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Opinion
A Network Model of the Emotional Brain

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Emotion is often understood in terms of a circumscribed set of cortical and subcortical brain regions. I propose, instead, that emotion should be understood in terms of large-scale network interactions spanning the entire neuroaxis. I describe multiple anatomical and functional principles of brain organization that lead to the concept of 'functionally integrated systems', cortical–subcortical systems that anchor the organization of emotion in the brain. The proposal is illustrated by describing the cortex–amygdala integrated system and how it intersects with systems involving the ventral striatum/ accumbens, septum, hippocampus, hypothalamus, and brainstem. The important role of the thalamus is also highlighted. Overall, the model clarifies why the impact of emotion is wide-ranging, and how emotion is interlocked with perception, cognition, motivation, and action.

Search for the Brain Mechanism of Emotion

Where does emotion reside in the brain? Thinking about the brain basis of emotion has fluctuated between a focus on regions and a focus on circuits. In the 1920s and 1930s, work by Cannon and Bard propelled the hypothalamus to the epicenter of the emotional brain [1]. At the same time, the idea that emotion depends on distributed circuits also was present in early work. In the 1930s, Papez proposed a distributed mechanism responsible for emotion involving, among others, the hypothalamus, hippocampus, anterior thalamus, and cingulate gyrus [2]. The region versus circuit tension was also present in subsequent developments, including MacLean's proposal of the visceral brain or 'limbic system' [3] (itself partly based on ideas by Broca in the previous century [4,5]), and Panksepp's framework of specialized subcortical circuits for basic emotions [6].

Today, characterizing circuit interactions is believed to be key to unraveling how emotion is organized in the brain. The key question addressed here is as follows: how is emotion instantiated in the brain? To quote Papez [2], what is the 'mechanism of emotion?' I propose the concept of cortical–subcortical 'functionally integrated systems' as a model of the emotional brain, which is based on large-scale networks and their interactions, and aimed at understanding the brain basis of emotion and interactions between emotion and perception, cognition, motivation, and action. I first outline six principles of brain organization that define the broader context needed for understanding the emotional brain. They are reviewed here not as a short tutorial on large-scale networks, but as concepts leading to the model of functionally integrated systems described subsequently. To anticipate, some of the consequences of the principles are as follows: the brain's anatomical and functional architectures are highly non-modular; signal distribution and integration are the norm, allowing the confluence of information related to perception, cognition, emotion, motivation, and action; in addition, the functional architecture comprises overlapping networks that are highly dynamic and context-sensitive.

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Principles of Brain Organization

Principle 1: Massive Combinatorial Anatomical Connectivity

Computational analysis of anatomical connectivity demonstrates that both cortical and subcortical brain regions are densely interconnected [7–11]. Rich connectivity is not limited to specific sectors of the brain (e.g., prefrontal cortex, PFC) but instead encompasses all of them (including the brainstem and cerebellum). Important anatomical properties include: (i) massive interconnectivity; (ii) high global **accessibility** (see Glossary) [12]; and (iii) the existence of a 'connectivity core' or 'rich-club' of regions marked by especially high levels of connectivity. Focusing on macaque cortical regions, one study described a core set of 17 regions spanning parietal, temporal, and frontal cortex that was marked by 92% connectivity density (92% of the connections that could exist were present) [12]. By combining multiple sources of data, another study described a core that was distributed across all major brain sectors (all cortical lobes, thalamus, and subcortical regions in the forebrain) [13].

Although progress has been made in elucidating properties of the large-scale anatomical architecture of the brain, computational studies likely underestimate existing connectivity, and provide a limited characterization of the existing organization. This is not only because current knowledge of existing pathways (and strength) is largely incomplete but also because several known properties of connectivity are not explicitly incorporated into computational analyses, which also focus mostly on cortical connectivity. Notably, specific cortical–subcortical anatomical **connectional systems** (involving long-range and large-scale pathways) have been characterized but are not generally considered, or are only partly incorporated. These include striatal, thalamic, cerebellar, hypothalamic, claustral, and brainstem circuits, to name some [14]. These connectivity systems have the potential to substantially alter overall architectural properties and to influence information exchange, as discussed next.

Principle 2: Cortical–Subcortical Anatomical Connectional Systems

The entire cortical sheet (with the exception of area V1) projects to the striatum [14]. Studies in the 1970s and 1980s led to the concept of cortico–basal ganglia–thalamo–cortical systems, or cortical–basal ganglia loops for short [15] (Figure 1A). This research attempted to map out how different parts of cortex are connected to different parts of the striatum, forming a series of possibly parallel and functionally segregated circuits. It was found that striatal territories receiving cortical input do not directly reciprocate their connections, which instead return via different parts of the thalamus (after an additional step in the pallidum), thus forming the loop.

The architecture described for cortical–basal ganglia loops was proposed to be more general and to apply to other structures at the base of the forebrain [16], including the septum and the **extended amygdala** (involving the central nucleus of the amygdala and a nearby area called the bed nucleus of the stria terminalis [17]). In identifying properties in line with the organization of cortical–basal ganglia loops (neuronal types, thalamic return projections, etc.), it was suggested that the 'cortical' projections should be thought of as originating in the **cortex-like** hippocampus in the case of the septum, and in the cortex-like basal and lateral amygdala in the case of the extended amygdala [16]. Another property of the connectional architecture is that regions at the base of the forebrain project along the brainstem, which is extensively connected to **subcortical forebrain** structures themselves as well as to the cortex (Figure 1B) [18].

Therefore, large-scale cortical–subcortical anatomical connectional systems are not confined to the traditional basal ganglia but involve additional subcortical forebrain structures, too. The importance of these systems is that cortical signaling must be understood in terms of an expanded framework in which cortical and subcortical mechanisms are intimately interrelated [19]. To reiterate, a subcortical forebrain target region (e.g., the ventral striatum or extended amygdala) receives extensive inputs, thus allowing it to be sensitive to a wealth of signals

Glossary

Accessibility: the extent to which information in one part of a system can reach other parts via direct and/or indirect pathways. Accessibility can be measured by using network measures of 'efficiency', which can be local or global.

Centrality: centrality analysis aims to identify the most important, or central, elements of a system (such as the most important person in a social group). Multiple mathematical definitions of centrality have been described in the literature.

Connectional system: large-scale anatomical pathways interlinking multiple regions, and typically spanning different levels of the neuroaxis. A prototypical example is the concept of cortico–basal ganglia–thalamo–cortical systems.

Coordination dynamics: seeks to identify and track the temporal evolution of collective states which reflect emergent properties of the system. The overarching idea is that the function of a complex biological system lies in the interaction between context-sensitive components.

Cortex-like: cortex is characterized by its layered pattern. Some brain regions have simple lamination and are at times called 'old cortex'. such as the hippocampus, referred to here as 'cortex-like'. The amygdala has both pallial and subpallial components (the 'pallium' refers to the dorsal part of the telencephalon); the basolateral amygdala appears to be mostly of pallial origin and is here referred to as 'cortex-like'.

Decerebrate: an animal preparation in which the entire cerebral cortex is removed from the brain.

Efficiency: measure of information transfer between nodes. In networks with high efficiency, information travels via short paths between different parts of the network.

Extended amygdala: the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis are at times described as the 'extended amygdala' given their shared cellular and developmental properties.

Functional connectivity: the extent of coherence between signals of two regions, often indexed by correlating the associated signal time series.

Functional diversity: a multidimensional characterization of

(sensory, cognitive, emotional, motivational, motor) (Figure 2A). From the target region two types of pathway exist: one projects back to cortex (or cortex-like regions) via the thalamus (Figure 2A); another descends along the brainstem (Figure 2B). The descending projections contact regions that: (i) have further descending projections; (ii) loop back within the brainstem; (iii) loop back to the subcortical forebrain; and (iv) have extensive (and at times diffuse) connectivity with subcortical and cortical regions (Figure 2C). Notably, the descending pathways contact sites that are components of ascending projection systems involving a broad range of neurotransmitters, including acetylcholine, dopamine, epinephrine, norepinephrine, and serotonin [14].

Principle 3: High Distributed Functional Connectivity

Understanding brain function requires characterizing how regions are **functionally connected**, that is, how their signals co-vary. What is important is not simply the anatomical location of a region but its position in a space of functional relationships to other regions [20–22]. From the perspective of a brain region, at a given time, a region affiliates (or clusters) with a set of other regions, thereby defining a momentary circuit.

The relationship between structural and functional connectivity is not a simple one. A structure–function dissociation is illustrated by an unusual population of adults without the corpus callosum. Although starkly different structurally relative to controls, individuals without the callosum exhibit similar patterns of functional connectivity (as measured during rest with fMRI). Thus, relatively spared coordinated activity can emerge in brains with substantially altered structural connectivity [23,24].

Anatomical architectural features support the efficient communication of information even when strong direct structural connections are not present, and allow functional interactions that vary as a function of context. More broadly, indirect connections may support functional relationships between regions that are not robustly linked by direct pathways ([25]; see also [26]), as exemplified by a study of functional connectivity in macaques [27]. Amygdala functional connectivity was more strongly associated with 'communicability' of structural connections, which considered both monosynaptic and polysynaptic links, than with monosynaptic

the involvement of a region across multiple mental functions or processes.

Heterarchy: a type of organization where the elements of a system are at the same 'horizontal' level, or where a clear hierarchy is not observed.

Hubs: brain regions with a high degree of connectivity.

Neuroaxis: main axis of the central nervous system (roughly vertical in bipedal humans); sometimes written 'neuraxis'.

Subcortical forebrain: subcortical regions at the base of the telencephalon.
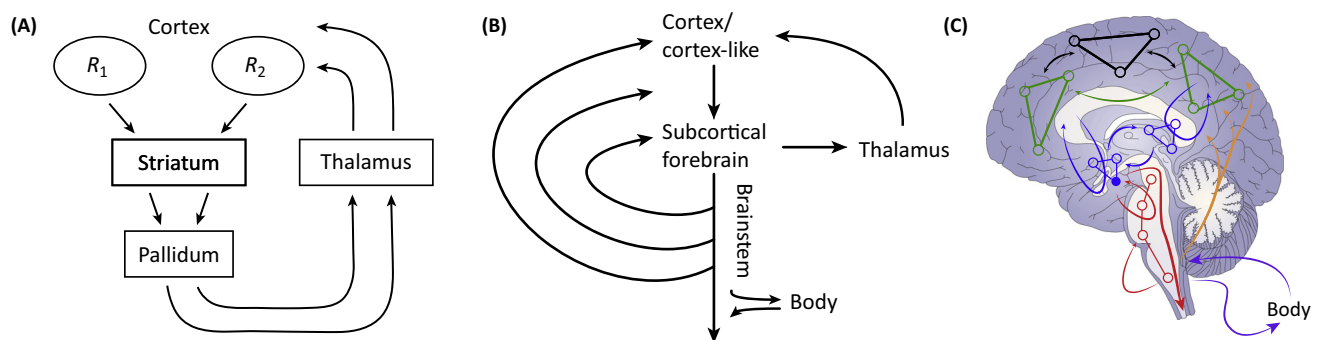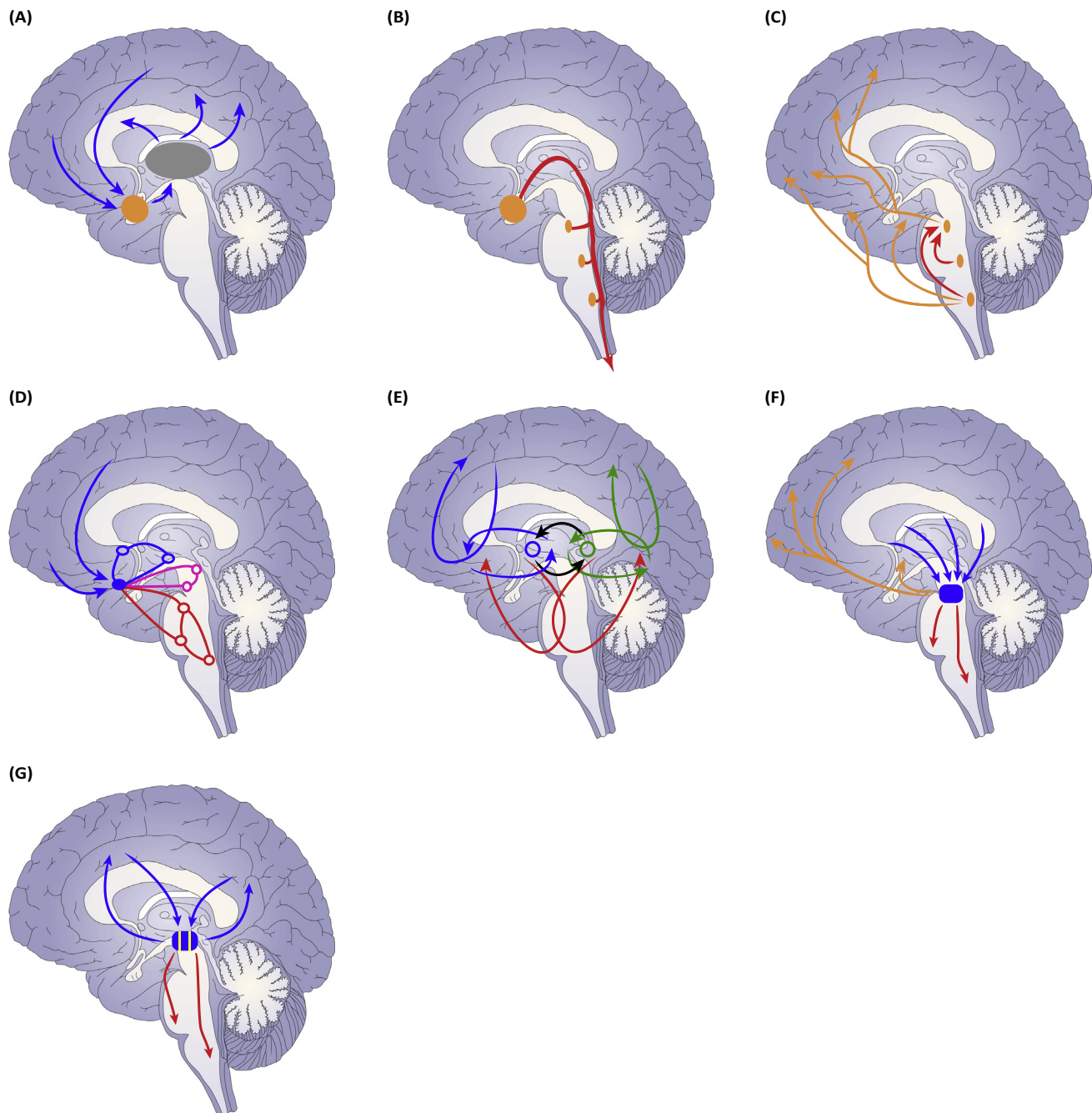

Trends in Cognitive Sciences

Figure 1. Cortical–Subcortical Anatomical Connectional Systems. (A) Cortico–basal ganglia–thalamo–cortical circuits (cortical–basal ganglia loops for short). Each thalamic region projects back to one of the cortical areas that feeds into the circuit, thus completing the 'closed loop' portion of the circuit. (B) Multiple regions at the subcortical forebrain are the target of cortical (or cortex-like) projections. Similarly to standard basal ganglia loop, the thalamus provides a route back to cortex (or cortex-like) regions. Notably, subcortical forebrain regions are also connected with caudally situated regions along the brainstem. (C) Network representation of cortical–subcortical connectional systems. Cortical regions, including those with strong connections to subcortical forebrain target regions (green) and other cortical networks (black). Subcortical forebrain regions (blue), including target regions such as the amygdala, striatum, and septum (blue, filled circle). Cortical–subcortical loops (blue lines with arrows returning to cortex) involve the thalamus (not shown). Subcortical forebrain and brainstem regions form loops (red lines with arrows); circuits are also present at the level of the brainstem (red lines with arrows). Ascending systems from the brainstem (orange lines) influence subcortical and cortical processing. Signals to and from the body are also exchanged (fuchsia arrows).

Figure 2. Properties of Cortical–Subcortical Anatomical Connectional Systems. (A) Target regions (orange) in the subcortical forebrain (thalamus shown in grey). (B) Descending projections along the brainstem. (C) Brainstem connections and diffuse projection systems. (D) A connectional system links multiple levels along the neuroaxis. (E) Connectional systems (in blue and green) interact with each other at the level of the subcortical forebrain (black lines). (F) Multiple systems merge at subcortical convergence hubs. (G) Partial segregation of systems.

connectivity. Furthermore, selective chemical inactivation of the amygdala degraded functional connectivity among other regions, including between medial prefrontal, orbitofrontal, anterior cingulate, and anterior temporal cortex. Thus, understanding brain circuits requires moving beyond structural connectivity and considering functional relationships.

Principle 4: Overlapping Brain Networks

Both anatomical (e.g., [13]) and functional (e.g., [28]) networks are typically described in terms of disjoint sets, such that each brain region belongs to a single community (a community or cluster comprises a set of closely associated regions). However, the importance of understanding and characterizing overlapping network structure has been discussed across multiple disciplines, because 'actual networks are made of interwoven sets of overlapping communities' [29].

Analysis of anatomical/functional data has repeatedly revealed regions with widespread connectivity [7–13,30], highlighting the limitations of parsing the brain into segregated networks. To assuage this problem, researchers have also described how regions behave as different types of **hubs** (particularly well-connected regions), so as to capture signal segregation and integration properties [31–33]. Although this approach may be satisfactory in relatively modular systems, given the degree of brain interconnectivity, it is more fruitful to consider networks as inherently overlapping [34,35].

A promising approach is to describe the brain based on networks (thus highlighting their relative independence), but allowing regions to belong to multiple networks simultaneously [36]. When we applied this approach to fMRI data during both taskless ('rest') and task conditions [35] it detected commonly observed communities, such as the task-negative (or default) network. However, the distribution of 'membership values' (the extent to which each region participated in each network; 0 and 1 in the extreme case of non-overlapping networks) indicated that nodes participated in multiple networks simultaneously. Distributed participation was even more evident in a community of frontal and parietal regions important for attention and executive control, consistent with a multifunctional role for these regions [32]. Supporting this notion, we found that 'membership diversity' (the extent to which regions participated across networks) during rest scans was positively related to **functional diversity** (which characterizes the involvement of a region in multiple mental functions, and can be assessed by interrogating large imaging databases [37]; see also [38,39]). Thus, regions that participated in more communities at rest tended to be activated by a wide variety of tasks – that is, they were functionally diverse.

Principle 5: Dynamic Brain Networks

Brain networks are not static but evolve temporally [40,41]. Although anatomical pathways change across the lifespan, the dynamics discussed here focuses on the functional connections between regions. Functional connections vary as a function of context, and are altered by cognitive, emotional, and motivational variables. Therefore, network organization must be understood dynamically. Indeed, the growth of methods to describe time-varying functional connectivity has begun to yield novel characterizations of how network organization evolves [42–44].

There are two important ways in which brain networks are dynamic. First, we can consider how specific networks evolve across time. For example, how does the **efficiency** [45] of the frontoparietal attentional network evolve as a function of task phase? More generally, it is important to characterize how multiple network properties change with time. Second, networks are not static and fixed collections of brain regions. Networks are suggested to be dynamic coalitions of brain regions that form and dissolve to meet specific computational needs. Accordingly, network descriptions must specify how groupings of regions evolve temporally. This poses several challenges because the very notion of a network as a coherent unit is possibly undermined. For instance, at what point does a coalition of regions become something other than, say, the salience network? Conceptualizing networks as inherently overlapping (principle 4) helps to mitigate this problem. For example, as previously discussed, each node

can be considered to be a member of every network with a specific probability-like 'membership value' [35] which fluctuates across time.

Implications of the Principles of Brain Organization

Together, the 'mechanism of emotion' of the brain should be consistent with the principles outlined above as well as with the principle of anatomical connectivity to and from the body (Box 1). Therefore, the brain basis of emotion involves large-scale cortical–subcortical networks that are distributed and sensitive to body signals. The high degree of signal distribution and integration provides a nexus for the intermixing of information related to perception, cognition, emotion, motivation, and action. Importantly, the functional architecture consists of multiple overlapping networks that are highly dynamic and context-sensitive. Thus, how a given brain region affiliates with a specific network shifts as a function of task demands and brain state.

Integrated Functional Systems: The Example of the Cortex–Amygdala System

The principles of brain organization outlined above set the stage for the concept of integrated functional systems. The starting point is the notion of a cortical–subcortical anatomical

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Box 1. Anatomical Connectivity To and From the Body

The contribution of the body to emotion has been debated since William James suggested its central role in emotional experience [96]. The precise status of the body notwithstanding, emotion is closely linked to bodily states. What is the anatomical connectivity to the body (expression) and from the body (interoception) that supports emotion-related processes?

To the Body: Hypothalamus and Cortex

The hypothalamus illustrates the to-the-body connectivity. This structure is involved in the regulation of endocrine functions and in the generation of autonomic reactions and basic behavioral patterns. To carry out these functions, the hypothalamus works in concert with a multitude of other sites, several of which are located in the brainstem and spinal cord. Preganglionic neurons in the spinal cord represent the final central nervous system output of the autonomic network, and produce bodily changes that maintain homeostasis (preganglionic fibers terminate in various autonomic ganglia). In particular, hypothalamic nuclei such as the paraventricular nucleus are among the few structures that innervate all levels of the sympathetic preganglionic outflow [97].

Connectivity affecting the body also originates in cortex, most notably in specific sectors of the cingulate gyrus ([98]; see also [99]). Descending projections to autonomic regulatory structures have been described, notably to the lateral hypothalamus, periaqueductal grey, parabrachial nucleus, and the nucleus of the solitary tract [14]. This connectivity is consistent with effects of cingulate electrical stimulation on virtually all autonomic processes, as well as many endocrine mechanisms.

From the Body: Nucleus of the Solitary Tract and Cortex

The general visceral pathways can be divided into four tracts – namely cardiovascular, pulmonary, respiratory, and gastrointestinal [100] – which innervate distinct subnuclei of the nucleus of the solitary tract, a structure that spans the caudal and rostral medulla. Visceral information reaches many other structures, including the parabrachial nucleus (in the pons), periaqueductal grey, the hypothalamus (paraventricular nucleus and lateral area), and amygdala (central nucleus). Most structures receiving these signals from lower structures feed back onto the lower ones.

Cortical regions with notable body-related signals include the medial orbitofrontal cortex, the cingulate gyrus, and the insula [101]. In particular, the physiological condition of the entire body is conveyed to the posterior insular cortex [101], which can be considered interoceptive cortex, much in the same way as parts of parietal cortex are somatosensory cortex, for example.

In conclusion, both cortex and subcortex are parts of extensive connectional systems that link the body to the brain. In this manner, the entire spectrum of brain signals can affect the body, and vice versa (see Figure 1B in main text).

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connectional system (principle 2; Figures 1B and 2A). I describe here the cortex–amygdala anatomical connectional system involving the basal, lateral, and extended amygdala. The basal and lateral (basolateral) amygdala are extensively interconnected with cortex [46]. They receive input from the visual, auditory, and somatosensory systems [46]. More broadly, they are connected with temporal, frontal, and insular cortices [46]. Connectivity with frontal cortex is densest for medial and orbital components, but weaker connectivity with lateral PFC has also been detected [47].

The basolateral amygdala is connected with the extended amygdala, thus gaining access to the hypothalamus and brainstem [14]. Extended amygdala outputs course down along the medial forebrain bundle to contact multiple structures along the brainstem [14,18]. By engaging the brainstem at multiple levels, the extended amygdala exerts widespread effects across the **neuroaxis**, from the brainstem itself, to midbrain, subcortical forebrain, thalamus, and cortex (Figures 2B,C). The extended amygdala is also interconnected with the thalamus, thus providing a separate source of influence on cortex [14] (Figure 2A).

More broadly, the basolateral amygdala plus extended amygdala anatomical system closely interacts with multiple subcortical regions (Figure 2D), establishing circuits at the level of the subcortical forebrain (with multiple hypothalamic nuclei, subiculum, substantia innominata, etc.), at the level of the midbrain (with periaqueductal grey, ventral tegmental area, substantia nigra, etc.), and at the level of the brainstem (parabrachial nucleus, nucleus of the solitary tract, etc.) [14]. Together, these architectural features allow the amygdala to be influenced by, and influence, a vast array of cortical and subcortical regions.

Interlinking Connectional Systems
An anatomical connectional system can be described as a more-or-less independent unit, with several of them defining parallel systems (much like the idea of multiple independent cortical–basal ganglia loops [15]). However, cortical–subcortical anatomical systems interact with one another at the level of the subcortical forebrain (Figure 2E).

Let us consider an example. The ventral striatum is a key region of the classical cortico–basal ganglia–thalamo–cortical loops [15]. Importantly, the ventral striatum and basolateral amygdala form a circuit [18], thereby interlinking their respective connectional systems (Figure 3, Key Figure). Whereas the basolateral amygdala projects robustly to the ventral striatum, the ventral striatum projects to the ventral pallidum, which in turn projects to the basolateral amygdala, thereby forming the circuit (Principle 3) [14]. Because each connectional system (amygdala anatomical system involving the basal, lateral, and extended amygdala; ventral striatum cortical–basal ganglia loop) is sensitive to a different spectrum of cortical and subcortical influences, the pathways between them expand the influences they receive, allowing them to integrate diverse types of signals. Indeed, recent studies are now characterizing interactions between systems. For example, optical stimulation of a basolateral amygdala pathway to the accumbens facilitates reward seeking [48] and decreases long-term fear ([49]; see also [50]). In sum, connectional systems communicate with each other at the level of the subcortical forebrain (Figure 2E), providing a substrate that affords greater integration and potential for context-dependence.

Subcortical Convergence Hubs
Anatomical systems also come together at subcortical convergence hubs (Figure 2F). For example, in the midbrain tegmentum, the pedunculopontine tegmental nucleus receives projections from amygdala, striatum, and septum connectional systems [18,51]. The pedunculopontine tegmental nucleus projects further downstream to other brainstem structures, and originates an ascending cholinergic projection system, which can then influence processing

Key Figure
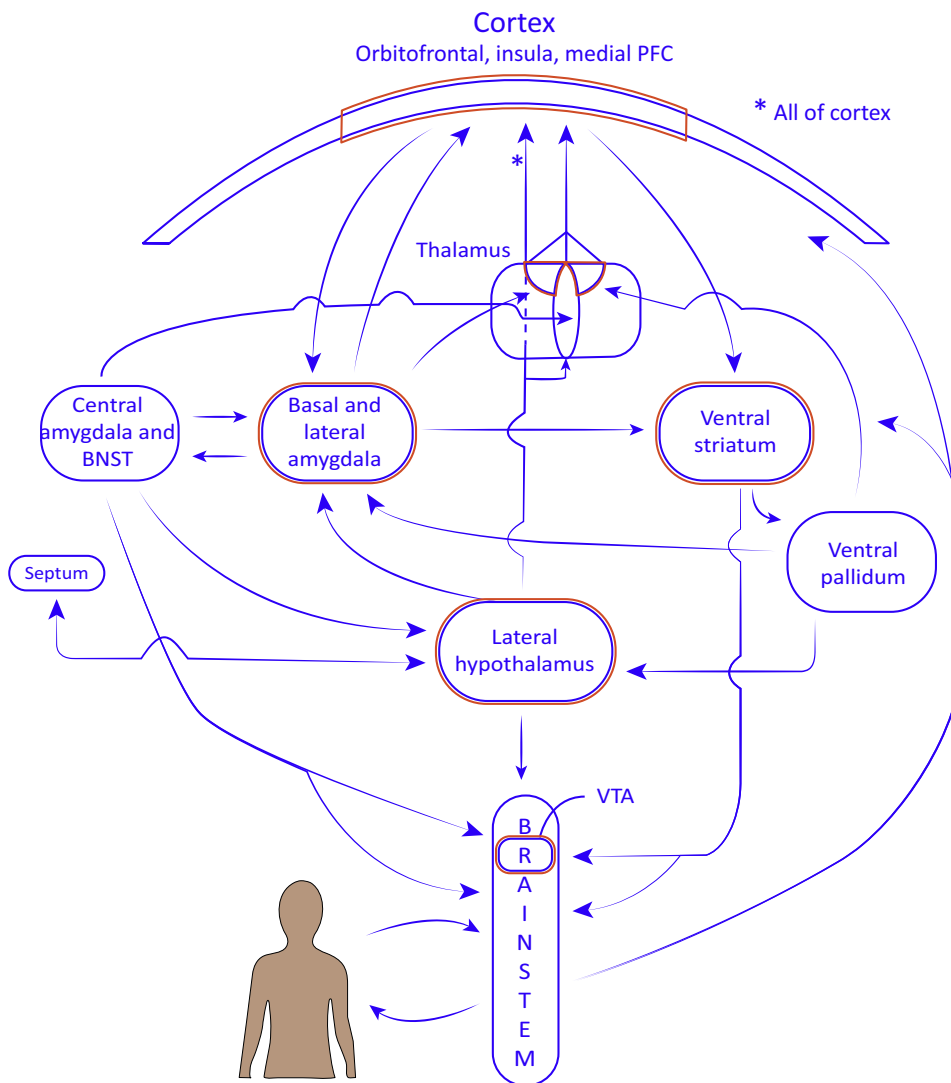
Functionally Integrated Systems

Figure 3. Connectivity between the amygdala and ventral striatal systems (only some of the connections are displayed). Regions outlined in orange indicate some of the convergence sites. The representation of cortex at the top is intended to represent all of cortex; the portion with the orange outline indicates the orbitofrontal cortex, insula, and medial prefrontal cortex. Within the thalamus, the ellipse represents midline nuclei, and the bilateral sectors represent the mediodorsal nucleus. Projections from the lateral hypothalamus reach all parts of cortex (denoted by asterisks). Abbreviations: BNST, bed nucleus of the stria terminalis; PFC, prefrontal cortex, VTA, ventral tegmental area.

across subcortical and cortical areas [18,51]. Signals impinging on convergence regions are not only influenced by different parts of cortex and subcortex but also have been further processed by multiple connectional systems. Thus, convergence onto subcortical hubs further enhances potential signal integration. Other convergence hubs include the lateral hypothalamus (as discussed below in the context of Figure 3) and possibly the ventral tegmental area.

Targets of connectional systems also converge onto partially segregated zones (Figure 2G), providing the substrate for some signal segregation and relative selectivity. For example, the accumbens and related parts of the ventral striatum project strongly to the ventral tegmental area [18]. By contrast, the extended amygdala appears to connect most robustly with the lateral parts of the substantia nigra (compact part) and adjacent retrorubral field ([18], but see [52]).

From Anatomical to Functional Systems

I call the large-scale cortical–subcortical connectional systems that have the properties summarized in Figure 2 'integrated functional systems', and these include the amygdala, dorsal striatum, ventral striatum, and septum–hippocampus systems. Together, the overall architecture contains a series of spiraling pathways that communicate and integrate signals across different spatial extents (Figure 1C). Although function is always anchored on anatomy, given the principles of functional connectivity, circuit overlap, and dynamics, the systems should be understood at the level of the functional relationships between regions.

The overall architecture comprises both 'closed' and 'open' loops, namely loops that return to the originating regions and loops whose return is less topographically organized. These circuits join cortex with the subcortical forebrain, the subcortical forebrain with the brainstem, and different components of the brainstem [19]. This organization leads to multiple convergence hub regions at all levels of the neuroaxis, including cortex, thalamus, subcortical forebrain, and brainstem (outlined in orange in Figure 3), which play important information processing roles given their relative **centrality** [53,54]. Functionally integrated systems involve cortical–subcortical loops, and, although loops via the thalamus play a prominent role, the systems span multiple levels of the neuroaxis. For related ideas, see the concept of 'macrosystems' [16,18]. The present proposal, however, emphasizes integration and coordination, while others have described specialization and relatively restricted communication between cortical–subcortical connectional systems ([18]; for more integrated proposals see [19,55]).

Figure 3 illustrates the general properties of the amygdala and ventral striatum systems, and why the systems are 'integrated.' Whereas the two systems have distinct connectional fingerprints, they converge at multiple stages. The architecture is organized around both vertical (e.g., between subcortical forebrain and brainstem) and horizontal (e.g., cortex to cortex) interactions (Figure 1C). In all, functionally integrated systems communicate with one another, thereby conferring organisms with greater behavioral flexibility via the integration of multiple signal types (including signals linked to appetitive and aversive processing; see below).

Coordinated Activity, Not Top-Down Regulation

Since the study of **decerebrate** animals in the 1850s, a hierarchical view of brain organization has enjoyed a dominant role in neuroscience [19]. In this view, subcortical structures are outflow stations that influence musculoskeletal and autonomic output. In the overall hierarchical plan, cortical structures regulate subcortical areas, thus guaranteeing appropriate behaviors. At first glance, some mechanisms fit this scheme, such as the role of the medial PFC in regulating the amygdala during fear extinction [56].

The architecture of integrated systems (Figures 2, and 3) stands in stark contrast to this viewpoint. The organization is not hierarchical but **heterarchical** [57], shifting the problem from one of understanding controller and controlled regions to understanding inter-region **coordination dynamics** [58,59] – that is, how signals from multiple regions collectively evolve. Understanding the latter is considerably more challenging because, although hierarchical interactions can be cast in terms of one region inhibiting (or exciting) another, coordination requires elucidating how distributed signals jointly bring about behaviors.

Let us consider the example of fear extinction in more detail. A top-down explanation emphasizes the role of the medial PFC in regulating the amygdala. However, considering the PFC as 'top' and the amygdala as 'down' does not take into account the richness of the existing interactions [60,61]. Multiple populations within the basolateral amygdala actually project to the medial PFC whose outputs in turn influence amygdala signals ([62]; see also [60]) (one study even suggested a 'top' role for amygdala 'extinction neurons' [62]; see also [63]). The ventral hippocampus also projects to multiple medial PFC sites [64] in addition to the basolateral amygdala, and hippocampal inputs to medial PFC appear to be potentiated during extinction [65]. Furthermore, medial PFC sites receive substantial inputs from mediodorsal thalamus [14], itself a major subcortical–cortical connectivity hub ([61] for an even broader set of interactions). More generally, during both fear expression and extinction, signals from the basolateral amygdala are integrated in the medial PFC with signals from multiple sources (including hippocampus and orbitofrontal cortex) to collectively determine whether or not to produce a response [60,61]. In this manner, interactions (including bidirectional ones) between the amygdala, medial PFC, and several other regions afford greater malleability when responding to threat. Taken together, top-down descriptions need to be expanded to mechanistic explanations in terms of coordination dynamics.

As an additional example, consider the hypothalamus, which is often conceptualized as the 'head ganglion' (or 'top') of the autonomic system [66,67]. However, as highlighted in Figure 3, the hypothalamus is deeply embedded within cortical–subcortical systems. In the context of emotion (see next section), it is particularly important because it interfaces with the amygdala, striatum, and septum systems. Thus, the hypothalamus is not simply a downstream controller. In particular, the hypothalamus projects to cortex via the thalamus (via midline and mediodorsal nuclei) [68]. In addition, the lateral hypothalamus (also the posterior hypothalamic area) projects to the entire cortical sheet. The hypothalamus thus illustrates again why coordinated activity across large-scale circuits needs to studied.

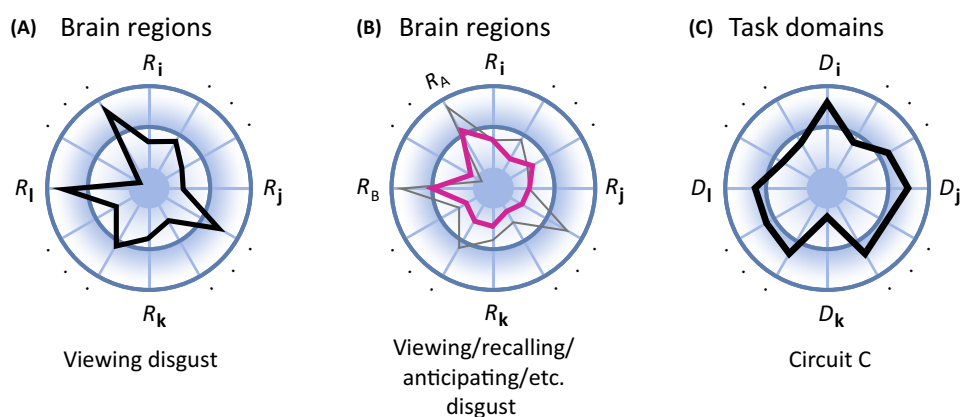## Implications for Emotion Research

How does the present model relate to other frameworks? According to the 'constructionist' approach, emotion is built via a set of domain-general, basic operations (such as core affect generation and body-related attention) [69]. Similarly to the constructionist framework, the present model advocates a distributed, network-based approach. However, there are important differences between the two models; I will briefly comment on two of these. (i) In the present model, there are no domain-general basic operations. The mind-brain is not built from a set of finite primitives but from dynamic emergent processes [70]. For example, the search for primitives in perception has produced limited success in understanding visual processing ([70] for dynamic alternatives). (ii) In the constructionist model, basic operations map onto distributed networks, notably those characterized during resting-state fMRI. In the present model the proposed functionally integrated systems are flexible and dynamic, and are thus highly context-dependent. Consider the cortex–amygdala system, for example. It does not have a core function such as 'affect generation'. Instead, its particular functional state determines how it will contribute to multiple mental operations, and these involve not only arousal, vigilance, and novelty but also attention, value determination, and decision-making more broadly [71].

In another framework, emotions are viewed as 'functional states' implemented by neural systems to regulate complex behaviors [72]. In particular, investigators should attempt to disentangle the neural correlates of emotions from all other processing with which they interact [73]. The present framework advocates, by contrast, to focus on interactions because the structural/functional organization of the brain is strongly non-modular.

The functionally integrated systems framework also speaks to current attempts to classify brain states, where distributed patterns of fMRI activation have been utilized to predict affective dimensions and discrete emotions with high levels of specificity [74]. Interestingly, in one study [75] predictive patterns spanned multiple cortical and subcortical systems, with no single system being necessary or sufficient for predicting affective experience. Furthermore, predictive patterns were not reducible to activity in traditional 'emotion-related' regions (e.g., amygdala) or resting-state networks (e.g., task-negative network). The present proposal is consistent with these results in that emotional states are highly distributed and should not cleanly map onto standard resting-state networks. However, the model also predicts that brain 'signatures' should be highly context-dependent, and not generalize well across tasks and conditions.

Returning to one of the central questions addressed here: are there specialized circuits in the brain for emotion? In an important sense the answer is 'no' because the very boundary between emotion and the 'rest of the brain' is ill-defined. How can the 'emotion researcher' then proceed? From the standpoint of studying specific tasks or conditions, multivariate (and distributed) activation fingerprints provide useful summaries of evoked responses or states (Figure 4A). Further insight can be obtained by studying multiple related tasks/conditions and determining a fingerprint that highlights the relative commonality of activation across regions; for instance, showing that regions R_A and R_B tend to participate together across some tasks/ conditions (Figure 4B). As an additional recommendation, a complementary summary can be generated by characterizing the (multiple) functions of specific circuits of interest which can be summarized via a 'functional diversity profile' [37] (Figure 4C). For example, in the case of the amygdala mentioned above, it would involve arousal, vigilance, novelty, attention, value determination, and decision making, among others.

Finally, the present framework underscores the importance of investigating large-scale circuits and their interactions in clinically oriented studies. To illustrate this point, consider a recent study targeting local central amygdala circuits involved in selecting between active

(A) Brain regions — R_i, R_j, R_k, R_l — Viewing disgust

(B) Brain regions — R_i, R_j, R_k, R_B, R_A — Viewing/recalling/anticipating/etc. disgust

(C) Task domains — D_i, D_j, D_k, D_l — Circuit C

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Figure 4. Distributed Characterization of Structure–Function Mapping. (A) The polar plot shows the distributed pattern of activation across regions R during an emotion task, such as viewing pictures eliciting disgust. The length of the segments indicates signal strength. (B) Multiregion pattern of activation across tasks. The profile in pink represents the activations that are (relatively) common across tasks (the grey outline is the same profile indicated in panel A). (C) Functional diversity profile of neural circuit of interest. The task domains D represent a set of potential mental functions of interest (spanning perception, cognition, emotion, motivation, and action). For example, this circuit is involved strongly in mental function D_i, but less so in function D_k.

and passive fear responses (flight vs freeze) [76]. A major finding of the study was that it revealed inhibitory connections between two subpopulations of central amygdala cells linked to the two behaviors. Suppose now that, with a future technology, we could identify and target the same cells in humans and modify the balance between the two subpopulations to (hypothetically) ameliorate maladaptive behaviors linked to anxiety disorders. The framework proposed here suggests that, without understanding how the local central amygdala circuit interacts with multiple regions (including hypothalamus, periaqueductal grey, and cortex), it would be unlikely that the treatment would be effective. Overall, a fuller understanding of neural circuit function that is clinically relevant will require an understanding of both local and large-scale circuit interactions, including those across multiple functionally integrated systems.

Functional Integrated Systems and the Emotional Brain

I suggest that, to understand the brain organization of emotion, it is necessary to consider general principles of brain organization (principles 1–5 and Box 1). I extend the concept of cortical–subcortical connectional systems (principle 2) and develop the idea of functionally integrated systems. I propose that they provide a unifying framework to understand the emotional brain, and how emotion is interlocked with perception, cognition, motivation, and action.

Emotion has been studied from multiple vantage points. Some investigators suggest that emotions are states elicited by rewards and punishers [77], while others focus on how emotions are involved in the conscious/unconscious evaluation of events [78]. Strong evidence also links emotions to the body [79]. Despite varying views ([73] for discussion), the brain basis of emotion has centered on a relatively small number of brain structures, including, subcortically, the amygdala, hypothalamus, periaqueductal grey, and ventral striatum, and, cortically, the insula, orbitofrontal cortex, and medial PFC [80,81].

All these structures (and several others discussed in the emotion literature) are important hub regions of the functionally integrated systems discussed here. In particular, the integrated systems of the amygdala, ventral striatum, and septum–hippocampus are intimately linked to both the evaluative and expression dimensions of emotion. For instance, the amygdala has been likened to a 'danger detector' and has been suggested to be part of an 'information gathering system' [82]. The close association of the amygdala with the hypothalamus, for example, assures that it influences homeostatic mechanisms and neuroendocrine signaling. The ventral striatum is closely associated with appetitive processing and reward-related mechanisms. The septum, a structure poorly studied in humans, is thought to play important roles related to affect and motivation [61,83].

As illustrated in Figure 3, not only are many structures of the 'emotional brain' chief components of integrated systems but they also participate across systems. This overlap is a central feature of brain networks (principle 4), and is one reason why multiple signal types are present in brain regions. Indeed, signal plurality is the norm in brain regions [84]. For example, the ventral striatum, which is recognized for its role in reward-related processing, also exhibits aversion-related signals [85,86] (in the case of the midbrain, see [87]); conversely, the bed nucleus of the stria terminalis, which is important during aversive states, is engaged by both aversive and rewarding stimuli [52,88] (in the case of the amygdala; see also [89,90]). In particular, the recent growth of neurotechniques will allow the disentangling of two scenarios: interdigitated but separate populations of positive and negative signals, or convergence at the synaptic/neuronal level. While the prevalence of these two types of organization remains to be determined [86,91], the discovery of multiple sites of convergence illustrates that opportunities for signal integration abound ([84] and references therein).

Concluding Remarks

Emotions mobilize the body (via autonomic, neuroendocrine, musculoskeletal systems) in part via functionally integrated systems that have access to the hypothalamus and to structures in the brainstem and medulla that are linked to the body. Emotions also mobilize brain responses, influencing attention, memory, and decision making. The mobilization of body and brain, which is closely associated with neurotransmitter systems, relies initially on the most robust anatomical pathways of connectional systems. However, the mobilization is rapidly expanded to include vast portions of the brain. This is accomplished through the general architectural principles of the brain, including combinatorial anatomical connectivity and distributed functional connectivity. These properties, in conjunction with extensive network overlap, assure that events of biological significance lead to the temporal reorganization of network affiliations to meet the demands faced by the organism.

In the proposed framework, the concept of emotion is not adequately summarized by the idea of a biasing mechanism, a metaphor frequently used in the literature. As discussed, descriptions in terms of coordination dynamics have the potential to capture interactions that go beyond simple biasing. In this context, at the spatiotemporal resolution of fMRI, we and others have started to characterize how emotion influences the temporal unfolding of large-scale network organization [92–95]. In a recent study [94], periods of 'anxious anticipation' were associated with transient and sustained changes to salience, executive, and task-negative networks in the human brain. Importantly, how the bed nucleus of the stria terminalis and the amygdala participated in network communication (as quantified by the measure of centrality) was altered during anxious states.

In conclusion, the model proposed here helps clarify why some structures are so important for emotion, such as the amygdala – they are important hubs of distributed cortical–subcortical functionally integrated systems. The framework also raises several important questions (see Outstanding Questions) while describing why the impact of emotion is so wide-ranging. It vividly highlights the limitations of pointing to specific structures as constituting the 'emotional brain', or even to specific levels of the brain, as in the focus on cortex of some human work and the focus on subcortex in some animal work (see also [73]). Ultimately, emotion is a large-scale network property of brain function.

Acknowledgments

Outstanding Questions

I proposed that cortical–subcortical connectional systems, and especially integrated systems, are central to the understanding of emotion in the brain. What is their role in processes traditionally described as cognitive? Is their importance also underappreciated in that case?

Do we need novel perspectives on causation in the brain? The architecture proposed here challenges simple models of causation (region *A* causes activity of region *B*). Can probabilistic causation, where causes change the probability of occurrence of their effects (e.g., investigated by quantifying the likelihood that a change in activity in one neuronal population affects the activity in another), provide a better approach?

Can the type of architecture described here be investigated without formal/mathematical tools? Given the complexity of the interactions, does neuroscience need to migrate to a model that is closer to that of physics? For example, experimental physicists are not lacking in mathematical sophistication. To some extent, neuroscience has evolved into extremely sophisticated 'laboratory techniques' that are at times divorced from formal approaches. How should we train future generations of brain scientists?

What is the role of functional specialization? Given the multitude of circuit interactions of the architectural framework, is there room for the functional specialization often ascribed by researchers to brain regions? Relatedly, can a relative degree of modularity be supported by the distributed interactions of the observed architecture?

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