

Opinion

Redefining the Role of Limbic Areas in Cortical Processing

Lorena Chanes^{1,2} and Lisa Feldman Barrett^{1,2,*}

There is increasing evidence that the brain actively constructs action and perception using past experience. In this paper, we propose that the direction of information flow along gradients of laminar differentiation provides important insight on the role of limbic cortices in cortical processing. Cortical limbic areas, with a simple laminar structure (e.g., no or rudimentary layer IV), send ‘feedback’ projections to lower level better laminated areas. We propose that this ‘feedback’ functions as predictions that drive processing throughout the cerebral cortex. This hypothesis has the potential to provide a unifying framework for an increasing number of proposals that use predictive coding to explain a myriad of neural processes and disorders, and has important implications for hypotheses about consciousness.

A General Organizational Framework for Predictive Coding in the Cerebral Cortex

Research and theory are converging on the idea that the brain actively constructs how we experience and act on the world. According to the principles of active inference and predictive coding, the brain functions as a hierarchical generative model of the world that follows the principles of Bayesian probability to explain sensory input based on past experience [1–3] (for an early proposal, see [4]). Signals based on this generative model, called ‘predictions’, are sent from higher areas in the processing hierarchy to lower areas; this corresponds to ‘feedback’ or descending projections [5–9]. Predictions modulate the firing of sensory neurons in advance of sensory signals arriving from peripheral receptors and are compared with incoming sensory input. The difference between predictions and sensory input (called ‘prediction error’) is sent back up the hierarchy; this corresponds to ‘feedforward’ or ascending projections. The reliability of the prediction error signal is also taken into account so that the impact of prediction error in updating the model is not fixed but weighted based on its reliability (or inverse of its variance, called ‘precision’) (see [2] for a review). Together, perceptions and actions are thought to derive from the brain’s best guess about the causes of sensory events, with incoming sensory input keeping those guesses in check. In a recent paper [10], we considered the notion of systematic variation of laminar structure of the cortex and integrated a structural theory of corticocortical connections ([11,12]; see [13] for a recent review) with the principles of predictive coding to propose an interoceptive system in the brain. In this paper, we extend this logic to the entire cerebral cortex. This redefines the role of cortical limbic areas in cortical processing.

Implementing predictive coding principles within the structural model of corticocortical connections reveals that the direction of predictions and prediction errors between two cortical areas is determined by the laminar structure of those areas, such that predictions flow from less to more laminated cortices and prediction errors flow in opposite direction (as discussed in [10]). Cortical limbic areas (cingulate cortex, ventral anterior insula, posterior orbitofrontal cortex, parahippocampal gyrus, and temporal pole) have the simplest laminar structure in the

Trends

The brain functions as a generative model of the world that, following the principles of Bayesian probability, explains sensory input based on past experience.

The structural model of corticocortical connections allows us to hypothesize that predictions flow from less to better laminated areas and prediction errors flow in opposite direction.

Limbic cortices, with their simple laminar structure, issue predictions from the top of the hierarchy within every sensory system. The lowest levels correspond to primary sensory cortices, with a well-developed laminar structure.

Owing to their position in cortical hierarchies and their connectivity, limbic cortices are well suited to integrate a neural ‘workspace’ for a unified conscious experience.

This model motivates novel hypotheses about the organization of intrinsic networks and has the potential to integrate a range of neural processes and disorders.

¹Northeastern University, Department of Psychology, Boston, MA, USA

²Massachusetts General Hospital, Department of Psychiatry and the Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, USA

*Correspondence: l.barrett@neu.edu (L.F. Barrett).

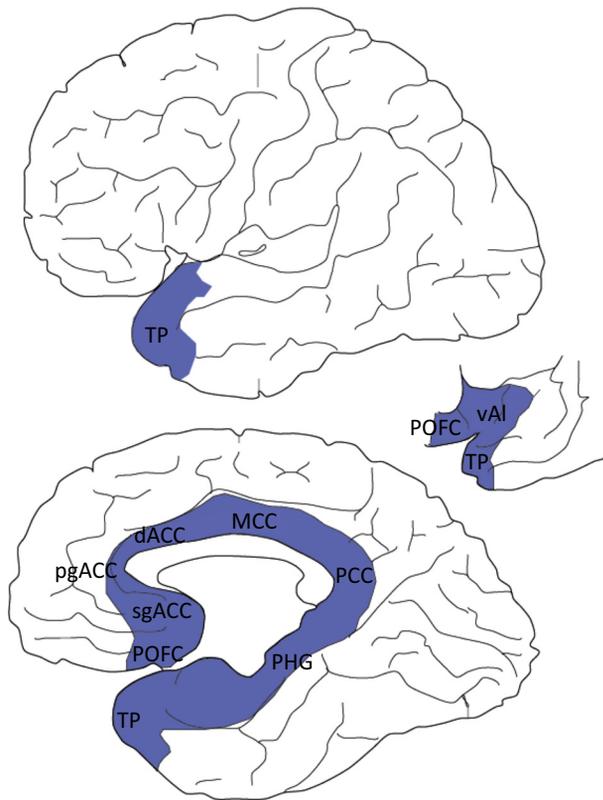


Figure 1. Limbic Cortices in the Human Brain. Cortical limbic areas (in blue) form a ring around the corpus callosum on the medial wall of each hemisphere, continuing along the temporal cortex and the base of the brain [13]. They are neocortical areas that either lack or have a rudimentary layer IV (i.e., are agranular or dysgranular, respectively). They are located between the simpler allocortex and the better laminated eulaminar cortex. Limbic cortices include the cingulate cortex (subgenual anterior cingulate cortex, sgACC; pregenual anterior cingulate cortex, pgACC; dorsal anterior cingulate cortex, dACC; mid-cingulate cortex, MCC; posterior cingulate cortex, PCC), the ventral anterior insula (vAI), the posterior orbitofrontal cortex (POFC), the parahippocampal gyrus (PHG), and the temporal pole (TP). Modified from [110].

Trends in Cognitive Sciences

neocortex (see [Glossary](#)) (Figure 1; Box 1). As a result, we hypothesize that they are at the top of the predictive hierarchy in all cortical systems, sending predictions, while the most laminated areas (e.g., primary sensory cortices) are at the lowest levels, receiving predictions. We further propose that owing to (i) their anatomical location abutting every sensory system [13], (ii) their position at the top of predictive hierarchies, and (iii) their strong connectivity to each other [14–19], as well as to subcortical structures such as the amygdala, the ventral striatum, and the hypothalamus [20–27], **limbic cortices** create a highly connected, dynamic functional ensemble for information integration and accessibility in the brain. We then hypothesize that limbic cortices, by virtue of their structural and functional properties, contribute to creating a unified conscious experience. We further suggest that our hypotheses provide novel insights about the flow of information within intrinsic brain networks. Finally, we discuss how our approach may offer a unifying framework for the growing number of predictive coding models of neural processes and disorders.

Box 1. Systematic Variation of Laminar Structure in the Cerebral Cortex and Cortical Limbic Areas

The cerebral cortex varies systematically in its degree of laminar differentiation [29,30]. Laminar differentiation increases progressively, from agranular cortices (which lack a layer IV) to dysgranular areas (with a rudimentary layer IV), then to eulaminar areas (with six layers including a well-developed layer IV), and finally koniocortices (with six layers including the most developed layer IV). For the purpose of the present paper, we operationally define cortical limbic areas or limbic cortices cytoarchitecturally, rather than by location or function (following [13]). Limbic cortices are those neocortical areas that either lack a layer IV (i.e., are agranular) or have a rudimentary layer IV (i.e., are dysgranular). Limbic cortices are located between the simpler allocortex and the better laminated eulaminar cortices [29,30]. They are also sometimes referred to as periallocortex (agranular parts) and proisocortex (dysgranular parts).

Glossary

Agranular cortex: part of the neocortex that lacks a layer IV.

Allocortex: part of the cerebral cortex with the simplest structure (two or three layers). It comprises the primary olfactory cortex (part of the cerebral cortex that receives the projection from the olfactory bulb) and the hippocampus.

Allostasis: process of activating physiological systems (such as hormonal, autonomic, or immune systems) with the aim of returning the body to homeostasis.

Dysgranular cortex: part of the neocortex with a rudimentary layer IV.

Eulaminar cortices: part of the neocortex with a well-developed layer IV. Eulaminar II areas have a better developed layer IV than eulaminar I areas. Also called granular cortex.

Interoception: the perception and integration of autonomic, hormonal, visceral, and immunological homeostatic signals that collectively describe the physiological state of the body.

Koniocortices: the eulaminar cortices with the most well-developed layer IV.

Limbic cortices or cortical limbic areas: part of the neocortex with agranular or dysgranular structure.

They are sometimes referred to as periallocortex (agranular) and proisocortex (dysgranular) cortex.

Neocortex: part of the cerebral cortex with three or more layers and columnar organization. Sometimes referred to as 'isocortex'.

Visceromotor limbic cortices: limbic (agranular and dysgranular) cortices that modulate the regulation of the autonomic nervous system, as well as of the hormonal and immune systems.

Predictive Coding within the Laminar Architecture of Corticocortical Connections

Predictive coding and active inference approaches to cortical processing have been implemented anatomically within the laminar architecture of the cortex. There are several models of corticocortical processing to choose from. The first papers (e.g., [6–9]) used the Felleman and Van Essen model of connections [28]. More recently, we implemented predictive coding hypotheses using the structural model of corticocortical connections [11,12] (Box 2) to propose the Embodied Predictive Interoception Coding (EPIC) model [10]. The Felleman and van Essen model identified laminar patterns for feedback and feedforward projections. The structural model went one step further to show that those patterns are predicted by the degree of laminar differentiation of the connected areas. This, together with the systematic variation in cortical structure across the cerebral cortex [29,30], has important implications for information flow. Moreover, the structural model generalizes to the entire cerebral cortex; it has successfully predicted the flow of information in frontal, temporal, parietal, and occipital cortices in experiments with macaques and cats, using both experimental and computational techniques (Box 2). Other models (e.g., using the distance rule [31,32]) have proven powerful and valid for some

Box 2. The Structural Model of Corticocortical Connections

In 1997, Barbas and Rempel-Clower introduced a structural model of corticocortical connections by analyzing projection patterns within prefrontal cortices and their laminar structure in the monkey [12]. Using anterograde and retrograde tracers, they showed that there is a relationship between laminar structure in cortical columns and the distribution of projection neurons that connect those columns (for a recent review, see [13]). Feedback projections originate in less differentiated cortical areas (such as **agranular cortex** with undifferentiated layers II and III and without a layer IV) primarily in the deep layers (layers V and VI) and terminate in superficial layers of areas with a more developed laminar structure (such as eulaminar cortices) (e.g., the blue neuron in Figure 1). Feedforward projections originate in areas with higher degree of laminar differentiation (e.g., eulaminar cortices with a fully expressed layer IV) primarily in the superficial layers (II–III) and terminate in middle deep layers (IV–VI) of areas with less differentiated laminar architecture (e.g., dysgranular cortex) (e.g., the red neuron in Figure 1). The structural model successfully predicts the flow of information in frontal, temporal, and parietal cortices in experiments with monkeys and cats (see [13] for a review) and outperforms other models of corticocortical connections [111].

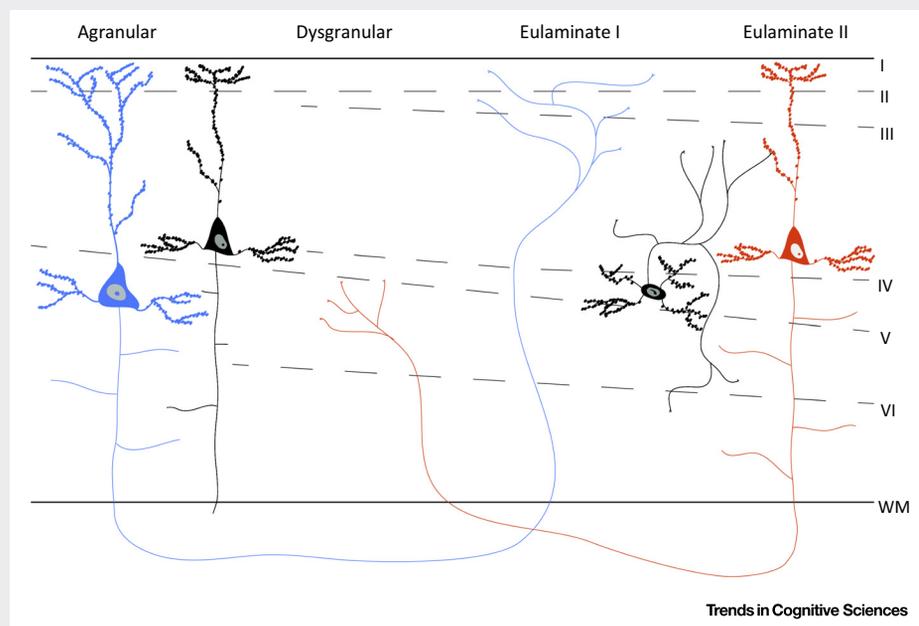


Figure 1. Structural Model of Corticocortical Connections. Feedback connections originate in deep layers of less laminated areas and terminate in superficial layers of more laminated areas (blue neuron). Feedforward connections originate in superficial layers of more laminated areas and terminate in deep layers of less laminated areas (red neuron).

systems (e.g., visual areas), but are known to be less suitable for predicting information flow within other systems (e.g., prefrontal areas; specifically, see Figure 6 legend in [32]).

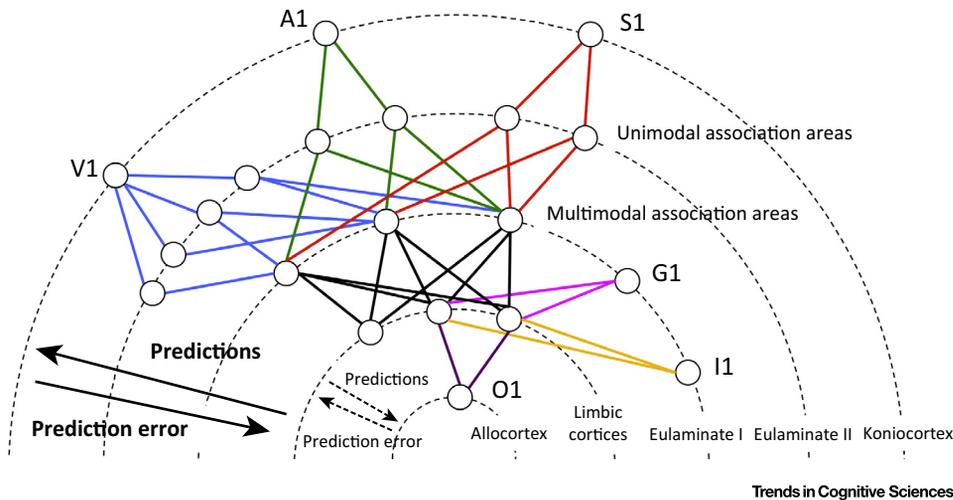
A direct consequence of using the structural model to implement predictive coding is that the direction of predictions ('feedback' connections) and prediction errors ('feedforward' connections) is determined by the relative degree of laminar differentiation of the cortical areas involved [10]. Predictions originate primarily in the deep layers of cortical areas with less laminar differentiation and terminate primarily in the superficial layers of more differentiated areas. By contrast, prediction errors originate primarily in the superficial layers of cortical areas with more laminar differentiation and terminate in the deep layers of less differentiated areas. When two areas have a comparable laminar structure, their projections originate and terminate both in superficial and deep layers (they are 'lateral'). This implies that some cortical areas, such as limbic cortices (which have the least differentiated laminar structure in the entire neocortex) primarily send predictions to better laminated cortical areas and primarily receive prediction error. Moreover, primary sensory cortices (with the most differentiated laminar structure) receive predictions from less laminated cortical areas and send prediction error. Other cortical areas (with intermediate degrees of laminar differentiation) send both predictions and prediction error depending on the relative laminar differentiation of the receiving cortices.

In the EPIC model [10], we used evidence from tract tracing studies in monkeys, as well as functional imaging evidence in humans, to propose that **visceromotor limbic cortices** (notably the anterior and mid-cingulate cortices and the ventral anterior insula) send predictions to the primary interoceptive cortex in the mid-to-posterior insula (I1), which is eulaminar in structure (extending the logic in [6–9]). Visceromotor cortical limbic areas also send predictions to subcortical structures that control the autonomic, hormonal, metabolic, and immunological systems (e.g., the amygdala and the hypothalamus). In this paper, we further extend our implementation of predictive coding within the structural model of corticocortical connections to hypothesize that limbic cortices are at the top of each cortical sensory system. We call this the limbic workspace model.

Limbic Cortices in Sensory Systems

One hypothesis of the limbic workspace model is that all cortical sensory systems are structured similarly to the interoceptive system. This hypothesis builds on evidence from tract tracing studies in monkeys, indicating that limbic cortices can be identified in visual (e.g., [33–36]), auditory (e.g., [37–39]), and somatosensory (e.g., [36,40]) systems (also see [41,42]). The anatomical pathways in the description of the different sensory systems that follows are, as in [10], inferred in humans based on tract tracing studies performed in monkeys, unless otherwise noted; this is similar to what has been done elsewhere [42], as inferences about the human brain are commonly made studying other species such as the macaque monkey. We acknowledge, of course, that different species have some important differences in brain structure and function.

It is well established that visual and auditory systems work via predictive coding (e.g., [5], [43–45] in humans, for a review on visual processing see [46]), and there is increasing evidence that the olfactory and gustatory sensory systems work via predictive coding as well ([47–49] in rodents, [50,51] in humans), along with a proposal that somatomotor system works similarly [6–9]. We propose that limbic cortices are at the top of each hierarchical cortical system and send predictions to better laminated areas. Primary sensory cortices are at the bottom and send prediction error back to areas with simpler laminar structure. Evidence in support of our hypothesis can be most clearly seen in the visual, auditory, and somatosensory systems (Figure 2, blue, green, and red respectively), where predictions flow from cortical limbic areas (agranular and **dysgranular cortex**) to multimodal association areas (e.g., lateral temporal



Trends in Cognitive Sciences

Figure 2. Schematic Representation of Exteroceptive and Interoceptive Cortical Sensory Systems. This figure is not meant to be exhaustive but representative. Each ring represents a different type of cortex, from greater (exterior circles) to less (interior circles) laminar differentiation. Primary sensory cortices (lower level of each sensory system) are indicated: A1, primary auditory cortex; G1, primary gustatory cortex; I1, primary interoceptive cortex; O1, primary olfactory cortex; S1, primary somatosensory cortex; V1, primary visual cortex. Unimodal association areas include extrastriate areas (V2, V3, V4, MT/V5) for the visual system, superior temporal areas surrounding A1 for the auditory system, and the superior parietal lobule for the somatosensory system. Multimodal association areas include the dorsolateral prefrontal cortex, lateral temporal cortex, and posterior parietal cortex. Predictions flow from cortical areas with less laminar differentiation to areas with greater laminar differentiation. Prediction error flows in opposite direction. The number of cortical steps (hierarchical levels) is less in interoceptive, gustatory, and olfactory systems than in exteroceptive visual, auditory, and somatosensory systems.

cortex and posterior parietal cortex) (e.g., [14–17] and based on intrinsic connectivity analyses in humans [52]). These multimodal areas are eulaminate in structure (i.e., they have a well-defined layer IV) and are shared across the three systems. From there, predictions are sent to unimodal association areas (extrastriate areas for the visual system, superior temporal areas surrounding primary auditory cortex for the auditory system, and the superior parietal lobule for the somatosensory system) (e.g., [36,41,53]). Unimodal association areas are **eulaminate cortices** with a better developed layer IV. From these areas, predictions flow to primary sensory cortices {primary visual cortex or V1 (e.g., [33,54–56]), primary auditory cortex or A1 (e.g., [37,57]) and primary somatosensory cortex or S1 (e.g., [36,40])}, which are **koniocortices** in structure (i.e., they contain the most well-developed layer IV).

Sensory input from the periphery (visual, auditory, and somatosensory input via the thalamus) arrives at the cortex at primary sensory areas (V1, A1, and S1). In those areas, sensory information is represented in great detail (see, for example, the early experiments for primary visual cortex [58]) and prediction error is computed. From there, prediction error (the sensory evidence that did not match the prediction) flows through the gradients of laminar differentiation to progressively less well laminated areas (unimodal association areas to multimodal association areas and finally to limbic cortices). Note that even though predictions and prediction errors flow hierarchically, areas within each system are not necessarily physically placed in a strictly linear manner (for a discussion see [42]). Moreover, these systems likely influence each other at every level of the hierarchy through lateral connections.

At higher levels of the predictive hierarchy (in areas with relatively less laminar differentiation), information becomes more integrated. This integration across sensory domains comes with progressive dimensionality reduction (meaning sensory detail is summarized and compressed). For example, multimodal association areas are shared across visual, auditory, and

somatosensory systems (e.g., [41]; see [42,59] for reviews; for evidence of a multimodal integration network in humans, see [52]).

Moreover, there are differences across systems in the amount of cortical processing. Compared with **interoception** (Figure 2, yellow), information from visual, auditory, and somatosensory modalities is processed more extensively in the cerebral cortex. In these exteroceptive systems, predictions and prediction errors are computed across several levels of cortical processing (i.e., there are several synaptic connections between primary sensory cortices in which representations are more specialized and cortical limbic areas in which they are more integrated), whereas there are fewer steps in the interoception system. Accordingly, primary interoceptive cortices in mid- and posterior insula (I1) are eulaminar in structure (i.e., they have a less developed layer IV than koniocortices of primary visual, auditory, and somatosensory cortices) (see [10]). This difference in degree of laminar differentiation along which predictive signals are coded [smaller in the interoceptive system (eulaminar to limbic) versus larger in the visual, auditory, and somatosensory systems (koniocortex to limbic)] may be one reason why interoceptive perception is less differentiated and lower in dimensionality when compared with exteroceptive perception (for a description of other reasons, such as the anatomy of the ascending interoceptive circuitry, see [60]).

The gustatory system (Figure 2, pink) is structurally similar to the interoceptive system. It has few steps between limbic and primary gustatory cortex (G1) (see, e.g., [14,15,17]), as G1 is eulaminar in structure (i.e., not as well laminated as koniocortices) (for a review in humans, see [61]).

The olfactory system (Figure 2, purple) is structured in a way that likely reflects its ancient evolutionary origin: the primary olfactory cortex (O1) is three-layered **allocortex**. It abuts the anterior insula and receives olfactory input directly from the olfactory bulb without a thalamic relay (see [62] for a review in humans). Because O1 is allocortical (rather than neocortical), the neurons are not structured in columns [63,64] and, therefore, strictly speaking, it is not known whether the structural model of corticocortical connections holds. Furthermore, axons leaving O1 to ipsilateral limbic cortices travel through the superficial layer I to the targeted areas [65] rather than through white matter tracts. Thus, they will reach target areas via superficial cortical layers. We can speculate, however, that predictions flow similarly from limbic cortices to O1, as odor expectations alone, even in the absence of olfactory input, are associated with activity in the main olfactory bulb [66] in rodents; for a review of 'top-down' influences on olfaction, see [49]).

Taken together, these findings are consistent with the hypothesis that predictions issued in limbic cortices involve more integrated, lower dimensional (multimodal) information, and these predictions become higher in dimensionality (as predictions issued at lower hierarchical levels within each sensory system are more specialized) until they reach primary sensory cortices, where the most specialized cortical processing occurs. As prediction error is sent from primary sensory to limbic cortices, it is compressed and summarized (for evidence consistent with this hypothesis, see [52,67–69]; for a discussion of the energy efficiency of this arrangement, see [70]). Therefore, the limbic workspace model proposes a general role of limbic cortices in cortical processing, which is compatible with more specific functions of these areas and the existence of differences across them; different cortical limbic areas may be more heavily associated with specific systems.

In a predictive coding framework, perception and action are tightly coupled, such that action can reduce prediction error (e.g., [6,7]; see also [10]). Extending this logic to the limbic workspace model, we speculate that both action and perception arise from the brain's hypotheses about the world and the body beginning as predictions in limbic cortices. Predictions are then

constrained by sensory inputs, such that perceptions are largely constructions based on past experiences and their allostatic relevance, kept in check by the actual state of the world and the body, rather than the other way around.

A Dynamic Global Workspace for Conscious Experience

The brain works as a generative model of the world using past experience to construct the present. We speculate that it is not an objective, accurate model, but one that is shaped by the information that the organism has encoded in its history and tailored to its allostatic needs and motivations (see also [10]). In addition to their anatomical position at the top of sensory and motor processing hierarchies, limbic cortices are strongly interconnected [14–19], and have strong bidirectional connections with subcortical structures such as the amygdala, the ventral striatum, and the hypothalamus [20–27]. Therefore, highly integrated neural representations in limbic cortices are easily accessible by virtually the whole brain. Interestingly, information accessibility and sharing, as well as the idea of a ‘workspace’, have been consistently described as key features of conscious access (e.g., [71–73]). ‘Global workspace’ [74] theories of consciousness propose the rapid activation or ‘ignition’ of a long-range neuronal system as the neural basis of consciousness ([71], for a review see [72]). Other theories emphasize the importance of corticothalamic loops (‘dynamic core’ theory, reviewed in [73]), or areas with dense anatomical connections known as ‘rich club’ hubs [75] (Box 3). We contribute to these ideas by proposing that limbic cortices, owing to their connectivity and position in hierarchical cortical information flow, are in a privileged position to contribute to the neural basis of conscious access and may provide a ‘workspace’ for conscious experience. Representations of information in a given cortical system (e.g., visual, auditory, motor, etc.) or a combination thereof can be dynamically selected and prioritized because of their predicted relevance for the organism in a specific context [67,76]. This implies that limbic cortices issue their predictions based primarily on the selected content. For example, as you read these lines there are many sensory details that you are not currently aware of, but you could be if those became suddenly relevant to you (e.g., the pressure of your back against the chair). As you read, these words are gaining privileged access to a workspace for consciousness, which we propose is integrated largely by cortical limbic areas. The content of specific cortical systems may be selected for its situation-specific relevance (based on priors) for the organism and sent to the workspace. From there, prioritized information can be accessed by virtually all systems in the brain, allowing a unified conscious experience. In every conscious moment, all modalities are represented, but the type of content that is prioritized may determine whether we categorize the experience as ‘emotion’, ‘perception’, or ‘cognition’. This dynamic selection of contents in the workspace and its flexibility guarantees both differentiation and integration, which are key properties of consciousness [73], as well as overall brain function [77]: differentiation because an immense number of possible

Box 3. Functional Organization of Intrinsic Brain Networks and ‘Rich Club’ Hubs

‘Resting state functional connectivity magnetic resonance imaging’ is the measurement of correlations of low frequency blood oxygen level-dependent (BOLD) signal fluctuations while a participant lays ‘at rest’ during functional magnetic resonance imaging (i.e., is not probed with an external stimulus). Analyses reveal a number of ‘intrinsic’ brain networks that are anatomically constrained [112–115], can be observed under light sedation [116], and account for a large proportion of the brain’s metabolic budget [117]. ‘Rich club’ hubs are the most highly connected brain areas and have been identified using diffusion tensor imaging of white matter tracts in humans [86] and reviewing tract tracing studies in monkeys [87,88]. A large proportion of the rich club hubs are contained in two of the brain’s intrinsic networks [75], conventionally known as the ‘default mode’ network [82] and the ‘salience’ network [80]; these two networks contain most of the brain’s cortical limbic circuitry, and many rich club hubs are, in fact, limbic (e.g., dorsal ACC and anterior insula). Furthermore, different intrinsic networks such as sensory networks overlap in these hubs, communicating with each other through them [75]. These findings provide a conceptual replication for the macaque tract tracing data, because they indicate that all sensory systems share cortical areas with core networks that contain limbic cortices. They suggest the intriguing hypothesis that these two networks are at the nexus of the brain’s architecture for predictive coding.

representations from each cortical system can be prioritized in the limbic workspace; integration because it provides a plausible explanation for a unified conscious experience and ‘stream of consciousness’.

Implications

Intrinsic Networks and ‘Rich Club’ Hubs

The limbic workspace model provides insight on the relationships between different cortical areas within and across intrinsic networks (Box 3). The brain can be thought of as one large structural network showing continuous, intrinsic activity [78]. This activity has been parsed as interconnected subnetworks that follow the white matter tracts within the brain (see [79] for a review of networks). Empirically, an intrinsic network is defined as those areas whose low frequency blood oxygen level-dependent (BOLD) signal correlates over time when a person is ‘at rest’ (i.e., not being probed with an external stimulus). Each intrinsic network includes areas with varying degrees of laminar differentiation (including limbic cortices) such as the ‘salience network’ [80] (which bears a strong resemblance to the ‘ventral attention’ [81] and ‘multimodal’ networks [52]) and the ‘default mode network’ [82] (sometimes called the mentalizing network [83], the construction network [84], or semantic knowledge network [85]). Within the limbic workspace model, intrinsic networks can be understood as hierarchical systems, with the flow of prediction signals within each network dictated by the structure of the cortical areas involved. In these networks, limbic cortices (e.g., the ventral anterior insula and dorsal anterior cingulate cortex for the ‘salience’ network and the posterior cingulate cortex and sub/pregenual cingulate cortex for the ‘default mode’ network) issue predictions to better laminated areas in the network. This way, a single network may contain a diverse population of representations across multiple levels of cortical processing.

Similarly, the limbic workspace model provides insights into the functions of brain areas that have the strongest structural connections, known as ‘rich club hubs’ [75,86–88], because these hubs also include areas with different degrees of laminar differentiation (Box 3). Structural and functional imaging in humans indicates that rich club hubs are ‘connector nodes’ for intrinsic networks [75] and they have been shown to play an important role in brain communication [67,89]. Mathematical modeling indicates that when one or more rich club areas are damaged (e.g., the anterior insula or the dorsal anterior cingulate cortex, as occurs in psychopathology or chronic stress), modularity in the brain increases dramatically [90].

Integrating Different Functional Domains and Disorders

In the past several years, there has been an explosion of predictive coding approaches beyond the sensory domain, including memory [91–93], pain [94–97], emotion [10,98–100], conscious presence [101], self-recognition [102], **allostasis** [103], the placebo effect [104], ‘fear’ learning [105], as well as neuropsychiatric disorders [106–108]. Each of these phenomena arises from the dynamic interaction of systems that contain cortical areas that vary in their degree of laminar differentiation. We speculate that limbic cortices, because they are at the core of the brain’s architecture for prediction, serve as shared neural relevant substrate for varied phenomena whose circuitry is usually assumed to be distinct. For example, in the case of neural processing of nociception, similarly to interoception, visceromotor limbic areas (e.g., dorsal anterior cingulate) might issue predictions, while areas with higher degree of laminar differentiation such as the dorsal mid-to-posterior insula or subcortical structures such as the periaqueductal gray (PAG) will be at lower levels in the hierarchy and will send prediction error back to limbic (agranular and dysgranular) areas (for a review on connections between the PAG and limbic areas, see [109]). In fact, evidence of predictions in expectance of pain in the anterior insula has been reported [94] and prediction error signals have been described in the PAG [96]. Our proposed model also suggests fruitful avenues to explore the common visceromotor predictive basis for psychiatric,

metabolic, and immunological symptom convergence in illnesses such as depression, heart disease, and cancer (see [10]).

Concluding Remarks

Research and theory are converging on the idea that the brain's architecture constructs a vast repertoire of functional states as a generative model of the world. This model of the world is shaped by the organism's history and tailored to its allostatic needs and motivational goals. In this paper, we hypothesized that limbic cortices send predictions within all cortical systems, driving cortical processing across the gradients of laminar differentiation. We hypothesized that limbic cortices issue low-dimensional, multimodal predictions that are specified into high-dimensional representations as they cascade to lower level cortical areas with better laminated cytoarchitectural structure. We further speculated that cortical limbic areas, owing to their privileged position in cortical hierarchies, their anatomical position within the brain (abutting all sensory systems), and their dense interconnectivity, are well suited to provide an integrated workspace enabling a unified experience. Ultimately, the limbic workspace model may offer a unifying anatomical and functional account to better understand the organizational principles of intrinsic networks and rich club hubs, as well as unify many healthy and pathological phenomena that have, until now, been considered as having separate circuitry (see Outstanding Questions).

Because limbic cortices function to represent integrated information across different modalities according to their allostatic relevance based on past experience, this may be why scientists continue to identify limbic cortices with goals, values, or motivation. The present model of cortical processing emphasizes the importance of information integration and segregation in the brain and may help explain how the brain constructs a diverse population of representations across multiple scales of organization within a relatively constrained architecture.

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Outstanding Questions

How flexible is our generative model of the world? How easily can it be modified with new experiences?

To what degree is our generative model of the world anchored in visceromotor changes and interoception? How much do interoceptive predictions contribute to ongoing experience? Are there individual differences in this regard?

Are there structural and functional differences between cortical rich club hubs of different degree of laminar differentiation?

Are there differences in limbic predictions during the mental events that are experienced as emotions, cognitions, and perceptions?

How is a generative model of the world altered in different neuropsychiatric conditions? Are there transdisorder vulnerabilities?

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