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Emotion and the Interactive Brain: Insights From Comparative Neuroanatomy and Complex Systems

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Abstract

Although emotion is closely associated with motivation, and interacts with perception, cognition, and action, many conceptualizations still treat emotion as separate from these domains. Here, a comparative/evolutionary anatomy framework is presented to motivate the idea that long-range, distributed circuits involving the midbrain, thalamus, and forebrain are central to emotional processing. It is proposed that emotion can be understood in terms of large-scale network interactions spanning the neuroaxis that form “functionally integrated systems.” At the broadest level, the argument is made that we need to move beyond a Newtonian view of causation to one involving complex systems where bidirectional influences and nonlinearities abound. Therefore, understanding interactions between subsystems and signal integration becomes central to unraveling the organization of the emotional brain.

Keywords

cognition; comparative neuroanatomy; emotion; networks

Emotion is closely associated with motivation, and interacts with perception, cognition, and action. Whereas such interactions are well documented in the literature, many conceptualizations treat emotion as fairly separate from other mental domains (see Pessoa, 2014, 2015 and associated commentaries). This article will discuss a framework for understanding the brain basis of emotion that is centered on these types of interactions, several of which have been emphasized in the recent literature (e.g., Blakemore & Vuilleumier, 2017; Brosch, Pourtois, & Sander, 2010; Iordan, Dolcos, & Dolcos, 2013; Lindquist & Barrett, 2012; Okon-Singer et al., 2017; Phelps & LeDoux, 2005).

The argument made here is that the brain basis of emotion needs to be understood from the perspective of the “interactive brain,” a view that contrasts with a more modular/hierarchical viewpoint (e.g., Ohman & Mineka, 2001). To understand some of the origins of the more traditional view, the article will initially consider early theoretical and empirical work in neuroscience in the 19th century which relegated emotion to the subcortical “basement” of

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the brain, and comparative neuro-anatomy work in the beginning of the 20th century which described the brain in terms of “old” and “new” parts. Combined, these “formative years” have heavily influenced how neuroscientists conceptualize the brain—and hence the organization of emotion in the brain.

To motivate the interactive-brain idea, initially, a simple appetitive/defensive system will be described from a comparative neuroanatomy perspective. As discussed, the brains of amphibians, reptiles, and mammals are comprised of long-range, distributed circuits that span multiple levels of the neuroaxis (involving the midbrain, thalamus, and forebrain). It is argued that these circuits provide the behavioral flexibility needed to handle complex environments, while at the same time blurring the distinction between cortical and subcortical systems, as well as between emotion and other functions. Thus, the brain architecture of vertebrates in general allows for complex forms of signal interaction and integration—even in animals with simpler behavioral repertoires. From this perspective, to understand the organization of the brain it is important to consider distributed cortical-subcortical anatomical systems. The resulting high degree of signal distribution and integration provides a nexus for the intermixing of information related to perception, cognition, emotion, motivation, and action. It is argued that the resulting “functionally integrated systems” are not hierarchically organized; instead, control is distributed throughout the system, where multiple bidirectional influences and nonlinearities are present. Because of the inherent challenges in characterizing such systems, it is argued that tools from complex systems theory are needed to advance current understanding. What is more, when systems are not isolable, understanding the interrelatedness between “subsystems” means that we should consider both interactions between them and potential signal integration as central elements to be unraveled.

Emotional Baggage From Victorian England and Early Evolutionary Thinking

In the conclusion of *The Descent of Man*, Darwin (1871) wrote that “the indelible stamp of his lowly origin” could still be discerned in the human mind, such that it was necessary to suppress the beast within—a notion that hearkens back to Aristotle (Finger, 1994, p. 271). The decades following the publication of the *Origin of Species* (Darwin, 1859) were a time of much theorizing not only in biology but also in the social sciences. The philosopher Herbert Spencer and others applied central concepts of biological evolutionary theory to social issues, including culture and ethics. A critical element in this thinking was that of *hierarchy*. It was argued, for example, that it is necessary to legitimize a hierarchical governing structure and a sense of self-control for the survival of evolved societies (see Parvizi, 2009).

These ideas, in turn, had a deep impact on neurology and neuroscience. In particular, Hughlings Jackson (one of the founders of neurology), embraced a hierarchical view of brain organization deeply rooted in the notion that the evolution of the nervous system involved the gradual building of more complex structures “on top of” more primitive ones. Thus, “higher” centers in cortex controlled “lower” centers in subcortex, and any “release”

from higher control could make even the most civilized human being act more like his or her primitive ancestors (Finger, 1994, p. 271). Decades later, this hierarchical scheme was also central to Freud's hierarchical framework of *id* (the lower level) and *super-ego* (the higher level; see Parvizi, 2009). Interestingly, Freud was trained as a clinical neurologist and was a great admirer of Jackson.

Against this backdrop, the study of decerebrate animals flourished in Europe in the last decades of the 19th century (see Cannon, 1927; Finger, 1994). Goltz was among a group of researchers trying to understand the contributions of cortical and subcortical brain regions to behaviors, and the question of the localization of function more generally (see Finger, 1994). He published several influential articles that showed that animals exhibited uncontrolled rage reactions after the cerebral cortex was removed. Another early researcher, Bekhterev, argued that emotional expression must be independent of the cortex for multiple reasons: at times the expression cannot be inhibited (e.g., laughing from tickle and crying from pain); because visceral changes occur which are beyond one's control; and because it is seen just after birth before cortical action is putatively important (see Cannon, 1927, p. 115). Bekhterev discussed studies in which he removed the entire cerebral cortex, after which the animals produced responses of an affective character. For instance, noxious stimuli would cause cats to snarl, and dogs to whine, show their teeth, and bark.

Comparative neuroanatomy was another important line of research that has had important consequences for the understanding of emotion. The late 19th and early 20th centuries witnessed vigorous interest in the organization of vertebrate brains. Edinger (1900), considered to be the founder of comparative neuroanatomy, proposed that the forebrain evolved by means of the *sequential addition* of parts. According to him, the forebrain contains an "old encephalon," found in all vertebrates, and a "new encephalon." He proposed that the new encephalon exists in animals "higher" than cartilaginous fishes, but is only more prominent in mammals. To illustrate this additive effect, he suggested that one could imagine precisely inserting a reptilian brain into that of a marsupial (a "simple" mammal). In another example, Edinger (1908, p. 446) described how, in the brain of the cat, the old encephalon "persists unchanged underneath the very important" new encephalon. Edinger thus speaks of "a new mechanism [that] has been *added* [emphasis added]" to the old encephalon (p. 449). These ideas, which clearly influenced MacLean (1990) in formulating his triune brain concept, have greatly impacted thinking about emotion in the brain.

I contend that modern-day neuroscience (neurology and psychiatry, too) has been, and continues to be, influenced by these ideas in many subtle and not-so-subtle ways—it is part of the field's intellectual heritage. The early research colors the overall conceptual framework in which research is done presently. To motivate the interactionist framework defended here, let's consider comparative functional neuroanatomy from a contemporary framework, and discuss potential implications.

A Simple Appetitive and Defensive System

At a given moment, animals face a three-way decision: stay the course, move away, or move toward. How is a stimulus classified as harmless, which may or may not be worth investigating further, as opposed to signaling an emergency that requires immediate action (Dean, Redgrave, & Westby, 1989)? For many animals, the stimulus's position in the visual field plays an important role in determining its significance. In small rodents, unexpected movement overhead (much like that of a predator) is more likely to elicit flight than movement at floor level (possibly a prey), which is more likely to elicit approach (Peek & Card, 2016).

An important system for both appetitive and defensive behaviors involves the superior colliculus in the midbrain (Basso & May, 2017; Dean et al., 1989; DesJardin et al., 2013; Forcelli et al., 2016; Furigo et al., 2010; Peek & Card, 2016; Pereira & Moita, 2016). It receives retinal inputs and has outputs that give it access to movements of head and neck, for example. In rodents, the superior colliculus could be involved in implementing the following rule: If unexpected movement is overhead, flee; otherwise, if movement is in the lower field, consider further exploration. However, simple rules based on stimulus features do not capture the flexibility of rodent behavior (think how hard it is to catch a rat). In particular, rats freeze more frequently to novel stimuli in unfamiliar environments, such as an open field (Peek & Card, 2016; Pereira & Moita, 2016). Clearly, the context in which a stimulus occurs is very important.

How about toads and frogs (of the Anuran family) which have relatively limited behavioral repertoire? Anurans generate tongue snapping when stimuli are in certain parts of their visual field, and the optic tectum is centrally involved in this behavior (Ewert, 1984, 1987b). The optic tectum (how the superior colliculus is called in nonmammals) is a layered structure at the top of the midbrain ("tectum" means "roof" in Latin). Whereas this structure is the recipient of retinal fibers and has important visual functions, it is a multisensory area with "maps" of the external world and the body that are in register with one another (Stein & Meredith, 1993). In anurans, the optic tectum is considered to be a sensorimotor interface because it receives retinal projections carrying visual signals and projects to brainstem and medullary motor circuits (Figure 1A; see Figure 1C for a schematic of the frog brain).

Although anurans produce fairly stereotypical behaviors, motivation-, learning-, and attention-related factors contribute to their behavior (Figure 1B). All of these factors influence activity in the optic tectum. For example, in the context of motivation, during the mating season, the threshold for escape is high (that is, animals are less defensive) and prey-catching is minimal (Ewert, 1987a, 1987b), whereas approach behavior by males toward females is high (Kondrashev, 1976). In the context of attention, effective prey-related stimuli elicit an orienting movement and evoke considerably stronger responses in the optic tectum when the animal is prepared to attack (Ewert et al., 2001). In terms of learning, toads fed on mealworms presented by hand eventually respond to the hand alone, demonstrating an association between food and hand (Brzoska & Schneider, 1978).

What connections contribute to these effects (Ewert, 1987a, 1987b; Neary, 1990; Nieuwenhuys, Donkelaar, & Nicholson, 1998; Wilczynski & Northcutt, 1983)? For example, in the context of motivation-related signals, the hypothalamus projects to the deep layers of the tectum, which have connections to motor areas. In the context of learning, the acquired mealworm–hand association just described is abolished in animals with lesions of the medial pallium, and the same lesion abolishes learning in naïve animals (Finkenstadt & Ewert, 1988). More generally, in addition to circuits that are more local (such as between the optic tectum and the adjacent periaqueductal gray), the optic tectum participates in several long-range anatomical loops (see Figure 2), which involve multiple thalamic nuclei, as well as multiple parts of the forebrain, including the striatum and the medial pallium. The medial pallium is believed to be a precursor to the hippocampus, and to be an integrative structure for olfactory and other types of sensory signals.

A simplified view of the optic tectum in anurans considers it to be a relatively direct sensorimotor interface, such that retinal inputs lead to motor actions. However, as seen, the optic tectum is embedded in multiple circuits that considerably expand the repertoire of signals that can influence sensorimotor behaviors that involve this structure (including prey-catching), as shown via lesion studies (Ewert, 1987a, 1987b; Nieuwenhuys et al., 1998). In all, the optic tectum not only listens to multiple cues from the sensory world, but to additional signals related to motivational state, recent history, and alertness, among others.

Rodent behavior is considerably less stereotypical (see following lines for further discussion of mammalian neuroanatomy). As stated, rats freeze to novel stimuli in unfamiliar environments more so than in familiar places. This observation reflects, again, an important principle of brain function—context sensitivity. The brain does not simply react to sensory stimuli; instead, sensory signals are incorporated into ongoing processing that encompasses the states of the brain and the body, such that the same stimulus exerts very different effects depending on context.

What implications can be drawn from the discussion in this section? Comparative neuroanatomy reveals the existence of multiple long-range circuits that interlink cortex and subcortex. This is the case even for “simple” animals. Supported by thalamic-forebrain anatomical loops, the outputs of a structure such as the optic tectum reflect multiple variables simultaneously, allowing context sensitivity to emerge as a consequence of its wiring and processing.

Implications for the Architecture of Emotion

The preceding ideas directly inform the common description of the amygdala’s role in the expression of emotional behaviors (see Figure 3). The processing of a stimulus with negative affective significance in the central amygdala engages a set of brain regions that allow reacting to the stimulus, thus impacting musculoskeletal and visceral systems, among others. In this regard, Anderson and Adolphs (2018, p. 34) state:

However, there are *many more projections* [emphasis added] than the ones shown here [in a figure similar to the present Figure 3], including projections to cortex, and there are also inputs to the amygdala from almost all of the targets to which it

projects, making it *complicated to disentangle cause and effect* [emphasis added] within the system.

Although “many more connections” are acknowledged by these and many other researchers, typically they are not considered more fully. Here it is argued that bearing in mind the connectivity is critical for a thorough understanding of the system (see following lines).

For now, let’s return to the architecture of the optic tectum in other animal classes. The objective is to further highlight the implications of vertebrate anatomical connectional systems that interlink disparate brain regions. In reptiles, the basic connectional architecture shown in Figure 2 is considerably expanded (Neary, 1990; Nieuwenhuys et al., 1998). The reptilian fore-brain receives many more thalamic projections, including those to the medial pallium and dorsal pallium (containing three layers and believed to be the precursor of six-layered neocortex). In mammals, the connectivity is in turn substantially elaborated relative to reptiles, and the number of potential long-range circuits is very large. In fact, in mammals, the superior colliculus is one of the most densely connected regions of the brain (May, 2006; Strehler, 1991).

Why this degree of complexity involving subcortical-cortical loops and extensive connectivity even in “simple” animals? One possibility is that it confers a high degree of flexibility that allows animals to cope with the complex interactions in their habitats, involving predators, prey, potential mates, and so on. In species with relatively malleable behaviors, survival is suggested to benefit from circuits that can form *combinatorially*, as the interactions of conditions related to the internal and external worlds of the animal are exceedingly high.

In particular, the optic tectum/superior colliculus is involved not only in multiple types of sensorimotor transformations (Ewert, 1984, 1987a, 1987b), but also in attention (Basso & May, 2017; Shipp, 2004) and appetitive/defensive behaviors (Dean et al., 1989; DesJardin et al., 2013; Forcelli et al., 2016; Furigo et al., 2010; Peek & Card, 2016; Pereira & Moita, 2016). Thus, sensory and motor components are “decoupled” (see Figure 4) via the type of loops shown in Figure 2 (see also Figures 5–6), which are proposed to be central to behavioral capabilities. By “decoupled” it is meant that sensory signals do not necessarily trigger motor actions, and that, when an action ensues, the sensorimotor transformation takes into account a broad range of influences. Thus, multiple variables are considered that cancel, enhance, or otherwise refine the types of actions undertaken (as in the case of motivational, learning-related, and attentional influences in anurans discussed earlier). The argument made here is that this “decoupling” property is not particular to the optic tectum/superior colliculus, but is shared with regions important for emotion. For example, the central amygdala targets multiple areas that impact behavior (see Figure 3) but, critically, is part of large-scale connectional systems (see following lines) in ways that allow it to influence and be influenced by sensory processing, action, and cognition.

Another implication of looped architectures (such as in Figure 2) is that the study of “isolated systems” (e.g., the amygdala by itself or together with a few target areas) is only a first (and coarse) step in understanding emotional processing during complex behaviors. This is further exacerbated because subcortical-cortical circuits are not independent. As

further discussed next, there are multiple pathways linking the loops that contribute to their potential interactions. Thus, dissecting how long-range, large-scale circuits bring about behavior is necessary for understanding emotional processing.

Large-Scale Circuit Integration and Embedding

Let's return to the discussion of brain evolution in view of the considerations of the previous section. In many conceptual treatments, emotion is motivated from an evolutionary perspective; for example, its mechanisms are said to promote survival. While this is true, all brain processes are the result of evolutionary processes.¹ In this respect, emotion is no different from perception and cognition. Cognitive abilities, in particular, are not present for abstract reasoning, but to support problem solving that impacts survival. The scheme of Figure 2 illustrates a simple circuit that affords appetitive/defensive capabilities in combination with context sensitivity. Other regions, including the hypothalamus, amygdala, periaqueductal gray, and striatum, also have circuits that participate in appetitive/defensive behaviors. How did long-range circuits involving these regions evolve?

A cortico-centric framework suggests that “newer” cortex controls subcortical regions, which are typically assumed to be relatively unchanged throughout evolution. Cortical expansion, in particular, is thus a matter of establishing circuits such that cortical regions can control “lower” centers. It is fair to say that some version of this idea is commonly accepted. I believe this is in good part due to the lingering effects of the hierarchical framework that was deeply entrenched in neuroscience in the 19th century and the first decades of the 20th century (see section Emotional Baggage From Victorian England and Early Evolutionary Thinking).

With developments in anatomical tracing methods and genetics, comparative neuroanatomy has greatly advanced knowledge of the organization of the vertebrate brain (see the four volumes by Meek & Nieuwenhuys, 1998). The new knowledge is particularly important in the context of the mammalian brain given the flourishing of cladistics in the 1960s (see Butler & Hodos, 2005; Hennig, 1999). Thus, for example, current understanding is that the evolutionary history of mammals is entirely separate from that of sauropsids (reptiles and birds; Carroll & Carroll, 1988; Evans, 2000; Liem, Bemis, Walker, Grande, 2001). Thus, no reptile was ancestral to any mammal or vice versa, a fact that is at times missed outside comparative biology circles.

Multiple large-scale connectional systems share important properties across vertebrates, including thalamo-cortical bidirectional connections (Butler, 2008), basal ganglia loops (Medina, 2009), and amygdala circuits (Medina, Abellán, Vicario, Castro-Robles, & Desfilis, 2017). These systems have important implications for how information is communicated and integrated in the brain. In addition, the basic plan of the vertebrate brain includes all of its major components (Striedter, 2005). This is not to say that all vertebrate brains are the same; but all major parts are present across the different animal classes.

¹Including genetic “random drift” via so-called neutral processes, that is, processes independent of selective pressures (Kimura, 1983).

The hypothesis advanced here is that older and newer elements of the brain changed in a more coordinated fashion. This does not exclude new circuits in which cortical areas have opportunities to exert control upon lower ones. But, overall, the resulting circuitry is one in which cortex and subcortex, for one, are mutually *embedded*. That is to say, cortical regions are not just regulators of subcortical ones, but integrally participate in the circuits in a way that expands the repertoire of functions the older territories are involved in.

A possible example of this type of mutual embedding is provided by the amygdala. The amygdala of mammals is composed of a dozen or more subregions. Chareyron, Banta Lavenex, Amaral, and Lavenex (2011) found that the lateral, basal, and accessory basal subregions are dramatically more “developed” in monkeys than in rats (based on morphological characteristics, such as cell counts and the volume of subregions). One possibility, as described by the authors, is that the differences in the relative size and neuron numbers between rats and monkeys are linked to their degree of connectivity with other brain structures, in line with the proposal of correlated evolution between components of functional systems (Barton & Harvey, 2000). Thus, the lateral, basal, and accessory basal nuclei are more developed in primates than in rodents, and parallel the greater development of the cortical areas with which these nuclei are interconnected in primates. Chareyron and colleagues propose that such correlated evolution may be responsible for a higher convergence and integration of information in the primate amygdala, and that the relative development of these amygdala nuclei might be influenced by their interconnections with other brain structures, namely their afferent and efferent connections (Amaral, Price, Pitkanen, & Carmichael, 1992).²

In this context, work by Barger and colleagues (Barger, Hanson, Teffer, Schenker-Ahmed, & Semendeferi, 2014; Barger et al., 2012; Barger, Stefanacci, & Semendeferi, 2007) has compared the volumes of amygdala nuclei across humans, apes, and monkeys. In particular, the lateral nucleus of the amygdala in humans is significantly larger than predicted (for an ape of human brain size). Indeed, the differences observed were substantial. Neuron numbers in the human lateral nucleus were nearly 60% greater than predicted.³ For reference, in terms of volume, the human neocortex is 24% larger than expected for a primate of our brain size (Rilling & Insel, 1999), whereas the human frontal lobe, frequently assumed to be enlarged, is approximately the size expected for an ape of human brain size (Semendeferi, Lu, Schenker, & Damasio, 2002).⁴

Cortical-Subcortical Connectional Systems

In the preceding sections, the argument was made that circuits relevant for emotion and motivation involve long-range circuits spanning the midbrain, thalamus, and forebrain that provide the substrate for interactions between diverse brain regions. This is suggested to be a property of circuits in general, even the “simple” appetitive/aversive system discussed.

²Parsing the reasons for changes in brain region size is not possible at the moment and likely will always constitute a major challenge. Both “concerted” and “mosaic” evolution proposals have been described (Striedter, 2005).

³Although this value seems exceedingly large and probably reflective of the small sample studied and less representative of population values.

⁴In the examples of amygdala and cortical differences, the neuron count and volume values are of course not directly comparable, and are given to provide an idea of the types of differences observed.

Indeed, interactions are a property of the brain of vertebrates, although anatomical pathways supporting them are considerably more exuberant in birds and mammals (Butler, 2008; Medina, 2009; Nieuwenhuys et al., 1998). This section will discuss examples of this *interactionist architecture* in mammals that illustrate the high degree of signal communication and aggregation.

Work focusing on mammals in the 1970s and 1980s uncovered important cortical-subcortical connectional systems. Notably, the entire cortical sheet (with the exception of Area V1) projects to the striatum (Nieuwenhuys, Voogd, & van Huijzen, 2008). Different parts of the 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. Together, these studies led to the important concept of cortico-basal ganglia-thalamo-cortical systems, or cortical-basal ganglia loops for short (Alexander, DeLong, & Strick, 1986).

The connectional architecture that was unraveled for cortical-basal ganglia loops was proposed to be more general and to apply to other structures at the base of the forebrain (Alheid & Heimer, 1988) including the septum and the extended amygdala (involving the central nucleus of the amygdala and parts of the bed nucleus of the stria terminalis; Alheid & Heimer, 1988; de Olmos, Alheid, & Beltramino, 1985; Fox, Oler, Tromp, Fudge, & Kalin, 2015). In identifying properties of the organization of “cortical”-basal ganglia loops (neuronal types, thalamic return projections, etc.), in the case of the septum and extended amygdala, it was suggested that the “cortical” projections should be thought of as originating in the cortex-like hippocampus in the case of the septum system, and in the cortex-like basal and lateral amygdala in the case of the extended amygdala system (Alheid & Heimer, 1988). Another property of the connectional architecture is that regions such as the septum and extended amygdala project along the brainstem; the latter is extensively connected to subcortical forebrain structures themselves as well as to the cortex (Heimer, van Hoesen, Trimble, & Zahm, 2007).

Taken together, large-scale cortical-subcortical anatomical connectional systems are not confined to the traditional basal ganglia but involve additional subcortical forebrain structures too (see Figure 5A). 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 (Parvizi, 2009). To reiterate, a subcortical forebrain target region (including the ventral striatum) receives extensive cortical inputs, thus allowing it to be sensitive to a wealth of signals (sensory, cognitive, emotional, motivational, motor). From the target region two types of pathway exist: one projects back to the cortex (or cortex-like regions) via the thalamus; another descends along the brainstem. The descending projections contact regions that loop back to the subcortical forebrain, and have extensive (and at times diffuse) connectivity with subcortical and cortical regions. Notably, the descending pathways contact ascending projection systems involving a broad range of neurotransmitters, including acetyl-choline, dopamine, epinephrine, norepinephrine, and serotonin (Nieuwenhuys et al., 2008).

Functionally Integrated Systems

The original concept of cortical-basal ganglia loops (Alexander et al., 1986; DeLong & Georgopoulos, 1981) emphasized independence between parallel and functionally distinct circuits (including sensorimotor, cognitive, and affective systems). However, anatomical pathways that allow communication and integration between systems have been described and highlighted in more recent proposals (see also Averbeck, Lehman, Jacobson, & Haber, 2014; Haber, 2003, 2014; Shipp, 2017). When we consider additional systems involving the amygdala, for example, further opportunities for communication exist.

Let us consider an example involving two connectional systems: an (a) amygdala system involving the basal, lateral, and extended amygdala, and (b) a ventral striatum cortical-basal ganglia loop (see Figure 6). The ventral striatum is a key region of the classical cortical ganglia-thalamo-cortical loops (Alexander et al., 1986), and receives robust connections from the basolateral amygdala. Importantly, the ventral striatum and basolateral amygdala form a circuit (Heimer et al., 2007), thereby interlinking their respective connectional systems. 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 establishing the circuit (Nieuwenhuys et al., 2008).⁵

Because each connectional system is sensitive to a different spectrum of cortical and subcortical influences, the pathways between them expand the influences they receive, allowing them to integrate increasingly diverse types of signals (Swanson & Lichtman, 2016). In particular, this affords interactions between appetitive, aversive, and contextual circuits involving both cortical and subcortical structures. For example, optical stimulation of a basolateral amygdala pathway to the accumbens facilitates reward seeking (Stuber et al., 2011) and decreases long-term fear (see also Britt et al., 2012; Correia, McGrath, Lee, Graybiel, & Goossens, 2016). Interactions between the hippocampus and amygdala, and between the hippocampus, medial prefrontal cortex (PFC), and amygdala, participate in contextual effects of aversive processing (Maren, Phan, & Liberzon, 2013). In sum, connectional systems communicate with each other at the level of the subcortical fore-brain, providing a substrate that affords greater integration and potential for context dependence.

The abundant pathways that link anatomical systems suggest that we should seek to understand brain function at the *functional level*. Indeed, the boundary between anatomy and function becomes blurred very quickly once one starts considering factors that characterize the anatomy (Lee, Harrison, & Mechelli, 2003). For instance, the type of receptor subtypes involved, the laminar profile of the connections (often interpreted in terms of “modulatory” vs. “driving” inputs), the presence of excitatory or inhibitory interneurons (and the ratio of these), the strength of the connection, and so on (for further discussion, see Pessoa, 2014). Hence, a fruitful strategy is to characterize how regions are *functionally connected*, that is, how their signals covary. From that viewpoint, what is important is not simply the anatomical location of a region but its position in a space of functional relationships to other

⁵Although functionally integrated systems involve the cortex in important ways (see Figure 6), space constraints preclude discussion of the contributions of its diverse sectors, including orbitofrontal, insula, and medial prefrontal cortex (see Pessoa, 2013).

regions (Aertsen & Preissl, 1991; Friston et al., 1997; Pessoa, 2014). From the perspective of a brain region, at a given time, a region affiliates (or groups) with a set of other regions, thereby defining a momentary circuit. Thus, although function is always anchored on anatomy, systems should be understood at the level of the functional relationships between regions. Recently, the large-scale cortical-subcortical connectional systems of the type illustrated in Figure 6, called “functionally integrated systems,” were proposed to be a central component of the emotional brain (for further discussion of additional interaction and integration properties, see Pessoa, 2017b). Together, the overall architecture contains a series of spiraling pathways that communicate and integrate signals across different spatial extents (see Figure 5B).

Taken together, it is proposed that the brain basis of emotion involves large-scale cortical-subcortical networks that are distributed and sensitive to bodily 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—that is, depending on internal and external world states.

Top-Down Control Versus Bi-Directional Circuits

In this section, some implications of the overall interactionist framework discussed thus far are illustrated in the context of “top-down control.” Since the study of decerebrate animals (where some or most of the cortex was removed) in the 19th century, a hierarchical view of brain organization has enjoyed a dominant status in neuroscience (see section Emotional Baggage From Victorian England and Early Evolutionary Thinking). 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. In the context of emotion, some mechanisms appear to fit this scheme, such as the role of the medial PFC in regulating the amygdala during fear extinction (Morgan, Romanski, & LeDoux, 1993).

The architecture of functionally integrated systems (see Figures 5B and 6) stands in stark contrast to this viewpoint. The organization is not hierarchical but heterarchical (where a clear hierarchy is not evident; McCulloch, 1945), shifting the problem from one of understanding controller and controlled regions to understanding interregion coordination (Grossberg, 1980; Tognoli & Kelso, 2014)—that is, how signals from multiple regions collectively evolve. Understanding the latter is considerably more challenging because, whereas 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 (Sotres-Bayon & Quirk, 2010; Tovote, Fadok, & Lüthi, 2015). Multiple populations within the basolateral amygdala actually project to the medial PFC whose outputs in turn influence amygdala signals (Herry et al., 2007; see also Sotres-Bayon & Quirk, 2010), and one study even suggested a “top” role for amygdala “extinction neurons” (see also Do-Monte, Manzano-Nieves, Quiñones-Laracune, Ramos-Medina, & Quirk, 2015; Herry et al., 2008). The ventral hippocampus (putatively “bottom”) also projects to multiple medial PFC sites (Hoover & Vertes, 2007) in addition to the basolateral amygdala, and hippocampal inputs to medial PFC appear to be potentiated during extinction (Hugues & Garcia, 2007). Furthermore, medial PFC sites receive substantial inputs from the mediodorsal thalamus (Nieuwenhuys et al., 2008), itself a major subcortical-cortical connectivity hub (see Tovote et al., 2015, 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 (Paré & Quirk, 2017; Sotres-Bayon & Quirk, 2010; Tovote et al., 2015). 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, more frequently emphasized top-down descriptions of underlying mechanisms need to be expanded so as to incorporate explanations in terms of multiregion coordination (Grossberg, 2017).

Causation in the Brain and Implications for Emotion

At the broadest level, the foregoing discussion speaks to how we should study systems as complex as the mind/brain. When we consider how emotion is represented in the brain and interacts with perception and cognition, among others, we tend to think in terms of a few brain regions interacting in fairly simple ways (see Figure 3). For instance, a brain region may excite another region, or have an inhibitory effect on it. In other words, we tend to default to a Newtonian way of reasoning about systems (with simple forces applied to separate components) and to adopt what could be called a “billiard ball” causality framework (upon being hit by the pool cue, a ball moves and hits another ball; Pessoa, 2017a, 2018; Pessoa & Najafi, 2015).

But for complex systems, such as the brain, different models are needed, especially when multiple bidirectional influences and nonlinearities are present (Grossberg, 1980, 2017). Increasingly, it is recognized that nonlinear dynamics are ubiquitous (e.g., Sugihara et al., 2012). In particular, when systems are not isolable, understanding the interrelatedness between “subsystems” means that we should consider interactions between systems and potential integration of signals as central elements to be unraveled.

As advocated elsewhere (see Maturana & Varela, 1987; Thompson, 2007), the focus should not be on parts but on *processes*, which must be understood not solely in terms of their putative constituent elements (brain regions in the present case) but in terms of interactions and temporal evolution. In the brain, we will be often interested in describing the joint state of a set of regions, and how this joint state evolves through time. Consider the set of activity strengths for a set of brain regions: $x_1, x_2, \dots, x_n$. The vector $\mathbf{x}$ describes the current state of

the system and $\mathbf{x}(t)$ describes its trajectory across time. At a particular time, the state of a set of regions can be represented as a point in multidimensional state space in which each axis represents a region's activity. Therefore, the evolution of the system can be described as a spatio-temporal trajectory (Buonomano & Maass, 2009; for an example involving cell recordings, see Mante, Sussillo, Shenoy, & Newsome, 2013).

Whereas thinking of causation in complex systems is challenging, the foregoing discussion suggests that understanding can be advanced by characterizing how multiple regions interact with one another across time. Therefore, instead of focusing solely on causation as the inherent goal of explanations in neuroscience, a fruitful research avenue is to develop formal tools that describe—and critically allow prediction of—the *multivariate structure of brain data*. In other words, we are interested in describing and predicting the joint state of a set of brain regions, and how this joint state evolves through time. In addition, the properties of a system can be characterized via graph/network measures (Newman, 2010). For example, some “efficiency” measures use all pairwise correlations between regions' time series to estimate how well signals can potentially “flow” through the network, revealing how information can spread and thereby influence regions that are not immediately connected with each other. At the spatio-temporal resolution of fMRI data, we and others have started to characterize how emotion influences the temporal unfolding of large-scale network organization (Hermans, Henckens, Joëls, & Fernández, 2014; Hermans et al., 2011; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014; Pessoa & McMenamin, 2016). In a recent study (McMenamin et al., 2014), periods of “anxious anticipation” were associated with transient and sustained changes to the salience, executive, and task-negative networks in the human brain. Notably, 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.

Conclusions

The framework to understand the emotional brain described here (see also Pessoa, 2013, 2017a) proposes that large-scale cortical-subcortical systems—functionally integrated systems—are critically important to understand the brain basis of emotion (given space limitations, most of the issues discussed here were only briefly described). Some may object that the framework is too complex and that more parsimonious descriptions should be sought. So, why should we embrace complexity?

The central reason is the context sensitivity, flexibility, and richness of behavior (Alcock, 2009). Many natural behaviors can be viewed in terms of a cost–benefit analysis, in which the benefits of certain actions are weighed against their drawbacks. And, at any given time, multiple actions may be contemplated, each of which with its own benefits and costs. It is suggested that functionally integrated systems enhance flexibility to solve environmental problems, thus promoting survival. To be true, in many cases, animals resort to actions that are based on relatively simple forms of association, including classical conditioning and habits. However, natural environments are sufficiently open-ended that behavioral malleability benefits greatly from circuits that are *combinatorial* in nature. Intersecting long-range circuits offer interactions between multiple classes of signals: exteroceptive signals

about the world, interoceptive signals about the internal state of the organism, signals related to learning and memory, signals related to ongoing computations (including attention and forms of online maintenance), among others. More generally, this type of architecture affords the interaction between systems that are typically described as perception, cognition, action, motivation, and emotion.

At the broadest level, the suggestion is that simple models of (Newtonian) causation are insufficient to understand complex systems with bidirectional influences and nonlinearities. At the root of it, the suggestion is that an important focus should be on understanding circuits involving multiple regions simultaneously. More controversially, the framework also questions the idea that “standard causation” should be the gold standard of explanations in neuroscience. This is not only because, as Anderson and Adolphs (2018) state, given the rich connectivity of some brain systems it is “complicated to disentangle cause and effect within the system.” It is because unraveling collective, or emergent, behavior of multicomponent systems is crucially important. The understanding of brain function will thus benefit from mathematical and computational tools from complex systems, dynamical systems, and control theory (Csete & Doyle, 2002; Grossberg, 2017; Hirsch, Smale, & Devaney, 2012; Sugihara et al., 2012). Such models will be increasingly important in refining our intuitions about brain and behavior, not to mention testing predictions about experimental manipulations. Other domains of knowledge, including ecology and evolution, benefit from such tools for the study of, for example, indirect effects in ecological networks (Guimaraes, Pires, Jordano, Bascompte, & Thompson, 2017), higher order interactions in large ecological communities (Grilli, Barabas, Michalska-Smith, & Allesina, 2017), and detecting causality in complex ecosystems (Sugihara et al., 2012).

To conclude, it is suggested that the study of the “emotional brain” will benefit from the interactionist framework described here. It could be countered that the architecture of emotion—and the brain in general—is considerably more modular than outlined in the present article. If true, the proposal described here would be unnecessarily unwieldy. I contend, however, that more modular, hierarchical approaches, which originate from a conceptual zeitgeist that can be traced back at least to 19th-century Victorian thinking, are too limited. While this is ultimately an empirical question, it can only be fully tested if we broaden our theoretical thinking and consider potential alternatives. Therefore, to let empirical research flourish, it is time to embrace complexity.

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Figure 1.

Simple defensive/appetitive system. The general scheme is proposed to apply across vertebrates. (A) The superior colliculus (called optic tectum in nonmammals) is located in the midbrain (top of the brainstem), and can be viewed as a sensorimotor interface. It receives retinal inputs (among others) and projects to regions that generate motor output. (B) Even in frogs and toads which have a limited behavioral repertoire, the optic tectum receives signals related to learning, attention, and motivation. In this manner, its responses are context-dependent, and support greater behavioral flexibility. (C) Schematic representation of a frog brain with some of its parts highlighted. The cross-section of the telencephalon on the right indicates its two main subcomponents, pallium and subpallium (related to cortex and subcortex in mammals, respectively), with the part of the subpallium that contains the striatum shown.

Note. Abbreviations: DP: dorsal pallium; MP: medial pallium (a precursor to the hippocampus); LP: lateral pallium.

Figure 2. Looped architecture involving the superior colliculus/optic tectum. (A) In amphibians and reptiles, long-range loops spanning the midbrain–thalamus–forebrain considerably extend the range of signals the colliculus/tectum is sensitive to. (B) The loops also involve the most dorsal parts of the telencephalon (called pallium).

Figure 3. Central amygdala and emotional expression. The central amygdala engages multiple anatomical sites that are believed to participate in the functions indicated. Figures like this are frequently shown in the literature (see Davis, 1992, for an early version of this figure).

Figure 4.

Decoupling of sensory and motor components. (A) In a direct sensorimotor transformation, a simple processing area (black circle) conveys sensory signals to motor outputs with minimal processing. (B) The direct mapping can be “decoupled” when intervening brain areas (black circles) allow sensory inputs to be combined with multiple types of signals, leading to context sensitivity and flexibility in the mapping. The ellipses represent different spatial scales of potential circuits.

Figure 5.

Cortical-subcortical anatomical connectional systems. (A) Multiple regions at the subcortical forebrain are the target of cortical (or cortex-like) projections; the thalamus provides a route back to cortex (or cortex-like) regions. Subcortical forebrain regions are also connected with caudally situated regions along the brainstem. (B) Network representation of cortical-subcortical connectional systems. Green: cortical regions with connections to subcortical forebrain regions (green) and other cortical networks (black). Blue: subcortical forebrain regions involved in cortical-subcortical loops. Red: Subcortical forebrain and brainstem regions form loops; circuits are also present at the level of the brainstem (red lines with arrows). Orange: ascending systems from the brainstem influence subcortical and cortical processing. Purple: signals to and from the body are also exchanged. *Note.* Reprinted with permission from Pessoa (2017a).

Figure 6.

Functionally integrated systems. Connectivity between the amygdala and ventral striatal anatomical 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 the 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 the cortex (denoted by asterisks). *Note.* BNST: bed nucleus of the stria terminalis; PFC: prefrontal cortex; VTA: ventral tegmental area. Reprinted with permission from Pessoa (2017a).