

perception loops might be reused for more advanced cognitive abilities such as planning, mindreading, and executive function (Barsalou 2008; Jeannerod 2006; Pezzulo 2012; 2014; Pezzulo et al. 2011; 2013; 2014). This suggests that the same “affective tuning” of neuronal hierarchies naturally biases higher cognitive abilities, too.

In sum, various active inference mechanisms reviewed here – embodied predictive coding, precision dynamics, and the affective tuning of neural representations – offer a rich substrate for cognitive-emotional interactions. At the same time, they are prone to vulnerabilities and misregulations, which might produce psychopathological states such as anxiety disorders and psychotic symptoms (Adams et al. 2013; Friston et al. 2014). Some forms of psychopathology might depend on (precision-mediated) misregulations at the cognitive-emotional interface. For example, eating disorders could arise from the failure to handle conflicting information at the level of interoceptive signals (e.g., hunger) versus body schema and (false) belief (e.g., seeing oneself as fat). In active inference, this deficit is not purely representational but determines how subjects act (and think); for example, anorexics plan their actions as if they had an enlarged body (Keizer et al. 2013). Conceptualizing psychopathological states in terms of active inference may shed light on this intriguing domain, where cognitive-emotional interactions are clearly evident in both a clinical and neuropsychological sense.

The cognitive-emotional brain: Opportunities and challenges for understanding neuropsychiatric disorders¹

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Abstract: Many of the most common neuropsychiatric disorders are marked by prominent disturbances of cognition and emotion. Characterizing the complex neural circuitry underlying the interplay of cognition and emotion is critically important, not just for clarifying the nature of the mind, but also for discovering the root causes of a broad spectrum of debilitating neuropsychiatric disorders, including anxiety, schizophrenia, and chronic pain.

Until the twentieth century, the study of cognition and emotion was largely a philosophical matter. But recent years have witnessed the emergence of powerful new tools for interrogating the brain and new areas of multidisciplinary research focused on identifying the neurobiological mechanisms underlying cognition, emotion, and their role in mental health and disease. In *The Cognitive-Emotional Brain*, Luiz Pessoa (2013) provides an authoritative perspective on this recent work and its implications for our understanding of the basic building blocks of the mind. Here, we highlight four of the book’s most important implications for understanding neuropsychiatric disorders, including anxiety, schizophrenia, substance abuse, chronic pain, and autism. These disorders cause enormous suffering for millions of patients and their families, outstripping the global burden of cancer or

cardiovascular disease (Collins et al. 2011; Goldberg & McGee 2011; Kessler et al. 2012; Whiteford et al. 2013). Notably, these disorders involve prominent alterations in both cognition and emotion (Millan et al. 2012), pointing to the need for a deeper understanding of the cognitive-emotional brain.

First, *The Cognitive-Emotional Brain* reminds us that mental faculties emerge from the coordinated interactions of large-scale brain networks. Put simply, fear, reward, attention, and other psychological processes cannot be mapped to isolated brain regions because no one region is both necessary and sufficient. Conversely, similar symptoms can emerge from damage to different regions in the same functional network (Karnath & Smith 2014). Pain, which is among the most prevalent clinical disorders (Institute of Medicine 2011), nicely illustrates this point. Pain is a multidimensional experience, involving systematic changes in both cognition and emotion: painful stimuli elicit anxiety, capture attention, and motivate action. Neurobiologically, pain is associated with a complex pattern of regional activation, often termed the “pain matrix” (Iannetti et al. 2013). Stimulation of individual components of the pain matrix does not consistently elicit pain, suggesting that pain and its disorders are emergent properties of regional interactions. This is not a new or contentious idea; pioneers like Mesulam, Goldman-Rakic, and LeDoux highlighted the importance of distributed neural circuits more than two decades ago, and there is widespread agreement among basic and translational researchers (Bullmore & Sporns 2012; Fornito et al. 2015; Goldman-Rakic 1988; LeDoux 1995; 2012; Mesulam 1998; Turk-Browne, 2013; Uhlhaas & Singer 2012). *The Cognitive-Emotional Brain* is a bracing call for accelerating the transition from localization strategies (i.e., mapping brain structures to function; sometimes termed “neophrenology”) to a network-centered approach. From a clinical neuroscience perspective, this suggests that understanding neuropsychiatric disorders will require embracing the kinds of analytic tools (e.g., functional connectivity fingerprinting, graph theoretic and machine learning approaches) that are necessary for elucidating how psychological constructs and mental disorders are realized in brain circuits (Turk-Browne 2013; Woo et al. 2014).

Pessoa’s second key conclusion is that the identity of brain functional networks, including the circuitry that underlies clinically relevant phenotypes, cannot be inferred from neuroanatomy alone. Pessoa makes it clear that the networks identified by functional magnetic resonance imaging (fMRI) and other neurophysiological techniques do not necessarily recapitulate the pattern of direct connections revealed by invasive anatomical tracing techniques. Indeed, there is ample evidence of robust functional connectivity between brain regions that lack direct structural connections (Adachi et al. 2012; Birn et al. 2014; Honey et al. 2009; Vincent et al. 2007) and increasing evidence that regulatory signals can propagate across complex, indirect pathways (Ekstrom et al. 2008). From a clinical perspective, this indicates that fMRI-derived measures of functional connectivity are particularly useful because they can be used to assay dysfunctional networks that encompass polysynaptically connected nodes (Birn et al. 2014), just as viral tracers can be used to delineate polysynaptic anatomical pathways in the nervous system (Dum et al. 2009). More broadly, *The Cognitive-Emotional Brain* implies that many of the signs and symptoms of mental disorders – anhedonia, hypervigilance for threat, working memory impairments, drug seeking, and so on – will reflect complex brain circuits (Okon-Singer et al. 2015; Seminowicz et al. 2004; Shackman et al. 2013; Stout et al. 2013).

The third key conclusion is that emotion and cognition are not different in kind but are instead deeply interwoven in the fabric of the brain. Subjectively, we often experience cognition and emotion as fundamentally different. Emotion is saturated with feelings of pleasure or pain and manifests in readily discerned changes in the body, whereas cognition often appears devoid of substantial hedonic, motivational, or somatic features. These apparent differences in phenomenological experience and peripheral physiology have led many scholars to treat emotion and cognition as categorically distinct, even oppositional, mental forces that presumably

reflect the operation of segregated brain circuits (de Sousa 2014; Schmitter 2014). A similar dichotomy pervades psychiatric nosology. But careful scrutiny reveals contrary evidence; cognition can arouse the face and body; conversely, emotion can profoundly alter attention, working memory, and cognitive control (Grupe & Nitschke 2013; Okon-Singer et al. 2015; Shackman et al. 2011). *The Cognitive-Emotional Brain* provides a useful survey of recent brain imaging research demonstrating the integration of emotional and cognitive processes in the brain (Shackman et al. 2011). Largely on the basis of brain imaging data, Pessoa joins with other theorists in rejecting claims that emotion and cognition are categorically different (Barrett & Satpute 2013; Damasio 2005; Duncan & Barrett 2007; Lindquist & Barrett 2012). Elucidating the contribution of the cognitive-emotional brain to psychopathology mandates the joint efforts of cognitive, affective, computational, and clinical neuroscientists. This kind of multidisciplinary research would refine our understanding of the mechanisms that give rise to “mixed” cognitive-emotional symptoms, such as hypervigilance or aberrant reinforcement learning (Cavanagh & Shackman 2014), and provide novel targets for intervention.

Pessoa’s fourth and most original conclusion is a powerful synthesis of the first three. Pessoa argues that widely held beliefs about the constituents of “the emotional brain” and “the cognitive brain” are fundamentally flawed. Regions such as the amygdala are not “emotional,” and regions such as the dorsolateral prefrontal cortex (dlPFC) are not “cognitive” (Birn et al. 2014; Buhle et al. 2014; Fox et al. 2005; Shackman et al. 2009). Both regions play a central role in the regulation of adaptive behavior. This should not be surprising—the human brain did not evolve to optimize performance on artificial laboratory probes of “pure” cognition or emotion. Pessoa also makes it clear that brain regions can dynamically assume different roles. Just as an individual can perform psychologically distinct roles in different social networks (e.g., executive, mother, sister, daughter), brain regions are poised to perform a range of functions (a property termed functional “superimposition”) in different neural “contexts” corresponding to their level of participation in particular functional networks. To paraphrase Pearson and colleagues (Pearson et al. 2014), key brain regions, such as the orbitofrontal cortex, are functionally heterogeneous, with individual neurons dynamically multiplexed into different functional roles. As such, they will “evade a single, modular, functional role assignment” (p. 954). Our brain reflects evolutionary pressures that demanded distributed neural systems capable of using information about pleasure and pain, derived from stimuli saturated with hedonic and motivational significance, to adaptively regulate attention, learning, somatic mobilization, and action in the service of maximizing reproductive fitness. From this perspective, it is easy to imagine how dysfunction of circumscribed territories of the brain can have a deep impact on distal regions and circuits, as recent work by our group and others demonstrates (Fox & Kalin 2014; Fox et al. 2010; Gratton et al. 2012). This may help to explain the co-occurrence of cognitive and emotional symptoms, as well as frequent comorbidities, among psychiatric and neurological disorders. Clarifying the nature of the cognitive-emotional brain is likely to have substantial benefits for our understanding of disorders marked by symptoms that blend elements of cognition and emotion (e.g., hypervigilance to potential threat or overgeneralization of threat, in the case of the anxiety disorders [Grupe & Nitschke 2013]).

Although many challenges remain, *The Cognitive-Emotional Brain* provides a road map to the most fruitful avenues for future research. One of the most important unresolved questions concerns the functional significance of regions activated by both cognitive and emotional challenges. For example, Pessoa highlights a recent meta-analysis from our group demonstrating that the elicitation of negative affect, pain, and cognitive control are all associated with activation in an overlapping region of the MCC (Shackman et al. 2011). A key unresolved question is whether the MCC and other regions implicated in both cognitive and emotional processes, such as the anterior insula, perform a single general function (e.g., adaptive control [Cavanagh &

Shackman, in press; Shackman et al. 2011]) or salience detection (Iannetti et al. 2013) or multiple specific functions.

On a broader note, much of the evidence surveyed by Pessoa comes from the human brain imaging literature. Accordingly, his conclusions are ultimately tempered by questions about the origins and significance of the fMRI signal and the measures of functional connectivity that underlie network-centered approaches to understanding the cognitive-emotional brain (Akam & Kullmann 2014; Cabral et al. 2014; Logothetis 2008). An important challenge for future studies will be to combine mechanistic techniques in animal models (e.g., optogenetics) with the same whole-brain imaging strategies routinely applied in humans (Birn et al. 2014; Borsook et al. 2006; Casey et al. 2013; Narayanan et al. 2013; Oler et al. 2012; Roseboom et al. 2014). Combining noninvasive mechanistic techniques (e.g., transcranial magnetic stimulation or transcranial direct current stimulation) or pharmacological manipulations with fMRI provides another opportunity for understanding how circumscribed perturbations can produce distributed dysfunction (Chen et al. 2013; Guller et al. 2012; Paulus et al. 2005; Reinhart & Woodman 2014).

For many disorders marked by cognitive and emotional disturbances, extant treatments are inconsistently effective or associated with significant adverse effects (e.g., Bystritsky 2006). *The Cognitive-Emotional Brain* provides an insightful survey of state of the science and a useful stimulus for the next generation of basic and clinical research, reminding us that we have a remarkable opportunity to use new tools for understanding brain function to discover the origins of neuropsychiatric disease.

NOTE

1. Owing to a printer’s error, the word “Opportunities” was misspelled in the title of this commentary. The title has been corrected.

Strengthening emotion-cognition integration

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Abstract: Pessoa’s (2013) integrative model of emotion and cognition can be strengthened in two ways: first, by clarification and refinement of key concepts and terminology, and second by the incorporation of an additional key neural system into the model, the locus coeruleus/norepinephrine system.

We agree with Pessoa’s (2013) integrative view of emotion and cognition in *The Cognitive-Emotional Brain*, and we agree with his network view of the brain’s cognitive-affective architecture. We suggest, however, that these viewpoints can be strengthened in two ways. First, their key concepts and terminology need clarification and refinement, in order to foster exchange between the parallel but mutually insulated research streams of affective science and the science of decision making. Second, Pessoa’s “dual competition model” of cognition-emotion would benefit from the incorporation of an additional key neural system for the affective biasing of attention, decision making, and control processes—the locus coeruleus/norepinephrine system. In this commentary, we address these two points in turn.

Concepts and terminology. Pessoa states that he will not define the terms “emotion” and “cognition,” but instead will use them “*descriptively*” to refer to paradigms, task conditions, or “processes” that are closer to the traditional, intended meanings of emotion and cognition” (p. 3). Although he observes that these meanings