed by the extension and reallocation of developmental genes that regulate brain development, particularly those expressed by the hem and antihem.

For Karten, the neocortex was proposed to have developed from the “reshuffling” of patterning zones, particularly of the contribution of the zone that gives rise to the dorsal ventricular ridge (DVR), a pallial structure in birds and reptiles that receives sensory thalamic inputs, relayed through the tectum (i.e., collothalamic). From this perspective, cells (including input and output types) that make up the DVR became incorporated, through tangential migration, into the dorsal pallium. Puelles et al. (L. Puelles, 2017), while believing that the neocortex reflects expansion of the dorsal pallium with no contributions from DVR pallial equivalents, also recognized that the development of the neocortex could arise through both tangential migration of cells from the ventral pallium to the dorsal pallium, as well as some alterations in the developmental mechanisms underlying the dorsal pallium.

Broadly, Karten was correct in so far as the reptilian DVR is considered equivalent to the ventral pallium and modern evidence shows tangential migration of ventral pallium cells during embryonic development. However, other specifics of Karten’s prediction have not been supported (Luis Puelles, 2011). For example, output neurons of the cortex (i.e., infragranular layers) are more related to the medial pallium than the ventral pallium (see below).

The attractiveness of Karten’s hypothesis for understanding both pallial and subpallial contributions is that it attempts to explain the similarity between the mammalian collothalamic inputs (discussed below) into the neocortex (particularly the lateral regions of the brain such as

the auditory and extrastriate visual cortex) and the DVR, which clearly has collothalamic inputs in reptiles. Relative to the Pax-6 ventral pallial patterning, using a Pax-6 knock-out mouse model it has been shown that development of the collothalamic pallial recipients (e.g., lateral occipito-temporal cortex and amygdala) is altered. Rather than forming a cortical sheet, a mound that bears resemblance to the reptilian DVR is produced (Butler & Molnár, 2002). The parallels between ventral pallium and the reptilian DVR are thus fairly strong.

Montiel and Aboitiz (Montiel & Aboitiz, 2015) also recognized the potential significance of patterning center modifications and specific thalamic inputs to the evolution of the mammalian neocortex. In their proposal, they make explicit the patterning mechanisms that may give rise to expansion of the dorsal pallium and development of the six-layered isocortex (**Figure 4**). According to them, the neocortex — while retaining its position within the dorsal pallium — expanded through the elaboration of both the hem and antihem. Specifically, the dorsal pallium grew through enhancement of hem transcription factors (e.g., Wnt). The antihem, expressing Pax-6, increased neuronal proliferation, contributing to cells in the upper layers of the neocortex. Through the spatio-temporal expansion of the patterning bases of the hem and antihem, and to some extent also a rostral patterning center, tangential migration of their respective cells overlapped in the dorsal pallium. The shifting of the dorsal, ventral and lateral pallial fields in this scenario also brought along the collothalamic projections that target the DVR in reptiles and birds.

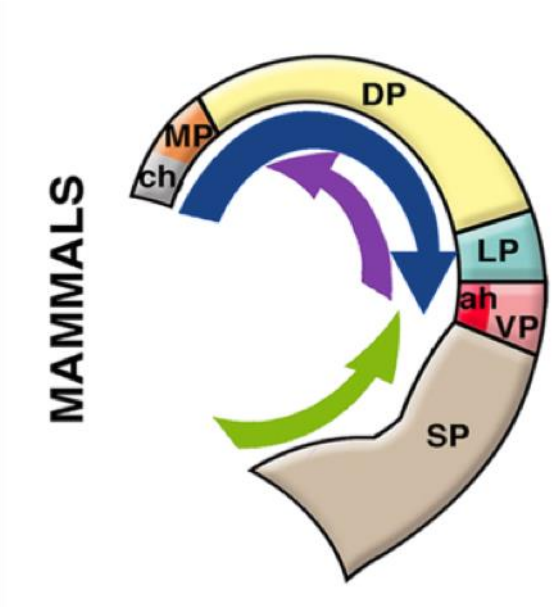


Figure 4. Hypothetical model of telencephalic signaling driving pallial expansion in mammals (from Montiel & Aboitiz, 2015). ah, antihem; Ch, cortical hem; DP, dorsal pallium; LP, lateral pallium; MP, medial pallium; SP sub pallium; VP, ventral pallium. Blue arrow illustrates dorsal signaling (Wnt) upregulation from the Ch to expand the DP. Purple arrow illustrates ventral signaling (Pax-6) upregulation into the DP. Green arrows illustrate subpallial signals.

Several findings support this proposal of Montiel and Aboitiz (2015). Teissier et al. (Teissier, Waclaw, Griveau, Campbell, & Pierani, 2012) showed that neural progenitor cells derived from the ventral pallium migrate tangentially throughout the pallium. Selective ablation of this population of cells results in a reduction in cortical thickness, particularly the supragranular layers. Pollen, et al. (Pollen et al., 2015) showed that another class of neural progenitor cells, known as outer radial glial cell — and abundantly located in the outer subventricular zone — contribute heavily to development of neurons of the supragranular layers (Molnár et al., 2019). Although the outer subventricular zone is seen in the dorsal pallium, which may seem at odds with the proposal that antihem patterning contributes to the superficial layers, Pollen, et al. (Pollen et al., 2015) showed that in early human embryonic development, genetic expression of outer radial glial cells appears in the ventricular zone. That they may have origins in the ventricular zone of the ventral pallium is seen by their generation in the ventral (as well as lateral) pallium in mice, where there is not a distinct outer subventricular zone.

Complementing these findings, Cajal-Retzius cells, which guide development of pyramidal cells, derived from the ventral pallium and can migrate into other pallial zones during

development and bring with them the patterning basis specified by their origin (Bielle et al., 2005). Bielle et al. found that when Cajal-Retzius cells derived from the ventral pallium and septum are ablated during development, the lateral cortex is compromised (showing a reduced thickness). In contrast, regions of archicortical origins, such as the cingulate cortex, develop normally. Interestingly, a special class of Cajal-Retzius cells (lot cells), possibly originating from the ventral pallium (Frade-Pérez, Miquelajáuregui, & Varela-Echavarría, 2017), guide development of the lateral olfactory tract and olfactory cortex. These cells go through a secondary migration during development towards the dorsal pallium. When this secondary migration is prevented, development of pyramidal cells in cortical layers 2/3 is compromised (de Frutos et al., 2016), consistent with the embryological origins of supragranular layers 2/3 from ventral pallial regions.

Additional evidence shows that cells of upper layers (2/3) of the neocortex express more genes that are shared with the olfactory cortex, when compared to deep layer (5/6) cells (Luzzati, 2015). Similarly, cells of deep layers (5/6) are more related to the archicortex, from the perspective of cytoarchitectural continuity of the deep layers of the dorsal pallium with the subiculum, and that expansion of medial pallial patterning mechanisms likely explains the archicortical cytoarchitecture in the dorsal pallium (Hevner, 2016).

Thus, considering the dual archicortical and paleocortical roots of neocortical evolution, several findings suggest that the neocortex can be seen to represent a stacking of the two (archi in 1, 5/6 and paleo in 2/3) allocortices (Luzzati, 2015; Shepherd, 2011). The functional specializations of archicortical and paleocortical divisions of the cerebral cortex are thus woven together with the dominant cytoarchitectonics of the limbifugal and limbipetal directions of processing, in ways that are complex but can be interpreted to support the feedforward (limbifugal) control bias of the dorsal division versus the feedback (limbipetal) bias of the ventral division.

The organization of a 6-layered neocortex not only involved embryological mutations that fused elements of the ventral paleo pallial field into layers 2/3 of the neocortex but also incorporation of inhibitory GABAergic neurons from the ganglionic eminences into all cortical layers (Rakic, 2009). Layers 2/3, together with layer 4, reviewed below, may provide the unique inhibitory (constraint) control influences of the collothalamic aligned system. In this way, the evolutionary incorporation of the subpallial GABAergic elements to form the 6-layered neocortex seems to have emphasized the role of layers 2/3 and 4 within the paleocortical-derived ventral division, giving this division of neocortex its granular-dominant appearance as observed by Eidelberg and Galaburda (1984).

In the primitive allocortices, inputs come in the from the top layers (i.e.,. through contacts with apical dendrites). However, in the neocortex, thalamic inputs arrive in layer 4 and project to excitatory stellate cells. It is the stellate cells — a new type of neuron that appears with the evolution of the neocortex — within layer 4 that give this layer its granular appearance. Luzzatti (Luzzati, 2015) found that cells of layer 4 are closely related to cells of layers 2/3, from the perspective of shared genes. Yet layer 4 cells also show some relation (albeit less) to layers 5/6.

Stellate cells start out as pyramidal cells and take on their stellate appearance through the retraction of apical dendrites. This retraction is dependent on input from the thalamus (Callaway & Borrell, 2011). Because of the importance of thalamic input — for formation of stellate cells — positional control of cells during developmental migration is revealing. Doublecortin (DCX) is a protein abundantly expressed by cells in layer 2. DCX is prominent in cortex that forms a network involved in object (i.e., non-spatial) processing ((Luzzati, 2015), see **Figure 5**), overlapping with the ventral network of feedback control as described above. Oishi et al., (Oishi et al., 2016) showed that DCX (along with the protocadherin20 protein, Pcdh20) specifies accurate positioning of cells to layer 4. Pcdh20 is interesting in that it also appears to regulate apical dendritic morphogenesis, such that in its absence, Oishi et al. postulated that the apical dendrites can be "stuck" to the marginal zone (where Cajal-Retzius cells reside), reducing their retraction in response to thalamic activity.

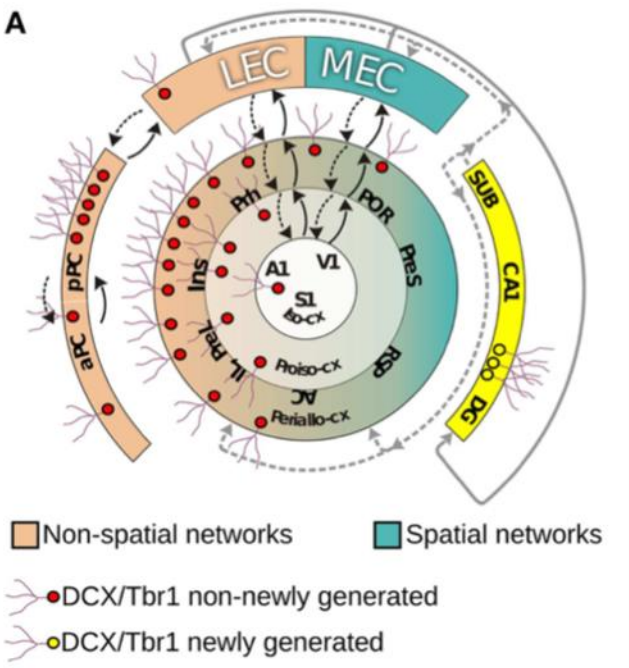


Figure 5. From Luzzati (2015). Distribution of DCX/Tbr1 cells (red). Cortex is organized according to concentric rings (after Sanides, 1964) with primary sensory cortices (A1, S1, V1) at the center and olfactory (anterior and posterior piriform cortex, aPC and pPC, respectively), hippocampus cortices (SUB, subiculum; CA1; DG, dentate gyrus) and lateral and medial enthorhinal cortex (LEC and MEC) at the edges. AC, anterior cingulate cortex; IL, infralimbic cortex; Ins, insula; PreL, prelimbic cortex; PreS, presubiculum; Prh, perirhinal cortex; POR, postrhinal cortex; RSP, retrosplenial cortex.

Further insights into the development of stellate cells are gained by examining the primary motor (i.e., agranular) cortex, where layer 4 was found to be missing as in Brodmann's initial characterization (Shipp, 2005). However, more recent observations have identified a layer 4 (García-Cabezas & Barbas, 2014; Yamawaki, Borges, Suter, Harris, & Shepherd, 2014). Importantly, Yamawaki et al. identified the layer 4 microcircuitry within primary motor cortex. Specifically, putative layer 4 cells — that receive afferents from the motor thalamus — project to layers 2/3. Furthermore, there is a lack of long-rage input-outputs from cells within this layer. A unique feature, however, is that in the motor cortex, the layer 4 neurons are more like pyramidal cells than stellate cells in that they show greater branching and lower density of arborization in layers 2/3. This architecture is more similar to a higher-order association cortex than a primary sensory area. Yamawaki et al. suggest that the evolution of layer 4 for primary sensory cortex,

when compared to agranular motor cortex, may reflect a change in cytomorphology rather than a change in circuitry (Yamawaki et al., 2014).

According to the dual-origin, double-layered model of neocortical evolution, recognizing that the neocortex receives direct thalamic input into layer 4 (even as projections to layer 1 are retained), speaks to the following hypothesis for the evolution of layer 4. The progressive lamination — namely, the addition of layers 2, 3 and 4 within the primordial allocortical architecture of 1, 5, 6 — reflects a co-option of ventral pallial (collothalamic regulated) developmental mechanisms, consistent with the DCX nature of stellate cells.

Perhaps consistent with this general evolutionary trend for differentiation of columnar architecture in the neocortex, in the primitive allocortex (including dorsal pallium of turtles) inhibitory neurons are relatively sparse and their types are few. In contrast, in the mammalian neocortex and also the hippocampus, inhibitory neuron types are many and make up about 20-30% of all cells (Markram, Toledo-Rodriguez, Wang, Gupta, Silberberg, & Wu, 2004). Unlike pyramidal cells, inhibitory neurons, for the most part, are restricted in their arborization. Within the canonical microcircuit framework, the evolution of granular cortex has involved increasing intralaminar inhibition compared to the primordial allocortical function, which reflects a more diffuse 3-layered auto-associative network architecture (Beul & Hilgetag, 2015).

Predictive Coding and Laminar Organization

Considering these several lines of evidence — on the origins of the 6-layered neocortex— an attractive speculation is that the evolved origins of cortical laminar development could explain the proposed role of supra and infragranular layers in predictive coding theory See **Box 1**. Bastos et al. (Bastos, Usrey, Adams, Mangun, Fries, & Friston, 2012) propose that pyramidal cells of the infragranular layers represent expectations that are passed (in a limbifugal direction) as predictions to supragranular layers of lower-order cortex, where they are mediated by interneurons of the superficial layers. These cells then pass the expectations downward (in the cortical column rather than to another cortical area) to infragranular cells to update predictions of that particular column for the next stage of limbifugal prediction outflow. Supragranular pyramidal cells represent prediction errors and pass (in a limbipetal direction) these to layer 4 of the next higher-order cortical area, where they are received and represented by cells of this layer.

The prototype origin of limbifugal projections — in the primitive pallium — is the archicortex, wherein multimodal sensory inputs arrive in the archicortex, and spatial-navigation maps are constructed. This information is then passed out in the limbifugal direction. On the other hand, the paleocortex is inherently limbipetal in nature, passing information that it receives from the olfactory bulb towards the archicortex and other pallial and subpallial structures (e.g., the amygdala). The cortical process of predictive coding, combining the formation of predictions in the limbifugal direction with the attending error-correction in the limbipetal direction, clearly occurs in both dorsal and ventrolateral divisions of neocortex. However, in line with our hypothesis of duality of control pathways, there may a different emphasis or bias — implemented via modulatory (precision) control – in the dorsal and ventral corticolimbic divisions. There are limbifugal predictions in the ventral neocortical division, to be sure, but perhaps the overall processing is dominated by the prominent granular layer in ways that support the constraint and restriction of processing that is consistent with focus on objects; i.e., affording more precision to object-related prediction errors. We might think that the prediction of an object has inherently greater constraint (in the ventral division) than the prediction of a context or exploratory space (in the dorsal division).

The cognitive skills of the dorsal division require error-correction as well as prediction, but the bias toward the primordial pallial pyramidal architecture, emphasizing layers 1, 5 & 6, might be specialized to elaborate predictions, thereby providing the dorsal division with not only spatial memory, but the capacity for generative, exploration of context (Tucker & Luu, 2023).

The overall effect is that active inference not only takes different forms in the two divisions, but the combined function of the neocortex (and the organism's adaptive success) requires a superordinate balance of the dorsal and ventral biases, combining both impulse (prediction bias) and constraint (error-correction bias) in the functional networks of the cerebral cortex.

This characterization of different adaptive biases of the dorsal and ventral neocortical processing streams is based on our observations of different behavioral and cognitive biases of the dual limbic divisions, including the impulsive bias of the dorsal limbic Papez circuit and the constraint bias of the ventral limbic Yakovlev circuit (Tucker & Luu, 2023). In the next sections we describe how subcortical structures, and their organization may align with what we see as the dual cybernetic systems of the neocortex. It is then the continuity of these systems and their vertical integration across the neuraxis (achieved in large part by what we describe as the collothalamic midbrain and lemnothalamic brainstem control systems) that may help explain the motive control for the primitive behavioral mechanisms of active affordance. These are then the evolved patterns of control that we propose may underlie the neocortical cognitive mechanisms of active inference.

Cortical Duality from Subcortical Duality

Dual Pathways Through the Thalamus

The lemnothalamic and collothalamic pathways were first described by Butler (Ann B Butler, 1994b) in an evolutionary-developmental analysis of the continuity of projection systems to the thalamus in pallial evolution. She observed that there are certain projections from the midbrain to specific nuclei of the thalamus that are highly conserved in vertebrates. Drawing from the term *colliculus* of the midbrain, Butler described these pathways as *collothalamic.* In early vertebrates, collothalamic nuclei target the subpallial striatum. As the pallium expanded and collothalamic inputs appeared in the pallium, these collothalamic projections were restricted to certain cortical regions. Butler (Ann B Butler, 1994a) observed that the collothalamic division of the cortex includes the auditory cortex, the lateral aspects of the temporal lobe, temporoparietal areas and insula.

It is remarkable that Sanides (1970) proposed a coherent evolutionary framework, based on cytoarchitectonics, that aligns these cortical regions along a single axis (paleocortical-ventral) that is now recognized as being defined by its collothalamic recipients. As noted above, Butler and Molnar (Butler & Molnár, 2002) showed that Pax-6 knock-out mice exhibit a developmental abnormality of the lateral aspects of the pallium, such that the structure is more like a pallial mound that resembles the reptilian DVR, a target of collothalamic projections in reptiles.

In complement to the collothalamic division, Butler described *lemnothalamic* nuclear group that receives afferents from lower brainstem areas through the lemnisces (ribbon-like fiber

tracts), bypassing the midbrain (also see (W. J. H. Nauta & Karten, 1970). The lemnothalamic projections target the pallium specifically. The lemnothalamic division of the cortex includes both limbic regions (such as the hippocampus and cingulate areas) and neocortical areas (such as the primary visual and somatosensory cortices), which are part of the archicortical, dorsal corticolimbic trend identified by Sanides (1964; 1970). **Figure 6** shows Butler's conceptualization of the *morphotypes* or generic forms of the lemnothalamic and collothalamic projections in jawed vertebrates (left), with a simple separation of lemnothalamic and collothalamic projections. A stem reptile is shown at right, with increasing complexity of lemnothalamic targeting and continued specificity of collothalamic projections for the striatum, but now with complementary pallial projections. Thus, in these morphotypes, the basic pallial-subpallial division of forebrain thalamic projections is clear. In mammals, a major theme for interpretation is how these two thalamic projection divisions came to influence the functions of the increasingly complex cerebral cortex in evolution.

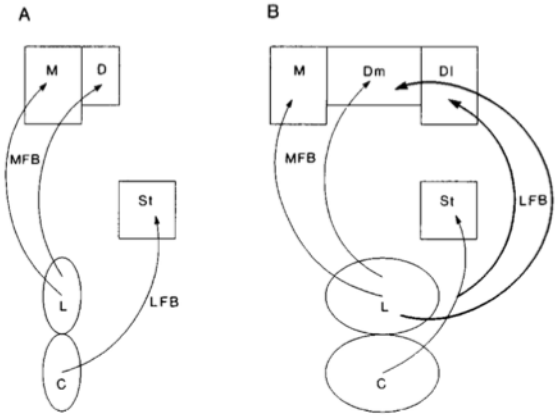


Figure 6. Morphotype for jawed vertebrates (A) and stem reptile (B). C, collothalamus; D, dorsal pallium; Dm, medial division of dorsal pallium; Dl, lateral division of dorsal pallium; L, lemnothalamus; LFB, lateral forebrain bundle; M, medial pallium; MFB, medial forebrain bundle; St: striatum, (From Butler, 1994b).

Duality in the Posterior Hypothalamus

Figure 7c shows the prosomeric model of the organization of the neuraxis based on the pioneering work of Puelles and colleagues (e.g., (Luis Puelles, Harrison, Paxinos, & Watson, 2013; Luis Puelles & Rubenstein, 2015). This model has superseded the classical columnar model **7A** that imagined longitudinal zones, extending from the brainstem to the forebrain, as the model of brain organization and development (Herrick, 1910). While no longer accurate as a model, an important aspect of the columnar model that still holds clues to understanding forebrain functional organization lies in the viscerosensory and visceromotor longitudinal domains. As can be seen in Figure **7B**, only the viscerosensory and visceromotor zones continue throughout the full extent of the forebrain, now reflected as the alar and basal plates (**7C**, (Nieuwenhuys, 2017). Although the boundary (sulcus limitans groove) that separates the viscerosensory and visceromotor zones sits slightly higher than the alar-basal boundary, putting the visceromotor nuclei in the alar plate, the progenitor domain of visceromotor brainstem cells lies in the basal plate (Luis Puelles, Tvrdik, & Martínez-de-la-torre, 2019). The basal plate nature of visceromotor organization continues into the mesencephalon (Figure 7C).

In light of rostral continuity of these two longitudinal zones, the insight provided by the prosomeric model, that the hypothalamic nuclei are part of the prosencephalon and not part of the diencephalon, becomes a key to understanding motor-related control of the basal forebrain. The posterior basal hypothalamic nuclei (particularly the subthalamic nucleus — STN, para-STN, premammillary nucleus, and mammillary body) are aligned in ways that reveal that the classic indirect (cortex-striatum-external component of the globus pallidus-STN-internal component of globus pallidus-thalamus-cortex) and hyperdirect (cortex-STN) circuitries of the basal ganglia are paralleled by indirect and hyperdirect circuits of the pallial amygdala and

hippocampus through to their posterior basal hypothalamic equivalents (Barbier & Risold (2021), which will be reviewed below.

The implication is that the posterior hypothalamic nuclei, arising from the basal plate, provide the visceromotor basis for integration of sensory functions of the entire telencephalon, which itself is derived from the viscerosensory domain of the alar plate (hp1 in Figure 7C) according to the prosomeric model. How this apparently general theme of pallial-striato-pallido-hypothalamo-thalamic organization of the forebrain relates to function and control remains to be understood fully. However, here we can already begin to see the unique ways these hypothalamic connections are differentially important to the classic dorsal Papez circuit and ventral limbic Yakovlev circuit. Barbier and Risold (2021) detail how the posterior hypothalamic nuclei control behavior differentially based on spatial (mammillary body) or internal contexts linked to visceral responses (e.g., the premammillary nucleus). In the following sections on the amygdala and septum, we discuss these hypothalamic loops in the context of dual cortical organization.

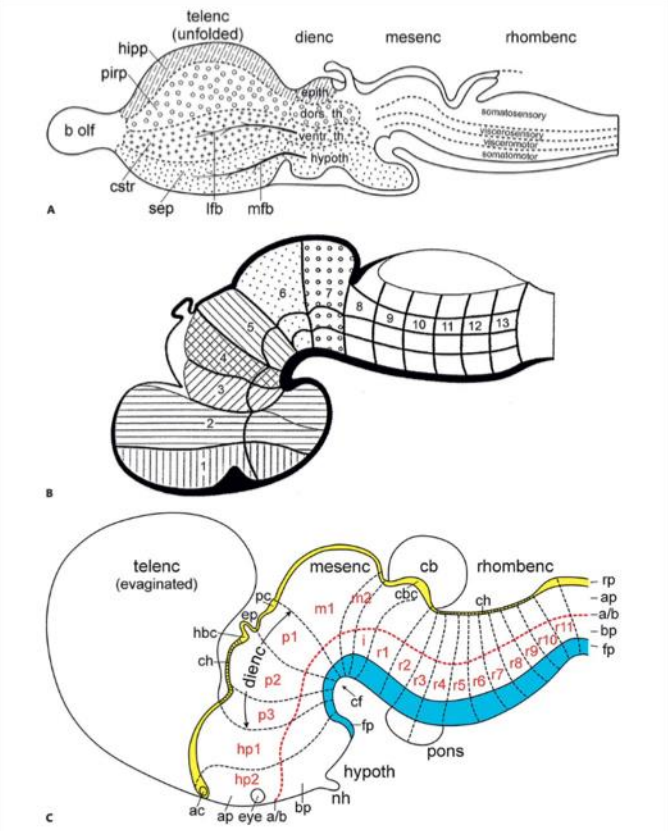


Figure 7. From Nieuwenhuys (2017) **A**. Columnar model illustrating continuity of longitudinal zones. **B**. Cellular proliferative zones that predated the prosomeric model (from Bergquist and Källen's, 1954 work). Note the extension of the viscerosensory and visceromotor zones into the most rostral aspect of the forebrain, which is captured by the alar and basal plates of the prosomeric model **C**. The prosomeric model. Note that the telencephalon is derived from the alar plate of hypothalamus (hp1). From Nieuwenhuys (2017). a/b, alar/basal boundary; ac, anterior commissure; b olf, olfactory bulb; bp, basal plate; cb, cerebellum; cbc, cerebellar commissure; cf, cephalic flexure; ch, tela choroidea; cstr, corpus striatum; dors th, dorsal thalamus; ep, epiphysis; epith, epithalamus; fp, floor plate; hbc, habenular commissure; hipp, hippocampal pallium; hp1 and hp2, hypothalomo-prosencephalic neuromeres; hypoth, hypothalamus; i, isthmic neuromere; lfb, lateral forebrain bundle; mfb, medial forebrain bundle; m1 and m2, mesomeres; nh, neurohypophysis; pc, posterior commissure; p1– p3, prosomeres; pirp, piriform pallium; rp, roof plate; r1–r11, rhombomeres; sep, septum.

Striatal and Collothalamic Bases of Amygdala Evolution

The amygdala, comprising both pallial and subpallial components, is an important integrative structure for the ventral limbic division. The pallial components of the amygdala are derived from a separate pallial field positioned caudal to the ventral pallium (Aerts & Seuntjens, 2021; L. Medina, Abellán, & Desfilis, 2019). Interestingly, Puelles et al. (Luis Puelles, 2022b; Luis Puelles et al., 2019) showed that this progenitor domain is not part of the cortical pallium at all but rather is a distinct pallial field. The connectional data suggest an alignment of the pallial amygdala with the collothalamic regulatory system. The pallial amygdala receives not only olfactory inputs but also sensory inputs from collothalamic nuclei. This collothalamic connectivity parallels the primordial avian and reptilian collothalamic connectivity with the DVR (see **Figure 8**) (L. Medina, Abellán, & Desfilis, 2019).

Certain subpallial nuclei of the amygdala are striatal-like (capsular and lateral parts of the central nucleus of the amygdala—CEAc and CEAl; medial nucleus of the amygdala—MEA). Others are more pallidal-like (bed nucleus of the stria terminals—BST, also sometimes referred to as the extended amygdala). In development, cells of the CEA and MEA primarily originate in the lateral and medial ganglionic eminences, areas that give rise to GABAergic inhibitory neurons of the striatum (Loreta Medina, Bupesh, & Abellán, 2011). In addition to receiving inputs from the pallial amygdala, the striatal amygdalar nuclei receive inputs from the insula.

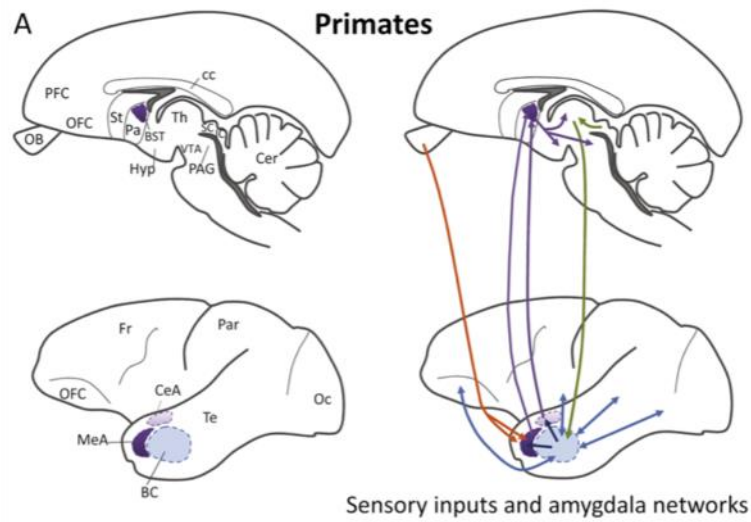


Figure 8. Major sensory inputs from the olfactory bulb and collothalamus to the amygdala and amygdalar connections with the basal ganglia (Pessoa et al., 2019). Note green arrows illustrate collothalamic inputs to the pallial amygdala. BC: Basal Amygdalar Complex, BST: Bed Nucleus of the Stria Terminalis, CC: Corpus Callosum, CeA: Central Amygdala, Der: Cerebellum, Fr: Frontal Lobe, Hyp: Hypothalamus, MeA: Medial Amygdala, OB: Olfactory Bulb, Oc: Occipital Lobe, OFC: Orbitofrontal Cortex, PA: Pallidum, PAG: Periaqueductal Gray, Par: Parietal Lobe, PFC: Prefrontal Cortex, SC: Superior Colliculus, St: Striatum, Te: Temporal Lobe, Th: Thalamus, VTA: Ventral Tegmental Area.

As described above, the analogous position of the premammillary nucleus and paraSTN of the posterior hypothalamus with the STN of the basal ganglia is appreciated by recognizing that the premammillary nucleus and paraSTN main afferents are from the BST. The BST receives inputs from the striatal amygdalar nuclei, which in turn receive inputs from the pallial amygdalar and pallial fields (analogous to the indirect loop). The BST also receives direct inputs from the insular and pallial posterior amygdalar nucleus (analogous to the hyperdirect loop, see (Barbier & Risold, 2021). Pesoa and associates (Pessoa, Medina, Hof, & Desfilis, 2019) also recognized the basal-ganglia like structure of the pallial and subpallial amygdalar circuitry.

Striatal and Lemnothalamic Origins of the Septum and Hippocampus

The anatomical coupling of the hippocampus and septum is evolutionarily primitive, and is seen in all vertebrate classes (Iyer & Tole, 2020). The common assumption is that the septum is a ventral component of the telencephalon. However, the prosomeric model shows that it is in fact developed from the roof plate of the neural tube (Luis Puelles & Rubenstein, 2015). These embryonic origins become significant in light of the new evidence showing that the hippocampus, septum and mammillary body of the hypothalamus form loops analogous to the hyperdirect and indirect loops of the basal ganglia (Barbier & Risold, 2021). Equivalent to the hyperdirect loop of the basal ganglia is the direct projection from the hippocampus to the mammillary body, which is analogous to the STN, via the fornix. The indirect loop equivalent consists of hippocampal projections to the lateral septum (striatal), which then project to the medial septum (pallidal). The medial septum in turn projects to the mammillary body.

In development, the cells of the septum are derived from multiple progenitor domains, which accounts for the different populations that make up the septum. Of particular significance for the

present review are the origins of the GABAergic neuronal population of the lateral and medial septum. The progenitors of this population arise outside of the septum itself, originating in the medial ganglionic eminence and preoptic area, suggesting that this neuronal population is subpallial. These cells then migrate tangentially into the septum during development (Iyer & Tole, 2020). In contrast, the cholinergic cells of the medial septum arise locally. The implication is that the inhibitory nature of the hippocampal-striatal loops reflects the GABAergic developmental mechanism common to the basal ganglia.

Reorganization of the Basal Ganglia to Accommodate the Dual Trends of Neocortical Evolution

The prosomeric model shows that the basal ganglia is derived from four subpallial patterning domains (Del Rey & García-Cabezas, 2022). In mammalian evolution, there appears to be considerable basal ganglia influence on both the dorsal and ventral limbic divisions, even though the primordial model of control over the basal ganglia by collothalamic projections is clear (as in Figure 6). In this section, we use additional connectivity evidence, together with the unique organization of the basal ganglia (striatal) organization in mammals, to observe that while the basal ganglia receive inputs from both dorsal and ventral cortical trends, the regulatory influence is biased towards dopaminergic (collothalamic system) control, even for lemnothalamically aligned inputs.

In the striatum of fish, amphibians, reptiles, and birds, medium-sized spiny neurons make up the majority of neurons, and they can be grouped into two neurochemically distinct types: striosomes and matrisomes. In mammals, these two classes of neurons are organized as distinct compartments (Anton Reiner, Medina, & Veenman, 1998). One way of understanding the striosome and matrix compartments is through recognizing that they receive different cortical afferents, with limbic inputs to the striosome compartment and sensorimotor inputs to the matrix compartment (Gerfen, 1992; Prager & Plotkin, 2019). How could this unique input pattern to the striatum be related to the dorsal-ventral cortical organization?

Recognizing that the pallium developed along both dorsal and ventral limbic divisions, we propose that the organization of the striosome and matrix striatal compartments might be related to the patterning of cortical evolution. As noted by some researchers, this unique mammalian organization of the striatum appears to parallel the ontogeny of thalamo-cortico-striatal connectivity (Hamasaki & Goto, 2019)(Prager & Plotkin, 2019). As reviewed below, in the mature brain these connectivity patterns provide clues to the alignment of the striosomes with the dorsal (lemno) cortical division and the matrix compartment to the ventral (collo) cortical division. In general, this alignment with basal ganglia compartments is consistent with the evidence that the dorsal cortical division is specialized for feedforward, limbifugal control (and thus striosomes) whereas the ventral division, and its dominant granular layer, is specialized for feedback, limbipetal control (and thus greater regulation by the matrix compartment).

Evidence of the changes in thalamo-striatal connectivity in evolution suggests a loss of direct sensory thalamic input to the striatum in amniotes (Anton Reiner, Medina, & Veenman, 1998). In modern day mammals, thalamic inputs into the striatum arise from the intralaminar and midline thalamic nuclei (Butler, 2008). In general, thalamic afferents to the striatum tend to target the matrix compartment, but examination of specific thalamic nuclei projections shows intriguing specific patterns. Cortical projections to the rostral intralaminar group (central median, centrolateral, and paracentral) originate from both dorsal and ventral cortical regions, including medial prefrontal cortex, orbitofrontal cortex, insula, primary motor cortex, primary somatosensory cortex and primary visual cortex (Vertes, Linley, & Rojas, 2022). Reflecting the

mix of both lemno and collo aligned cortical inputs, these nuclei do not show a bias in projections to either striosomes or matrix compartments (Fujiyama, Unzai, & Karube, 2019).

On the other hand, the paraventricular, rhomboid and paratenial nuclei of the midline thalamus preferentially project to the striosome compartment (Fujiyama, Unzai, & Karube, 2019). The rhomboid nucleus receives projections from the primary somatosensory cortex, a lemnothalamic target, as well as regions aligned with the dorsal cortical trend, such as the medial agranular cortex and ACC (Cassel et al., 2021). Cortical inputs to the paraventricular and paratenial nuclei largely overlap, and arise from the medial aspects of the frontal lobe and the hippocampus (both of dorsal cortical origin) as well as the insula (Vertes, Linley, & Rojas, 2022). Importantly, the input from the insula, aligned with the ventral cortex, is restricted to the posterior aspect of the paraventricular nucleus, suggesting an overall bias of lemno aligned inputs to this nuclear group.

Corticostriatal projections are usually understood and grouped according to cortical region (i.e., limbic vs sensorimotor). However, understanding the possible differential evolutionary origins of supragranular and infragranular layers allows a new interpretation of an important finding reported by Gerfen (Gerfen, 1992): cortical projections to the *striosome* compartment originate in infragranular layers of the mammalian neocortex, specifically deep 5 and 6, whereas the *matrix* compartment of the striatum receives inputs from the superficial aspects of layer 5 and the supragranular layers (particularly layer 3). Gerfen's findings have been disputed (Smith et al.,

2016), but this could be due to the methodology employed by Smith et al. (Prager & Plotkin, 2019).

A question that arises from the cortical projections is why the matrix compartment has commingled inputs from both layer 3 and upper layer 5, which are of different cortical origins. A feature of layer 3 and upper layer 5 neurons is that layer 3 neurons project to upper layer 5 neurons (layer 3 neurons are not connected to deep layer 5 neurons). Thus, to Thompson and Bannister (Thomson & Bannister, 2003) the layer 3 to upper layer 5 connectivity pattern (compared to deep layer 5), is more like a limbipetal pattern, from a cortical column perspective. This pattern aligns layer 3-upper layer 5 inputs with the limbipetal (i.e., collo) nature of cortico-striatal inputs to the matrix compartment and is consistent with the predictive coding account, with passing of expectations downward to infragranular cells in the same cortical column to update predictions of that particular column: see Figure 5 in (Bastos et al., 2012) and **Box 3** for schematics that consider these intralaminar projections under various predictive coding schemes.

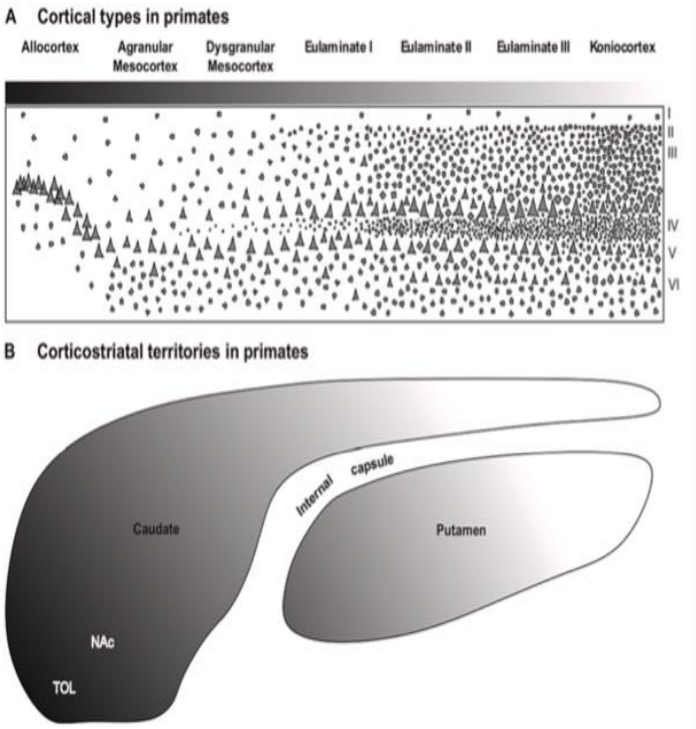
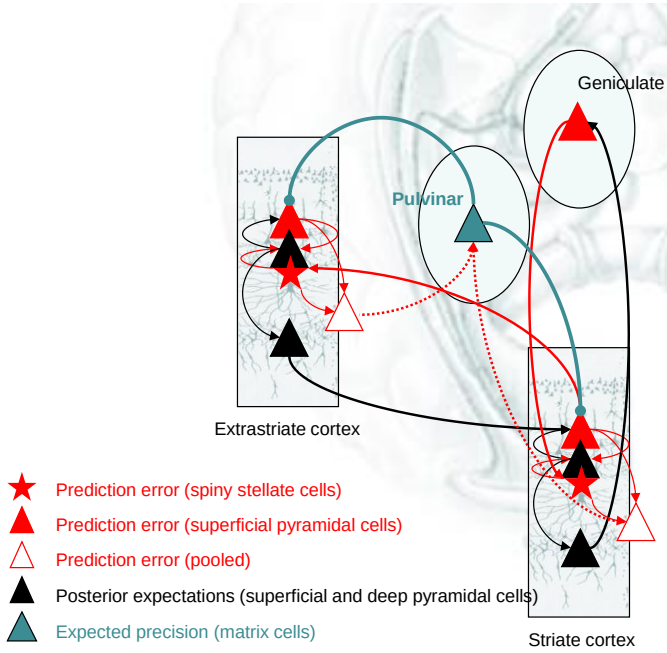


Figure 9. Laminar complexity of the cortex in primates and cortical projections to the striatum (from (Del Rey & García-Cabezas, 2022). Cortical types reflecting laminar complexity are coded by the black-white shading gradient under the cortical type labels. Note that isocortex encompasses eulaminate cortex and koniocortex. The same gradient shading is used to show cortical projections to the striatum. NAc, nucleus accumbens; TOL, olfactory tubercule.

Box 3. Predictive coding and laminar connectivity



This schematic is a more detailed version of Figure 1 that includes putative laminar-specific connections that are consistent with the precision-based predictive coding described in (Kanai et al., 2015). This architecture is based upon (Bastos et al., 2012) and conforms roughly to the known neuroanatomy and physiology of canonical microcircuits in the visual system and the laminar specificity of extrinsic connections. The key aspect of this figure is the inclusion of deep pyramidal cells encoding the amplitude of (pooled) prediction error that inform posterior expectations about precision in the (matrix cells) of the pulvinar. These cells reciprocate descending projections to modulate the gain of superficial pyramidal cells in cortex. Ascending (limbipetal) connections are in red, and descending (limbifugal) connections are in black. First-order prediction errors are shown as full red lines and second-order (pooled) prediction errors are shown as broken red lines. This schematic ignores inhibitory interneurons that mediate inferences vicariously.

This way of understanding the alignment of striosome and matrisome compartments with the dorsal cortex (lemno targeted) and ventral cortex (collo targeted) is complemented by a cortico-striatal projection scheme based on the Structural Model. In this scheme, there is a graded pattern of cortical projections to the striatum (**Figure 9**) (Del Rey & García-Cabezas, 2022), and regardless of dorsal or ventral nature of the cortical inputs, if they are of the same cortical type, their projections will overlap in the striatum. This Structural Model of cortico-striatal connectivity is complimented by the standard view of limbic cortico-striatal projections being biased towards the striosome compartment whereas sensorimotor cortico-striatal projections are biased towards the matrix compartment. That is, the presence of striosome compartment is much more prominent in the allocortico-striatal targeted regions whereas the matrix compartment is most prominent in the isocortico-striatal targeted region (Graybiel & Matsushima, 2023).

In summary, the lemno (to striosome compartment) vs collo (to matrix compartment) striatal organization scheme provides a more explicit and comprehensive explanation for the functional interpretation of the striosome (feedforward) and matrix (feedback) compartments to behavioral control, and yet it remains consistent with prior functional models of these compartments. For example, the idea that the striosome compartment is involved in predictions is captured in prior striosome compartment models by the concepts of reinforcement prediction (Houk & Adams, 1995) or mental templates for directing actions (Graybiel & Matsushima, 2023). Similarly, feedback control of the matrix compartment is also mirrored by concepts of motor generation (Houk & Adams, 1995) or state switches (Graybiel & Matsushima, 2023)) guided by predictions.

The differential controls of these two compartments are extended through their outputs. Allocortical-striatal outputs are biased toward SNc whereas isocortico-striatal loops outputs are biased to substantia nigra pars reticulata (SNr) (Gerfen, 1992). Intermediate cortical-type striatal loops output to both SN divisions. For Gerfen, this implies that they differentially affect feedback to the cortex via their connections to the SNc (more broadly modulating) or SNr (more specific).

In this explanatory framework the striosome may be more aligned with lemnothalamic (dorsal) system because of the inherent predictive nature of this system; the bias is also shown in the midline nuclei (predominantly lemno) projections to the striosome compartment (Fujiyama, Unzai, & Karube, 2019), as reviewed. However, as noted in the Overview section, dorsal and ventral divisions of neocortex have both limbipetal as well as limbifugal directions of connection, and this is acknowledged here as well.

Based on the particular bias of DA function in the basal ganglia (to be reviewed below), the type of prediction control to the cortex may be biased towards the collo form of control. An example of this bias may be given in a recent review by Amemori et al. (Amemori, Graybiel, & Amemori, 2021). These researchers showed that in the pregenual ACC to striatal loop, the pregenual ACC appears to be related to optimistic predictions of rewards. However, an anxiety network that they identify as consisting of the orbitofrontal cortex, insula and amygdala also sends projections to the striosome compartment and appear to modulate DA activity of the SNc to provide a pessimistic prediction (an avoidance response) bias, an important component of our theoretical analysis of differential neural mechanisms of impulse and constraint (Tucker & Luu, 2012).

Summary of Cortical Duality from Subcortical Duality

We focused on how the apparent cybernetics of cortical duality can arise out of subcortical duality, first by understanding a fundamental organization of the thalamus. This understanding of lemnothalamic and collothalamic organization allows a way of understanding not only cortical organization but also how to understand the organization of the posterior hypothalamus, amygdala, septum and basal ganglia. With this understanding and the insight that the STN is part of the posterior hypothalamus, and the evidence that the hypothalamus develops within the visceromotor domain of the basal plate of the neural tube, we can see the subpallial domains of the telencephalon forms three broad striatal circuits (perhaps reflecting a general motif of pallial-subpallial organization). The various nuclei of the posterior hypothalamus thus provide the visceromotor basis of the striatal loops for lemnothalamic and collothalamic sensory integration. The basal ganglia are particularly unique in this light, exhibiting an evolved organization that parallels cortical expansion, incorporating inputs from both dorsal and ventral evolutionary trends while appearing to keep the feedforward and feedback control somewhat separate, as reflected by in the organization of the striosome and matrix compartments. Even as the basal-

ganglia receives and retains the organization of extensive cortical inputs, the fundamental nature of mesencephalic influence on its function (as shown by collothalamic alignment in early vertebrate evolution and dopaminergic projection, as reviewed further below) is retained, perhaps providing an overall feedback bias of control.

Catecholamine Duality and Cybernetic Control

We started the anatomic and development review of the pallium and subpallium with evidence that the cortex is organized along dual trends that reflect the developmental origin of the cortex; showing that the limbic bases of archicortical and paleocortical pallial fields give rise to the neocortex and are organized by developmental patterning centers. Furthermore, we reviewed evidence that shows that the dorsal (lemno) trend is pallial in nature whereas the ventral trend, while arising out of the co-option of ventral pallial developmental mechanisms, is strongly aligned with subpallial (i.e., collo) evolution. However, it has long been apparent that the vertical integration of motive control in the neuraxis involves not only the extensive linked networks of the frontal lobe with the basal forebrain and hypothalamus (W. J. H. Nauta & Haymaker, 1969), but also essential midbrain and lower brainstem roles, contributing both to specific adaptive postures and to more general arousal states (Moruzzi & Magoun, 1949) and (Derryberry & Tucker, 2006; Lindsley, 1960). In this section, we propose that — in the presence of considerable overlap — there is a duality of catecholamine regulation of the cortex, with NE of rhombencephalic origins being more important to the lemnothalamic regulation of the dorsal limbic division and its associated neocortex, whereas DA of mesencephalic origins is more important for the collothalamic regulation of the ventral limbic division and its associated ventral division of the cerebral cortex.

Classical anatomical studies in monkeys show that DA innervates frontal and temporal cortical regions preferentially, whereas NE projects to widespread cortical areas (Brown, Crane, & Goldman, 1979; Levitt, Rakic, & Goldman-Rakic, 1984). Perhaps more important for the present proposal was the selectivity observed for cortical control *over* brainstem NE, which was limited to the dorsal frontal lobe, and not observed for the ventral, orbital frontal lobe (Arnsten & Goldman-Rakic, 1984). This pattern would be consistent with the alignment we propose between the dorsal corticolimbic division and brainstem NE control.

In the next section we aim to show how the midbrain and brainstem catecholaminergic systems, particularly the LC and VTA/SN, were initially aligned in the forebrain according to the pallial-supballial duality, consistent with the initial evolution of lemnothalamic control of the pallium and collothalamic control of the subpallium. During evolution, as subpallial development came to be incorporated into the pallium to create the 6-layered mammalian neocortex, so did DA innervation. Even as DA came to innervate the pallium, it did so while maintaining continuity in alignment with collothalamic organization, and in a generally complementary arrangement to NE and the lemnothalamic regulation of the dorsal corticolimbic division.

Norepinephrine Distribution and Lemnothalamic Pallial Evolution

There are multiple brainstem NE nuclei, but the LC provides the bulk of NE innervation to the pallium of the forebrain (Robertson, Plummer, De Marchena, & Jensen, 2013). Other NE nuclei provide the majority of inputs to the amygdala and hypothalamus. Developmentally, LC cells predominantly come from a source in the dorsal aspect of the rhombencephalon (r1 in Figure 7C). Consistent with its dorsal developmental position, the bone morphogenic protein

(BMP) signaling factor of the roof plate plays a role in the specification of LC neurons (Goridis & Rohrer, 2002). Also consistent with the its dorsal position, and with the lemniscal nature of the LC NE projections, is the continuity of LC projections to the dorsal horn of the spinal cord, which constitute the start of the lemniscal system. NE projections to the ventral horn of the spinal cord, in contrast, arise primarily from other NE cell groups (Bruinstroop et al., 2012; Grzanna & Fritschy, 1991).

In frogs and toads, in contrast with limited dopaminergic innervation of the pallium, NE innervation is present in all pallial areas, as well as in medial aspects of the septum (González & Smeets, 1994). NE also projects to subpallial areas as well, including collothalamic structures (such as the amygdala and striatum). In reptiles, the specificity of NE distribution patterns to the lemnothalamic trend become more distinct. At the level of the striatum and amygdala, NE innervation is weak (Smeets, 1994). At the level of the pallium, DVR NE innervation is almost absent. At the level of the cortex, the medial pallium is well innervated by NE whereas the ventral pallium is weakly innervated (Smeets, 1994).

In avians, NE innervation to the telencephalon is much sparser when compared to DA and generally more uniformly distributed (forming a thin superficial band) across the telencephalon (Reiner et al., 1994). In mammals, NE innervation of the striatum is observed but it is extremely sparse (A. Reiner, 1994). In the amygdala, denser levels of NE innervation are observed. At the cortical level, there is more variability between species. In rodents NE innervation is seen in all cortical areas with the particularly strong innervation of layers 1, 4 and 5 (B. Berger & Gaspar, 1994). Agster et al. (Agster, Mejias-Aponte, Clark, & Waterhouse, 2013) showed that the cingulate cortex (the cortical base of the dorsal limbic division) in rodents contains the densest distribution of NE projections among cortical areas, whereas the olfactory cortex (ventral limbic) had less NE projections. When LC innervation to the hippocampus was examined, abundant NE fibers were found (Takeuchi et al., 2016; Wagatsuma, Okuyama, Sun, Smith, Abe, & Tonegawa, 2018). In primates (including humans), cortical regional differences are more apparent, with the densest regions being the primary motor and somatosensory areas and decreasing rostrally and caudally from these regions (B. Berger & Gaspar, 1994).

In summary, our proposal for alignment of NE via the LC with lemnothalamic organization is based on the following evidence: 1) developmental origin of LC neurons, both in terms of position and requirement of the BMP dorsal transcription factor, 2) the paucity of NE innervation of striatal areas (excluding amygdala, see below) in reptiles and mammals and 3) the relatively denser NE distribution in the pallium (particularly archicortex and cingulate cortex) in reptiles and mammals compared to the olfactory cortex and striatum.

Dopamine Distribution and Collothalamic Pallial Evolution

VTA/SNc neurons originate along the floor plate of the mesodiencephalic tegmentum continuum. The ventralizing sonic hedgehog (SHH) protein, which has a role in specifying floor plate cells of the neural tube and subsequently the ventral forebrain (Diaz & Puelles, 2020), is also involved (although not exclusively, see (Goridis & Rohrer, 2002)) in the development of VTA/SNc DA neurons.

The collothalamic morphotype in amphibians and reptiles, as noted previously, is characterized by thalamic projections that are restricted to the striatum and do not reach the pallium (Figure 6). Consistent with this anatomy, in amphibians such as frogs, toads and salamanders, the dopaminergic innervation of the pallium is limited. In contrast, the olfactory bulb, striatum and amygdala show dense innervation by DA (Gonzalez & Smeets, 1994). In reptiles, the midbrain dopaminergic projections innervate the olfactory bulb, striatum

(particularly the nucleus accumbens), and the DVR (particularly for lizards and snakes, Smeets, 1994). In the pallium, DA innervation is sparse except for the ventral pallium. Thus, from a pallial vs subpallial organizational perspective, dopaminergic innervation patterns, while increasingly complex, generally parallel collothalamic projections in amphibians and reptiles.

In avians, DA innervation is dense in the striatum, amygdala (such as the BST) and septum (Reiner et al., 1994). In the pallium, the DVR is also densely innervated. The Wulst (an enlarged part of the avian brain involved in vision), and medial pallium show dense DA distribution as well. In mammals, with the more extensive development of the pallium, we find a continuation of the parallel between DA innervation and the collothalamic trend. At the level of the striatum, DA distribution is remarkably similar across species (Reiner, 1994). The dorsal striatum (caudate and putamen) displays dense DA innervation whereas the pallidum displays less, but still high levels. The central nucleus the amygdala and BST are also high in DA innervation.

At the level of the pallium, there are more regional differences in DA distribution. In rodents, DA innervation is densest in the ventral limbic division (Yakovlev circuit) (W. Nauta, 1985), including the orbitofrontal region, the insula, and primary olfactory cortex (Berger & Gaspar, 1994; (Björklund & Dunnett, 2007). However, in the hippocampus proper (the central allocortex of the dorsal limbic Papez circuit), DA innervation is very sparse (Takeuchi et al., 2016; Wagatsuma et al., 2018). Elsewhere (i.e., primary sensory and motor, sensory association), DA innervation is also sparse. Examining the layered distribution of DA terminals shows that for the collothalamic aligned cortical fields, DA innervation is dense across all cortical layers. One dorsal limbic region that is densely targeted by DA in mammals (in contrast with our simple hypothesis) is the ACC, which is proposed to be of archicortical derivation and aligned with the lemnothalamic trend.

In primates (including humans) and similar to rodents, the densest DA innervation is to the ACC, premotor cortex and insula (B. Berger & Gaspar, 1994; B. Berger, Gaspar, & Trottier, 1988). However, unlike rodents, primates show an additional area of particularly dense innervation, the primary motor cortex (Berger & Gaspar, 1994). Furthermore, particularly dense innervation in primates is seen in the SMA. The pattern in primates can be summarized by the Williams and Goldman-Rakic (Williams & Goldman-Rakic, 1993) findings, who showed that DA innervation in the frontal cortex follows rostral-to-caudal and medial-to-lateral gradients, with increases in DA innervation density more caudally (peaking at the SMA) and decreases more laterally. Williams and Goldman-Rakic noted that the regions of dorsal cortex of primates that show the densest DA innervation are involved in motor functions, which may reflect the incorporation of subpallial (striatal) motor control into these areas and may be explanatory for the DA presence in what we argue are primordially lemnothalamic cortical fields.

In summary, the proposal for alignment of DA via the VTA/SNc with collothalamic organization is based on the following evidence: 1) floor plate position of the mesencephalic VTA/SNc progenitors and the importance of SHH in their initial specification, 2) the subpallial (striatal and amygdala) and not pallial distribution in amphibians, 3) the striatal (including amygdala) and pallial DVR (collothalamic) pallium reptiles and avians and 4) DA targeting of striatal (including amygdala) and ventral cortices in mammals.

A Note on the Olfactory Cortex and LC

Although the olfactory cortex is aligned with the collothalamic trend, from the perspective of pallial patterning it does not receive thalamic projections. Rather, olfactory inputs arrive directly from the olfactory bulb. Thus, in this sense, it is not strictly a collothalamic structure. Because LC innervation to the forebrain appears to favor pallial structures (Robertson et al., 2013),

particularly in animals with primitive pallial fields, the dense olfactory cortex innervation by NE is the exception. Although NE innervation of the amygdala is high, this originates from other NE cell groups rather than the LC, as shown by Robertson et al. (2013). Clearly, from these examples and others, there is considerable overlap in neuromodulator projections to the forebrain, so that our model of differential NE and DA regulation of lemno and collo forebrain divisions must remain a general one, with considerable overlap that must be recognized.

Dual Modes of Vertical Integration

Although the extensive cerebral cortex is the focus of much of the research in human neuroimaging and neuropsychology, the importance of vertical integration — the regulatory support for the telencephalic hemispheres from thalamic, midbrain, and brainstem control systems — can be seen from examples of now classic systematic studies of the neural control of emotional vocalizations in squirrel monkeys by Jürgens and Ploog. These researchers showed that social calls could be elicited by electrical stimulation not only in limbic areas but also in midbrain and brainstem periaqueductal gray areas (Jürgens & Ploog, 1970). A hierarchical organization of these areas was implied by the emotional quality of the vocalizations. Whereas species-specific calls could be elicited by midbrain stimulation, these vocalizations were brief and fragmentary. Only with limbic stimulation did the calls appear to have a strongly emotional quality integrated with the ongoing behavioral context (Ploog, 1981).

Such observations are reminiscent of pseudobulbar palsy in human patients, in which lesions that release brainstem/midbrain responses cause emotional outbursts such as crying, yet patients report these as being dissociated from the subjective experience of emotion (MacLean, 1987). Thus, the evidence points to highly conserved anatomical pathways in vertebrate evolution that

recruit arousal and motive control systems of the midbrain and brainstem to support

Box 4. Active inference, arousal and attention

The regulation and selection of ascending (e.g., limbipetal) afferents in active inference rests upon the precision afforded the implicit prediction errors. This precision can be read as implementing a kind of gain control that contextualizes the selection of limbic predictions that underwrite action and the attention afforded various sources of prediction errors (Feldman and Friston 2010, Moran, Campo et al. 2013, Vossel, Bauer et al. 2014, Auksztulewicz and Friston 2015, FitzGerald, Moran et al. 2015, Parr and Friston 2019).

In brief, predictive coding formulations of active inference cast neuronal processing as a process of Bayesian belief updating, in which ascending (limbipetal) prediction errors (e.g., from superficial pyramidal cells) revise expectations at higher levels in any given hierarchy (Bastos, Usrey et al. 2012). These expectations (e.g., encoded in deep pyramidal cells) generate predictions of the level below that are reciprocated to the source of prediction errors, in an attempt to minimize prediction error or surprisal.

Crucially, the ascending limbipetal prediction errors themselves have to be selected based upon their predicted precision (Kanai, Komura et al. 2015, Shipp 2016). In other words, only precise prediction errors that report dependable 'newsworthy' information have privileged access to update expectations. Psychologically, this selective precision-weighting can be read as attentional selection and—in the context of limbic adaptive control—sensory attenuation (Brown, Adams et al. 2013, Wiese 2017, Allen, Levy et al. 2022, Limanowski 2022).

Physiologically, precision-weighting can be read as regulating the postsynaptic gain, based upon descending (limbifugal) predictions of precision. The mechanisms of this modulatory or regulatory aspect of predictive coding are generally ascribed to the ascending modulatory neurotransmitter systems (e.g., DA, NE, acetylcholine, et cetera) and, crucially—from the point of view of the current thesis—the fast phasic interactions between superficial pyramidal cells and inhibitory interneurons (Lisman 2012, Pinotsis, Brunet et al. 2014, Auksztulewicz and Friston 2015, Shipp 2016). In short, inhibitory interneurons may play a special role in the selection and regulation of horizontal and vertical message passing that underwrites predictive coding formulations of active inference.

hypothalamic, basal telencephalic, and limbic control processes. At the same time, the complex function of the brain, such as emotional elaboration of vocalization, only emerges as higher telencephalic structures regulate the lower neuraxis through vertical integration.

In the following sections, we review the evidence of continuity and vertical integration of motor control from the perspective of the dual organization framework reviewed thus far. We aim to show that the control of behavior can be understood to reflect primordial themes of arousal control that can be traced to brainstem (phasic arousal, NE) and midbrain (tonic activation, DA) networks, projected to the forebrain through coherent vertically-integrated networks

(lemnothalamic and collothalamic, respectively), thereby organizing two major control systems for behavior in the basal forebrain, limbic system, and neocortex. Our theoretical interpretation emphasizes that the unique properties of these different forms of arousal and motor control — constituting active affordance in vertebrate behavioral regulation — have been maintained by, and have led to, the architecture of the mammalian neocortex, which then elaborated the elementary, largely homeostatic, capacity for active affordance into the more fully allostatic capacity for active inference (see Box 4).

Midbrain and Brainstem Bases of Locomotor Control

As we detailed in the early sections of this paper, the dual foundations of the dorsal and ventral divisions of the limbic system can be traced to 1) the dual (septo-hippocampal-hypothalamic and striatal-amygdalar-hypothalamic) bases of the basal forebrain, 2) the lemnothalamic and collothalamic pathways through the thalamus and 3) the rhombencephalic LC and the mesencephalic SNc/VTA cell groups that may be primary drivers of these dual pathways and regulatory systems. This organization sets the context for the basic themes of vertical integration of motor control organized across the thalamus, midbrain, and lower brainstem.

Figure 10 shows the vertical hierarchy of motor control from Grillner et al. (2008). Forming the base of the hierarchical neuraxis are the central pattern generators (CPG) of the spinal cord that are responsible for the sequential activation of muscles that form a movement pattern (such as walking). Controlling these CPGs are the locomotor regions of the mesencephalon (mesencephalic locomotor region, MLR) and forebrain (diencephalic locomotor region, DLR) through their regulation of the spinal cord projection neurons in the brainstem. These reticulospinal neurons are located in the medial aspects of the brainstem reticular formation. By their connections to the CPGs, they are the initiating neurons for movement (Brownstone & Chopek, 2018). The reticulospinal area contain neurons that receive inputs from both the MLR and DLR. A central structure of the MLR is the pedunculopontine nucleus (PPN) that contains cholinergic, glutamatergic and GABAergic cells (Mena-Segovia & Bolam, 2017).

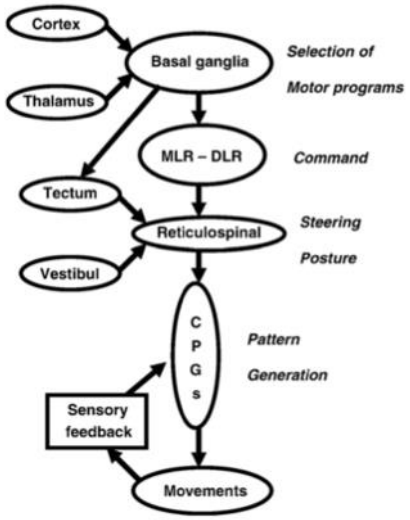


Figure 10. Subsystems of motor control (from Grillner et al., 2008). CPG: Central Pattern Generator, DLR: Diencephalic Locomotor Region, MLR: Mesencephalic Locomotor Region.

From the perspectives of both anatomical organization and electrophysiological properties, it has been suggested that the PPN should be considered part of the basal ganglia (Mena-Segovia, Bolam, & Magill, 2004). The implication is that the basal ganglia may be involved in regulation of arousal control, in addition to motor control, through vertical integration with the PPN.

A particularly important aspect of the PPN in locomotion is its interaction with the SNc and VTA DA cell groups, with which it is prominently connected. Local modulation of PPN cholinergic projections to the VTA increases motor activity (Mena-Segovia & Bolam, 2017). The PPN also shows phasic short latency responses to cues, rewards and reward omission, similar to DA cell responses. The PPN response is relayed to the DA neurons that cause them to burst. Mena-Segovia et al. proposed that the main function of the PPN is to signal the occurrence

of salient stimuli, regardless of value. Thus, it may be that the significance of the signal is only adaptive when relayed to other structures that can employ the signal relative to the behavioral context. With the signal relayed to DA neurons, which then innervate the basal ganglia, associations with motor and reinforcement outcomes can be learned. This appears to be achieved through a specific regulatory control, the redundancy or repetition bias, supported by DA activity (Redgrave, Vautrelle, & Reynolds, 2011), as we explain below.

Recognizing that the reticulospinal region is involved in both locomotor control, via projections to the CPGs, and arousal regulation, via the NE projection neurons of the LC throughout the forebrain, we can see the tight coupling between motor activity and specific forms of neural arousal at an elementary level. LC stimulation produces both wakefulness and increased locomotion (Carter et al., 2010). The increase in locomotion is supported by the direct effect of NE on muscle tone, with antagonists producing loss of muscle tone and agonists increasing muscle tone (Burgess & Peever, 2013).

Through this coupling of arousal and motor action, the LC projection system appears to be the core of the phasic arousal system of the brainstem that regulates the dorsal division of the forebrain particularly. LC neuronal activity responds in a phasic fashion to novel and salient stimuli in all sensory modalities; the phasic quality of this response is integral to its cybernetics (regulatory influence) and appears to be created by its rapid habituation. Changes in the environment (that induce uncertainty about contingencies), relative to a stimulus to which LC responses have already habituated, will reengage neurons of the LC. Bouret and Sara (Bouret & Sara, 2005) proposed that the function of LC NE activity is to serve as a reset signal that reconfigures brain networks appropriate for the processing of new contexts that require a behavioral shift.

The dorsal limbic specialization for the orienting response — the phasic response to novel events — may explain the classic sign of *hypermetamorphosis* (immediate orienting to every change in the environment) observed by Kluver and Bucy following lesions to the amygdala and ventral limbic cortex (Kluver & Bucy, 1939). The removal of the amygdalar regulation of constraint (based on anxiety) may *release* the intrinsic phasic arousal orienting response of the dorsal limbic division (Tucker & Luu 2023). When active, NE activity may facilitate sensory processing, through a signal-to-noise amplification (Aston-Jones & Waterhouse, 2016), and facilitate action, through enhancement of muscle tone. In between periods of phasic activity, low NE activity prevents shifts that would otherwise be induced by irrelevant stimuli. Bouret and Sara (Bouret & Sara, 2005) argued that enhanced NE tone represents a state of expectancy, consistent with our reasoning that the feedforward bias of the dorsal limbic division is integral to the generation of predictions and plans in active inference (Tucker & Luu, 2023).

We propose that the control dynamics of the MLR, regulated by DA inputs from the SNc (Ryczko et al., 2016), and reticulospinal (regulated by NE) centers for motor control give rise to two arousal control bias modes that emanate from the midbrain and brainstem to regulate the functions of the forebrain. DA provides a *redundancy* or status quo bias whereas NE provides a *habituation* or phasic arousal bias (D. M. Tucker & Luu, 2012; D. M. Tucker & Williamson, 1984). The term redundancy was used by Pribram & McGuinness (1975) to describe the tonic activation that maintains stability and focus in action regulation. Redundancy provides a focus of attention to determine casual relations between actions and stimuli (Redgrave, Vautrelle, & Reynolds, 2011), and is thus uniquely suited to feedback control of actions based on ongoing monitoring of specific environmental contingencies. In contrast, the habituation bias of phasic

arousal supports rapid shifting of attention to anticipate future actions and is thus suited to active, feedforward control of imaginative expectancies.

LC, Septum and Hippocampus in Feedforward Control

A forebrain complement to the collothalamic basal ganglia — extending motor control from the midbrain to the forebrain — occurred with the evolution of lemnothalamic motor control mediated by the septum and hippocampus. Nauta and Karten (1970) recognized the continuity of the fiber tracts of the brainstem reticular formation to the septum, and they proposed that the septum should be thought of as the telencephalic extension of the brainstem reticular activating system. We suggest further that in addition to extending aspects of arousal control, and given the tight link between arousal and locomotor control in the reticulospinal locomotor center, locomotor control from the brainstem should also be considered to be extended to the septum, particularly in light of the indirect (hippocampo-lateral septum-medial septum-MB) and hyperdirect (hippocampal-MB) loops described above.

With their close interconnections, the septum and hippocampus can together be considered as a forebrain locomotor/arousal region that may be rooted in the head-direction functions of the MB (Don M. Tucker & Luu, 2023). Furthermore, we propose that this vertically-integrated circuitry may provide an elemental basis for organismic intention. Indeed, stimulation of the medial septum has arousing effects, as well as effects on motor activity (Mocellin & Mikulovic, 2021). Both these effects appear to be supported by the direct LC projections to the septum (España & Berridge, 2006).

Early evidence of behavioral changes following electrical stimulation applied to the medial septum shows broad behavioral changes, such as reinforcing effects, increases in grooming and feeding, and general hyperactivity (for review see (Mocellin & Mikulovic, 2021)). More specific effects associated with lesions to the medial septum include deficits in exploratory behavior and impaired performance on spatial tasks. Importantly, lesioned animals also showed a slower rate of habituation (the cybernetic mechanism for selecting for novelty). With more precise methods for activating or inactivating the medial septum and diagonal band of Broca (DBB) in recent studies, a close link of the medial septum-DBB complex is seen with tasks requiring memory and navigation. As summarized by Mocellin and Mikulovic, the medial septum-DBB complex generally provides locomotion output that has behavioral specificity, depending on the involvement of different types of cells within the medial septum-DBB complex. In this way, the medial septum-DBB complex can be regarded as providing the motivational impetus for locomotion.

The role of the hippocampus in spatial representation is now well established across the vertebrate class (Broglio et al., 2015). Studies that have examined the direct effect of LC innervation of the hippocampus in learning show that inhibition of LC impairs learning in a novel environment (Takeuchi et al., 2016; Wagatsuma et al., 2018). In control animals, exposure to a new environment produces exploration and then habituation, reflected by decreases in exploratory behavior. In animals with the LC directly inhibited during initial exposure to the new environment, exploratory behavior remains high when exposed to the same environment on a subsequent day. This deficit in habituating to novelty leads to impairment in the learning of spatial relations, as assessed by the differentiating responses of place cells.

The primitive dorsal pallium in amphibians and reptiles is a three layered cortex. As with the olfactory cortex and hippocampus, inputs from the lemnothalamic sensory nuclei (somatosensory and visual) arrive in the top layer. Aboitiz and Montiel (Aboitiz & Montiel, 2015) suggest that the dorsal pallium in reptiles can be compared with the entorhinal cortex and subiculum of

mammals, thereby providing additional inputs into the olfactory-hippocampus architecture for navigation.

An important aspect of this neural architecture, as suggested by Aboitiz and Montiel, is that lemniscal sensory inputs into the primitive pallium may not be for sensing per se. Indeed, this may also hold true for the olfactory cortex as well, because odor identity can be achieved by neurons the olfactory bulb themselves, after which this identification is relayed to the olfactory cortex via layer 1. Afferents arriving in the top layer provide inputs to the apical dendrites of pyramidal cells, suggesting that they are strongly *modulatory* (rather than sensory representational) in function, consistent with a role in providing predictions of precision that underwrite attentional selection. The tangential nature of both the contacts with apical dendrites of pyramidal cells as well as the convergence of multimodal inputs to this top layer may argue for a learning and memory role (specifically for the purpose of navigation). From this perspective, one interpretation may be that the mammalian neocortex evolved from the dorsal pallium to act as a memory interface between the olfactory cortex and the septum-hippocampus system for navigation (see Aboitiz and Montiel, 2015).

A related and potentially compatible theory put forth by Jacobs (Jacobs, 2012; Jacobs & Schenk, 2003) for functional integration of the olfactory cortex and hippocampus is known as the *parallel map theory*. Parallel map theory proposes that navigation (an inherently feedforward process) is based on two elemental maps: a global bearing map used for directional navigation and a local map based on positional cues provided by a constellation of object (local landmarks) positions. Jacobs noted that the properties of olfaction provide for both directional and object information. The role of hippocampus in spatial representation has long been recognized from studies showing place cells and other spatially-related cell types (e.g., head direction cells, border cells and grid cells) in the hippocampus supporting a general role in learning spatial relations (Moser, Rowland, & Moser, 2015). The increasing recognition of the septal-hippocampal function in generative imagination (Comrie, Frank, & Kay, 2022) is consistent with our theoretical proposal that active affordance begins with feedforward exploration. This exploration increases knowledge about the world, with the initiative for exploration supported by the flexible generation of spatial navigational maps in the dorsal limbic division (Don M. Tucker & Luu, 2023).

SNc-VTA, the Basal Banglia, Tectum, and MLR in Feedback Control

To understand striatal motor control, an essential insight is the recognition that outputs of the dorsal striatum to the SNr (the direct route composed of cortex-striatum-internal component of globus pallidus-thalamus-cortex) and STN (the indirect route discussed above) target the MLR (Grillner, Wallén, Saitoh, Kozlov, & Robertson, 2008). As noted by Nauta & Karten (1970) pallidal outputs do not directly go beyond the mesencephalon in reptiles, birds and mammals. Thus, prior to expansion of sensory inputs into the pallium and neocortical elaboration, sensorimotor control can be considered striatal and collothalamic with primary control in the midbrain.

In its basic form, perhaps most prominent in anamniotes (fish and amphibians), striatal and collothalamic movement control involves the orienting and tracking of objects (predator/prey) in the environment (e.g., Grillner et al., 2008). While seemingly simple in principle, orienting and tracking objects in the presence of eyes that are mobile in their orbits is a challenge, as sensory spatial relation to visual inputs and other body senses are decoupled. Merker (Merker, 2007) persuasively argued that the tectum provides the necessary support, via sensory integration along with motor control (in this case eye control) as a solution to the problem and serves as a target

selection structure. The basal ganglia via the SNr serves as an action selector (as noted above in the work of (Houk & Adams, 1995) but also see Redgrave et al., 2011) through its connection with the superior colliculus which controls eye and orientation movements (and regulating the MLR more generally). This mode of motor control can be thought of as *feedback* control, in the cybernetic sense of direct regulation of action to match continuous sensory input. From the perspective of the second stage of active affordance —feedback error-correction and regulation by closed-loop environmental input — this cybernetic mode of feedback control is aligned with satisfying organismic values (either escape or consumption) in the local, proximal acts of exploitation (Cisek, 2022; Schwartenbeck, Passecker, Hauser, FitzGerald, Kronbichler, & Friston, 2019; Don M. Tucker & Luu, 2023).

The action selection function of the basal ganglia is supported by the feedback architecture of the basal ganglia reentrant loops and dopaminergic inputs. The reentrant loops of the basal ganglia represent different channels of sensory/motivation information that course from their respective origins (e.g., different parts of the cortex) through the basal ganglia and back again. As noted by Redgrave et al. (Redgrave, Vautrelle, & Reynolds, 2011), the multiple reentrant loops of the basal ganglia are able to support *selection,* because different loops can be selectively inhibited or disinhibited. Driving the selection, and thus differentiating and constraining actions, are dopaminergic inputs from the SNc and VTA.

The notion that SNc/VTA phasic sensory responses code *reward prediction errors* has been popular because it supports the idea of reinforcement learning. However, Redgrave et al. (2011) argued persuasively that the short latency of the SNc/VTA response (which is ~100ms) is inconsistent with a reward prediction error explanation. The phasic sensory response is more consistent with a sensory (arriving from the tectum) prediction error. In parallel, tectal outputs are also relayed to the PPN, which provides input to the SNc/VTA and as noted, previously, also responds physically to significant stimuli to provide salience signals to the SNc/VTA (Mena-Segovia & Bolam, 2017). Indeed, it is now recognized that the early dopaminergic response provides a way to code precision or salience, rather than strictly to reward-related features of sensory data. Given its more complex architecture, the tectum itself is readily trained to respond to differential values of sensory inputs.

This emerging picture of vertical integration of collothalamic, DA-mediated regulation may characterize mechanisms of active affordance, consistent with the precision or accuracy designation of the error-feedback that regulates action selection (Karl Friston, Schwartenbeck, FitzGerald, Moutoussis, Behrens, & Dolan, 2014; K. J. Friston et al., 2012; Schwartenbeck, FitzGerald, Mathys, Dolan, & Friston, 2015). In parallel with the converging sensory, motivational and motor inputs to the basal ganglia, a coincident phasic dopaminergic signal may serve to promote the re-selection of the motor command (Redgrave, Vautrelle, & Reynolds, 2011). The notion of re-selection (i.e., the tendency to repeat the motor act) is consistent with the well known fact that enhanced dopaminergic activity, such as with drugs, readily produces behavioral stereotypy. Thus, increased dopaminergic control appears to promote a *redundancy bias* (Tucker & Williamson, 1984) or a *repetition bias* in the term of Redgrave et al. Here redundancy and repetition share a common conceptual meaning, which is the bias for repeating the same act. We suggest this is translatable to cognitive control as well, in the sense of maintaining stability in representation (Pribram & McGuinness, 1975) that is now sometimes referred to as "status quo" maintenance (Little & Brown, 2014). In this sense, Redgrave et al. noted that the phenomenology of such a bias would be similar to *wanting* or motive anticipation

rather than the *liking* that has been widely but mistakenly attributed to a dopamine-mediated hedonic response (Berridge, 2009).

Through the redundancy/repetition bias, motor acts will recur in a particular sensory context, and the differential enhancement and inhibition of various basal ganglia reentrant loops allow for a convergence on causation, enabling an animal to learn to repeat the motor sequence (creating a habit) that produces a desire outcome. These control mechanisms are integral to the concept of an *affordance*, an adaptive configuration of sensing and acting (Gibson, 1970). Extending the logic of active affordance to basal ganglia selection, the implication is that DA is a teaching signal that incentivizes subsequent behavior. The computational anatomy that follows from work on active inference follows exactly this logic: see Figure 10 in (K. J. Friston, Parr, & de Vries, 2017) for a technical illustration of the requisite neuronal message passing.

In our analysis of subcortical control of active affordance, the dopaminergic routinization of habits is a key component of an *affordance*: an organized, well-routinized, and historically adaptive perception-action sequence. Thus, the elementary cybernetic mechanisms the collothalamic control system produce is an active affordance in subcortical circuits, and we propose these mechanisms — with substantive neuronal adaptations to be sure — have been incorporated within the neocortical error-correction and belief updating in the higher level cognitive process of active inference.

Regulation of Dorsal and Ventral Limbic Memory Systems

Returning to the observation of unique genetic markers of cortical networks that make up object (non-spatial) vs spatial processing (see Figure 5) observed by Luzzati (Luzzati, 2015), the reviewed evidence makes it clear that the ventral and dorsal cortical trends are not just rooted in their respective limbic bases (Tucker & Luu, 2023) but also that the organization reflects deeper evolutionary and organizational roots. In the following, we highlight how the control biases of the lemnothalamic and collothalamic systems may regulate these forms of memory.

Initially evolving with dopaminergic and midbrain regulation of the subpallial structures (basal ganglia and amygdala) collothalamic regulation through GABAergic inhibitory control may explain the unique functions of primate and human ventral stream of the neocortex that supports object memory. These collothalamic regulatory influences on the GABAergic interneurons in 2/3 and 4 are less apparent, and less dominant (Galaburda, 1984), although still present and important of course, in the archicortical dorsal division of the neocortex (Luzzati, 2015; Montiel & Aboitiz, 2015; D. M. Tucker & Luu, 2012).

Tucker and Luu (2012) emphasized that the separation of an object from its context may be supported by the inhibitory surround processing that can be traced to the GABAergic interneurons of the basal ganglia that are now in the cortex. The midbrain DA systems are integral to the collothalamic projections to the basal ganglia (Ikemoto, 2010), contributing to the stabilization of cortical motor processing signaled by beta rhythms (Engel & Fries, 2010; Nelson et al., 2017). This stabilization may be the underlying mechanism of the redundancy bias for attentional control in earlier neuropsychological theory (Pribram & McGuinness, 1975; D. M. Tucker & Williamson, 1984). Maintenance of the status quo supports the sensitization of neural activity that focuses attention to allow differentiation of objects in perception and memory from the contextual surround.

Thus, the midbrain DA systems are integral to the collothalamic arousal control that regulates the basal ganglia, amygdalar-striatal complex, and (we propose) ventral limbic and neocortical networks. In primitive vertebrates, DA regulation of behavior is engaged during attack and ingestion of prey, but is switched off during exploratory approach behavior (Cisek,

2022). As noted above, although DA modulation has been interpreted in relation to reward mechanisms broadly in the neuroscience literature, it is clearly not associated with simple pleasure (Ikemoto, 2010) but rather to incentive salience (Berridge, 2009). In mammals DA may perform a more specific regulation of learning and cognitive control through sustaining focused attention to support recognition of prediction discrepancy (Lau, Monteiro, & Paton, 2017; Schultz, Dayan, & Montague, 1997). This unique cybernetic role may be consistent with the *constraint* bias in the face of prediction discrepancy hypothesized to be applied by ventral limbic regulation (D. M. Tucker & Luu, 2012; Don M. Tucker & Luu, 2023).

The specific thalamocortical control of the ventral, paleocortical division of the limbic system by the mediodorsal nucleus of the thalamus is illustrated in **Figure 11** (Jones, 2007)**.** The principle seems to be that, whereas the mediodorsal thalamic nucleus receives projections from the amygdala, it does not project to the amygdala directly, but rather to the subcallosal cingulate area that is closely interconnected with the amygdala (Jones, 2007). The preferential collothalamic regulation of the mediodorsal thalamus has been suggested in anatomical studies in monkeys. Tracer injected into the mediodorsal nucleus of the thalamus was taken up by the tectum and ventral midbrain areas (as well as by the claustrum) (Erickson, Melchitzky, & Lewis, 2004). Also consistent with collothalamic specificity of the mediodorsal nucleus of the thalamus, other injections of tracer to the mediodorsal nucleus were taken up in the ventral tegmental area of the midbrain (Erickson, Melchitzky, & Lewis, 2004).

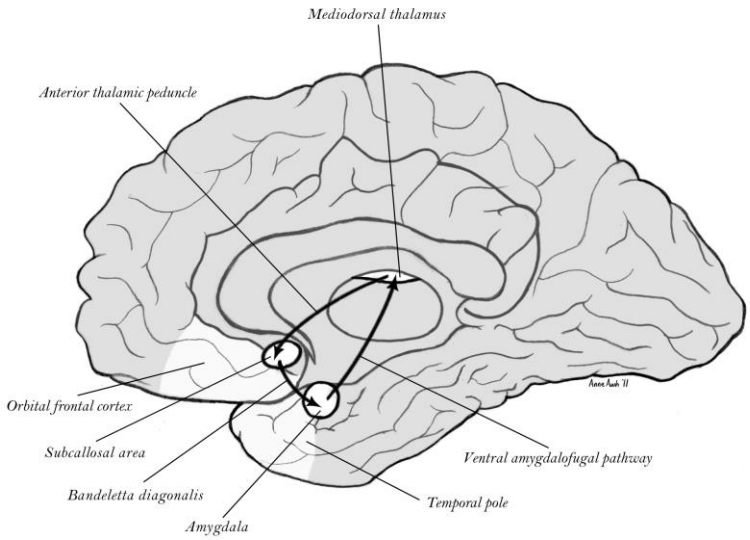


Figure 11. The "triangular circuit" is formed by an unusual 3-way interconnection between the extended amygdala, the subcallosal area of the orbital frontal lobe, and the mediodorsal nucleus of the thalamus. The strong connections of the mediodorsal nucleus of thalamus and the midbrain may be an integral component of the collothalamic regulation of the ventral, paleocortical division of the limbic system. From Tucker and Luu (2012).

Thus, the ventral division of the limbic system and neocortex seems to have achieved novel forms of object memory by incorporating subpallial, collothalamic algorithms of neural control within the pallial (limbic and neocortical) architecture. Apparently in a complementary cybernetic balance, the dorsal division of the limbic system and associated neocortex appears to have retained the more primordial pallial architecture and processing reflected by the excitatory pyramidal network organization, regulated by lemnothalamic arousal control. Of course, the eulaminar (highly articulated layered) columnar architecture of neocortex (Barbas & Rempel-Clower, 1997) is also found in the dorsal neocortex, with layer 4 integrated within the 6-layer architecture. Importantly, layer 4 in the dorsal frontal lobe does not include stellate cells, at least as seen in sensory areas, and as observed by Brodmann, does not evidence a distinct granular

layer in the dorsal frontal lobes (Shipp, 2005). This relatively undifferentiated architecture is observed in these dorsal frontal regions, even as these are often seen as the apex of executive control in the human neocortex.

Our theoretical interpretation has been that the specialization of the dorsal division for contextual memory — with broad representations of conceptual as well as perceptual space — can be attributed to the more pyramidal-dominant cytoarchitectonics of the dorsal division of neocortex, exemplified by pyramidal cells of infra-granular layers 5/6 (Eidleberg & Galaburda, 1984; Galaburda, 1984) and reminiscent of the elementary 3-layered architecture of the pallium. The diffuse, excitatory representational mode of a pyramidal-dominant architecture may be supportive of the broad allocation of working memory regulated by the habituation bias of the dorsal division, continually allocating limited working memory to novel rather than static features of the environment (Tucker & Luu, 2012, 2021).

Here the work of Marin-Padilla (Marin-Padilla, 1998) provides a clue to how the infragranular layers of the neocortex are derived from the archicortex in mammals. The dorsal pallium of amphibians is characterized by afferent fibers and sparse presence of Cajal-Retzius cells and their efferent fibers. Marin-Padilla refers to this primitive pallial layer as the *primordial plexiform neuropil*, and he considers this to be the ancestral layer I. In amphibians, cells near the periventricular zone have their apical dendrites extending into the primordial plexiform neuropil, resembling cells of the dentate gyrus of the hippocampus. In reptiles, the periventricular zone cells migrate into the primordial plexiform neuropil and become stratified and have basal dendrites in addition to the apical dendrites. The morphology of these cells resembles CA cells of the hippocampus.

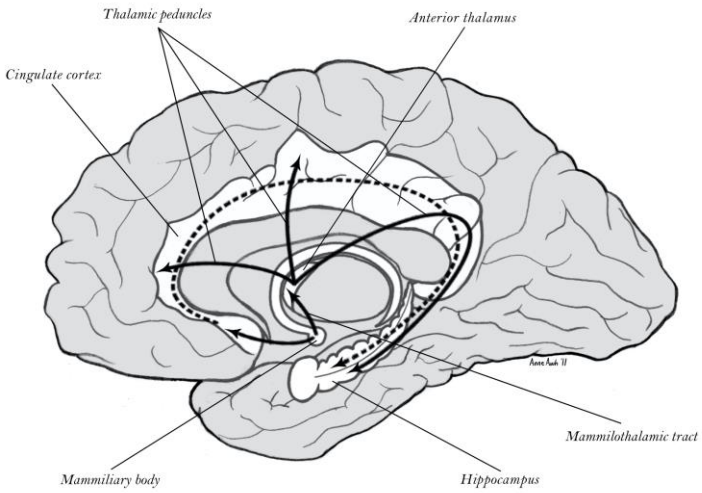


Figure 12. The Papez circuit of the dorsal limbic division connects dorsal cortical (cingulate) with basal forebrain (septal), hippocampal, and hypothalamic (mammilary bodies) areas to the anterior nuclei of the thalamus. The anterior nuclei of the thalamus appear to have preferential interconnections with the lemnothalamic projections from the brainstem. From Tucker and Luu (2012).

This account of the archicortical origin of the infra-granular layers is consistent with Ishizuka's (Ishizuka, 2001) proposal that the subiculum of the hippocampal formation corresponds to layers 5 and 6 of neocortex. His reasoning is based on the following observations: 1) both subiculum and infragranular cells have projections to the basal ganglia, thalamus and mammillary body and 2) the size of the efferent fibers of each type of subcortical projections are ordered similarly in both subiculum and infragranular layers.

The alignment of the anterior nuclei of the thalamus with the dorsal limbic division is shown by the classic Papez circuit (**Figure 12**) (Jones, 2007). Perhaps consistent with the parallel between the dorsal neocortical architecture and the primitive 3-layered pallium, the anterior

thalamic nuclei have preferential connections with the lemnothalamic pathways from the lower brainstem (Poremba, Kubota, & Gabriel, 1994). Using retrograde labeling from horseradish peroxidase injections in the anterior thalamic nuclei of rabbits, Poremba et al observed brainstem labeling in the lateral dorsal and the pedunculopontine tegmental nuclei, LC, dorsal raphe nucleus, as well as Gudden's dorsal tegmental nucleus and the pretectum, brainstem regions that appear to be sources of lemnothalamic projections. Particularly important may be the *head direction cells* found in rats both in the anterior nuclei of the thalamus and the lower brainstem reticular formation (Taube, 1995), linking the lemnothalamic foundations of the dorsal limbic Papez circuit to the egocentric foundation of motive, and locomotive, control in the dorsal limbic division (Don M. Tucker & Luu, 2023).

Feedforward and Feedback Cybernetics of Action and Affordance

In reviewing the evolution of neural mechanisms for behavior across the vertebrate lineage, Cisek (2022) emphasizes the feedback relations between motive states, environmental threats, and behavioral control systems in two primitive classes of behavior, exploration (such as foraging) and exploitation (such as ingesting prey). Although feedback controls are integral to homeostasis, linking internal set points to corrective actions, we emphasize that the lemnothalamic mediation of exploratory behavior operates under feedforward rather than feedback control. Consistent with the generative nature of hippocampal processing of memory (Comrie, Frank, & Kay, 2022), the dorsal limbic circuitry does not regulate action under feedback control from sensory monitoring of environmental data (which is the ventral limbic mode). Rather, the projective, impulsive nature of urges and expectancies in the dorsal division is more specifically a feedforward form of control, an expectancy that can be seen as a kind of prediction, where a fast and loose behavioral regulation is directed toward a goal but not guided by sensory feedback control, which is typically slower to engage (Don M. Tucker & Luu, 2023).

This distinction in cybernetic modes of the organism's arousal status (phasic arousal versus tonic activation) is important to another observation from Cisek's recent review that is highly relevant to the current theoretical questions. Work in the Graziano laboratory, now replicated and extended by a number of studies, has suggested that the control of action in motor cortex is organized, not just in control of specific muscle movements, but in coherent patterns of ecologically relevant behavior, such as climbing/leaping, moving a hand in lower space, or manipulating something in central space (Graziano, 2016). These action patterns in motor cortex are closely aligned with action monitoring networks in parietal cortex, suggesting to Cisek that these are *affordance* representations in fronto-parietal networks that underly integrated adaptive behavior.

This characterization of the role of motor cortex and its linked parietal cortex fits well with the theoretical analysis of active inference in motor control (Adams, Shipp, & Friston, 2013). That analysis suggests that, rather than muscle commands, the motor cortex organizes predictions of (expectancies for) the evaluative effects of actions that are then matched by the brainstem motor control networks. These expectancies for the anticipated effects of actions — we might say they are imagined feelings — may be, at the most elementary level, responsible for the feedforward control of active affordance.

Conclusion: From Active Affordance to Active Inference

Active affordances are anticipated species-specific patterns of interacting with the environment. Although they evolved as elementary neural mechanisms of vertebrate behavior control, with direct roots in the hypothalamus, the primitive representations of exploratory goals

have evolved in mammals to become allostatic rather than homeostatic controls. Whereas affordances may be seen as reflex-like behavioral patterns, we propose that active affordances (perhaps in reptiles and certainly in mammals) are elementary allostatic anticipations for coping: preparations for the future. By tracing the subcortical control of active affordances, we propose they evolved from elementary subpallial patterns of action habits (exploitation) as organized in relation to pallial capacities for representing the adaptive context (exploration) (Cisek, 2022). We propose that the dorsal and ventral corticolimbic divisions each regulate half the story of active affordances, in ways that have formed the basis for the evolution of the feedforward and feedback controls of active inference in the mammalian cerebral cortex.

The dorsal division is the active half of active affordance: the lemnothalamic generative (feedforward, imaginative) expectancies in dorsal corticolimbic networks model the desired outcomes of behavior. The ventral division then regulates the other half that is equally important: the collothalamic (feedback, constrained) organization of routinized perception-action sequences that form effective habit systems that have been learned through extensive feedback in repetition and practice. It is this ventral limbic constraint of feedback control of routinized habit patterns in active affordance that forms the foundation for the more complex error-correction (i.e., belief updating) in the cognitive process of active inference.

As the pallium evolved, and the highly laminated structure of the neocortex emerged in mammals, these primordial modes of action regulation became interdigitated, as reflected in the stacking of the two primitive allocortices and incorporation of GABAergic inhibitory control into the 6-layered neocortex, forming the inhibitory (interneuron) architecture that, when combined with the excitatory (pyramidal, glutamatergic) networks, form the architecture of the canonical cortical microcircuit (Douglas and Martin, 2004). These influences can be seen to maintain the excitatory-inhibitory balance, perhaps optimized at criticality (Plenz, Ribeiro, Miller, Kells, Vakili, & Capek, 2021), in the management of feedforward and feedback control in the limbic-cortical dialog.

Yet, even as the architecture is combined, the elemental cybernetic modes remain separable in the *directional flow of control* (feedforward-limbifugal and feedback-limbipetal). The result is that these dual, complementary control modes are balanced in network architecture of the cerebral cortex, with feedforward control leading to impulsive character of the dorsal corticolimbic division, and feedback control leading to the greater constraint provided by the ventral corticolimbic division (Tucker & Luu, 2023). This architecture can be seen to provide unique modes for the excitatory-inhibitory anatomy described by the structural model of cortical organization (Barbas & Rempel-Clower, 1997; García-Cabezas, Zikopoulos, & Barbas, 2019). Our theoretical proposal is that this interdigitated — balanced excitatory-inhibitory — anatomy of the cerebral cortex is motivated by dual limbic controls as the mammalian neocortex evolved complex representational capacities from the more homeostatic species-specific mechanisms of active affordance to create the more allostatic and general cognitive process of active inference.

Together, these dual control modes appear to engage primordial subcortical arousal control systems, which we propose are aligned with rhombencephalic lemnothalamic and mesencephalic collothalamic pathways, bringing their integral mood and motivation properties to support both the generation of predictions and the correction of ongoing expectancies by the sensory-motor evidence of the world in the ongoing process of active inference (Bastos et al., 2012; K. Friston, 2008).

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