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Emotion and the Prefrontal Cortex: An Integrative Review

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The prefrontal cortex (PFC) plays a critical role in the generation and regulation of emotion. However, we lack an integrative framework for understanding how different emotion-related functions are organized across the entire expanse of the PFC, as prior reviews have generally focused on specific emotional processes (e.g., decision making) or specific anatomical regions (e.g., orbitofrontal cortex). Additionally, psychological theories and neuroscientific investigations have proceeded largely independently because of the lack of a common framework. Here, we provide a comprehensive review of functional neuroimaging, electrophysiological, lesion, and structural connectivity studies on the emotion-related functions of 8 subregions spanning the entire PFC. We introduce the *appraisal-by-content model*, which provides a new framework for integrating the diverse range of empirical findings. Within this framework, appraisal serves as a unifying principle for understanding the PFC's role in emotion, while relative content-specialization serves as a differentiating principle for understanding the role of each subregion. A synthesis of data from affective, social, and cognitive neuroscience studies suggests that different PFC subregions are preferentially involved in assigning value to specific types of inputs: exteroceptive sensations, episodic memories and imagined future events, viscero-sensory signals, viscero-motor signals, actions, others' mental states (e.g., intentions), self-related information, and ongoing emotions. We discuss the implications of this integrative framework for understanding emotion regulation, value-based decision making, emotional salience, and refining theoretical models of emotion. This framework provides a unified understanding of how emotional processes are organized across PFC subregions and generates new hypotheses about the mechanisms underlying adaptive and maladaptive emotional functioning.

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Keywords: decision making, emotion, prefrontal cortex, value, ventromedial

Life is filled with color through emotion—the happiness of a good first date, the fear instilled by reports about climate change, and the sadness and compassion evoked by news of Syrian refugees. Central to emotion is a suite of *appraisal* processes that evaluate the meaning of actual or imagined events with respect to our well-being and survival. When on a first date, one might evaluate the other person in terms of sensory features (e.g., attractiveness), their gestures and actions, and unobservable mental states (e.g., how intelligent and funny they are), and also evaluate oneself (e.g., "I am making a great first impression"), and what one imagines might happen at the end of the date. Emotion is multifaceted, involving many evaluative components, but also embodied components including physiological changes (e.g., increased heart rate), subjective feelings (e.g., excitement), and action tendencies (e.g., the urge to go in for a kiss).

Uncovering the neurobiological basis of emotion is essential for a complete understanding of the healthy and unhealthy operation of emotional mechanisms. Emotion influences, and is in turn influenced by, multiple brain systems ranging from the brainstem to the prefrontal cortex (PFC), as demonstrated by decades of neuroscientific research using rodents, nonhuman primates, and humans. Among these emotion-related brain systems, the PFC is generally considered to be primarily involved in elaborating upon and regulating the more basic emotional processes occurring in subcortical and brainstem regions (Barbas, 2000; Bechara & Damasio, 2005; Cunningham & Zelazo, 2007; Davidson, 2004; Dixon & Christoff, 2014; Haber & Behrens, 2014; Lane et al., 2015; McDannald et al., 2012; Ochsner & Gross, 2005; Ochsner & Gross, 2014; Rolls, 2004; Rudebeck & Murray, 2014; Rushworth et al., 2011; Shackman et al., 2011; Sharpe & Schoenbaum, 2016; Vogt, 2009b; Wager et al., 2008; Wallis, 2007). In doing so, the PFC makes a critical contribution to the organization and flexible regulation of emotional responses and goal-directed behavior. That

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the PFC plays a significant role in emotion also becomes obvious when considering that dysfunction of the PFC has been implicated in the etiology of nearly all of the affective disorders, including depression (Drevets, Savitz, & Trimble, 2008; Farb et al., 2010; Greicius et al., 2007; Mayberg et al., 2005), anxiety (Bishop, Duncan, Brett, & Lawrence, 2004; Chamberlain et al., 2008; Davidson, 2002; Goldin et al., 2009), and bipolar disorder (Blumberg et al., 2003, 1999; Frye et al., 2007).

Despite this well appreciated importance of the PFC in emotion and an ever expanding empirical literature, we still lack a detailed, integrative framework for understanding the specific contributions that the PFC makes to emotion and how these contributions relate to overall prefrontal functional and anatomical organization at the subregional level. Here we provide a comprehensive review of the neuroscientific literature on emotion-related functions of the PFC, with specific emphasis on anatomical precision. Our review expands upon prior work in several important ways. First, we examine the functional roles of eight subregions covering the entire expanse of the PFC, thus providing a comprehensive review of PFC functions in emotion. Second, we bring together research findings from multiple fields (affective, social, and cognitive neuroscience), and multiple methodologies (neuroimaging, brain lesions, and electrophysiological recordings). Third, we also take advantage of psychological models of emotion to organize and synthesize a broad range of neuroscientific findings. The result is a new framework that offers an improved understanding of the unity and diversity of the PFC's emotion-related functions, with relevance to both healthy and unhealthy emotional functioning.

The present review is founded upon three core ideas: (a) anatomical and functional connectivity constrains function, and can be used to infer differences in function across regions (Barbas, 2000; Beckmann, Johansen-Berg, & Rushworth, 2009; Haber & Behrens, 2014; Passingham, Stephan, & Kotter, 2002; Passingham & Wise, 2012; Rushworth, Behrens, Rudebeck, & Walton, 2007; Vogt, 2009b); (b) it is critical to bridge psychological theory and neuroscientific findings (Brosch & Sander, 2013; Lewis, 2005; Poeppel, 2012); and (c) a global framework of PFC function should explicitly specify both the unity and diversity of function across subregions (Teuber, 1972).

Challenges in Understanding the Role of the PFC in Emotion

Theoretical Considerations

Because of the overwhelming complexity and wealth of empirical findings, literature reviews and theories have often focused on specific emotional process (e.g., threat; decision making; pain; Etkin, Egner, & Kalisch, 2011; Rushworth et al., 2011; Vogt, 2005) or specific anatomical regions (e.g., the orbitofrontal cortex; Dixon & Christoff, 2014; Kringelbach & Rolls, 2004; Rushworth et al., 2007; Schoenbaum & Esber, 2010; Shackman et al., 2011). Furthermore, there has been a relatively low degree of integration across different areas of inquiry. Different areas of emotion research have often become focused on some prefrontal subregions, often to the exclusion of others. For example, research on reward and decision making has predominantly focused on the orbitofrontal and ventromedial prefrontal cortices, whereas research on emotion regulation has predominantly focused on the lateral PFC and the anterior mid-cingulate cortex (also known as the dorsal anterior cingulate cortex). Each research area has developed its own terminology and distinct theoretical concepts, which has further contributed to the lack of integration across fields. Finally, there has been a surprising paucity of cross-talk between the theoretical and neuroscientific emotion literatures (Brosch & Sander, 2013). Generally speaking, neuroscience research has not made use of the fine-grained taxonomies and sophisticated psychological models of emotion that have emerged from decades of theoretical/behavioral research. Concepts from psychological models may help in refining ideas about core emotional mechanisms, and potentially offer a unifying framework for organizing and integrating neuroscientific findings.

Anatomical Considerations

The PFC is a large expanse of brain tissue that can be subdivided into multiple anatomically and functionally distinct areas (Figure 1; Barbas, 2000; Carmichael & Price, 1996; Mackey & Petrides, 2010; Ongur, Ferry, & Price, 2003; Petrides & Pandya, 1999, 2002; Vogt, 2009b). Advances in technology and the use of well-designed tasks has enabled researchers identify cognitive processes associated with neural activity in localized PFC zones. While critical for advancing the field, this increased focus on functional localization has made it difficult to build a comprehensive and integrative perspective. Another challenge is that we lack a standard (i.e., widely adopted) parcellation scheme and corresponding nomenclature for the PFC. As a result, there is considerable variability in how different prefrontal subregions are defined and labeled. In some cases, the same label has been used to describe distinct and anatomically nonoverlapping brain regions. For example, the label "ventromedial prefrontal cortex" (VMPFC) has been used across different fMRI studies to describe activations that may fall in area 14, area 25, area 32, or area 10 (see Figure 1; e.g., Boorman, Behrens, Woolrich, & Rushworth, 2009; Chib, Rangel, Shimojo, & O'Doherty, 2009; Glascher, Hampton, & O'Doherty, 2009; Hunt et al., 2012; Kim, Shimojo, & O'Doherty, 2011; Smith et al., 2010; Strait, Blanchard, & Hayden, 2014; Winecoff et al., 2013). This is problematic considering that areas 10 and 14 emerged later in mammalian evolution than areas 25 and 32, and are likely to be functionally distinct (Passingham & Wise, 2012; Wise, 2008). The lack of consistent and commonly adopted nomenclature for prefrontal subregional parcellation has made it difficult to work toward a systematic account of PFC's role in emotion.

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The Current Review

Here we provide a comprehensive review of how the PFC contributes to emotion. We examine the distinct functions of eight PFC subregions spanning the medial, ventral, and lateral prefrontal surface (Figure 1). To discern potential differences in relative functional specialization across subregions, we review functional neuroimaging, electrophysiological, lesion, and structural connectivity findings for each subregion. To organize this large set of findings, we introduce a novel theoretical framework—the *appraisal-by-content* (ABC) model—which accounts for both the commonalities and differences across different PFC subregions.

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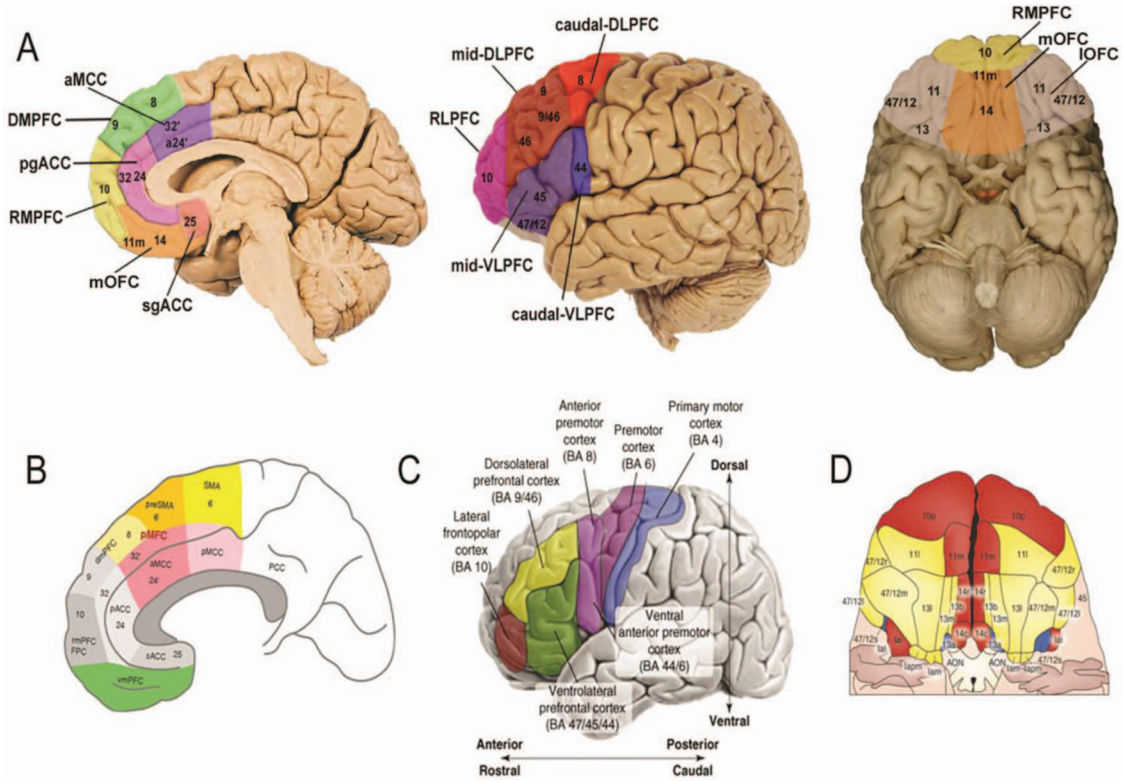

Figure 1. Functional-Anatomic Parcellation of the prefrontal cortex (PFC) (A). Current PFC parcellation. sgACC = subgenual anterior cingulate cortex; pgACC = pregenual anterior cingulate cortex; aMCC = anterior mid-cingulate cortex; lOFC = lateral orbitofrontal cortex; mOFC = medial orbitofrontal cortex; RMPFC = rostromedial prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; RLPFC = rostrolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; DLPFC = dorsolateral prefrontal cortex (B). Our parcellation is similar to other recent work. Parcellation of the cingulate cortex and medial PFC from Ullsperger et al. (2014) (C). Parcellation of lateral PFC from Badre (2008) showing dorsal/ventral and rostro-caudal gradients (D). Parcellation of the OFC into lateral (yellow/light) and medial (red/dark) subregions based on anatomical connectivity from Price and Drevets (2010). See the online article for the color version of this figure.

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This model proposes that appraisal, the process of evaluating the affective significance of an event, can serve as a unifying functional principle that governs the role of the entire PFC in emotion. The model further suggests that different PFC subregions exhibit relative specialization, or biases, to support appraisal of different types of content. This relative specialization is influenced by differences in the anatomical and functional connectivity across regions. The proposed appraisal-by-content model is informed by the theoretical and neuroscientific literatures, and allows for a synthesis of a wide range of empirical findings by translating diverse anatomical and functional terminology into a single, unified framework. The model, however, is not meant to provide an exhaustive account of PFC function beyond its role in emotion, nor to imply that emotional appraisal only relies on the PFC. Rather, it aims to provide an organizational structure for understanding the role of the PFC in emotion.

In the following sections, we begin by briefly reviewing key concepts from psychological models of emotion, and outline the proposed appraisal-by-content model. We then describe the nomenclature and PFC parcellation that our model adopts. Then, we review empirical findings regarding the patterns of functional contributions and anatomical connectivity associated with eight PFC subregions: lateral orbitofrontal cortex; medial orbitofrontal cortex; subgenual anterior cingulate cortex; pregenual anterior cingulate cortex; anterior mid-cingulate cortex; rostromedial prefrontal cortex; dorsomedial prefrontal cortex; and lateral prefrontal cortex. We then use the present integrative framework to offer a novel perspective on several topics: emotion regulation; value-based decision making; dissociating salience detection from subjective feelings and action tendencies; and how we can use neuroscientific findings to refine theoretical models of emotion. Finally, we highlight methodological and theoretical issues that will be important to address in future research.

Theoretical Framework

Theoretical Approaches to Emotion

Decades of theoretical and behavioral research have produced fine-grained taxonomies and sophisticated psychological models of emotion. Yet this rich history has not been well integrated into neuroscientific investigations of emotion. Many psychological the-

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ories of emotion emphasize that an emotional episode involves multiple distinct, yet interacting components: (a) appraisal mechanisms that evaluate the significance of an event for an individual's survival and well-being; (b) changes in peripheral physiology (e.g., cardiovascular, respiratory, hormonal); (c) action tendencies; and (d) subjective feeling states that influence attention and decision making (Barrett, Mesquita, Ochsner, & Gross, 2007; Damasio, 2003; Frijda, 1987; Gross, 1998; Keltner & Gross, 1999; Lewis, 2005; Moors, Ellsworth, Scherer, & Frijda, 2013; Russell, 2003; Scherer, 2001, 2005). Appraisal is at the heart of these models. It specifies whether something is good or bad for me, informed by prior experience and current context (Arnold, 1960; Barrett et al., 2007; Barrett, Wilson-Mendenhall, & Barsalou, 2014; Brosch & Sander, 2013; Cunningham & Zelazo, 2007; Ellsworth & Scherer, 2003; Lazarus & Smith, 1988; Moors et al., 2013; Scherer, 2001; Smith & Ellsworth, 1985; Tracy & Robins, 2004). Appraisal is highly similar to the concept of "valuation" that is often used in the neuroscientific literature (Gross, 2015; Ochsner & Gross, 2014; Rangel, Camerer, & Montague, 2008). The theoretical concept of appraisal is particularly useful because it has been decomposed into multiple distinct dimensions. We summarize some of the major dimensions that are of relevance for understanding the brain regions considered here.

Goal-relevance appraisal. This appraisal dimension reflects an evaluation of the environment—objects, people, and places—based on their implications for one's *current goals and needs* (Brosch & Sander, 2013; Ellsworth & Scherer, 2003; Scherer, 2001). Because goals continuously change, brain mechanisms that evaluate goal-relevance must be flexible and provide real-time updates regarding the value of stimuli with respect to those goals. In the context of emotion theory, goal-relevance refers to a variety of hierarchically organized goals and needs, from survival to the desire to attend a concert. Objects and events are assigned value commensurate with their position within the individual's hierarchy at a given moment in time.

Appraisal of intentionality. This appraisal dimension reflects the extent to which others' intentions have implications for hindering or facilitating one's goals (Brosch & Sander, 2013; Ellsworth & Scherer, 2003; Lazarus & Smith, 1988; Scherer, 2001). The same action may have different emotional consequences based on the intentions behind it. Discerning others' intentions requires information about their current mental states. This ability, often referred to as *mentalizing*, requires stepping out of one's own perspective, and recognizing that others have independent and unique thoughts, beliefs, and desires that govern their behavior (Gallagher & Frith, 2003). Others' mental states can be inferred based on a variety of information including observable cues (e.g., facial expression) and personality traits.

Self-evaluation based on social norms. Humans' highly developed capacity for self-awareness allows for the construction of a self-image (the idea of "me") consisting of particular attributes and goals, and that exists within a temporally extended personal narrative (Markus, 1977). To maintain social standing and bonds with others, individuals often evaluate themselves as good or bad based on the alignment or discrepancy between their actions and social norms (Ellsworth & Scherer, 2003). Self-evaluations may be triggered by stored knowledge about social values, or by direct feedback from others, and often lead to complex emotions such as pride and embarrassment that are believed to promote socially valued behaviors and discourage socially inappropriate behavior (Scherer, 2001; Tracy & Robins, 2004).

Other appraisal dimensions. Beyond the traditional theoretical literature, reinforcement learning models suggest that there may be a specific appraisal mechanism that evaluates action plans based on the outcomes they are expected to yield (Sutton & Barto, 1998). Thus, rather than have action selection result indirectly from the valuation of objects and events, adaptive actions are learned directly based on their association with valenced outcomes. There may also be specific appraisals related to physiological arousal. Barrett and Simmons (2015) proposed a predictive coding model of body states suggesting that there is a mechanism that generates predictions about the upcoming requirements of the body, and that this triggers changes in physiological arousal in *anticipation* of the actions that are likely to be executed in a given situation (Barrett & Simmons, 2015). In this way, the body is prepared to rapidly execute any required actions to cope with an emotionally significant event. This prediction can be conceptualized in terms of an appraisal mechanism that assigns value to endocrine and autonomic signals. In particular, this appraisal mechanism may involve the strengthening and weakening of associations between specific configurations of bodily activation and contextual cues based on experienced outcomes. Finally, Ochsner and Gross (2014) have proposed that the initiation of emotion regulation can be framed in terms of a second-order appraisal system that evaluates the emotions generated by first-order appraisal mechanisms (e.g., a negative evaluation of anger will initiate regulatory strategies that alter the emotion; see also Gross, 2015). The notion of appraisal thereby provides a unifying framework for understanding the nature of emotion generation and regulation.

Appraisal as a Unifying Principle of PFC Function in Emotion

We suggest that appraisal can be seen as a unifying principle of PFC function. The term appraisal is useful because it provides a bridge to the theoretical emotion literature, and allows us to integrate findings that have used different terminology and concepts. We use this term synonymously with valuation and evaluation. In line with recent perspectives, we suggest that both emotion generation and emotion regulation can be understood in terms of appraisals at various levels of complexity (Gross, 2015; Ochsner & Gross, 2014). The suggestion that every PFC subregion participates in appraisal is consistent with evidence that value signals are observed across the entire PFC (Bartra, McGuire, & Kable, 2013; Clithero & Rangel, 2014; Dixon & Christoff, 2014; Vickery, Chun, & Lee, 2011). This is not to say that the PFC as a whole is selectively involved in appraisal; on the contrary, it is known contribute to other functions outside of emotional contexts. Furthermore, appraisal depends on many regions beyond the PFC, and occurs at multiple levels of complexity, from simple associations between perceptual inputs and physiological and action-related outputs to high-level conceptual appraisals that include a variety of contextual information (Barrett et al., 2014; Cunningham & Zelazo, 2007; Ochsner & Gross, 2014; Scherer, 2001). The PFC may be primarily involved in the latter type of appraisals, but heavily interacts with subcortical and brainstem regions that support other types of appraisals.

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Appraisal-By-Content Specialization as a Differentiating Principle of PFC Function in Emotion

We propose that while the overall unifying function of PFC in emotion is that of assigning value (appraisal), what distinguishes different PFC subregions is a relative functional specialization for carrying out appraisal on specific types of inputs (or contents). Although different brain regions work together within functional networks to support complex functions (Buckner, Krienen, & Yeo, 2013; Bullmore & Sporns, 2009; Fox & Raichle, 2007; Medaglia, Lynall, & Bassett, 2015; Petersen & Sporns, 2015), some brain regions are better suited to perform certain functions than others—a phenomenon reflected in the concept of *functional specialization* (Aron, Robbins, & Poldrack, 2004; Beckmann et al., 2009; Epstein & Kanwisher, 1998; Fedorenko, Duncan, & Kanwisher, 2012; Gilbert et al., 2006; Kanwisher, 2010; Kanwisher, McDermott, & Chun, 1997; Poldrack et al., 1999; Ungerleider & Haxby, 1994; Zeki et al., 1991). Each brain region has a unique anatomical connectivity fingerprint and therefore access to different types of information, and this may promote an intrinsic bias to perform a specific function (Barbas, 2000; Beckmann et al., 2009; Haber & Behrens, 2014; Passingham et al., 2002; Passingham & Wise, 2012). Consistent with this, there is a long history of brain lesion studies revealing distinct cognitive and emotional deficits depending on the source of brain damage (Bechara, Damasio, Tranel, & Anderson, 1998; Stuss & Alexander, 2007; Stuss & Knight, 2002; Szczepanski & Knight, 2014). Moreover, different brain regions emerged at different points in mammalian evolution (e.g., the pregenual cingulate cortex is evolutionarily older than the adjacent rostromedial prefrontal cortex), suggesting variations in functional contribution (Passingham & Wise, 2012; Wise, 2008).

We propose that each prefrontal subregion is characterized by a relative specialization to assess the value of specific types of inputs. Critically, we favor the idea of *relative rather than absolute* functional specialization. That is, we suggest that each PFC subregion is *preferentially* involved in evaluating specific inputs—a relative bias that emerges because of the combined constraints of anatomical and functional connectivity. These biases emerge flexibly when certain task demands need to be met (e.g., during emotional appraisal) but may not be present in other contexts (e.g., during visuospatial reasoning). In the case of injury, neighboring regions may be able to compensate, to some extent, through plasticity in structural pathways or functional interactions. The idea of relative rather than absolute functional specialization is consistent with evidence of adaptive tuning of single neurons in the PFC (Duncan, 2001; Miller, 2000; Miller & Cohen, 2001), and previous theorizing of subregional specialization in lateral PFC outside of emotion (Christoff & Keramatian, 2007; Christoff, Keramatian, et al., 2009). A combination of relative functional specialization and adaptive neural coding may provide an ideal balance that supports structured neural responses that exploit statistical regularities in external and internal events, but also the capacity to flexibly adjust to changes in the environment. Lesion work is consistent with the idea that PFC organization may reflect a combination of domain-general and domain-specific processing (Szczepanski & Knight, 2014). Similarly, work on other PFC-related processes such as executive functions have also emphasized the idea of "separable but related functions that share some underlying commonality" (Miyake et al., 2000, p. 88). Thus, while our review addresses differences in function across PFC subregions, our discussion should not be interpreted as implying the existence of a modular architecture. Instead, the function of each region should be understood as a relative and highly flexible functional specialization.

Finally, PFC subregions are likely *necessary but not sufficient* for the different types of appraisals reviewed here. Many brain structures outside the PFC are known to contribute to each of the appraisals we describe. Indeed, regions are structurally and functionally embedded within networks, and are subject to unique "fingerprint-like" interactions (Passingham et al., 2002; Pessoa, 2015). Thus, the findings reviewed here need to be interpreted within a network context (Barrett & Satpute, 2013; Pessoa, 2015). Furthermore, we do not claim that PFC subregions are *selective* for the described appraisals. In other words, it would be invalid to draw reverse inferences from activations in specific prefrontal subregions to specific types of emotional appraisal. Prefrontal subregions are likely involved in multiple other functions outside of appraisal. Thus rather than identify the core function of prefrontal subregions, the purpose of the review is to discern the principles of PFC organization and its specific contributions to emotion.

Functional–Anatomical Parcellation of the PFC

The brain can be parcellated at various scales, however it is critical to use a scheme that matches the level of resolution of functional differences observed in the neuroscientific literature. In the current review, we parcellate the PFC into eight subregions based on data from invasive tracer studies in macaque monkeys, noninvasive fiber tracking (i.e., diffusion tensor imaging), functional connectivity patterns in humans, and functional considerations. The regional distinctions made here are very similar to other recent efforts (Etkin et al., 2011; Morecraft et al., 2012; Price & Drevets, 2010; Ullsperger, Danielmeier, & Jocham, 2014; Vogt, 2009c). However, the current review is unique in covering the functions of all subregions.

Orbitofrontal Cortex

The ventral surface of the frontal lobe is known as the orbitofrontal cortex (OFC), and is composed of four main architectonic areas (caudal-central area 13, lateral area 47/12, rostral area 11, and medial area 14; Mackey & Petrides, 2010; Ongur & Price, 2000; Wallis, 2011). These areas can be grouped into two major functional regions based on patterns of anatomical connections (Carmichael & Price, 1996; Ongur & Price, 2000), and functional coactivation patterns (Zald et al., 2014): (a) the lateral OFC which encompasses architectonic areas 13, 47/12, and most of area 11; and (b) the medial OFC, which encompasses area 14 and the medial aspect of area 11. The medial orbital sulcus provides a boundary between these functional zones. Although the OFC contains multiple different architectonically distinct subregions, reviews and meta-analyses frequently divide OFC into medial and lateral territories (Cavada et al., 2000; Elliott, Dolan, & Frith, 2000; Kringelbach & Rolls, 2004; Rudebeck & Murray, 2011a; Rushworth et al., 2011; Zald et al., 2014). This division of the OFC in two regions is ideal for the level of resolution of current neuroscientific findings, however greater specificity reflecting the

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known anatomical divisions of the OFC may be possible in the future.

Medial Prefrontal Cortex

The rostromedial prefrontal cortex (RMPFC) corresponds to the medial part of frontopolar area 10. A rough approximation of the dorsal/ventral boundary separating RMPFC from the medial OFC is $z = -10$ in MNI space (Mackey & Petrides, 2014; Sallet et al., 2013). It is critical to separate the medial OFC from the RMPFC because of well-established functional differences. For example, meta-analyses have shown that tasks involving explicit self-reflection are associated with activation that is restricted to the RMPFC and does not extend into the medial OFC (Denny, Kober, Wager, & Ochsner, 2012; Murray, Schaer, & Debbane, 2012; van der Meer, Costafreda, Aleman, & David, 2010). The dorsomedial prefrontal cortex (DMPFC) corresponds to areas 9 and 8B on the medial wall (Petrides & Pandya, 1999) and is located between the RMPFC and the presupplementary motor area (pre-SMA; area 6). Recent functional connectivity-based parcellations suggest that DMPFC and RMPFC belong to distinct functional networks, and a rough approximation of the dorsal/ventral border between these regions is $z = 20$ in MNI space (Andrews-Hanna, Reidler, Sepulcre, et al., 2010; Sallet et al., 2013; Yeo et al., 2011). A rough approximation of the anterior/posterior border separating DMPFC and pre-SMA is $y = 25$ in MNI space (see Figure 4 in Sallet et al., 2013).

Cingulate Cortex

Vogt and colleagues have outlined an exquisitely detailed parcellation scheme and nomenclature for the cingulate cortex (Vogt, 2009c; Vogt, Vogt, Farber, & Bush, 2005). The subgenual anterior cingulate cortex (sgACC) is a small region situated below the genu of the corpus callosum, and is mainly comprised of architectonic area 25, but also includes a small portion of areas 24 and 32. The pregenual anterior cingulate cortex (pgACC; areas 24 and 32) is located rostral to, and slightly above and below, the genu of the corpus callosum. Roughly speaking, the cingulate cortex lying rostral to $y = 30$ in MNI space is the pgACC. This region is distinguished from adjacent cingulate regions by virtue of strong functional connectivity with default network (Yeo et al., 2011). The mid-cingulate cortex (MCC) occupies most of the cortex sitting dorsal to the corpus callosum, and can be divided into anterior (aMCC; areas a24′ and a32′) and posterior (pMCC; area p24′) sectors, with their approximate border being the vertical plane that passes through the anterior commissure. Because the pMCC is mainly a motor region and not directly involved in emotion, it was not included in the current review. The aMCC is often referred to in the literature as the dorsal anterior cingulate cortex; however, recent evidence has conclusively demonstrated that this part of the cingulate cortex can be distinguished from the anterior cingulate cortex based on cytoarchitecture and connectivity, and hence, should be referred to with a distinct name (Vogt, 2009c; Vogt et al., 2005).

Lateral PFC

The lateral PFC contains numerous anatomically distinct subregions (Petrides & Pandya, 1999, 2002, 2007). At the broadest level, the lateral PFC can be divided into dorsolateral (DLPFC), ventrolateral (VLPFC), and rostrolateral (RLPFC) sectors. Furthermore, anatomical connectivity and functional activation patterns also suggest a rostro-caudal (anterior-posterior) organization (Badre, 2008; Badre & D'Esposito, 2009; Christoff & Gabrieli, 2000; Christoff & Keramatian, 2007; Koechlin & Summerfield, 2007; Petrides, 2005). In the current review, we consider the lateral PFC as a whole, given that its role in emotional valuation processes are only beginning to be investigated (Dixon & Christoff, 2014). However, in the section entitled Relationship to Other Models of PFC Organization we touch upon potential functional distinctions along the rostro-caudal axis. AQ: 4

Inclusion Criteria

The goal of the present review is to provide a comprehensive and integrative review of empirical findings on emotion pertaining to the entire PFC. The scope of this goal renders an exhaustive review of empirical findings impossible. To be as comprehensive and unbiased as possible in selecting literature for review, we adopted the following approach: (a) we used highly cited authoritative review papers and meta-analyses covering each PFC subregion to guide our search for the most relevant literature; (b) we focused on findings that replicated across multiple methodologies (fMRI, electrophysiology, lesion) and across different species (humans, nonhuman primates, and rodents); and (c) we integrated findings from multiple fields that have traditionally remained segregated (affective, social, and cognitive neuroscience; anatomical connectivity, and network neuroscience). We used 67 review papers and meta-analyses to guide our literature search (Table 1). T1

Review of Neuroscientific Evidence for Relative Functional Specialization

The Lateral Orbitofrontal Cortex: Appraisal of Exteroceptive Sensations

Psychological models of emotion suggest that there is a dedicated appraisal mechanism that assesses the goal-relevance of objects/events (Brosch & Sander, 2013; Ellsworth & Scherer, 2003; Sander, Grafman, & Zalla, 2003; Scherer, 2001). Considerable evidence suggests that lateral orbitofrontal cortex (OFC) function aligns with this appraisal dimension. This region is specifically involved in the appraisal of exteroceptive sensations, that is, sensory information arising from the external environment, based on current context and goals (Figure 2A). This function has F2 been variably referred to as stimulus-reinforcement learning, evaluating the subjective value of stimuli, or signaling outcome expectancies (Padoa-Schioppa, 2011; Padoa-Schioppa & Assad, 2006; Rolls, 2004; Rudebeck & Murray, 2014; Schoenbaum & Esber, 2010; Wallis, 2007; Walton et al., 2010). By correlating brain activation with subjective evaluations of stimulus valence or the objective magnitude of reward outcomes, functional neuroimaging and electrophysiological studies have shown that lateral OFC activation reflects the value of food items (Howard, Gottfried, Tobler, & Kahnt, 2015; Kringelbach, O'Doherty, Rolls, & Andrews, 2003; Padoa-Schioppa & Assad, 2006; Stalnaker et al., 2014), odors (Anderson et al., 2003; Gottfried, O'Doherty, & Dolan, 2003), auditory stimuli (Frey, Kostopoulos, & Petrides,

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Table 1
Review Papers and Meta-Analyses That Guided Literature Selection for the Current Review

Authors	Type of manuscript	Region(s) of focus	Topic
Morrison and Salzman (2009)	Review	lOFC	Value of sensory input
Padoa-Schioppa (2011)	Review/Model	lOFC	Value-based decision making
Rolls (2004)	Review	lOFC, mOFC	Stimulus-reinforcement learning
Rudebeck and Murray (2011a)	Review	lOFC, mOFC	Sensory values and comparisons
Wallis (2007)	Review	lOFC	Value learning and decision making
Schoenbaum and Esber (2010)	Review	lOFC	Outcome expectancies
Sharpe and Schoenbaum (2016)	Review	lOFC	Comparing OFC and amygdala functions
Levy and Glimcher (2012)	Review/Model	mOFC	Value-based decision making
Bartra et al. (2013)	Meta-analysis	mOFC, RMPFC, pgACC, sgACC	Value-based decision making
Clithero and Rangel (2013)	Meta-analysis	mOFC, RMPFC, pgACC, sgACC	Value-based decision making
Bechara and Damasio (2005)	Review/Model	mOFC	Somatic marker theory
Zald et al. (2014)	Meta-analysis	mOFC, lOFC	Coactivation patterns
Domhoff and Fox (2015)	Review/meta-analysis	mOFC	Dreaming
Etkin et al. (2011)	Review	mOFC, aMCC	Threat expression vs regulation
Barrett and Simmons (2015)	Review/Model	sgACC	Interoception and prediction
Vogt and Derbyshire (2009)	Review	sgACC, pgACC	Visceral circuits
Vogt (2005)	Review	sgACC, pgACC, aMCC	Pain
Vogt (2009c)	Review	sgACC, pgACC, aMCC	Physiological arousal, feelings, action values
Lane et al. (2015)	Review	pgACC	Subjective feelings, alexithymia
Lee and Siegle (2012)	Meta-analysis	pgACC, lOFC	Stimulus evaluation, subjective feelings
Shackman et al. (2011)	Review/ Meta-analysis/Model	aMCC	Adaptive control of defensive actions
Rushworth et al. (2007)	Review	aMCC, lOFC	Stimulus and action values
Rushworth et al. (2012)	Review	aMCC, lOFC	Decision making, foraging
Botvinick et al. (2001)	Review/Model	aMCC	Conflict monitoring
Ridderinkhof et al. (2004)	Review/Meta-analysis	aMCC	Performance monitoring
Alexander and Brown (2011)	Model	aMCC	Action-outcome learning
Ullsperger et al. (2014)	Review	aMCC, lateral PFC, lOFC, mOFC	Performance monitoring
Devinsky et al. (1995)	Review	aMCC, pgACC, sgACC,	Pain, action, visceral processing
Holroyd and Coles (2002)	Model	aMCC	Error processing, reinforcement learning
Picard and Strick (1996)	Review	aMCC	Motor functions
Gallagher and Frith (2003)	Review	DMPFC	Mentalizing
Mar (2011)	Meta-analysis	DMPFC	Mentalizing
Van Overwalle and Baetens (2009)	Meta-analysis	DMPFC	Mentalizing
Saxe (2006)	Review	DMPFC	Mentalizing
Wagner et al. (2012)	Review	DMPFC, RMPFC	Reflection on self and other
Murray et al. (2012)	Meta-analysis	RMPFC	Reflection on self and other
Van der Meer et al. (2010)	Meta-analysis	RMPFC	Self-reflection
Amodio and Frith (2006)	Review/Model	RMPFC, aMCC, mOFC	Monitoring self, actions, outcomes
Denny et al. (2012)	Meta-analysis	RMPFC	Reflection on self and other
Buckner et al. (2008)	Review	RMPFC, pgACC, mOFC	Default network
Christoff et al. (2016)	Review/Model	RMPFC, mOFC	Default network, spontaneous thought
Schmitz and Johnson (2007)	Review	RMPFC, mOFC	Self-reflection, emotion
Ochsner et al. (2012)	Review/Meta-analysis	lateral PFC, aMCC, DMPFC	Emotion regulation
Ochsner and Gross (2014)	Review/Model	lateral PFC, aMCC, mOFC	Emotion regulation and valuation
Etkin et al. (2015)	Review/Model	lateral PFC, aMCC	Reinforcement learning and emotion regulation
Buhle et al. (2013)	Meta-analysis	lateral PFC, aMCC	Emotion regulation
Dixon and Christoff (2014)	Review	lateral PFC	Value learning and decision making
Dixon (2015)	Review/Model	lateral PFC	Value-based emotion regulation
Buckholtz (2015)	Review/Model	lateral PFC	Model-based decision making
Badre and D'Esposito (2009)	Review/Model	lateral PFC	Rostro-caudal organization
Christoff and Gabrieli (2000)	Review/Meta-analysis	lateral PFC	Rostro-caudal organization
Koechlin and Summerfield (2007)	Review/Model	lateral PFC	Rostro-caudal organization
Watanabe and Sakagami (2007)	Review	lateral PFC	Emotion-cognition interactions
Pessoa (2008)	Review	lateral PFC	Emotion-cognition interactions
Wager et al. (2008)	Meta-analysis	lateral PFC, aMCC, DMPFC	Emotion regulation
Petrides (2005)	Review	lateral PFC	Rostro-caudal organization
Brosch and Sander (2013)	Review	DMPFC, lOFC, lateral PFC	Various appraisals
Christoff (2012)	Review	RMPFC, pgACC, mOFC	Default network, internally directed processing
De la Vega et al. (2016)	Meta-analysis	aMCC, pgACC	Pain, cognitive control, social
Dixon et al. (2014b)	Review/Model	RMPFC, pgACC, mOFC	Internal vs external processing
Fox et al. (2015)	Meta-analysis	RMPFC, pgACC, lateral PFC pgACC, mOFC	Mind wandering

(*table continues*)

Table 1 (*continued*)

Authors	Type of manuscript	Region(s) of focus	Topic
Lindquist et al. (2016)	Meta-analysis	All regions	Positive and negative affect
Passingham and Wise (2012)	Review/Model	lateral PFC, lOFC, MPFC	Cognition and emotion
Rushworth et al. (2011)	Review	lateral PFC, lOFC, mOFC, aMCC	Value-based decision making
Shulman et al. (1997)	Meta-analysis	RMPFC, pgACC, mOFC	Default network, task-induced deactivations
Haber and Behrens (2014)	Review	lOFC, aMCC	Stimulus and action values

Note. lOFC = lateral orbitofrontal cortex; mOFC = medial orbitofrontal cortex; RMPFC = rostromedial prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; sgACC = subgenual anterior cingulate cortex; pgACC = pregenual anterior cingulate cortex; aMCC = anterior mid-cingulate cortex.

2000), somatosensory stimulation (Rolls et al., 2003), and visually presented images of scenes and other individuals (e.g., erotic images; Chikazoe, Lee, Kriegeskorte, & Anderson, 2014; Sescousse, Redoute, & Dreher, 2010; Watson & Platt, 2012; Wright et al., 2008). Furthermore, the lateral OFC contains face-responsive neurons (Rolls, 2004), and is sensitive to changes in facial expression that signal reward (e.g., smile) or punishment (e.g., angry expression; Kringelbach & Rolls, 2003). Thus, the lateral OFC signals the value of stimuli across a variety of sensory modalities. Furthermore, monkey lateral OFC neurons encode the reward magnitude of visual stimuli with a median latency of 60 ms following cue presentation (Bouret & Richmond, 2010), consistent with a role in the rapid valuation of external sensory objects.

A wealth of neuroimaging studies in humans and neurophysiological recordings in rodents and monkeys have further demonstrated that the lateral OFC is involved in learning associations between arbitrary visual cues and rewarding or aversive outcomes (e.g., learning the relationship between a restaurant sign and the quality of the food inside; Azzi, Sirigu, & Duhamel, 2012; Bouret & Richmond, 2010; Gottfried et al., 2003; Kennerley, Dahmubed, Lara, & Wallis, 2009; Morrison & Salzman, 2009; Noonan, Mars, & Rushworth, 2011; Padoa-Schioppa & Assad, 2006; Raghuraman & Padoa-Schioppa, 2014; Roesch & Olson, 2004; Schoenbaum, Chiba, & Gallagher, 1998; Schoenbaum & Esber, 2010; Sharpe & Schoenbaum, 2016; Tremblay & Schultz, 1999; Wallis & Miller, 2003). One study recorded the activity of lateral OFC neurons while monkeys were presented with visual cues that predicted the subsequent occurrence of a large juice reward, a small juice reward, or an aversive air-puff to the face (Figure 2B; Morrison & Salzman, 2009). The results showed that some lateral OFC neurons exhibited a large increase in activity when presented with the cue that predicted the large reward, a smaller increase when presented with the cue that predicted the small reward, and the least activity when presented with the cue that predicted the aversive air-puff (Morrison & Salzman, 2009). Notably, a separate population of lateral OFC neurons exhibited the opposite pattern, displaying the largest increase in activity when presented with the cue that predicted the air-puff (Morrison & Salzman, 2009). These studies have shown that lateral OFC activity correlates with the magnitude, probability, and temporal delay of expected outcomes based on sensory cues. Moreover, different lateral OFC neurons will respond to different cues even if they signal the same value, suggesting that this region learns specific associations between the identity of sensory objects and their value (Sharpe & Schoenbaum, 2016). Lesion studies corroborate this idea (Walton et al., 2010).

Critically, the lateral OFC contributes to the evaluation of sensory stimuli based on current needs and goals. In one study, during a first scanning session, hungry participants learned associations between visual images and food-based odor rewards (Gottfried et al., 2003). This was followed by a selective satiation period during which participants were fed on a meal related to one of the odors from the scanning session until it was no longer pleasant. A second scanning session was then used to identify regions that tracked the diminished value of the odor based on the change in goal-relevance as a result of the meal. The results demonstrated that the visual cue associated with the devalued odor relative to a cue associated with a different (rewarding) odor elicited reduced activation in the lateral OFC (Gottfried et al., 2003). Numerous studies have found results consistent with this finding (Critchley & Rolls, 1996; Kringelbach et al., 2003; O'Doherty et al., 2000). Additionally, lateral OFC lesions disrupt the ability to evaluate the relevance of stimuli based on current physiological needs; control but not lateral OFC-lesioned animals exhibit a preference for nondevalued over devalued rewards (Izquierdo, Suda, & Murray, 2004; Murray & Rudebeck, 2013; Pickens et al., 2003; Rudebeck & Murray, 2011b). Other work has shown that the lateral OFC is also sensitive to social goals (Azzi et al., 2012; Campbell-Meiklejohn et al., 2012; Nitschke et al., 2004; Singer et al., 2004; Watson & Platt, 2012). These findings suggest that the lateral OFC flexibly assesses the current relevance of sensory input by combining expectations about reward/punishment magnitude with real-time updates regarding physiological and social needs and goals (Wallis, 2007).

Together, these findings suggest that the lateral OFC may support a rich, multidimensional representation of external sensory events that can be used to contrast the desirability of different outcomes (Rudebeck & Murray, 2011a). This idea is consistent with convergence of sensory inputs in this region (Barbas, 2000; Rolls, 2004). The fact that neurons in this region convey information about both the specific sensory features of objects and their value distinguishes the contribution of the lateral OFC from other PFC value-coding regions that are insensitive to sensory information. While multiple regions including the amygdala may also contribute to evaluations of sensory stimuli (Cunningham, Van Bavel, & Johnsen, 2008; Sander et al., 2003), lesion work suggests two critical roles of the lateral OFC. First, the lateral OFC is necessary for credit assignment, that is, the ability to learn precise relationships between the identity (sensory features) of external stimuli and the value of the outcomes they predict (Walton et al., 2010). Second, the lateral OFC is necessary for *inferring* the value of sensory objects based on contextual information including task structure (Jones et al., 2012; Stalnaker et al., 2014). This information may be particularly useful for decision making. Consistent with this, neural activity in this region encodes the subjective value

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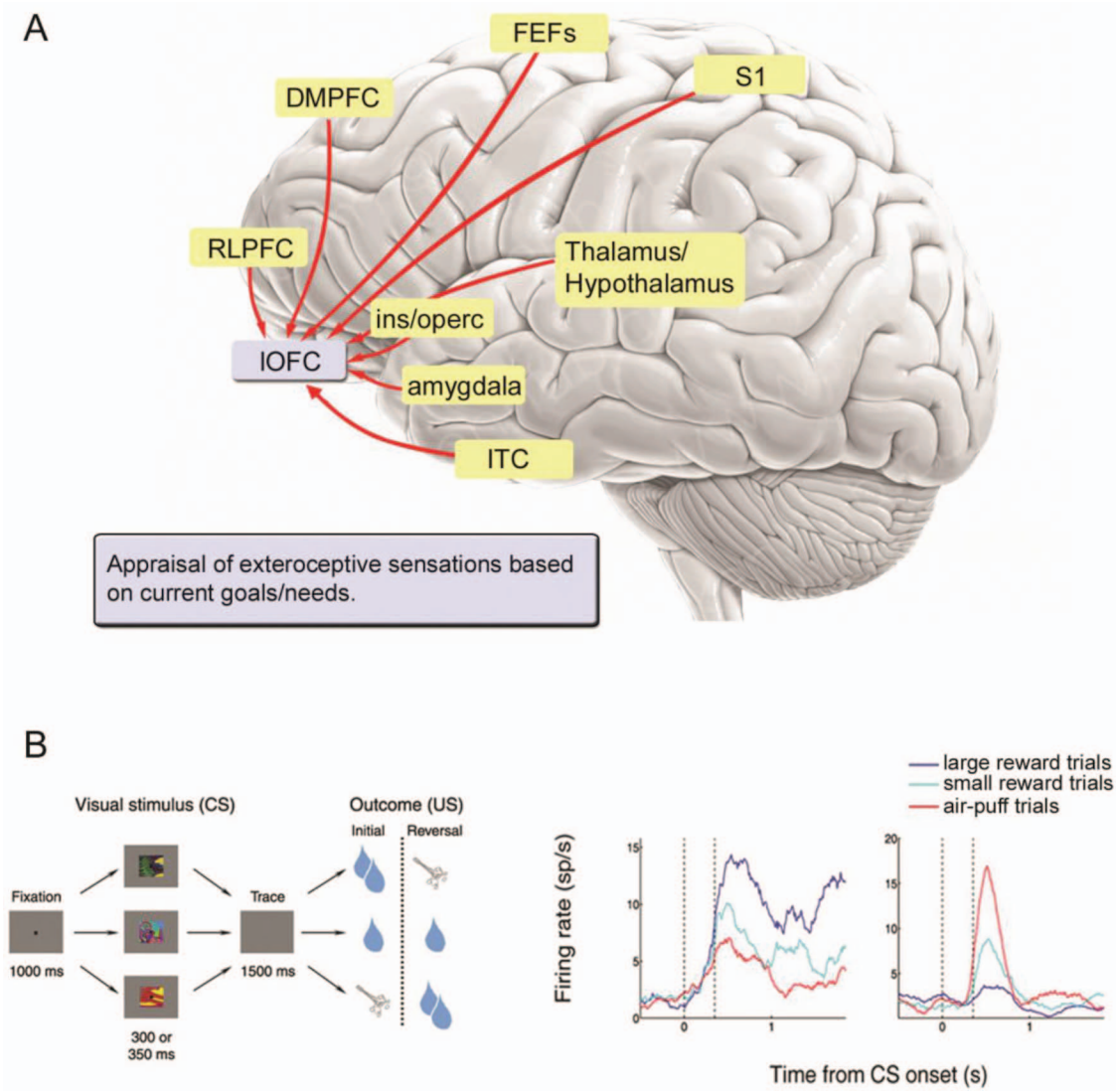

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Figure 2. Contributions of lateral OFC to emotion (A). Schematic overview of relevant anatomical inputs to lateral OFC, based on anatomical connectivity findings. Not shown: connections with pyriform (olfactory) cortex and auditory cortex. lOFC = lateral orbitofrontal cortex; RLPFC = rostrolateral prefrontal cortex; ins/operc = insula/frontal operculum; ITC = inferotemporal cortex; DMPFC = dorsomedial prefrontal cortex; S1 = primary somatosensory cortex; FEFs = frontal eye fields (B). Task design and results from Morrison and Salzman (2009). Monkeys viewed a visual cue that predicted the subsequent occurrence of one of three outcomes: large reward, small reward, or an aversive air puff. An example "appetitive" neuron shows the greatest increase in activity in response to the cue that predicts the large reward, and diminishing activity for the other two outcomes, whereas an example "aversive" neuron shows the reverse pattern. Thus, OFC neurons carry information about the value of the outcomes associated with the visual stimuli. See the online article for the color version of this figure.

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of choice options (Padoa-Schioppa & Assad, 2006), and dynamically alternates between states associated with the value of the two available options prior to choice, and predicts how quickly subjects will make a decision (Rich & Wallis, 2016).

The present conceptualization of lateral OFC as involved in the evaluation of external sensory stimuli based on current goals and needs provides a bridge to psychological models of emotion, and specifically, the notion of a goal-relevance appraisal. Consistent with this conceptualization, the lateral OFC receives direct anatomical input from all sensory modalities, and is particularly distinguished from neighboring cingulate and medial PFC regions in terms of being richly interconnected with regions involved in visual object processing and visual attention, including the inferotemporal cortex, perirhinal cortex, and frontal eye fields (Barbas, 2000; Cavada et al., 2000; Morecraft, Geula, & Mesulam, 1993; Petrides & Pandya, 2007; Rolls, 2004; Rushworth et al., 2011).

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The lateral OFC is also interconnected with the amygdala, hypothalamus, and periacqueductal gray—regions that may supply signals conveying rewards and punishment, as well as information about current physiological needs (Bandler, Keay, Floyd, & Price, 2000; Cavada et al., 2000; Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Petrides & Pandya, 2007; Rempel-Clower & Barbas, 1998). Additionally, connections with the medial and lateral PFC (Cavada et al., 2000; Petrides & Pandya, 2007) may provide the lateral OFC with information about social, task-related, and long-term goals (Dixon & Christoff, 2012, 2014; Gallagher & Frith, 2003; Saxe, 2006; Van Overwalle, 2009). Thus, the lateral OFC has access to a rich multidimensional representation of the current internal and external environment that can be used to assess the value of sensory objects.

The Medial Orbitofrontal Cortex: Appraisal of Episodic Memories and Imagined Future Events

The medial orbitofrontal cortex (OFC) has often been examined as part of a larger territory often referred to as the ventromedial prefrontal cortex. Damasio and Bechara and colleagues were among the first to provide an in-depth examination of behavioral consequences of damage to the ventromedial prefrontal cortex and observed severe decision making impairments on a gambling task that varied the risk of monetary gain and loss (Bechara & Damasio, 2005; Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, & Damasio, 2003; Bechara, Damasio, Tranel, & Damasio, 1997). Since then, electrophysiological and fMRI studies have searched for the key computations supported by this region using a variety of reward-based decision making tasks. One influential idea is that the ventromedial prefrontal cortex supports a "common currency" subjective value signal that allows for the comparison of options that differ on multiple dimensions (e.g., an apple vs. an orange; Levy & Glimcher, 2012). The idea here is that the various attributes of objects are mapped onto an abstract value space that serves as a single common scale for comparison (Levy & Glimcher, 2012). Plassmann et al. (2007) used a Becker-DeGroot-Marshak auction procedure to look for neural correlates of a subjective value signal. Participants were allotted $3, and then viewed images of 50 sweet and salty junk food items, and placed bids on each food item, from $0 to $3. At the end of the experiment, participants received and could eat the food item from a randomly selected trial, and also received the remaining money from their bid. This procedure encouraged participants to accurately report the amount of money they were willing to pay for each food item, and hence, revealed the subjective values assigned to each item. The results of this simple decision making task revealed that ventromedial prefrontal cortex activation correlated with trial-to-trial variation in subjective values (i.e., bid amounts; Plassmann, O'Doherty, & Rangel, 2007). Other studies have shown that overlapping parts of the ventromedial prefrontal cortex are responsive to the subjective value of diverse outcomes, including monetary rewards, social rewards, and food rewards (Kim et al., 2011; Levy & Glimcher, 2011; Lin, Adolphs, & Rangel, 2012; Smith et al., 2010). Furthermore, neural recordings from this region reveal a variety of response properties consistent with a role in decision making (Strait et al., 2014).

However, there are several problematic issues with the common currency value interpretation. First, as noted earlier, the ventromedial prefrontal cortex includes four architectonically distinct regions, and the location of subjective value signals within the ventromedial prefrontal cortex varies considerably across studies. Indeed, numerous distinct regions exhibit correlated activation with subjective value (Bartra et al., 2013; Clithero & Rangel, 2014), including the lateral OFC (Padoa-Schioppa, 2007; Rich & Wallis, 2016), medial OFC (Plassmann et al., 2007), pregenual anterior cingulate cortex (area 24/32; Chib et al., 2009; Litt, Plassmann, Shiv, & Rangel, 2011), subgenual anterior cingulate cortex (area 25; FitzGerald, Seymour, & Dolan, 2009), rostromedial PFC (area 10; Hunt et al., 2012; Smith et al., 2010), as well as regions outside of the PFC. This suggests that subjective value (or subjective value comparison) as a construct may be composed of numerous cognitive processes. Additionally, selective medial OFC lesions do not cause a global deficit in decision making as would be expected if a core common currency value computation was disrupted. Rather, medial OFC lesions only impair difficult decisions (Noonan et al., 2010). Furthermore, the lateral OFC exhibits stronger coding of the value of external objects than the medial OFC (Bouret & Richmond, 2010). Finally, the medial OFC is activated by stimuli that elicit negative relative to neutral affect (Chikazoe et al., 2014; de la Vega et al., 2016; Lindquist et al., 2016), which is inconsistent with the idea that greater medial OFC activation primarily signals positive subjective value.

Below, we review evidence pertaining specifically to area 14/11m, which we refer to as medial OFC, and arrive at a different functional interpretation of this region. Based on a synthesis of findings from outside of neuroeconomics, including literature on the default network, episodic memory and prospection, and anatomical connectivity we suggest that the medial OFC is involved in appraisal of internally generated events—episodic memories and imagined future events (Figure 3). This proposal is quite similar to F3
the prescient theoretical work of Damasio and Bechara (Bechara & Damasio, 2005; Bechara et al., 2003). In a recent study, Benoit et al. (2014) examined the neural correlates of assigning value to episodic future simulations. Participants first provided a list of familiar people and places and rated the familiarity and pleasantness of each. Then during scanning, participants were presented with pseudorandom person/place combinations (in written words), and were asked to simulate in their mind a *novel and vivid* interaction with the person in that specific location. Following scanning, participants rated the anticipated affective value of the simulated episode. The results demonstrated that medial OFC signal correlated with: (a) the familiarity of the simulated episodes, consistent with a role in using elements of episodic memory to construct a simulated future scenario; (b) the anticipated pleasantness of the episodes (i.e., the specific person/place combination), controlling for the effect of familiarity, and controlling for the pleasantness of the individual components; and (c) the anticipated pleasantness of person/place combinations that were completely novel, based on post scanning ratings (Benoit, Szpunar, & Schacter, 2014). Thus, medial OFC signal tracked the affective value of the overall person/place episodic simulation.

In another study, Bray, Shimojo, and O'Doherty (2010) found AQ: 6
overlapping activation in the medial OFC when subjects earned money in a reversal learning task and when they mentally visualized something that was personally rewarding in the absence of an external stimulus. Andrews-Hanna et al. (2010) observed that the medial OFC was more activated when participants reflected on

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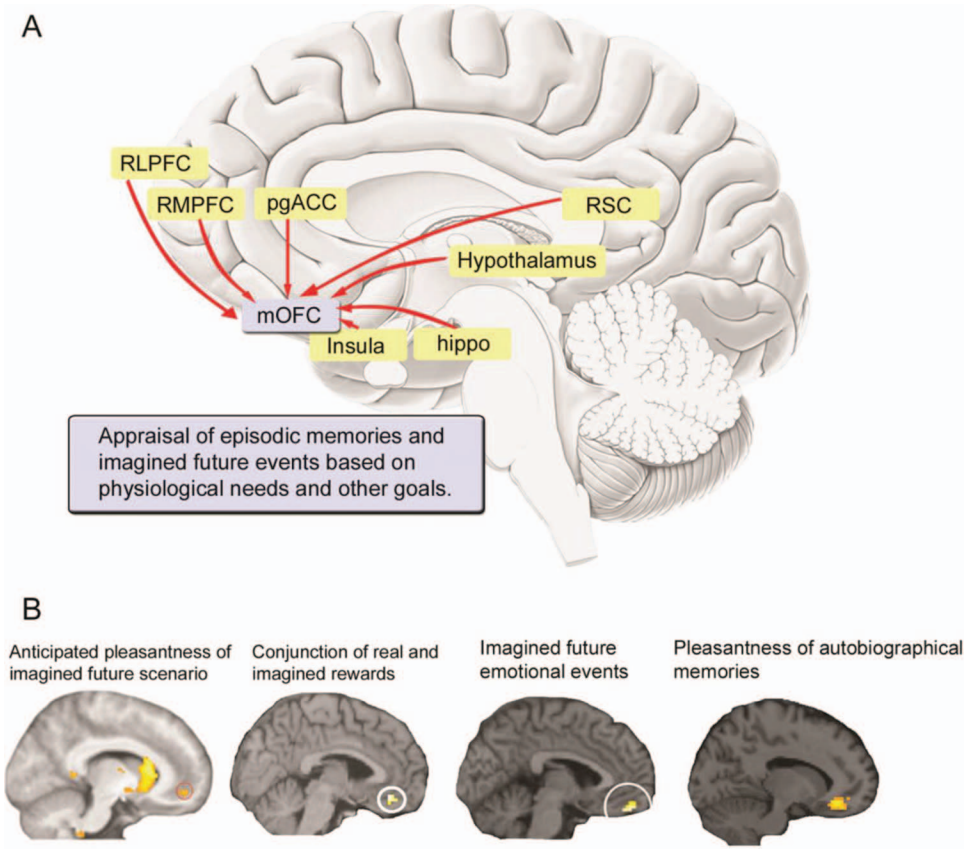

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Figure 3. Contributions of medial OFC to emotion (A). Schematic overview of relevant anatomical inputs to medial OFC, based on anatomical connectivity findings. mOFC = medial orbitofrontal cortex; RLPFC = rostrolateral prefrontal cortex; RMPFC = rostromedial prefrontal cortex; pgACC = pregenual anterior cingulate cortex; hippo = hippocampus; RSC = retrosplenial cortex (B). From left to right: activation in medial OFC exhibits a positive correlation with the anticipated pleasantness of future scenarios involving combinations of familiar people and places, from Benoit et al. (2014); conjunction effect showing overlapping medial OFC activation for real monetary rewards and imagined rewarding scenarios, from Bray et al. (2010); medial OFC activation is stronger when participants imagined positive and negative events in the future relative to routine events, and this contrast was more pronounced for events imagined in the far future relative to the near future, from D'Argembeau et al. (2008); medial OFC activation parametrically increases with the reported pleasantness of recalled autobiographical memories, from Lin et al. (2016). See the online article for the color version of this figure.

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personally relevant future events compared with personal concerns of the present moment. D'argembeau at al. (2008) found greater medial OFC activation when participants imagined positive and negative events in the future (e.g., related to friends and family) relative to imagined routine events (e.g., showering) that did not require future thinking. This effect was especially pronounced for imagined events in the far relative to near future (D'Argembeau et al., 2008). Lin et al. (2016) had participants recall and rate autobiographical memories, and found that medial OFC activation positively correlated with the reported pleasantness of the memories. Furthermore, studies of dreaming have consistently reported medial OFC recruitment (Domhoff & Fox, 2015; Fox et al., 2013), consistent with a role in evaluating the emotional significance of the internally constructed events that compose a dream (Domhoff & Fox, 2015). Supporting these findings, electrophysiological data indicate that medial OFC neurons are more responsive to rewards linked to internally generated information rather than external stimuli (Bouret & Richmond, 2010). Finally, lesions centered on the medial OFC disrupt schema-based memory processes (Warren, Jones, Duff, & Tranel, 2014).

Thus, when medial OFC activation is observed during the presentation of an external stimulus, it may reflect an appraisal of internal thoughts and memories triggered by the stimulus, rather than appraisal of the stimulus per se (Bechara & Damasio, 2005; Bechara et al., 2003; Phan et al., 2004). Several lines of evidence support this idea. First, the medial OFC has weak sensory-related connections, but robust anatomical connections with regions involved in episodic memory and simulating future events including the hippocampus, parahippocampus, and posterior cingulate/retrosplenial cortex (Aggleton, Wright, Rosene, & Saunders, 2015; Barbas, Ghashghaei, Dombrowski, & Rempel-Clower, 1999; Cavada et al., 2000). Notably, these memory-related connections are

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stronger for the medial OFC than the lateral OFC (Aggleton et al., 2015; Cavada et al., 2000). Second, the medial OFC exhibits strong functional connectivity with these memory-related regions (Andrews-Hanna, Reidler, Sepulcre, et al., 2010; Vincent et al., 2006), and individual differences in the frequency of past- and future-oriented thoughts correlate with the strength of functional coupling within this network (Andrews-Hanna et al., 2010). Third, the medial OFC is part of the core mnemonic network that is reliably engaged during tasks that require participants to construct past and future events in their mind (Addis et al., 2009; Andrews-Hanna, Reidler, Sepulcre, et al., 2010; Hassabis, Kumaran, & Maguire, 2007; Lin, Horner, & Burgess, 2016; Summerfield, Hassabis, & Maguire, 2010). Finally, the medial OFC is part of a collection of regions that are activated during internally oriented spontaneous thought and suppressed when attention is focused externally (Andrews-Hanna, Reidler, Huang, et al., 2010; Buckner, Andrews-Hanna, & Schacter, 2008; Christoff, Gordon, et al., 2009; Christoff et al., 2016; Raichle et al., 2001; Shulman et al., 1997; Stawarczyk, Majerus, Maquet, & D'Argembeau, 2011).

In the context of decision making, regions including the amygdala and lateral OFC may first encode information about the sensory features and subjective value of decision-related stimuli. The medial OFC may then add an additional layer of appraisal based on the simulated future outcomes of different choices. This idea is consistent with the neurophysiological response properties of neurons in medial OFC (Strait et al., 2014). While the medial OFC may encode the value of internally generated events whenever decision making is required, this information may only be *necessary* during difficult decisions when choice options are close in terms of their predicted value (Noonan et al., 2010), and a fine discrimination between simulated future outcomes is necessary. Such difficult decision making may rely on greater internal attention to different simulated outcomes and comparisons.

Numerous studies have shown that current physiological, task-related, and social goals modulate mOFC activation (Behrens, Hunt, Woolrich, & Rushworth, 2008; Bouret & Richmond, 2010; Hampton, Bossaerts, & O'Doherty, 2008; Hare, Camerer, & Rangel, 2009; Janowski, Camerer, & Rangel, 2013). Thus, mOFC may play a role in valuation of episodic memories and imagined future events based on current needs and goals. Indeed, in addition to strong anatomical connections with memory-related regions, the medial OFC also has significant connections with numerous limbic regions including the amygdala, insula, subgenual and pregenual anterior cingulate cortices, hypothalamus, and periacqueductal gray (Barbas et al., 1999; Carmichael & Price, 1996; Cavada et al., 2000; Croxson et al., 2005; Rempel-Clower & Barbas, 1998). These regions may supply information about reward and punishment, and interoceptive signals including physiological needs. Additionally, connections with the rostromedial PFC (Barbas et al., 1999; Carmichael & Price, 1996) may supply information about self-relevance and current personal concerns, while connections with the lateral PFC (Barbas et al., 1999; Petrides & Pandya, 1999, 2002, 2007) may supply information about task context and long-term goals.

The data reviewed here suggest that the medial OFC performs a parallel function to that of the lateral OFC: whereas the lateral OFC is preferentially involved in evaluating the goal-relevance of external sensory information, the medial OFC is preferentially involved in evaluating the goal-relevance of internally generated events. A recent model suggests that the lateral OFC is involved in value learning, whereas the medial OFC is involved in value comparison and decision making (Noonan et al., 2010). However, this model cannot easily account for medial OFC involvement in valuation of memories and future scenarios that do not include a decision making component. Our framework, which suggests that the lateral OFC and medial OFC differ primarily in their relative specialization with respect to the type of information being evaluated, provides a comprehensive account that explains the involvement of these regions across a variety of different tasks. It is difficult to know exactly what comprises the internal events that medial OFC evaluates. The network to which it belongs has been linked to scene construction (Andrews-Hanna, Reidler, Huang, et al., 2010; Hassabis et al., 2007) and the spontaneous generation of thoughts (Christoff et al., 2016; Ellamil et al., 2016). However, it is also possible that medial OFC plays a role in evaluating imagined actions (perhaps in combination with the anterior midcingulate cortex). Additionally, it is possible that the medial OFC also contributes to the process of elaborating memories in value-relevant ways. While there is still much to be learned about medial OFC function and differences with the lateral OFC, there is now compelling evidence to suggest a role for this PFC subregion in appraisal of internal mental simulations.

The Subgenual Anterior Cingulate Cortex: Appraisal of Viscero-Motor Signals

It has long been suggested that the subgenual anterior cingulate cortex (sgACC) is an autonomic control center (Vogt, 2005, 2009b). It operates alongside regions such as the hypothalamus and periacqueductal gray that trigger patterned physiological responses (e.g., coordinated changes in heart rate, blood pressure, hormone levels) to cope with emotionally significant events (Bandler et al., 2000; Saper, 2002; Tsigos & Chrousos, 2002). Barrett and Simmons (2015) suggest that the sgACC contributes to *predictions* about changes in physiological arousal that are required to cope with current or upcoming situations. These predictions exert a top-down influence on the hypothalamus and periacqueductal gray, triggering changes in physiological states in anticipation of the responses that are likely to be needed (Barrett & Simmons, 2015). We propose that these predictions reflect an appraisal of viscero-motor signals (Figure 4). By viscero-motor we mean *efferent* signals that modulate physiological states via the autonomic nervous system or neuroendocrine processes. F4

Consistent with a role in controlling autonomic arousal, electrical stimulation of the rat infralimbic cortex—the putative homologue of the primate sgACC based on cytoarchitecture and connectivity patterns (Vogt, 2009a)—causes changes in cardiovascular (heart rate, blood pressure), respiratory (frequency and drive to breathe), and metabolic (core temperature) processes (Burns & Wyss, 1985; Fisk & Wyss, 2000; Hassan, Cornish, & Goodchild, 2013). Furthermore, infralimbic cortex lesions in the rat impair the typical cardiovascular and respiratory changes that occur in response to impending threats (Frysztak & Neafsey, 1994; Vogt, Finch, & Olson, 1992). The sgACC may also regulate endocrine responses orchestrated by the hypothalamic-pituitary-adrenal (HPA) axis. For example, blood flow in the sgACC covaries with levels of cortisol (indicative of HPA activation) when monkeys are placed in a threatening context

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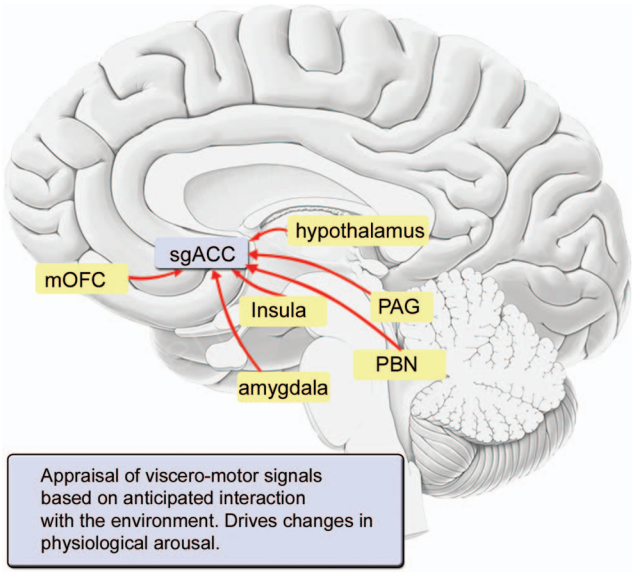

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Figure 4. Contributions of sgACC to emotion (A). Schematic overview of relevant anatomical inputs to sgACC = based on anatomical connectivity findings. sgACC = subgenual anterior cingulate cortex; mOFC = medial orbitofrontal cortex; PBN = parabrachial nucleus; PAG = periacqueductal gray. See the online article for the color version of this figure.

(Jahn et al., 2010). Consistent with this, rats with right infralimbic cortex lesions exhibit reduced stress-related corticosterone output (Sullivan & Gratton, 2002). These results are consistent with the idea that the sgACC may play a central role in modulating physiological arousal.

The sgACC may be particularly critical for sustaining autonomic arousal across time. One study presented monkeys with a cue that either signaled an impending reward (conditional stimulus (CS)+) or no reward (CS-) on each trial, followed by a delay, and then the delivery of the outcome (Rudebeck et al., 2014). Pupil size was monitored as an index of physiological arousal throughout the trial. Monkeys without brain lesions exhibited an increase in pupil size during the presentation of the CS+, and arousal remained elevated throughout the delay period until the reward was received (Rudebeck et al., 2014). In contrast, monkeys with sgACC lesions did not exhibit sustained changes in pupil size during the delay period. Interestingly, sgACC lesions did not interfere with the transient increase in pupil size elicited by the CS+ or by the reward itself; the lesion selectively interfered with the ability of the animals to sustain the change in pupil size (their proxy for physiological arousal; Rudebeck et al., 2014). Thus, sgACC appears to be critical in using predictive cues to generate and sustain physiological arousal in anticipation of emotionally significant events, consistent with the model proposed by Barrett and Simmons (2015).

We suggest that this predictive function of the sgACC can be conceptualized as a specific type of appraisal operating on viscero-motor signals. The sgACC integrates input about the meaning of the current situation from other regions such as the lateral OFC, medial OFC, and amygdala, and may assign value to different patterns of endocrine and autonomic signals based on their expected usefulness for the current situation. One possibility is that the sgACC appraisal process occurs in an implicit and automatic manner based on prior experience. A pattern of arousal for a given situation may be assigned a high value if, in similar situations in the past, that pattern was activated and was associated with a desirable outcome (i.e., the avoidance of an aversive outcome, or the acquisition of a rewarding outcome). That is, the sgACC may play a role in strengthening and weakening associations between specific physiological configurations of the body and situational cues based on experienced outcomes. In turn, the physiological state or configuration assigned the highest value would be encoded by the sgACC as a "prediction" that exerts a top-down influence on the hypothalamus and periacqueductal gray leading to the initiation of changes in the internal milieu. Stimulation studies with animals have provided insights into the nature of these patterned configurations of physiological arousal (Bandler et al., 2000). For example, stimulation of the caudal part of the lateral/dorsolateral periacqueductal gray results in fleeing behavior coupled with tachycardia and increased blood flow to skeletal muscles and diminished blood flow to the viscera, whereas stimulation of the ventrolateral periacqueductal gray results in hyporeactivity (recovery behaviors) coupled with bradycardia and opioid-mediated analgesia (Bandler et al., 2000). Future work that examines interactions between the sgACC and periacqueductal gray may shed further light on appraisals related to changes in physiological arousal.

Thus, convergent evidence suggests that the sgACC plays a critical role in appraisal of viscero-motor signals. Anatomical data supports this idea. The sgACC is the cortical region with the strongest connections to regions that monitor and control physiological arousal, including the dorsolateral periacqueductal gray, several hypothalamic nuclei, lateral parabrachial nucleus, and the bed nucleus of the stria terminalis (Bandler et al., 2000; Beckmann et al., 2009; Chiba, Kayahara, & Nakano, 2001; Fisk & Wyss, 2000; Freedman, Insel, & Smith, 2000; Johansen-Berg et al., 2008; Ongur, An, & Price, 1998; Ongur & Price, 2000; Petrides & Pandya, 2007; Vogt & Derbyshire, 2009). Furthermore, strong interconnections with the medial OFC, and amygdala (Aggleton et al., 2015; Barbas et al., 1999; Freedman et al., 2000; Johansen-Berg et al., 2008) may send information to the sgACC about the meaning of current or anticipated situations, which can be used to assign value to patterned physiological responses. Finally, connections with the hippocampus and parahippocampal gyrus (Aggleton et al., 2015; Barbas et al., 1999; Johansen-Berg et al., 2008) may allow for contextualization of the current situation in light of prior experience and contribute to the activation of context-appropriate arousal patterns.

The Pregenual Anterior Cingulate Cortex: Appraisal of Viscero-Sensory Signals

Neuroimaging and electrophysiological data suggest that the pregenual anterior cingulate cortex (pgACC) is a core part of the neural circuitry of valuation (Amemori & Graybiel, 2012; Bartra et al., 2013; Clithero & Rangel, 2014). The pgACC is often subsumed under the term "ventromedial prefrontal cortex", and not attributed a specific functional role, distinct from neighboring regions. However, Vogt and colleagues were among the first to provide an in-depth analysis of cingulate cortex subregions, and suggested that pgACC function is related to subjective emotional

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feelings, particularly happiness, and the aversiveness associated with pain (Vogt, 2005, 2009b; Vogt, Derbyshire, & Jones, 1996). Building upon this idea as well as more recent evidence, we suggest that the pgACC plays a role in assigning value to viscero-sensory signals based on self-referential and conceptual knowledge. By viscero-sensory we mean *afferent* signals reflecting the internal state of the body (also known as interoceptive sensations). Thus, the pgACC and sgACC play complementary roles: whereas the sgACC plays an effector role, contributing to an appraisal that initiates changes in physiological states, the pgACC plays an *input* role, contributing to an appraisal of the resulting interoceptive sensations (Figure 5). This appraisal role of the pgACC may contribute to, or elaborate upon, subjective feeling states of pleasure and displeasure.

The pgACC exhibits stronger activation when attention is directed internally rather than externally (Andrews-Hanna, Smallwood, & Spreng, 2014; Buckner et al., 2008; Dixon, Fox, & Christoff, 2014b; Ellamil et al., 2016; Raichle et al., 2001) and has weak sensory-related anatomical connections (Barbas, 2000; Chiba et al., 2001; Paus, 2001) suggesting that it is not involved in evaluating external stimuli. Rather, pgACC is robustly activated when individuals to attend internally to their subjective emotional feelings (Kulkarni et al., 2005; Lane, Fink, Chau, & Dolan, 1997; Lee & Siegle, 2012). Lane and colleagues (1997) had participants look at pleasant and unpleasant pictures and manipulated attentional focus. In one condition, participants were instructed to attend externally to the visual aspects of the pictures (i.e., whether they depicted indoor or outdoor scenes). In another condition, participants were instructed to attend internally to their subjective emotional feelings. Contrasting the attend to feelings condition with the attend to visual details condition yielded robust activation in the pgACC (BA 32) extending into the adjacent RMPFC (Lane et al., 1997). Additionally, pgACC activation is robustly driven by interoceptive signals related to visceral and somatic pain, and hypoglycemia (Kulkarni et al., 2005; Petrovic, Kalso, Petersson, & Ingvar, 2002; Teves, Videen, Cryer, & Powers, 2004; Vogt & Derbyshire, 2009), and is specifically associated with the subjective unpleasantness of these sensations. For example, one study found that the pgACC exhibited greater activation for painful versus innocuous thermal stimulation, and this pain-related activation was greater when participants attended to the *unpleasantness* relative to the location of the painful stimulation (Kulkarni et al., 2005). Furthermore, pgACC signal correlated with trial-by-trial variations in reported unpleasantness (Kulkarni et al., 2005). Consistent with this, opioid analgesia and subjective relief from pain unpleasantness has been linked to changes in pgACC activation, and its functional connectivity with the midbrain periacqueductal gray (Petrovic et al., 2002). Finally, rodents with pgACC lesions do not exhibit aversion to pain, but still have the capacity to detect the location and intensity of painful stimulation (Johansen, Fields, & Manning, 2001).

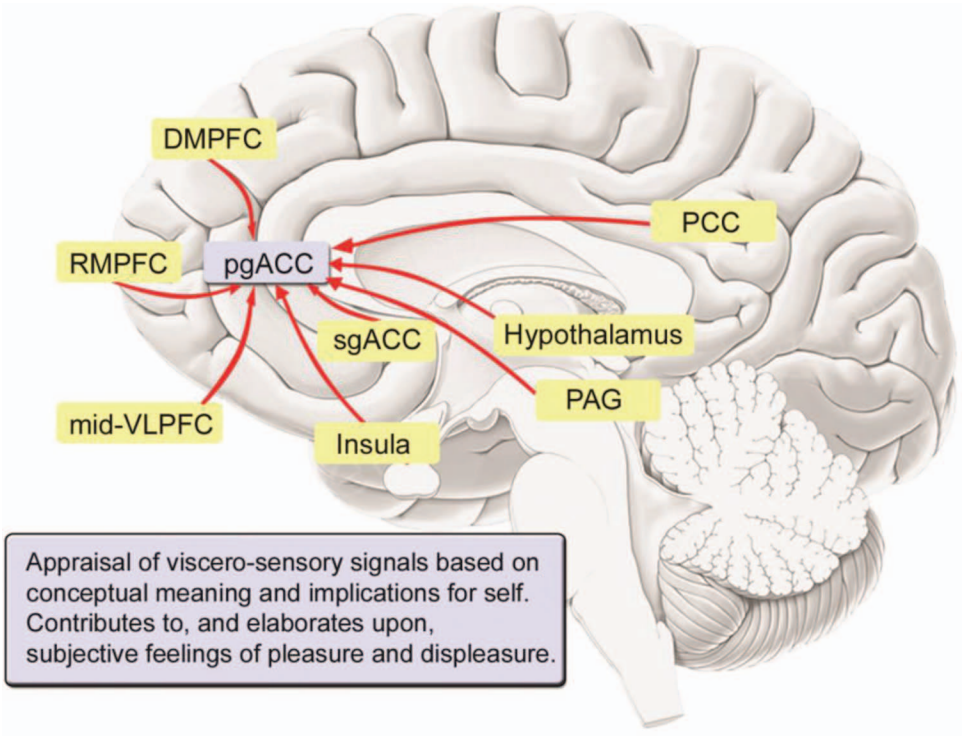

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Figure 5. Contributions of pgACC to emotion. Schematic overview of relevant anatomical inputs to pgACC, based on anatomical connectivity findings. pgACC = pregenual anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex; mid-VLPFC = midventrolateral prefrontal cortex; RMPFC = rostromedial prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; PAG = periacqueductal gray; PCC = posterior cingulate cortex. See the online article for the color version of this figure.

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Notably, pgACC activation is also observed in relation to pleasure and happiness (Grabenhorst et al., 2010; Lindgren et al., 2012; Vogt, 2005). Human patients with lesions of the pgACC (extending into sgACC and DMPFC) exhibit significant changes in the intensity and frequency of subjective feelings (Hornak et al., 2003). Beyond just an association with subjective feelings per se, several studies have now documented a relationship between pgACC structure and function and individual differences in the capacity to be aware of, describe, and understand emotional feelings (Ernst et al., 2014; Frewen, Lane, et al., 2008; Frewen, Lanius, et al., 2008; Lane et al., 2015; Paradiso et al., 2008). Alexithymia is associated with difficulty identifying and differentiating feelings, trouble communicating feelings, and a tendency of focusing attention externally rather than on internal states. Paradiso et al. (2008) found that individuals scoring higher on the Toronto Alexithymia Scale exhibited smaller pgACC volume, but exhibited no difference in subgenual anterior cingulate cortex or mid-cingulate cortex volume. Conversely, stronger pgACC activation for emotional relative to neutral imagery was found to negatively correlate with alexithymia (Frewen, Lanius, et al., 2008). Together these findings suggest that the pgACC plays a critical role in supporting the understanding of bodily sensations.

Considering these findings in light of pgACC's anatomical connectivity patterns helps to explicate the nature of its role in emotion. Like the subgenual anterior cingulate cortex, the pgACC has extensive connections with regions involved in processing physiological signals, including the hypothalamus, dorsolateral periacqueductal gray, insula, and parafascicular and paraventricular nuclei of the thalamus (Barbas et al., 1999; Chiba et al., 2001; Haber et al., 1995; Johansen-Berg et al., 2008; Morecraft et al., 2012; Petrides & Pandya, 2007; Vogt & Derbyshire, 2009). However, the pgACC is distinguished from the subgenual anterior cingulate cortex in terms of robust anatomical connections with regions of the default network including the rostromedial prefrontal cortex and posterior cingulate cortex, and with connections to lateral PFC, including the ventrolateral prefrontal cortex (VLPFC; Barbas et al., 1999; Carmichael & Price, 1996; Johansen-Berg et al., 2008; Pandya, Van Hoesen, & Mesulam, 1981; Petrides & Pandya, 1999, 2002, 2007). The default network contributes to a personal autobiographical narrative—the idea of "me"—consisting of self-referential thoughts, memories, and goals (Andrews-Hanna, Saxe, & Yarkoni, 2014; Andrews-Hanna, Smallwood, et al., 2014; Buckner et al., 2008; Raichle et al., 2001), while both the VLPFC and default network have been linked to the retrieval and use of conceptual knowledge (Badre et al., 2005; Binder, Desai, Graves, & Conant, 2009). The VLPFC in particular has been associated with attaching verbal labels to emotions (Lieberman et al., 2007).

Synthesizing this information, we propose that the pgACC contributes to an evaluation of viscero-sensory (interoceptive) signals based on self-referential and conceptual knowledge (including emotion knowledge). Categorizing and assigning value to interoceptive sensations through the filter of one's autobiographical narrative and conceptual knowledge may contribute to, or elaborate upon, subjective feelings of pleasure and displeasure (Berridge & Kringelbach, 2011). While a suite of cortical (e.g., insular cortex) and subcortical/brainstem regions (e.g., periacqueductal gray) are involved in processing interoceptive signals and are likely necessary for the experience of subjective feelings (Craig, 2002; Damasio & Carvalho, 2013; Farb, Segal, & Anderson, 2013), pgACC appraisal processes may play a role in attributing conceptual meaning to bodily sensations and facilitating the understanding of those sensations—a process compromised in alexithymia (Lane et al., 2015). Some psychological models have suggested the possibility of interactions between interoceptive signals and conceptual knowledge (Barrett et al., 2014). We view this as a type of appraisal whereby interoceptive sensations are assigned positive or negative value based on self-related and conceptual knowledge. While this idea can explain pgACC activation across a number of studies, more hypothesis-driven examinations of pgACC function are needed.

The Anterior Mid-Cingulate Cortex: Appraisal of Actions

Reinforcement learning models suggest that there is an appraisal mechanism that assigns value to actions based on the outcomes they are likely to produce, and the amount of effort they require (Rangel & Hare, 2010; Rushworth et al., 2007; Sutton & Barto, 1998). While several regions contribute to this type of appraisal, within the PFC, the anterior mid-cingulate cortex (aMCC) appears to be preferentially involved. An early influential model suggested that the aMCC (also referred to as the dorsal anterior cingulate cortex) supports a performance monitoring function and detects response conflict and errors in service of adjusting levels of cognitive control (Botvinick et al., 2001; Brown & Braver, 2005; Holroyd & Coles, 2002; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Ullsperger & von Cramon, 2001; Vogt, 2005). However, this model could not account for the robust activation of the aMCC during events that may not involve control demands, including pain, threats, and rewards (Behrens et al., 2008; de la Vega et al., 2016; Eisenberger et al., 2011; Etkin et al., 2011; Hayden & Platt, 2010; Hutchison et al., 1999; Lieberman & Eisenberger, 2015; Livneh & Paz, 2012; Milad et al., 2007; Mobbs et al., 2009; Mobbs et al., 2010; Phelps, Delgado, Nearing, & LeDoux, 2004; Rainville et al., 1997; Rushworth et al., 2007; Shackman et al., 2011; Vogt, 2005; Wager et al., 2013; Wager et al., 2004).

Accordingly, a more encompassing framework has emerged, and suggests that the aMCC is involved in using predicted outcomes—positive and negative—to evaluate actions and adaptively adjust behavior based on the current context (Figure 6; Alexander & Brown, 2011; Rushworth et al., 2007; Shackman et al., 2011; Shima & Tanji, 1998; Ullsperger et al., 2014; Vogt, 2009b). In a classic study, Shima and Tanji (1998) taught monkeys to make one of two actions—push or turn a handle—to obtain a juice reward. The monkeys learned that they should keep making the same action until the reward amount was reduced, at which point they should switch to the alternate action to obtain the maximum reward amount. In this task, reward was contingent on specific actions, rather than the selection of a specific visual object. Notably, a significant number of cells in the aMCC demonstrated increased activity following a reduction in reward, but only when the monkey then switched to the alternate action which would yield the maximum reward once again (Shima & Tanji, 1998). Moreover, following inactivation of the aMCC, monkeys were less likely to adaptively switch actions after the reward was reduced (Shima & Tanji, 1998). These findings suggest that the aMCC

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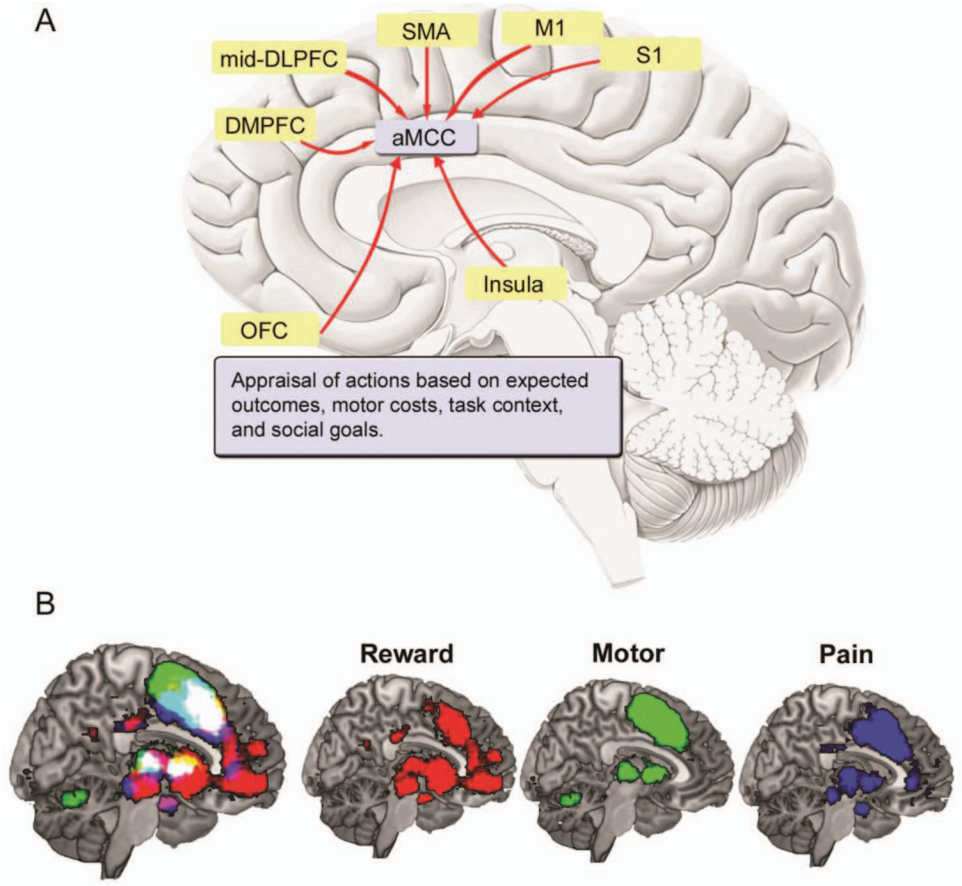

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Figure 6. Contributions of aMCC to emotion (A). Schematic overview of relevant anatomical inputs to aMCC, based on anatomical connectivity findings. aMCC = anterior midcingulate cortex; DMPFC = dorsomedial prefrontal cortex; mid-DLPFC = mid dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; SMA = supplementary motor cortex; M1, primary motor cortex, S1, primary somatosensory cortex (B). We performed three automated meta-analyses using NeuroSynth software (Yarkoni et al., 2011). The images reflect false discovery rate-corrected forward inference statistical maps (i.e., the probability of activation given the use of a particular term). Highlighted are regions of the brain that are likely to be activated in studies using the term "reward" (red), "pain" (blue), and "motor" (green). The aMCC contains a large area of white which reflects activations common to all three domains. This is consistent with a role in appraisal of actions based on positive and negative outcomes. See the online article for the color version of this figure.

contributes to an evaluation of actions based on anticipated outcomes. Numerous human and nonhuman primate studies have corroborated these results (Camille, Tsuchida, & Fellows, 2011; Hadland, Rushworth, Gaffan, & Passingham, 2003; Hayden & Platt, 2010; Kennerley et al., 2006; Noonan et al., 2011; Shima & Tanji, 1998; Williams et al., 2004). Indeed, affective information is registered in effector-specific motor zones in the aMCC (e.g., juice rewards specifically activate the aMCC region specialized for facial movements), providing compelling evidence that this region links affective information to somatomotor maps that contribute to the selection of actions (Procyk et al., 2016). The dissociation between object and action appraisal is important because the acquisition of a desired object may require different actions depending on context.

While aMCC activation is observed across a number of tasks, in each case it may reflect the valuation of actions and online adjustment of behavior to meet current demands (Alexander & Brown, 2011; Shackman et al., 2011; Ullsperger et al., 2014). Indeed, action values must be frequently updated in cognitive control tasks based on trial-to-trial changes in the relevance of different actions as specified by the task rules. Similarly, pain and threats (e.g., an approaching snake) are invariably associated with the valuation of action tendencies and the preparation of defensive action plans (Shackman et al., 2011; Vogt, 2009c). Several findings underscore the idea that the aMCC's role is fundamentally tied to action selection: (a) the aMCC demonstrates robust activation during the anticipation and execution of voluntary actions (Amiez & Petrides, 2014; Dixon, Fox, & Christoff, 2014a; Picard & Strick, 1996); (b) aMCC stimulation can elicit feelings of action planning and movement (Devinsky, Morrell, & Vogt, 1995; Talairach et al., 1973); (c) the aMCC contains an area within the cingulate sulcus with *somatotopic organization* (i.e., distinct occulomotor, facial, forelimb, and hind limb regions) which would be useful for evaluating specific action plans (Amiez & Petrides, 2014; Picard & Strick,

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1996, 2001; Wang, Matsuzaka, Shima, & Tanji, 2004; Wang, Shima, Sawamura, & Tanji, 2001); and (d) aMCC lesions disrupt the capacity to efficiently select actions (Gaymard et al., 1998; Stuss et al., 2005; Turken & Swick, 1999).

Notably, the aMCC is sensitive to the number and difficulty of actions that must be performed to obtain a desired outcome (Croxson et al., 2009; Kennerley et al., 2009; Kurniawan, Guitart-Masip, Dayan, & Dolan, 2013; Shidara & Richmond, 2002). Furthermore, rats with aMCC lesions become less willing to work for a large reward (Schweimer & Hauber, 2006; Walton, Bannerman, Alterescu, & Rushworth, 2003). This has led to the suggestion that the aMCC is sensitive to the *effort costs* of motor output (Rushworth et al., 2007). Additionally, recent work suggests that aMCC activation tracks foraging behavior, which is predicated upon integrating the possible value of outcomes that could be obtained by searching elsewhere in the environment with the energetic cost of doing so (Kolling, Behrens, Mars, & Rushworth, 2012). Thus, whether an action is good or bad for me is based upon a trade-off between the expected reward outcome and the expected effort costs. The fact that aMCC activation is modulated by this trade-off is key evidence that it plays a role in action appraisal.

The idea that the aMCC is preferentially involved in action appraisal provides a unifying account that can explain its involvement in many different tasks. The aMCC has robust anatomical connections with the motor system, including the premotor cortex, supplementary motor area, primary motor cortex, and the spinal cord (Beckmann et al., 2009; Dum & Strick, 1991; Morecraft et al., 2012; Pandya et al., 1981; Picard & Strick, 2001). Anatomical connections with the basolateral amygdala and OFC (Aggleton et al., 2015; Morecraft & Van Hoesen, 1998; Pandya et al., 1981; Petrides & Pandya, 2007; Shackman et al., 2011) may inform the aMCC about the value of sensory objects. Additionally, projections from the midline and intralaminar thalamic nuclei supply aMCC with nociceptive cutaneous, muscular, and visceral inputs that may lead to appraisal of defensive action plans (Vogt, 2005; Vogt, Rosene, & Pandya, 1979). The aMCC has a particularly strong connection to the anterior insula (Morecraft et al., 2012; Seeley et al., 2007; Yeo et al., 2011), which may allow for the coordination of skeletomotor and viscero-somatic changes during goal-directed actions. Finally, interconnections with the lateral and medial PFC (Morecraft et al., 2012; Pandya et al., 1981; Petrides & Pandya, 1999, 2007) may facilitate the dynamic appraisal of action tendencies based on changing social and task contexts.

The Dorsomedial Prefrontal Cortex: Appraisal of Other's Mental States and Traits

The ability to infer and evaluate others' internal thoughts and desires helps individuals to determine if others are likely to interfere with, or facilitate their goals, and this has considerable impact on emotional responses. Indeed, a core appraisal dimension in psychological models of emotion is the evaluation of others' intentions with respect to implications for one's well-being (Brosch & Sander, 2013; Ellsworth & Scherer, 2003; Lazarus & Smith, 1988; Scherer, 2001). Based on evidence from the social neuroscience literature on mentalizing as well as recent social reinforcement learning tasks, we suggest that the dorsomedial prefrontal cortex (DMPFC) shows a relative functional specialization that is well aligned with this appraisal dimension.

A wealth of functional neuroimaging evidence suggests that the DMPFC is robustly recruited during tasks that require mental state inference (i.e., "mentalizing"; Andrews-Hanna, Saxe, et al., 2014; Fletcher et al., 1995; Gallagher & Frith, 2003; Gallagher et al., 2000; Mar, 2011; Saxe, 2006; Van Overwalle & Baetens, 2009; Wagner, Haxby, & Heatherton, 2012). In these tasks, participants are often asked to read stories or view cartoons and interpret the actions of the characters with respect to their internal goals, beliefs, and feelings. For example, participants may be asked to predict the action that a story character will make, and can only do so correctly, if they infer that the character has a belief that conflicts with reality (e.g., inferring that Sally will search for her basketball where she left it in her room, even though in reality, her mom moved the basketball to the closet). The DMPFC is reliably activated when contrasting false belief conditions with well-matched control conditions that do not require mental state inference (e.g., a question pertaining to the physical actions themselves; Andrews-Hanna, Saxe, et al., 2014; Fletcher et al., 1995; Gallagher & Frith, 2003; Gallagher et al., 2000; Mar, 2011; Van Overwalle & Baetens, 2009; Wagner et al., 2012). Consistent with a role in discerning the intentions behind actions, the DMPFC shows greater activation when participants think about *why* an action (e.g., brush teeth) is performed (to clean teeth) as compared with *how* the action is performed (using a toothbrush; Spunt, Falk, & Lieberman, 2010).

In addition to a role in processing other people's transient mental states, the DMPFC is also involved in representing more enduring personality traits. The DMPFC is recruited when participants reflect on personality characteristics (e.g., assertive, energetic, liberal, etc.), particularly as they apply to other people (D'Argembeau et al., 2005; D'Argembeau et al., 2010; Denny et al., 2012; Mitchell, Heatherton, & Macrae, 2002; Mitchell, Macrae, & Banaji, 2006; Murray et al., 2012; Wagner et al., 2012). Moreover, multivoxel activation patterns within the DMPFC reliably distinguish representations of different personality types (Hassabis et al., 2014). Thus, DMPFC may be part of a network that represents social person knowledge.

In the context of emotion, we suggest that the DMPFC is preferentially involved in appraisal of others' intentions with respect to their implications for one's well-being (Figure 7). This F7
type of appraisal may come into play during competitive interactions with others (e.g., for limited resources), when an individual needs to infer others' mental states to predict the best course of action. O'Doherty and colleagues examined this type of scenario with the Inspection game (Hampton et al., 2008). A participant within the fMRI scanner interacted with a participant outside of the scanner, and alternated between playing the role of the employer or employee. On each trial, the employer chose whether to inspect or not inspect, while the employee chose whether to work or shirk. The employer gained a large sum of money if the employee worked and they chose not inspect, whereas the employee earned the most money when they chose to work and the employer inspected, and when they chose to shirk and the employer did not inspect. To earn the most money across trials, each player needs to generate a continuously updated model of how their actions are influencing the mental state and strategy of the opponent, so that they can predict and exploit the opponent's future actions. The results demonstrated that participant's choices were best fit by a model that incorporated such mental state inferences. Furthermore,

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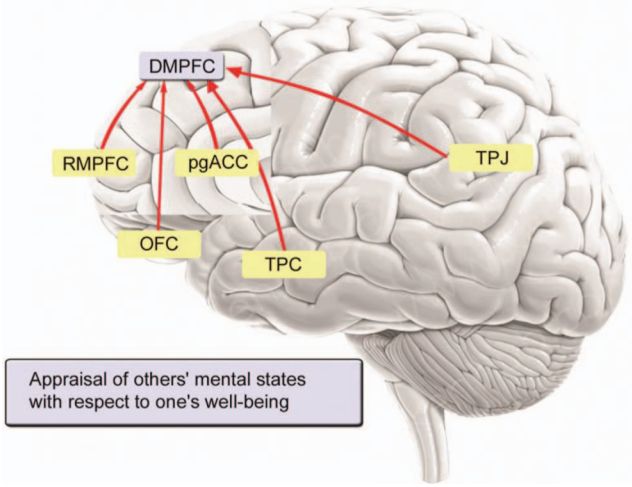

Figure 7. Contributions of DMPFC to emotion. Schematic overview of relevant anatomical inputs to DMPFC, based on anatomical connectivity findings. DMPFC = dorsomedial prefrontal cortex; RMPFC = rostromedial prefrontal cortex; pgACC = pregenual anterior cingulate cortex; OFC = orbitofrontal cortex; TPC = temporopolar cortex; TPJ = temporoparietal junction. See the online article for the color version of this figure.

DMPFC activation correlated with expected reward outcomes based on inferences about the intentions of the opponent, particularly in participants that were more likely to exhibit mental state strategizing (Hampton et al., 2008). In line with this, single neuron recordings from the monkey DMPFC have revealed signals related to the strategy of opponents during a competitive reward task (Seo, Cai, Donahue, & Lee, 2014). These findings suggests that the DMPFC is involved in evaluating others' mental states in relation to outcomes that affect one's well-being.

In another study, Behrens and colleagues (2008) had participants select between two choice options on each trial, and money could be earned based on their choices. Participants could learn about which option to choose based on two sources of information: (a) the probability of reward associated with each choice gleaned from prior experience; and (b) "advice" from a confederate that was provided on each trial prior to the choice period. On each trial, participants viewed the two choice options (visual cues) and monetary amounts associated with them, and then were provided with confederate advice about which option to choose, and then had to select a response, which was followed by feedback about which option was correct (rewarded). Across trials, the probability of reward and the truthfulness of confederate advice were varied. Accordingly, participants needed to track the confederate's trustworthiness to maximize their earnings. The results showed that DMPFC activation reflected trial-by-trial expectations about the confederate's trustworthiness before the outcome of the choice was revealed, and then reflected a prediction error signal at the time of the outcome if the confederate was more or less trustworthy than expected (Behrens et al., 2008). Trustworthiness is often thought of as a trait, but it was designed to vary across time in this task, rendering it closer to a mental state. Either way, these findings support the idea that the DMPFC plays a role in representing value information in relation to mental states and person knowledge.

While the OFC and other regions are involved in evaluating people in terms of their observable physical characteristics, the aforementioned findings indicate that the DMPFC is preferentially involved in evaluating people's unobservable mental states and traits with respect to their likelihood of facilitating or hindering one's goals. Supporting this idea, the DMPFC has weak anatomical connections with sensory cortices and memory regions (e.g., hippocampus; Barbas et al., 1999; Ray & Zald, 2012), but is well connected to, and frequently coactivated with, regions involved in perspective taking, evaluating agency, and storing social conceptual knowledge—the temporoparietal junction and temporopolar cortex (Andrews-Hanna, Saxe, et al., 2014; Barbas et al., 1999; Kestemont et al., 2015; Mar, 2011; Petrides & Pandya, 2007; Santiesteban, Banissy, Catmur, & Bird, 2012; Van Overwalle, 2009; Van Overwalle & Baetens, 2009; Zahn et al., 2007). Together, these regions are often referred to as the "mentalizing network." Interactions between these regions may allow individuals to focus on the perspective of others, and use social knowledge to infer their mental states, including motives for acting in particular ways. Notably, DMPFC tends to be more activated when individuals reflect on others as compared with themselves (Denny et al., 2012; Murray et al., 2012; van der Meer et al., 2010; Van Overwalle, 2009; Wagner et al., 2012), suggesting preferential involvement in evaluating others' mental states rather than a primary role in self-evaluation. Additional interconnections with the lateral orbitofrontal cortex, rostromedial prefrontal cortex, and pregenual anterior cingulate cortex (Barbas et al., 1999; Ongur & Price, 2000; Petrides & Pandya, 2007) may provide access to value information that can be combined with inferences about others' mental states.

The Rostromedial Prefrontal Cortex: Appraisal of Self-Related Information

The rostromedial prefrontal cortex (RMPFC) is consistently recruited in studies of emotion (Lindquist et al., 2016) and value-based decision making (Bartra et al., 2013; Clithero & Rangel, 2014; Smith et al., 2010), however the specific role of this region has remained elusive. This region has generally been incorporated within "ventromedial prefrontal cortex," and not given a unique functional interpretation. By integrating findings from the largely segregated literatures on emotion and self-referential processing, we propose a distinct role for the RMPFC. In the context of emotion, our review suggests that the RMPFC shows a relative functional specialization for appraisal of self-related information (e.g., assigning positive or negative value to self-image; Figure 8A). F8

Outside of the emotion literature, the RMPFC has a well-established role during tasks requiring reflection on the self and self-related attributes. When participants judge whether personality traits describe themselves, RMPFC activation positively correlates with the extent to which the traits are rated as self-descriptive and emotionally valued (D'Argembeau et al., 2005; D'Argembeau et al., 2012; D'Argembeau et al., 2010; Denny et al., 2012; Korn et al., 2012; Moran et al., 2006; Murray et al., 2012; Ochsner et al., 2005; Schmitz & Johnson, 2007; van der Meer et al., 2010; Wagner et al., 2012). Furthermore, the RMPFC is activated when participants recall episodic memories and imagine future events—particularly future goals that are closely tied to personal values

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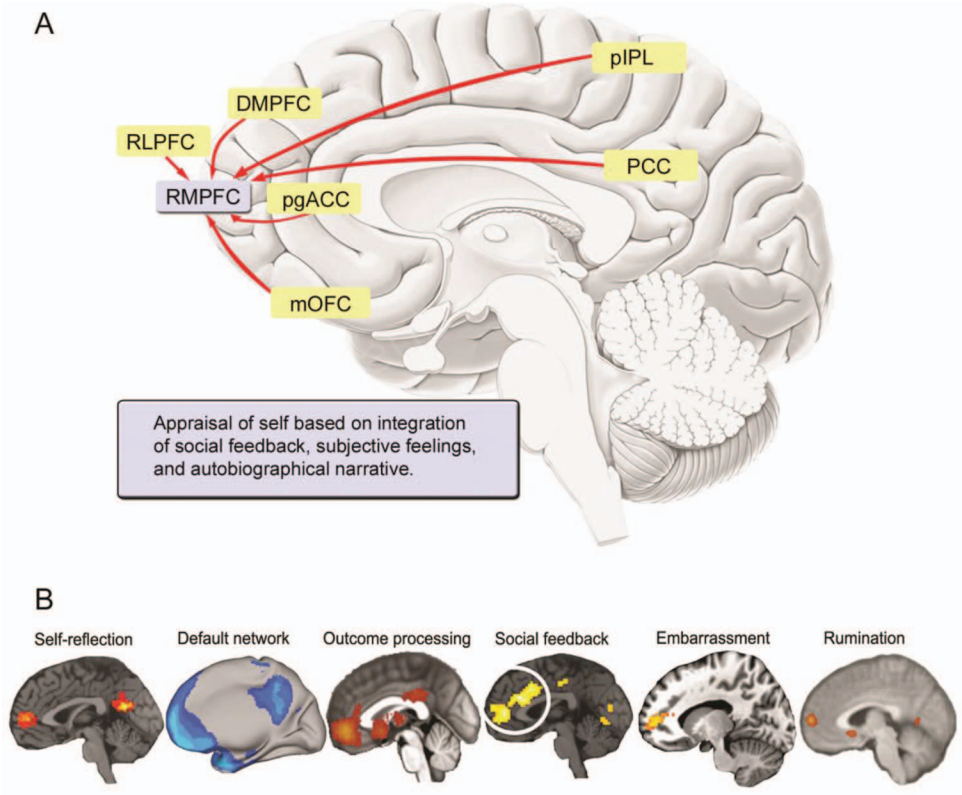

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Figure 8. Contributions of RMPFC to emotion (A). Schematic overview of relevant anatomical inputs to RMPFC, based on anatomical connectivity findings. RMPFC = rostromedial prefrontal cortex; mOFC = medial orbitofrontal cortex; RLPFC = rostrolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; pgACC = pregenual anterior cingulate cortex; pIPL = posterior inferior parietal lobule; PCC = posterior cingulate cortex. (B). The RMPFC is activated in studies of self-referential processing and value processing. From left to right: Meta-analytic activation map from van der Meer et al. (2010) demonstrating RMPFC involvement in self-reflection; RMPFC is a key hub of the default network (from Buckner et al., 2008); meta-analytic activation map from Bartra et al. (2013) showing RMPFC recruitment during the receipt of reward outcomes; RMPFC activation when participants received positive social feedback about themselves from Korn et al. (2012); RMPFC activation parallels age-related changes in self-reported embarrassment from Somerville et al. (2013); RMPFC activation correlates with subjective reports of negative affect when participants remember distressing memories and engaged in ruminative thinking, from Kross et al. (2009). See the online article for the color version of this figure.

(e.g., becoming a doctor; Addis, Wong, & Schacter, 2007; D'Argembeau et al., 2005; D'Argembeau et al., 2010; D'Argembeau et al., 2008; Hassabis et al., 2007; Schacter, Addis, & Buckner, 2007; Spreng et al., 2010). Additionally, the RMPFC is a core hub of the default network, and is activated during mind wandering and the resting state, both of which often involve self-referential processing (Andrews-Hanna, Reidler, Sepulcre, et al., 2010; Buckner et al., 2008; Christoff, Gordon, et al., 2009; Fox et al., 2015). While the RMPFC and medial orbitofrontal cortex show similarities in their activation profiles, the functions of these regions can be distinguished: meta-analyses have shown that the RMPFC but not the medial orbitofrontal cortex is consistently recruited in tasks involving explicit self-reflection (Murray et al., 2012; van der Meer et al., 2010). This suggests that the distinguishing role of the RMPFC in emotion is related to the integration of self-referential and value information.

Self-evaluation based on social norms is a key appraisal dimension in the theoretical emotion literature (Ellsworth & Scherer, 2003; Jarymowicz & Imbir, 2014; Scherer, 2001; Tracy & Robins, 2004). Individuals often evaluate themselves as good or bad based on the alignment or discrepancy between their attributes and behaviors and social norms. Self-evaluations may be triggered by stored knowledge about social values, or by direct feedback from others, and often lead to emotions such as pride and embarrassment that may encourage socially valued behaviors and discourage socially inappropriate behavior (Scherer, 2001; Tracy & Robins, 2004). Mounting evidence suggests that RMPFC may contribute to this type of appraisal (Figure 8B). Early studies found RMPFC activation when participants reflected on how they thought others perceived them (Amodio & Frith, 2006; Ochsner et al., 2005). More recent work has shown that RMPFC activation is modulated by the receipt of valenced feedback from others about one's personality, and this is particularly the case when it is positive relative to negative feedback (Izuma, Saito, & Sadato, 2008; Korn et al., 2012; Somerville, Kelley, & Heatherton, 2010). In one study (Korn et al., 2012) participants interacted with others during a

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game of monopoly and then rated each other on a list of personality traits (e.g., honest, friendly, stubborn, etc.). On a subsequent day, participants were scanned while they rated themselves on the traits, and while being informed about how the other participants rated them on the previous day. Following scanning, participants rated themselves on the traits once again. The results showed that participants exhibited a positivity bias: they often adjusted their self ratings upward based on positive social feedback, but were unlikely to adjust their self ratings based on negative feedback (Korn et al., 2012). Interestingly, RMPFC activation positively correlated with individual differences in the behavioral positive update-bias (Korn et al., 2012). That is, RMPFC was more activated in those participants that were more likely to selectively change ratings of themselves based on positive social feedback. Other work has shown that individuals with low self-esteem exhibit an exaggerated difference in RMPFC activation for positive relative to negative social feedback, consistent with the heightened salience of information related to acceptance and rejection for these individuals (Somerville et al., 2010). Because humans are thought to share an intrinsic goal of achieving belonging and social connection (Baumeister & Leary, 1995), social feedback has a powerful influence on emotions.

Although the RMPFC may often contribute to the filtering of social feedback to promote positive evaluations of self-image, it is also a key neural substrate underlying negative evaluations of self-image. One study had participants believe that they were being watched through a camera by a peer, and found that embarrassment increased from childhood to adolescence and then leveled off into adulthood. Embarrassment level was accompanied by a parallel age-related change in brain activation in the RMPFC (Somerville et al., 2013). This finding suggests that maturation of neural circuits involving the RMPFC may be associated with adolescents' growing self-awareness and tendency to evaluate themselves based on social feedback. Another study found RMPFC activation when participants read sentences about themselves engaging in actions that were likely to elicit embarrassment or guilt relative to actions that were affectively neutral (Takahashi et al., 2004). Patients with lesions that include the RMPFC exhibit increased socially inappropriate behavior and reduced embarrassment (Beer, John, Scabini, & Knight, 2006). These patients have intact knowledge of social norms, but fail to appropriately evaluate themselves in relation to such norms (Beer et al., 2006). This provides causal evidence that RMPFC contributes to self-evaluations. Finally, studies of rumination and maladaptive self-referential processing have consistently implicated the RMPFC (Farb, Anderson, Bloch, & Segal, 2011; Kross, Davidson, Weber, & Ochsner, 2009; Kucyi et al., 2014; Ray et al., 2005; Sheline et al., 2009). For example, the strength of functional connectivity between the RMPFC and the posterior cingulate cortex, medial thalamus, and periacqueductal gray is positively correlated with pain rumination in patients with chronic pain (Kucyi et al., 2014).

The findings reviewed above suggest that, in the context of emotion, the RMPFC is preferentially involved in evaluating self-related information, particularly on the basis of social feedback. Thus, the RMPFC contributes to an abstract appraisal that has been well described by psychological models of emotion: self-evaluations based on social norms (Ellsworth & Scherer, 2003; Jarymowicz & Imbir, 2014; Scherer, 2001; Tracy & Robins, 2004). While it is clearly the case that the RMPFC plays a general role in processing self-related content, in the context of emotion, it may specifically contribute to assigning value to one's self-image based on social feedback and norms. Anatomically, the RMPFC has significant connections with regions involved in autobiographical memory, including the posterior cingulate cortex, regions involved in multimodal semantic integration including the posterior inferior parietal lobule, and regions involved in mentalizing, including the dorsomedial prefrontal cortex, temporopolar cortex, and temporoparietal junction (Barbas et al., 1999; Burman, Reser, Yu, & Rosa, 2011; Mars et al., 2012; Petrides & Pandya, 2007). Interactions with these regions may allow relevant life details and mental states to be retrieved and reflected upon. Additionally, interactions between the RMPFC and mentalizing network may be important for interpreting social feedback. Finally, connections with the medial and lateral orbitofrontal cortex, pregenual anterior cingulate cortex, and anterior insula (Barbas et al., 1999; Burman et al., 2011; Cavada et al., 2000; Ongur & Price, 2000; Petrides & Pandya, 2007), may provide the RMPFC with access to value-related information and feeling states that can then be combined with self-referential information to generate evaluations of self-image.

The Lateral Prefrontal Cortex: Appraisal of Emotional States and Regulatory Strategies

The lateral PFC has a well-established role in contributing to cognitive control via flexible representation of task rules, abstract concepts, social context, and long-term goals (Bunge et al., 2003; Christoff & Keramatian, 2007; Duncan, 2010; McClure, Laibson, Loewenstein, & Cohen, 2004; Miller & Cohen, 2001; Rainer, Asaad, & Miller, 1998; Ruff, Ugazio, & Fehr, 2013; Stokes et al., 2013). In the context of emotion, the lateral PFC has received considerable attention in relation to emotion regulation—the use of a goal to alter the trajectory of an emotional response (Buhle et al., 2014; Ochsner & Gross, 2005; Ochsner, Silvers, & Buhle, 2012; Wager et al., 2008). In a classic study (Ochsner, Bunge, Gross, & Gabrieli, 2002), participants viewed neutral and negative pictures during fMRI scanning, and were instructed to adopt one of two strategies on each trial: (a) *attend* to the feelings elicited by the pictures without altering them in any way; or (b) *reappraise* the meaning of negative pictures so that they no longer elicited a negative response. Prior to scanning participants received instruction and practice in using the reappraisal strategy (e.g., reinterpreting a picture of a crying woman outside of a church as attending a wedding rather than a funeral). Reappraisal relative to attend trials were associated with diminished self-reported negative affect, and were accompanied by robust recruitment of lateral PFC, and a negative correlation between lateral PFC activation and amygdala and medial OFC activation (Ochsner et al., 2002). The authors concluded that the lateral PFC is part of the neural circuitry involved in implementing emotion regulation strategies and modulating processing in emotion generative regions (Ochsner et al., 2002).

Gross and colleagues have recently proposed that emotion regulation can be conceptualized in terms of multiple valuation mechanisms (Etkin, Buchel, & Gross, 2015; Gross, 2015; Ochsner & Gross, 2014). Emotion regulation is initiated by a *second-order valuation system* that assigns value to the emotional feelings that were generated by a first-order valuation system (Etkin et al.,

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2015; Gross, 2015; Ochsner & Gross, 2014). In this model, emotion generation results from an initial perception-valuation-action (PVA) cycle, and emotion regulation results from a second PVA cycle that takes the initial emotion as the target of perception that is itself evaluated. When there is a discrepancy between desired and actual emotions, specific emotion regulation strategies (e.g., reappraisal; attentional deployment; response modulation) are then evaluated to determine which to implement. Based on recent evidence suggesting that the lateral PFC plays a role in valuation processes we suggest that it may contribute to these high-level appraisal mechanisms that assign value to ongoing emotional states and to emotion regulatory strategies (Figure 9). F9

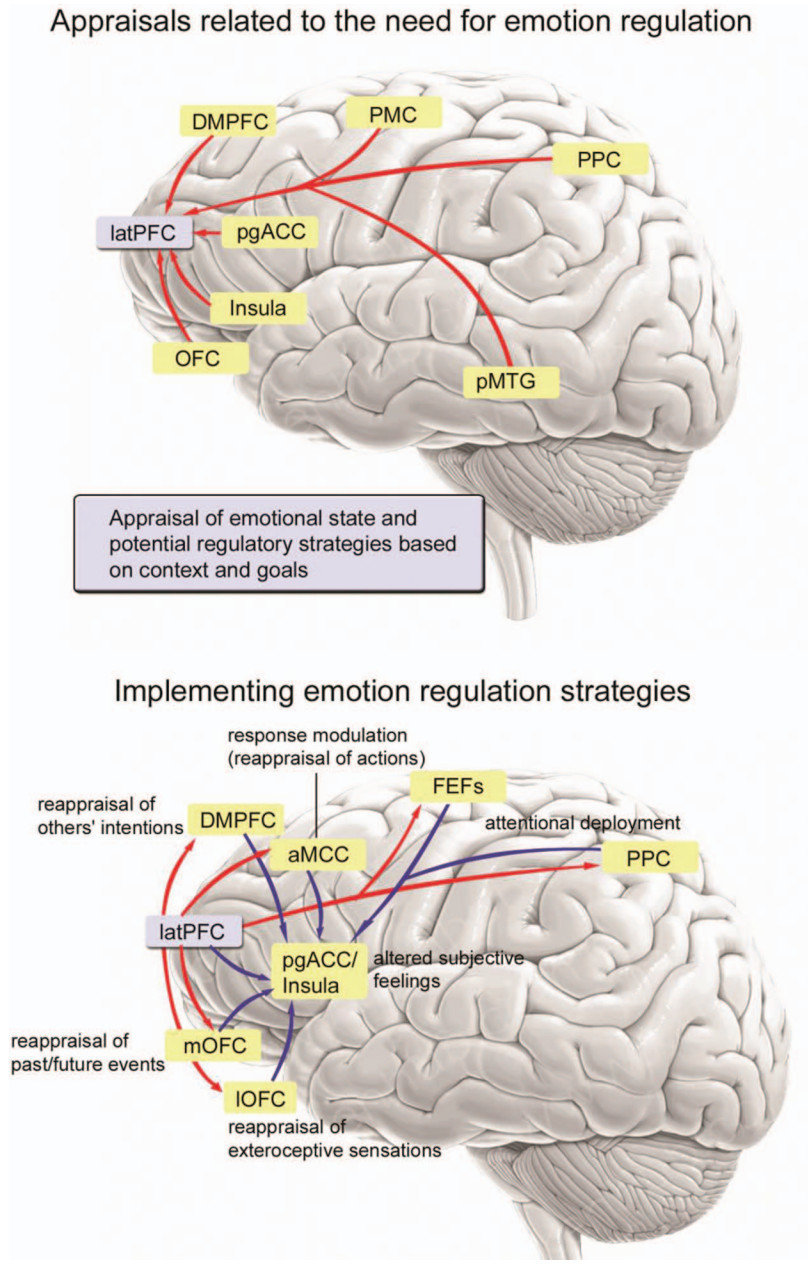

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Figure 9. Contributions of medial OFC to emotion. Schematic overview of relevant anatomical inputs to lateral PFC, based on anatomical connectivity findings. Top: appraisal of emotions and emotion regulatory strategies by integrating information about feelings, context, and task demands. Bottom: implementation of emotion regulation strategies to alter emotional state. Different types of emotion regulation may occur via distinct interactions between the lateral PFC and other PFC subregions. latPFC = lateral prefrontal cortex; lOFC = lateral orbitofrontal cortex; mOFC = medial orbitofrontal cortex; pgACC = pregenual anterior cingulate cortex; DMPFC = dorsomedial prefrontal cortex; FEFs = frontal eye fields; PPC = posterior parietal cortex; pMTG = posterior middle temporal gyrus; PMC = premotor cortex. See the online article for the color version of this figure.

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In contrast to the traditional view that the lateral PFC is strictly a "cognitive" region, there is now compelling evidence that lateral PFC plays a role in valuation (Dixon, 2015; Dixon & Christoff, 2014; Lee & Seo, 2007; Pessoa, 2008; Watanabe & Sakagami, 2007). For example, numerous electrophysiological studies have shown that lateral PFC neurons represent information about rewards and aversive outcomes (Asaad & Eskandar, 2011; Barraclough, Conroy, & Lee, 2004; Hikosaka & Watanabe, 2000; Kim, Hwang, & Lee, 2008; Kobayashi et al., 2006; Lee & Seo, 2007; Pan et al., 2008; Wallis & Miller, 2003; Watanabe, Hikosaka, Sakagami, & Shirakawa, 2002). Furthermore, the lateral PFC is involved in reward learning (Kahnt, Heinzle, Park, & Haynes, 2011) especially based on instructed knowledge about the reward probabilities associated with different stimuli (Li, Delgado, & Phelps, 2011). Neuroeconomic studies have frequently observed lateral PFC recruitment during value-based decision making, particularly during the selection of future over immediate rewards (Diekhof & Gruber, 2010; Essex, Clinton, Wonderley, & Zald, 2012; Figner et al., 2010; Hare et al., 2009; Jimura, Chushak, & Braver, 2013; McClure et al., 2004), during exploratory choices (Badre, Doll, Long, & Frank, 2012; Boorman et al., 2009; Daw et al., 2006), and during choices guided by an internal model of the current task context (Buckholtz, 2015; Glascher, Daw, Dayan, & O'Doherty, 2010; Smittenaar et al., 2013). Lesion studies and the use of transcranial magnetic stimulation to disrupt lateral PFC function have demonstrated a causal role in these valuation-related processes (Camus et al., 2009; Essex et al., 2012; Figner et al., 2010; Simmons, Minamimoto, Murray, & Richmond, 2010; Smittenaar et al., 2013).

Based on evidence that the lateral PFC is involved in processing information about value, context, and task rules, we suggest that lateral PFC activation in studies of emotion regulation may, at least in part, reflect an explicit appraisal of an ongoing emotional state based on context, goals, or task demands. The most rostral zone of the lateral PFC (i.e., BA 10) has been linked to internally oriented cognitive processes (Burgess, Dumontheil, & Gilbert, 2007; Christoff & Gabrieli, 2000) including metacognitive awareness—the ability to reflect on and accurately report one's mental contents (Baird, Smallwood, Gorgolewski, & Margulies, 2013; De Martino, Fleming, Garrett, & Dolan, 2013; Fleming et al., 2010; McCaig et al., 2011; McCurdy et al., 2013), and plays a reflective or monitoring function that integrates and evaluates the outputs of prior stages of cognitive processing (Christoff & Gabrieli, 2000; Fletcher & Henson, 2001; Petrides, 2005; Ramnani & Owen, 2004). This region may thus be involved in attending to, and evaluating, the emotional responses initially generated by other cortical and subcortical appraisals. Studies showing lateral PFC involvement when individuals regulate the temptation of immediate rewards in favor of acquiring more beneficial future outcomes can also be understood in terms of an appraisal mechanism. In one study, Hare and colleagues (2009) recruited individuals on a diet, and had them rate 50 images of food items for health and taste. Subsequently, they indicated their relative preference for each item compared with a reference item that was rated as neutral on health and taste. Based on these responses, participants were placed into one of two groups: (a) self-controllers (who made decisions based on health and taste); and (b) nonself-controllers (who made decisions primarily based on taste). The fMRI results revealed that medial OFC activation correlated with food value regardless of self-control, whereas lateral PFC activation was stronger on trials involving successful self-control (i.e., when a healthy but disliked item was chosen or when an unhealthy but liked item was not chosen), and this effect was stronger in the self-controllers. Additionally, lateral PFC activation was inversely correlated with medial OFC activation on trials in which an unhealthy but liked item was not chosen (Hare et al., 2009). Thus, lateral PFC may have contributed to a negative evaluation of the emotional response elicited by the taste of food items, thereby modulating medial OFC activation, and allowing health (which has future benefits) to have a greater impact on decision making.

In some cases, the mismatch between desired and actual emotional experience may engage explicit regulatory strategies such as reappraisal of an event's meaning, or controlling the focus of attention. Prior to initiation, these potential strategies need to be evaluated to determine which to implement (Gross, 2015). For example, higher value may be assigned to reappraisal over attentional control if task demands specified that reappraisal should be used, or if an individual has had more success with reappraisal in the past. The lateral PFC may contribute to this process. Recent work suggests that this region encodes associations between task rules and the value of expected outcomes (Bahlmann, Aarts, & D'Esposito, 2015; Dixon & Christoff, 2012) and allows value information to modulate cognitive processes (Etzel et al., 2016; Jimura, Locke, & Braver, 2010). Thus, the lateral PFC may contribute to both the valuation of emotional states, and the valuation of regulatory strategies (Dixon, 2015). It is important to note that we are not suggesting that lateral PFC is the only region involved in emotion regulation; rather, the suggestion is that it may be a key component of the neural circuitry involved in the type of appraisals that initiate forms of controlled emotion regulation.

Through its widespread connectivity, the lateral PFC has access to information about current goals, context, rules, and expected outcomes that would be important for the high-level appraisals related to emotion regulation. This region receives highly processed information about context, actions, and rules from the premotor cortex, posterior middle temporal gyrus, and posterior parietal cortex (Petrides & Pandya, 1999, 2002, 2007). Though it is often underappreciated, lateral PFC is also robustly interconnected with the orbitofrontal cortex, pregenual anterior cingulate cortex, and anterior insula (Barbas et al., 1999; Carmichael & Price, 1996; Johansen-Berg et al., 2008; Morecraft & Tanji, 2009; Pandya et al., 1981; Petrides & Pandya, 1999, 2002, 2007). Inputs from the pregenual anterior cingulate cortex and insula may inform lateral PFC about ongoing emotional feelings (Craig, 2002; Critchley et al., 2004; Farb et al., 2013; Kulkarni et al., 2005; Lane et al., 2015), while inputs from the OFC may supply information about the affective value of objects and events. Finally, interconnections with the dorsomedial and rostromedial prefrontal cortices may provide access to information about social context and self-referential processing (Barbas et al., 1999; Ongur & Price, 2000; Petrides & Pandya, 1999, 2007). By representing feelings states in relation to current goals and context, lateral PFC may contribute to the evaluation of current feelings and potential emotion regulation strategies.

Application of the Appraisal-by-Content Model

In the previous sections, we reviewed a large body of findings consistent with the idea that the PFC as a whole is involved in

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appraisal, with different subregions being preferentially involved in appraising different types of content. In this section, we demonstrate the utility of this appraisal-by-content model for generating new perspectives on key topics.

Implications for Emotion Regulation

Emotion regulation is the process by which implicit and explicit goals alter the trajectory of an emotional response, and is a fundamental aspect of adaptive human behavior (Gross, 1998). It is widely recognized that the PFC plays a central role in emotion regulation (Beauregard, Levesque, & Bourgouin, 2001; Etkin et al., 2015; Johnstone et al., 2007; McRae et al., 2012; Ochsner et al., 2002; Ochsner & Gross, 2005; Ochsner & Gross, 2014; Quirk & Beer, 2006; Wager et al., 2008). The present framework offers several novel perspectives on the role of the PFC in emotion regulation. We suggest that: (a) the PFC's regulatory role can be understood in terms of appraisals that are highly sensitive to the current context; (b) PFC appraisals contribute to both emotion generation and emotion regulation; (c) different forms of emotion regulation rely on specific combinations of PFC appraisals; and (d) PFC appraisals can sometimes contributes to emotional dysregulation. These ideas are addressed in turn.

PFC appraisals and emotion regulation. While it is well-established that the PFC is a critical neural substrate of emotion regulation, the specific ways in which its contributes to regulation have yet to be fully elucidated. Viewing the PFC's contribution through the lens of an appraisal-based framework provides novel insights into this issue (see also Etkin et al., 2015; Gross, 2015; Ochsner & Gross, 2014). Specifically, we suggest that the PFC contributes to regulating emotional responses by representing the value of events in a highly contextualized manner. We have reviewed evidence suggesting that PFC appraisals incorporate complex and abstract information about social context, task rules, self-image, and long-term goals (Cunningham & Zelazo, 2007; Daw, Niv, & Dayan, 2005; Dixon & Christoff, 2014; McDannald et al., 2012; Ochsner & Gross, 2014). These appraisals interact with, and modulate (that is, regulate), subcortical appraisals that may be more simple in nature, often reflecting prior learning about simple stimulus-outcome associations (Cunningham & Zelazo, 2007; Kaouane et al., 2012; Ochsner & Gross, 2014; Sharpe & Schoenbaum, 2016).

Emotion regulation can be assessed in a variety of ways. One example is fear extinction paradigms that involve an initial period of fear conditioning (that is, learning that a particular stimulus is predictive of an aversive outcome), followed by a period of fear extinction during which the stimulus is no longer paired with the aversive outcome. Fear-related responses often diminish during the latter period and this is attributable to new learning outcompeting old learning for expression in behavior. While subcortical regions including the amygdala are critical for initial learning of stimulus-outcome associations, several PFC subregions are critical for the expression of fear extinction (LaBar et al., 1998; Milad & Quirk, 2002; Milad, Rauch, Pitman, & Quirk, 2006; Phelps et al., 2004; Rauch, Shin, & Phelps, 2006; Reekie, Braesicke, Man, & Roberts, 2008). One interpretation is that PFC allows the extinction period to be understood as a *new spatiotemporal context* that is distinct from the previous spatiotemporal context, and appraises the meaning of the stimulus on the basis of this information. Whereas amygdala neurons mainly carry information about stimulus-outcome associations independent of context (Kaouane et al., 2012; Sharpe & Schoenbaum, 2016), the PFC may allow contextual information that goes beyond the stimulus itself (e.g., distinguishing past vs. present circumstances) to influence the attribution of value. In this way, the PFC plays an important role in adaptive emotional responses during sudden changes in the environment (including changes in stimulus-reinforcement contingencies) when prior learning must be, at least temporarily, overridden.

Another popular paradigm for examining emotion regulation is reappraisal tasks. Participants are asked to modulate their emotions to pictures or other affective stimuli based on a set of task demands (e.g., instructions for reinterpreting the meaning of the stimuli). Relative to just experiencing emotions, reappraisal often elicits recruitment of several PFC subregions accompanied by changes in subcortical activation (e.g., diminished amygdala activation when down-regulating negative affect; Buhle et al., 2014; Ochsner & Gross, 2005; Ochsner et al., 2012; Wager et al., 2008). The role of the PFC can be understood in terms of appraisals that incorporate abstract contextual information (in this case, *task demands* held in working memory). For example, if the task instructions were to downregulate negative affect, then the generation of fear by the stimuli may elicit a negative appraisal by the PFC that in turn triggers the engagement of a regulatory strategy. In this case, reappraisal would be assigned a high value by the PFC based on task instructions to use this strategy, and this would lead to implementation of this particular strategy. Thus, reappraisal may rely on a set of context-sensitive appraisals.

As a final example, emotions are often regulated based on the context imposed by one's self-image. For example, if one's self-image includes the desire to appear tough, evocation of sadness may be automatically assigned a negative value and suppressed. As reviewed earlier, a vast literature has suggested that PFC subregions including the RMPFC play central roles in representing self-related information and combining this information with valenced evaluations. In the example noted above, the RMPFC might play a role in negatively valuing the self when sadness is experienced, and this may naturally lead to a negative valuation (and regulation) of feelings of sadness to restore positive self-related feelings. To summarize, emotion regulation can be conceptualized in terms of PFC appraisals that are highly sensitive to contextual information—the current spatiotemporal context, task context, or the context created by one's self-image—and these appraisals may exert a modulatory influence on subcortical and brainstem emotion generative processes.

PFC subregions contribute to emotion generation and emotion regulation. While other frameworks predict that different PFC regions can be distinguished based on whether they are involved in emotion generation or emotion regulation, here we maintain that appraisal is the unifying principle of PFC contributions to emotion. As a corollary, we suggest that through appraisal, the same regions can contribute to both emotion generation and emotion regulation—with relative differences in content specialization along the lines that we have outlined. Etkin and colleagues (2011) suggested that the dorsal cingulate/medial prefrontal cortex is involved in emotion generation, whereas the ventral cingulate/medial prefrontal cortex is involved in emotion regulation, based on evidence that the former is engaged during fear conditioning tasks and associated with increased sympathetic arousal, whereas

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the latter is activated during fear extinction tasks and associated with diminished sympathetic arousal (Etkin et al., 2011). In contrast, we suggest that these regions participate in both processes. For example, the ventral cingulate/medial prefrontal cortex (e.g., medial OFC) may contribute to a wave of anxiety (emotion generation) when an individual mentally envisions an upcoming school exam, but then may also contribute to emotion regulation when the individual attempts to dampen the anxiety by recalling a memory of doing well on a prior exam. Similarly, the dorsal cingulate/medial prefrontal cortex (e.g., the aMCC) may indeed contribute to emotion generation (e.g., action tendencies such as freezing during the perception of a threat such as a large spider in one's bedroom). However, this region may also contribute to emotion regulation by updating action values based on goals (e.g., deciding to overcome one's fear and taking action to put the spider outside). As another example, the RMPFC may contribute to a negative self-evaluation and the generation of embarrassment when a friend makes a disparaging comment about one's dance moves, but a reassuring comment from another friend may restore one's pride and alleviate the embarrassment via updated self-evaluations. Finally, although the lateral PFC is most often linked to emotion regulation, it may also contribute to the generation of emotion. For example, its role in assigning value to complex and abstract information (e.g., task rules; Dixon & Christoff, 2012, 2014) may contribute to the generation of excitement in a physics student while they are attempting to solve a complex physics problem. Thus, while the distinction between emotion generation and regulation is important, it is unlikely to map cleanly onto different sets of brain regions, at least within the PFC.

Taxonomy of emotion regulation. Gross' (1998, 2015) process model of emotion regulation suggests that regulatory mechanisms can intervene and modulate an emotional response at any one of several points along the trajectory of an unfolding emotion, from stimulus input to response output. Several testable predictions regarding the neural correlates of emotion regulation can be gleaned by combining Gross' process model with the appraisal-by-content model of PFC function. In particular, our framework suggests that different regulatory strategies will depend on *specific combinations* of PFC appraisals. This can guide future research on the neurobiological basis of individual and group differences in emotional regulatory capacities. Below, we outline the neural predictions that our framework makes for each of the five forms of emotion regulation proposed by Gross:

Situation selection. This strategy involves using foresight to put oneself in situations that are expected to yield desirable emotions or to avoid situations that may yield undesirable emotions. An example would be deciding to avoid a party that is likely to involve drugs such as cocaine. Our framework predicts that this type of emotion regulation should draw upon the appraisal-related functions of the medial OFC. This region's role in constructing and evaluating the affective significance of imagined future events (Benoit et al., 2014; D'Argembeau et al., 2008; Gerlach, Spreng, Madore, & Schacter, 2014) may highlight the value of different possible situations. This region may work in concert with lateral PFC, which is recruited when individuals pursue beneficial future outcomes (Diekhof & Gruber, 2010; Essex et al., 2012; Figner et al., 2010; Hare et al., 2009; McClure et al., 2004), and choose to avoid situations that may interfere with the attainment of future rewards (Crockett et al., 2013).

Situation modification. This strategy involves taking direct action to change something about a situation to alter its emotional impact. For example, a parent may ask their teenage son to turn down the blaring music. We predict that this strategy would recruit the aMCC reflecting the updating of action values (Rushworth et al., 2007; Shima & Tanji, 1998; Williams et al., 2004), and the selection of new behaviors to modify the situation. Additionally, in some cases, there may be involvement of lateral PFC and medial OFC if individuals mentally simulate how things could be different, prior to taking action.

Attentional deployment. This strategy relies on the control of attention to change one's emotional response (Thiruchselvam et al., 2011). For example, actively attending away from dessert items on a restaurant menu when on a diet to attenuate the temptation. This type of regulation may rely on interactions between the lateral OFC and lateral PFC, given the well-established role of lateral PFC in directing attention based on current goals and task demands (Bishop et al., 2004; Buschman & Miller, 2007; Corbetta & Shulman, 2002; Hampshire, Thompson, Duncan, & Owen, 2009; Miller & Cohen, 2001). The lateral PFC may represent the goal of not succumbing to the temptation of dessert by negatively appraising the feeling of pleasure elicited by the thought of dessert. This may modulate lateral OFC appraisals such that the dessert section of the menu is assigned a lower value than it would in a nondieter. In turn this may guide the deployment of attention via lateral PFC and lateral OFC efferent projections to the frontal eye fields and inferotemporal cortex (Armony & Dolan, 2002; Morecraft et al., 1993; Rolls, 2004).

Cognitive change. The most commonly studied form of this strategy is reappraisal, which involves changing the meaning of a situation to alter its emotional impact (e.g., saying to oneself: "It's okay that I didn't get accepted into med school because being a doctor is not my true passion"). The lateral PFC has a well-established role in reappraisal, and may interact with several different PFC subregions depending on the specific target of reappraisal (Figure 9). Interactions with the lateral OFC are predicted to occur when changing the meaning of a specific sensory object. In other situations, reappraisal may target the intentions of another person, and this may rely on interactions between the lateral PFC and DMPFC. Finally, the lateral PFC may interact with the RMPFC when one's self-image is central to reappraisal, as in the example described above. We suggest that lateral PFC plays a role in choosing one of these reappraisal strategies via assigning value to each strategy based on their likelihood of producing a desired change in emotion in the current context. This role is predicated upon the integration of value, task demands, and context by the lateral PFC (Dixon, 2015; Dixon & Christoff, 2014).

Response modulation. This strategy involves the direct attempt to alter subjective feelings, behaviors, or physiological responses. To change feelings and physiological state, individuals often use coffee, alcohol, drugs, food, exercise, or meditation. A well-studied example of modulating behavior is expressive suppression, which involves the attempt to inhibit emotionally expressive behavior (e.g., trying not to display embarrassment). Our framework predicts that this strategy will involve different cingulate subregions depending on the target of modulation. Specifically, attempts to modulate subjective feelings should involve changes in pgACC recruitment. Both opioid and placebo induced changes in the subjective experience of pain are associated with

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changes in pgACC activation and the way it interacts with lateral PFC (Petrovic et al., 2010; Petrovic et al., 2002). In contrast, attempts to change physiological state should be accompanied by changes in sgACC activation, and its coupling with subcortical and brainstem regions (Vogt & Derbyshire, 2009). Finally, behavioral modulation should involve the aMCC, as the value assigned to particular actions are updated (Shima & Tanji, 1998; Williams et al., 2004). Given that individuals often inhibit or alter overt actions to gain positive or avoid negative reactions from others, behavioral modulation may often involve additional interactions involving DMPFC and RMPFC.

PFC function is not always adaptive. A prevalent assumption in the neuroscientific literature is that emotional well-being is predicated upon stoic PFC areas reigning in the nefarious activities of subcortical regions. PFC activation is frequently assumed to reflect an adaptive regulatory function based on reverse inference (assuming a particular mental state based on observed brain activation). Commensurately, affective disorders are widely thought to arise because of PFC dysfunction and a lack of regulatory control over subcortical regions. However, by considering PFC function in the context of appraisals, it is evident that the PFC may in some cases drive maladaptive processing in subcortical regions. For example, the data reviewed above suggested that the RMPFC contributes to self-evaluations, both positive and negative, and may play a role in rumination and the perpetuation of negative affect in some situations (Farb et al., 2011; Kross et al., 2009; Kucyi et al., 2014; Ray et al., 2005; Sheline et al., 2009). This could occur via RMPFC efferent signals to sadness-related or threat-related appraisals and physiological responses supported by subcortical and brainstem regions.

As another example, the capacity to evaluate episodic memories and future events can elicit negative emotion long after an event has passed or before an event occurs. Extreme cases include feelings of hopelessness and negative future expectations characteristic of depression and traumatic flashbacks characteristic of PTSD (APA, 2013; Beck, 1991; Miloyan, Pachana, & Suddendorf, 2014). Substantial evidence suggests that the medial OFC plays a role in evaluating internally generated events. Notably, medial OFC lesions are associated with a *lower* incidence of PTSD and depression (Koenigs, Huey, Calamia, et al., 2008; Koenigs, Huey, Raymont, et al., 2008), suggesting that its functional role may in some cases contribute to maladaptive emotional responses. This could potentially occur via interactions with the sgACC and top-down modulatory influences on the hypothalamus and periacqueductal gray that could trigger prolonged (and detrimental) changes in physiological arousal.

Finally, even the lateral PFC may sometimes contribute to maladaptive emotions. While it can be adaptive to pursue long-term goals over immediate gratification (e.g., studying instead of going to a party to do well in school; dieting instead of having dessert to change one's appearance), in some cases individuals may start to habitually deny immediate gratification and unintentionally sabotage their own well-being (most academics have at some point spent long days at the office working too hard to get ahead, and losing a healthy and balanced lifestyle that includes time for family, friends, hobbies, and relaxation). Given that the lateral PFC has been implicated in appraisals that allow long-term goals to outweigh immediate rewards (Diekhof & Gruber, 2010; Essex et al., 2012; Figner et al., 2010; Jimura et al., 2013; McClure et al., 2004), it may contribute to diminished well-being in such cases. To summarize, PFC regions have variable interactions with subcortical regions, and may have positive or negative influences on well-being.

The Neural Architecture of Value-Based Decision Making

Studies of the neural basis of decision making often present individuals with a choice between several options (e.g., different food items) and then look for activation that is correlated with the subjective value of the options. The "common currency" model suggests that the brain computes the subjective value of each option in an abstract (common currency) value space that allows for a comparison among the choice options, and then the motor system is informed of the winning option so that a response can be executed to procure the desired outcome (Levy & Glimcher, 2012; Padoa-Schioppa, 2011). According to this serial model, sensory signals are fed forward to become contextualized by cognitive and motivational signals by a variety of brain regions, and then passed to the ventromedial prefrontal cortex, where these different attributes are transformed into an abstract common currency value signal (Figure 10A; Levy & Glimcher, 2012; Padoa-Schioppa, 2011). After the ventromedial prefrontal cortex computes and contrasts the values of different choice options, this information is passed to the motor system where it is transformed into commands to drive action selection (in some variations of the model, value information for each option is sent to the aMCC for value comparison prior to motor selection; Levy & Glimcher, 2012; Rushworth, Kolling, Sallet, & Mars, 2012). This model has been influential and considered to be supported by empirical evidence. However, as noted earlier, there are also findings that are inconsistent with the model. Furthermore, others have suggested that a parallel processing model consisting of multiple distinct value mechanisms may better fit the empirical data, and may better capture decision making in naturalistic settings (Cisek, 2012; Cisek & Kalaska, 2010; Rushworth et al., 2012).

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A different account follows from our appraisal-by-content model (Figure 10B). We suggest that decisions emerge from the dynamic cooperative and competitive interactions between multiple *parallel* valuation mechanisms that appraise different types of content. When options are presented, distributed PFC and subcortical regions simultaneously engage in value-related assessments of the various attributes of each option under consideration, and interact through bidirectional feedback loops along the processing hierarchy from stimulus input to action output. When there is enough support for one option relative to the other(s), motor excitability crosses a critical threshold, action selection occurs and concludes the decision making process (Cisek, 2012). Thus, counter to the idea that the ventromedial prefrontal cortex is the site of a core valuation process, on this account, each region "casts a vote" for a particular option based on the specific inputs that it evaluates, and a winning option emerges from the combined influence of all votes. Thus, rather than serial information flow, this idea suggests large-scale reciprocal interactions. This is consistent with the fact that sensorimotor regions encode multiple potential action plans prior to a decision, suggesting that parallel valuation mechanisms may activate several candidate actions in sensorimotor cortex, thus allowing potential motor costs to be assessed in

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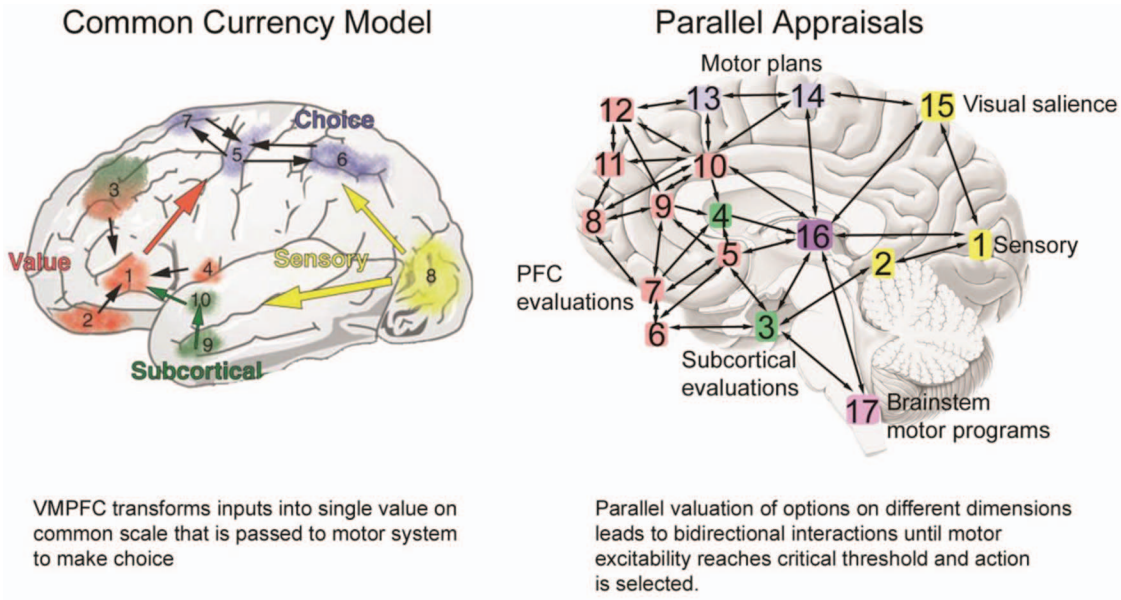

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Figure 10. Models of value-based decision making. (A) *Common currency model*. (1) ventromedial prefrontal cortex, (2) orbitofrontal cortex, (3) dorsolateral prefrontal cortex, (4) insula, (5) primary motor cortex, (6) posterior parietal cortex, (7) frontal eye fields, (8) visual cortex, (9) amygdala, (10) striatum. (B) Our framework leads to a different conception of decision making based on the idea of *parallel appraisals*. (1) sensory cortex (in this case visual cortex), (2) inferotemporal cortex (object recognition), (3) amygdala and other subcortical regions, (4) striatum, (5) subgenual anterior cingulate cortex, (6) lateral orbitofrontal cortex, (7) medial orbitofrontal cortex, (8) rostromedial prefrontal cortex, (9) pregenual anterior cingulate cortex, (10) anterior midcingulate cortex, (11) dorsomedial prefrontal cortex, (12) lateral prefrontal cortex, (13) presupplementary and supplementary motor areas, (14) primary motor cortex, (15) posterior parietal cortex (intraparietal sulcus), (16) thalamic nuclei, (17) midbrain and brain stem regions. It should be noted that all prefrontal cortex (PFC) subregions connect with the thalamus and striatum, and some PFC subregions connect directly to brainstem nuclei. See the online article for the color version of this figure.

parallel with the valuation of other factors (e.g., reward magnitude associated with each option; Cisek, 2012; Cisek & Kalaska, 2010).

To explicate this idea further, consider a simplified example in which you are making a decision between buying a flashy convertible sports car, or a more environmentally friendly hybrid. The lateral OFC may be involved in a rapid appraisal of the sensory qualities of the choice options (e.g., valuation based on the color and design of the cars). The medial OFC may add an additional layer of appraisal based on the simulated future consequences of selecting one option over the other (e.g., imagining wind flowing through one's hair in the convertible). The DMPFC may contribute to an evaluation of mental states (e.g., "Is this salesman just trying to sell me the more expensive option?"). The RMPFC may be involved in a self-related appraisal (e.g., "If I buy the convertible I will feel young again"). Activation of the aMCC may reflect the value of different actions based on motor/effort costs (e.g., the sports car may be assigned a lower action value because of the greater effort costs related to putting in extra hours at work for the next month to afford it). The sgACC may contribute to an appraisal of viscero-motor signals that modulates physiological arousal (e.g., heart rate) in anticipation of consuming a reward (i.e., owning a sports car), while the pgACC may contribute to an appraisal of viscero-sensory signals and the emergence of subjective feelings (e.g., excitement). Finally, the lateral PFC may be involved in higher-order appraisal processes that, for example, downregulate the temptation of immediate rewards to pursue desired future outcomes (e.g., negatively valuing the excitement associated with owning a convertible so that the long-term ecological benefits of owning a hybrid can have a stronger impact on choice). In this example, several appraisals favoring the sports car would compete against several appraisals favoring the hybrid, and these interactions would continue until there is convergence toward one option through excitatory and inhibitory interactions across the distributed network of appraisals. Here, we have focused on PFC subregions, but this idea can be extended to subcortical and brainstem regions.

The idea of multiple appraisals occurring in parallel across PFC subregions has several advantages of the common currency model: (a) it corresponds well with the fact that value signals are widely distributed throughout the brain (Vickery et al., 2011) and multiple value-related regions are activated during the decision making process (Bartra et al., 2013; Clithero & Rangel, 2014); (b) it is consistent with theoretical models of emotion that propose continuous bidirectional interactions between components of emotion (Barrett et al., 2014; Gross, 2015; Lewis, 2005; Scherer, 2001); (c) it explains why medial OFC lesions do not cause a global disruption of decision making; and (d) it generalizes beyond simple choice situations to offer predictions about how emotional behaviors are selected in any situation. By combining explicit ideas

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about the content that is evaluated by each PFC subregion with information about the strength of anatomical and functional connectivity across PFC subregions (and with the rest of the brain), predictions can be made about how certain appraisals may interact. For example, it is well-established that anatomical connections between lateral PFC and aMCC are much stronger than the connections between lateral PFC and sgACC. This information could be included as a modulatory weight on predicted interactions across appraisal dimensions, leading to a well-specified and biologically informed model of decision making. Indeed, recent work has shown that the strength of activation in a given brain region can be accurately predicted based on the strength of activation in other regions multiplied by the strength of their functional connectivity with that target region (Cole, Ito, Bassett, & Schultz, 2016). Employing this approach could offer a way of formally modeling the relative contribution of different types of appraisals to a given decision.

Dissociating Salience Detection From Subjective Feelings and Action Tendencies

An influential paper by Seeley and colleagues (2007) introduced the so called "salience network" (Seeley et al., 2007). This network included a collection of regions including the aMCC (called the dorsal ACC by Seeley et al.), the anterior insula, and periacqueductal gray, among other regions. This network is believed to play a general role in detecting salient internal and external events. Since the publication of this study, the neuroscientific literature has become filled with studies employing reverse inference (Poldrack, 2006) and assuming that activation in this network reflects salience detection. However, there are two problems with this practice. First, salience detection is a poorly defined construct. An object can be salient because of its intrinsic visual qualities (Itti & Koch, 2001), affective relevance (Anderson & Phelps, 2001; Markovic, Anderson, & Todd, 2014; Todd, Cunningham, Anderson, & Thompson, 2012; Vuilleumier, 2005), or relationship to current task demands (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Gottlieb, Kusunoki, & Goldberg, 1998). Second, in many circumstances, the detection of an affectively salient stimulus is highly correlated with changes in subjective feelings and the generation of action tendencies (that is, urges to move to acquire a positive outcome or avoid an aversive outcome). Accordingly, brain activation that correlates with salience detection may reflect any one of several appraisals related to stimulus properties, actions, or visceral signals. While emotion theory has long recognized the importance of distinguishing these components of emotion, neuroscientific studies generally have not. Thus, designing studies that orthogonalize appraisals related to different components of emotion could support greater precision in delineating the meaning of brain activation in neuroimaging studies.

Studies of pain provide an example that highlights the importance of considering distinct types of appraisals. Painful stimulation (e.g., noxious heat) is a potent activator of many brain regions, often referred to as the pain matrix, which bears similarity to the salience network, but also includes regions such as the pgACC (Craig, 2002; Hutchison et al., 1999; Kulkarni et al., 2005; Lieberman & Eisenberger, 2015; Petrovic et al., 2002; Rainville et al., 1997; Shackman et al., 2011; Vogt, 2005; Wager et al., 2013). Wager and colleagues (2013) demonstrated that a machine learning algorithm could distinguish painful heat from nonpainful heat, social pain, and pain anticipation and recall with remarkable accuracy based on patterns of activation within the pain matrix. But what exactly is the algorithm detecting? A painful stimulus will elicit a robust salience detection response (i.e., appraisal of exteroceptive sensations); increased physiological arousal; strong action tendencies (overt or covert) related to the reflex to prevent tissue damage; and subjective feelings of displeasure. The relationship between pain-responsive brain regions and appraisals related to these components of emotion is critical to address if the goal is to use brain patterns to identify feelings of pain in patients that are unable to communicate their level of pain, as proposed by Wager and colleagues (2013). It has recently been demonstrated that many pain-responsive regions (including the aMCC and insula) are activated by noxious stimulation in individuals with congenital insensitivity to pain (Salomons, Iannetti, Liang, & Wood, 2016). This suggests that many of these regions perform functions that are correlated with pain, but do not directly bear on the experience of displeasure/aversion associated with pain.

Our framework, predicated on knowledge of anatomical connectivity and findings from multiple methodologies, suggests possible functional distinctions within the pain matrix. As an example, our review suggests that the pgACC is involved in appraisals related to the subjective feeling component of pain, whereas the aMCC is involved in appraisals related to the action tendency component of pain. Anatomical connectivity patterns show that the aMCC is robustly interconnected with the motor system, whereas the pgACC is not. Moreover, our Neurosynth meta-analysis revealed that studies employing the term "motor" potently activate the aMCC but not the pgACC (Figure 6). In contrast, pgACC activation closely tracks subjective feelings of pain unpleasantness and is modulated by opioid- and placebo-induced changes in pain feelings (Kulkarni et al., 2005; Petrovic et al., 2002). Finally, lesion work has shown that aMCC lesions disrupt action-value processing (Rushworth et al., 2007; Shima & Tanji, 1998; Williams et al., 2004), whereas pgACC lesions disrupt subjective feelings including the aversiveness of pain (Hornak et al., 2003; Johansen et al., 2001). Thus, while numerous regions are frequently activated together during pain, their functions may be very different. Recently, there has been significant controversy over whether aMCC function is selective to pain processing (Lieberman & Eisenberger, 2015; Wager et al., 2016). The aMCC may be robustly recruited during pain because of the rapid updating of action values and preparation of defensive action tendencies, however this would not imply a selective role in pain, given that action values are computed in many other circumstances as well. Our framework, in conjunction with the psychological models of emotion, suggest that it is critical for future work to experimentally orthogonalize different appraisal dimensions. When this is not possible, the meaning of brain activations should be interpreted with caution, acknowledging that it may reflect any one of several correlated components of emotion.

Using Neuroscientific Findings to Refine Psychological Models of Emotion

Psychological models of emotion have emphasized the importance of decomposing appraisal into multiple constituent dimensions (Brosch & Sander, 2013; Ellsworth & Scherer, 2003;

Scherer, 2001; Smith & Ellsworth, 1985). We in turn have used this idea as a framework for organizing neuroscientific findings. However, in examining the functional roles of PFC subregions, it is clear that there are additional appraisal dimensions that have not been incorporated into most psychological models. Our review suggests that the lateral OFC plays a critical role in assigning value to stimuli that are present in the external environment based on current goals and needs. This is similar to theoretical descriptions of goal-relevance appraisals. However, emotions are often triggered by internally generated events including episodic memories and imagined future events. Consistent with this, the evidence reviewed here suggests that the medial OFC is preferentially involved in evaluating internally generated scenarios or events. The clear anatomical and functional differences between the lateral OFC and medial OFC suggests an important distinction between goal-relevance appraisals related to external and internally generated events that has yet to be emphasized in psychological models of appraisal. Indeed, the evaluation of internal (mentally simulated) events has unique adaptive properties such as contributing to foresight and adaptive decision making by helping individuals plan for the future based on the likely risks and opportunities that may occur (Bechara & Damasio, 2005; Boyer, 2008; Gilbert & Wilson, 2007; Miloyan & Suddendorf, 2015; Peters & Buchel, 2010). The idea that there are separate neural mechanisms for evaluating the relevance of external versus internal events is consistent with a large literature highlighting a division between internal and external streams of information processing (Chun, Golomb, & Turk-Browne, 2011; Dixon et al., 2014b; Fox et al., 2005; Golland et al., 2007; Lieberman, 2007; Vanhaudenhuyse et al., 2011). Incorporating an explicit distinction between internal versus external goal-relevance appraisals into psychological models of emotion may allow for more specific predictions about healthy and pathological emotion processing.

Our review also suggests that the internal appraisal dimension can be further decomposed into mnemonic and interoceptive streams. The medial OFC plays a role in evaluating events that have been simulated in mind, whereas the sgACC and pgACC play a key role in evaluating visceral (physiological) signals. Psychological models have postulated numerous appraisal dimensions, but rarely highlight specific appraisal triggering mechanisms related to bodily signals. Barrett and Simmons (2015) have recently proposed that the brain generates predictions about upcoming requirements of the body, and this leads to anticipatory changes in physiological arousal. We have suggested that this predictive process reflects the appraisal of efferent (motor) visceral signals by the sgACC. This type of valuation is based on concrete physiological states and quite different from an evaluation of external or imagined events (e.g., people and places). Furthermore, we suggest that feedback regarding changes in physiological states is registered and evaluated by the pgACC, which integrates afferent (sensory) visceral signals with self-referential and conceptual information (Lane et al., 2015). These sgACC and pgACC appraisals that operate on information about the body, are informed by, but are distinct from, evaluations of external and internally imagined events involving people and places. Accordingly, psychological theories of emotional appraisal may become further refined by incorporating these additional appraisal dimensions suggested by the neuroscientific evidence. An advantage of considering the possibility of distinct appraisal processes related to visceral signals is that it provides a means of understanding how changes in body state can occur to some extent independently of, and sometimes preceding, evaluations of external or mentally constructed events. Within this approach, emotion is not viewed as a linear process whereby the meaning of an event is registered and then causes changes in body state. Rather, both can occur in parallel as a result of simultaneous operation of distributed appraisal mechanisms that evaluate different types of information.

Relationship to Other Models of PFC Organization

In this section we consider other accounts of PFC organization and how they relate to our appraisal-by-content model. The three major models of PFC organization we discuss are: (a) a rostro-caudal organization based on different levels of abstraction in processing; (b) medial-lateral organization based on emotion versus cognition; and (c) hemispheric asymmetry based on approach versus avoidance. We address each in turn.

Rostro-Caudal Organization

Growing evidence suggests that PFC regions may be organized along a hierarchical rostro-caudal (anterior to posterior) gradient, with progressively more rostral regions supporting more abstract information. In addition to the idea of a hierarchically organized visual stream, there is also evidence that orbitofrontal, lateral prefrontal, and medial prefrontal cortices may also exhibit such an organization (Badre & D'Esposito, 2009; Bunge & Zelazo, 2006; Christoff & Gabrieli, 2000; Christoff, Keramatian, et al., 2009; de la Vega et al., 2016; Dixon et al., 2014a; Koechlin, Ody, & Kouneiher, 2003; Kouneiher, Charron, & Koechlin, 2009; Kringelbach & Rolls, 2004; Petrides, 2005; Venkatraman, Rosati, Taren, & Huettel, 2009). There is evidence for such an organization within and across areas. In the current review, we found an association between more caudal regions (aMCC, sgACC, and pgACC) and appraisals related to concrete visceral and motor processes. In contrast, we found an association between more rostral regions (RMPFC and DMPFC) and appraisals related to abstract information related to the self and mental states. Thus, the functional roles described by our framework align well with the rostro-caudal organization model.

This rostrocaudal functional organization parallels the evolutionary emergence and anatomical composition of PFC regions. Caudal regions (i.e., cingulate cortex and caudal OFC) are agranular (that is, they lack a well-developed layer IV) and emerged earlier in mammalian evolution than more rostral regions that are dysgranular (that is, they contain an incipient layer IV) or granular (that is, homotypical, containing a well developed layer IV; Figure 11A), and are only present in primates (Mackey & Petrides, 2010; Passingham & Wise, 2012; Wise, 2008). Furthermore, projections from limbic structures such as the amygdala and hypothalamus to the PFC exhibit a rostro-caudal gradient, with stronger projections to caudal regions (Aggleton et al., 2015; Ghashghaei, Hilgetag, & Barbas, 2007; Jin et al., 2016; Figure 11B). Finally, there is some evidence that connectivity between the PFC and posterior cortical areas (e.g., the temporal and parietal cortices) exhibits a rostro-caudal organization (Pandya & Barnes, 1987; Christoff & Keramatian, 2007).

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Rostro-caudal organization may also be present within each PFC region. For example, evaluation of concrete exteroceptive

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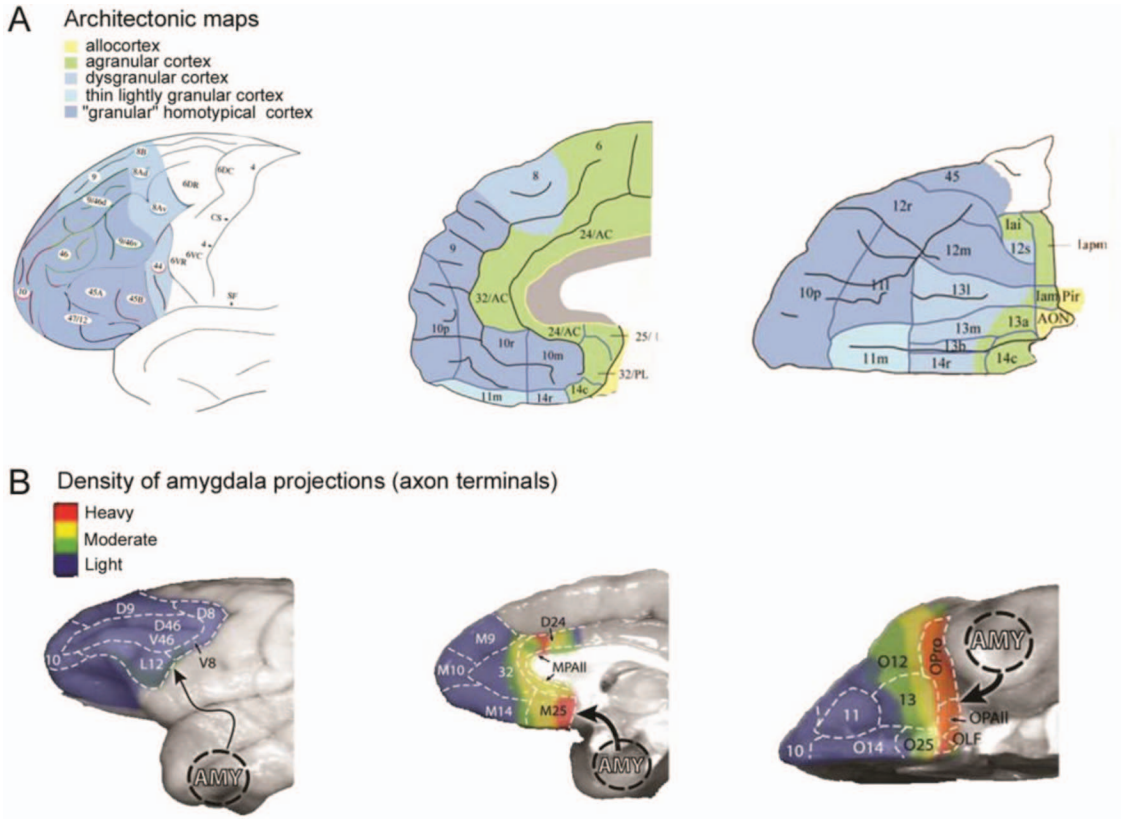

Figure 11. Rostro-caudal organization of the prefrontal cortex (PFC; A). Architectonic maps showing caudal to rostral progression from agranular to "granular" cortex. Lateral views modified from Petrides and Pandya (1999, 2002). Medial and orbitofrontal views modified from Wise (2008). (B) Anatomic inputs from the amygdala to the PFC exhibit rostro-caudal organization: the densest amygdala projections are to caudal PFC, while the rostral PFC receives very sparse amygdala inputs. Modified from Ghashghaei et al. (2007). See the online article for the color version of this figure.

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sensations (e.g., primary rewards such as food and odors) is associated with activation of caudal OFC, whereas evaluation of more abstract exteroceptive sensations (e.g., secondary reinforcers such as money) is associated with activation of rostral OFC (Kringelbach & Rolls, 2004). There is also robust evidence of rostro-caudal functional organization in lateral PFC. More rostral parts of lateral PFC have been associated with the processing of abstract concepts or rules that operate over long time-scales, whereas the caudal lateral PFC has been linked to concrete concepts and rules that regulate the immediate execution of actions (Badre & D'Esposito, 2009; Christoff & Gabrieli, 2000; Christoff, Keramatian, et al., 2009; Christoff, Ream, Geddes, & Gabrieli, 2003; Dixon et al., 2014a; Koechlin et al., 1999; Koechlin & Summerfield, 2007; Nee & D'Esposito, 2016; O'Reilly, Herd, & Pauli, 2010; Petrides, 2005). Based on this data, Dixon (2015) proposed a preliminary rostro-caudal model of the evaluative functions of the lateral PFC, according to which rostral lateral PFC (BA 10) contributes to directing attention internally to evaluate emotional states based on long-term goals; mid-lateral PFC contributes to the implementation of particular emotion regulation strategies by representing associations between rules/strategies (e.g., reappraisal) and desired outcomes (e.g., less sadness); and the caudal lateral PFC contributes to the execution of context appropriate actions. Thus, for each of the specific appraisals we have linked to different PFC subregions, there may be a finer level of organization within subregions, reflecting the same appraisal at different levels of abstractness. Accordingly, the appraisal-by-content framework and the rostro-caudal organization model are fully compatible and complementary. While the idea of rostro-caudal organization has received considerable attention in the cognitive neuroscience literature, it has only been touched upon by the emotion literature. This is an important avenue for future work.

Medial-Lateral Organization

An early model suggested that the PFC may be organized along a medial-lateral gradient, reflecting emotional versus cognitive functions. This model emerged from lesion work revealing conspicuous deficits in affective processes and decision making following medial PFC damage and conspicuous deficits in cognitive functions including working memory, rule use, and attention, following lateral PFC damage (Bechara et al., 1998; Glascher et al., 2012; Stuss & Alexander, 2007; Stuss & Knight, 2002). However, many studies employed tasks that generally conflated task difficulty and reward availability. Studies of complex cognition rarely used reward-incentives, and studies of reward process-

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ing and decision making often required minimal cognitive demands. Thus, these studies were unlikely to observe lateral PFC involvement in reward and decision making because they used simple tasks that did not require the complex motivational functions that may be supported by lateral PFC (Dixon & Christoff, 2014). In the current review and framework, we propose a fine-grained organization that goes beyond an emotion versus cognition dichotomy, with the proposal of specific appraisal dimensions distributed across the medial and lateral PFC. Indeed, several recent summaries of existing evidence argue that the medial/orbital (emotion) versus lateral (cognition) organizational heuristic for the PFC is no longer tenable given the growing empirical literature documenting a convergence of emotional and cognitive processes within multiple PFC subregions (Dixon & Christoff, 2014; Pessoa, 2008; Watanabe & Sakagami, 2007). For example, as noted earlier, there is a wealth of electrophysiological, neuroimaging, and lesion evidence that provides unequivocal evidence that lateral PFC plays a causal role in linking cognitive information such as task rules to reward and punishment outcomes. Moreover, given the robust anatomical connections between lateral PFC and the OFC and medial PFC, it could be argued that the lateral PFC is actually positioned at the top of the emotion hierarchy.

In a variation on the original medial-lateral distinction, Lieberman (2007) suggested that lateral frontoparietal regions are involved in externally focused processing, which is often nonemotional and focused on the physical aspects of the social world, whereas medial frontoparietal regions are involved in internally focused processes including self-reflection, emotion, and personal moral reasoning. While there is some evidence supporting distinct streams of internal and external processing, this division does not map onto a medial-lateral gradient (Dixon et al., 2014b). Recent network neuroscience findings have demonstrated that the lateral frontoparietal network often works in concert with the medial frontoparietal network to support a variety internally focused processes, including future planning, recollection, creativity, and mind wandering (Ellamil, Dobson, Beeman, & Christoff, 2012; Fornito, Harrison, Zalesky, & Simons, 2012; Fox et al., 2015; Gerlach et al., 2014; Spreng, Mar, & Kim, 2009; Spreng et al., 2010).

The current framework emphasizes both similarity and distinction between the medial and lateral PFC functions. We suggest that both are involved in emotion-related appraisal processes. However, we have proposed a medial-lateral distinction in the sense of first-order versus second-order evaluative mechanisms. Our review suggests that lateral PFC may often contribute to evaluations of emotional responses that arise following the appraisal of internal and external events supported by orbital and medial PFC regions. The evaluations associated with lateral PFC often take into account future goals, and may be more abstract and hence less visceral and grounded in current body states than the evaluations linked to orbital and medial PFC regions. Thus, although recent evidence is not compatible with existing models of medial-lateral organization, there may be functional differences that have yet to be fully appreciated. More research is necessary to evaluate this idea.

Hemispheric Asymmetry

A rich body of electroencephalography (EEG) work has shown that baseline differences in PFC activity between the two hemispheres predicts a host of outcomes relevant to well-being. Specifically, individuals with greater left versus right-sided alpha activity within PFC show increased psychological well-being (Urry et al., 2004), reduced stress hormone cortisol levels (Kalin, Larson, Shelton, & Davidson, 1998), and more robust immune response at baseline and because of challenges (Davidson, Coe, Dolski, & Donzella, 1999; Kang et al., 1991). State-based increases in anger also produce greater alpha asymmetry (Harmon-Jones, Gable, & Peterson, 2010), however it has been argued that such changes could reflect adaptive efforts to overcome thwarted goals rather than reflect negative valence (Davidson, 2004). Based on such data, prominent models of alpha asymmetry propose that greater left sided alpha activity track differences in motivation to approach versus withdraw from events in the world (Davidson et al., 1990; Harmon-Jones et al., 2010).

Davidson (2004) suggested that the electrocortical recordings that assess alpha asymmetry likely reflect signals from the dorsolateral PFC. Specifically, he argues that regions of the left dorsolateral PFC in particular may modulate activity in the amygdala, thereby shaping approach motivation (Davidson, 2000; Davidson, 2002). While our model does not address hemispheric differences in PFC functions, the idea that dorsolateral LPFC plays a central role in guiding organisms toward valued goals by modulating amygdala activity is consistent with our suggestion that lateral PFC contributes to the appraisal of ongoing affective states initially triggered by subcortical regions.

More broadly, Craig (2005) suggests that hemispheric asymmetry may extend beyond the lateral PFC, to the forebrain more generally, and reflect opposing parasympathetic and sympathetic nervous system roles in homeostatic regulation. According to this idea, the left forebrain is associated with parasympathetic activity and affiliative emotions that promote energy enrichment, whereas the right forebrain is associated with sympathetic activity and energy use in service of withdrawal and survival-related emotions (Craig, 2005). This idea is not inconsistent with our model: each PFC subregion may contribute to particular type of appraisal, with the left and right sides of each subregion performing a variation of that appraisal. For example, the left lateral OFC may contribute to the appraisal of sensory objects in a manner that is related to affiliation and the promotion of energetic resources, whereas the right lateral OFC may contribute to the appraisal of sensory objects in a manner that is related to threats and other challenges that require energy expenditure. This idea remains speculative at present, but could be investigated in future work.

Relationship Between the PFC and Subcortical Regions

Although the focus of the present review was the PFC, we do not intend to imply that the PFC is more important than other regions for emotion, or that appraisal processes are uniquely associated with the PFC. Quite the contrary, brainstem and subcortical regions are known to provide critical links to the body, and promote survival via monitoring and regulating deviations from homeostasis. Subcortical and brainstem regions support stereotypical, but rapid responses to challenges posed by the environment. In the course of evolution, the PFC has expanded considerably in primates: new areas have appeared (medial and lateral PFC), and older areas such as the cingulate regions have become rewired with

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connections to both subcortical regions and the new PFC regions (Passingham & Wise, 2012; Wise, 2008). In general, it seems that the PFC *elaborates upon and regulates* the basic appraisals supported by subcortical and brainstem regions. PFC subregions do so by assigning value to more complex and abstract information, thus facilitating *flexible and context-sensitive* emotional responses.

Theoretical Frameworks for Understanding Appraisals Across the Brain

Emotion theorists assume that appraisals occur at multiple levels of processing (Barrett et al., 2014; Ochsner & Gross, 2014; Scherer, 2001). At the simplest level, appraisals may reflect automatic and implicit associations between perceptual inputs and physiological and action-related outputs. At an intermediate level of processing, appraisals may involve the evaluation of stimuli in relation to current internal and external context (e.g., evaluating a previously threatening object as safe in the current context). Finally, at the highest level of processing, there are conceptual appraisals that may often be explicit and possible to verbalize. These latter appraisals situate current events within the context of semantic knowledge and an individual's autobiographical narrative. One possibility is that subcortical and brainstem regions are primarily involved in more basic, implicit appraisals, whereas PFC regions are more involved in more complex, explicit appraisals (Ochsner & Gross, 2014).

Expanding on this idea, the iterative reprocessing model suggests that objects and events are subject to an iterative sequence of evaluations reflecting interpretation and reinterpretation based on increasing levels of contextual information (Cunningham & Zelazo, 2007). Initial automatic appraisals by subcortical regions such as the amygdala are simple in nature, and followed by more reflective and contextualized appraisals by PFC regions, and this information is fed back to subcortical regions to refine the initial simple evaluations, and so on, as this sequence unfolds (Cunningham & Zelazo, 2007). This model thus suggests a dynamic process of interaction between simpler and more complex appraisals via subcortical-PFC communication.

Finally, reinforcement learning models suggest a distinction between model-based and model-free value learning (Daw et al., 2005; Dayan & Niv, 2008; Dolan & Dayan, 2013; McDannald et al., 2012). Model-free learning is characterized by trial-and-error learning about the outcomes that follow actions. When a stimulus or action is followed by an unexpected reward, this triggers a positive prediction error that drives learning (the updating of stimulus/action values), and will increase the probability that the same stimulus/action is selected in the future. Thus, model-free values are slowly and incrementally updated following actual experience with outcomes. In contrast, model-based learning is characterized by an internal model of current circumstances that specifies the relationships between stimuli, actions, and outcomes. Such models allow individuals to look *forward* in time to predict the likely outcomes associated with selecting particular stimuli and actions, even before outcomes are directly experienced. This distinction is useful because it can be captured with quantitative reinforcement learning models that can be fit to neuroimaging data. Recent work has shown that PFC regions primarily contribute to model-based learning (Dixon & Christoff, 2012; Glascher et al., 2010; Hampton, Bossaerts, & O'Doherty, 2006; Jones et al., 2012; Lee, Shimojo, & O'Doherty, 2014; Li et al., 2011; Smittenaar et al., 2013; Stalnaker et al., 2014).

To summarize, theoretical models suggest a hierarchy of appraisals based on complexity/abstractness, with some consensus that PFC regions support the valuation of highly contextualized information (e.g., stimuli in the context of mental states and current task structure), whereas subcortical regions may preferentially support the valuation of less contextualized information, but can incorporate more complex information via iterative reprocessing (that is, reentrant processing through feedback from higher level regions). Highly contextualized appraisals related to the PFC may modulate subcortical activation and enable flexible (rather than stereotypical) emotional responses and rapid adaptation to changes in the environment.

Contrasting PFC Appraisals With Subcortical and Brainstem Appraisals

Appraisals of sensory input. Both the lateral OFC and amygdala are involved in evaluating exteroceptive sensations (Cunningham et al., 2008; Gottfried et al., 2003; Sander et al., 2003). The amygdala may support simpler evaluations, often based on salient cues rather than broader contextual considerations (Kaouane et al., 2012), whereas evidence points to a key role for the lateral OFC in more complex evaluations based on a rich representation of current context (Pickens et al., 2003; Saddoris, Gallagher, & Schoenbaum, 2005; Schoenbaum & Esber, 2010; Wallis, 2007). During reversal learning, different sets of OFC neurons encode the value of cues pre- and post-reversal (Sharpe & Schoenbaum, 2016) and this can be conceptualized as a process by which the OFC treats post-reversal as a new temporal context, with a new population of neurons coming online to evaluate the sensory cues in this context. In contrast, amygdala neurons simply reverse firing during reversal and encode the new outcome value linked to sensory cues, consistent with a more cue-centric appraisal process that operates independent of broader contextual information (Sharpe & Schoenbaum, 2016). Furthermore, lesion studies have shown that OFC input is necessary for amygdala activity to integrate information about multiple cue-outcome associations (Sharpe & Schoenbaum, 2016). Finally, recent work has shown that the OFC is critical for the ability to use models of task context to infer the value of novel stimuli (Jones et al., 2012; Stalnaker et al., 2014).

Anatomical connectivity also provides a window into potential functional differences. The lateral OFC is strongly interconnected with the DMPFC and lateral PFC whereas the amygdala is not. Thus, the lateral OFC but not the amygdala has direct access to high-level information about others' mental states and task context that can be incorporated into valuations. Thus, the amygdala may provide a first-pass evaluation of stimuli based on prior learning (i.e., reinforcement history), whereas the lateral OFC may reprocess this information based on additional contextual information (Pickens et al., 2003; Schoenbaum & Esber, 2010; Wallis, 2007). Efferent signals from the lateral OFC may allow these more precise evaluations of value to shape ongoing processing in the amygdala, allowing it to become more sophisticated and flexible (Cunningham & Zelazo, 2007). Additionally, appraisals associated with the medial OFC further expand upon subcortical function by allowing for the valuation of mental simulations of sensory events

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via interactions with the hippocampus and retrosplenial cortex, among other regions. In this way, medial OFC function contributes to the process by which additional high-level contextual information (based on mental time travel to the past and future) shapes emotional responses.

Appraisal of actions. Dopaminergic midbrain-striatal pathways are involved in promoting the "wanting" motivational drive for rewarding objects (i.e., invigorating approach-related actions), and establishing habits to acquire those objects, via trial-and-error learning of action values (Berridge, 2007; Everitt & Robbins, 2005; O'Doherty et al., 2004; Tricomi, Balleine, & O'Doherty, 2009; Yin & Knowlton, 2006). When a particular stimulus-action-outcome association has been overtrained, a habit develops and an individual will continue to select an action linked to a stimulus even if the outcome has become devalued, and this process is associated with recruitment of the dorsolateral striatum (Tricomi et al., 2009). This region, via interactions with other brain structures, may support an implicit appraisal of actions based on reinforcement history (Daw et al., 2005). The aMCC is also involved in evaluating actions, but in contrast to the dorsal striatum, is preferentially involved in nonroutine situations that require the adaptive integration of numerous costs and benefits (Shackman et al., 2011). Indeed, the aMCC is invariably recruited in cognitive control and emotion regulation tasks that require the controlled, goal-directed selection of actions (Botvinick et al., 2001; Buhle et al., 2014; Dixon et al., 2014a; Kouneiher et al., 2009; MacDonald, Cohen, Stenger, & Carter, 2000). Thus, the appraisal processes supported by the aMCC may expand upon striatal function by allowing for the appraisal and selection of actions in a manner that is flexibly tailored to current goals and context.

Appraisals related to physiological arousal and interoception. The nucleus of the solitary tract and parabrachial nucleus register visceral input from multiple bodily organs via the spinothalamic tract and the vagus and glossopharyngeal nerves, providing an early representation of signals related to hunger, thirst, pain, nausea, as well as respiratory, cardiac, and other visceral sensations (Critchley & Harrison, 2013; Damasio & Carvalho, 2013; Saper, 2002). These regions interact with the hypothalamus and periacqueductal gray, which play roles in driving patterned changes in autonomic arousal and endocrine processes. Together, these regions support a suite of simple appraisals that reflexively initiate changes in body state to maintain homeostasis (e.g., the baroreflex which monitors and regulates changes in blood pressure), and pattered physiological responses (i.e., coordinated autonomic and neuroendocrine responses) that support stereotypical behaviors (e.g., freezing vs. fleeing) to cope with immediate challenges in the environment (Bandler et al., 2000; Critchley & Harrison, 2013; Saper, 2002; Ulrich-Lai & Herman, 2009). The sgACC expands upon these reflexive appraisals by using contextual cues to support a predictive appraisal mechanism that generates and sustains anticipatory changes in arousal. Additionally, interoceptive signals from subcortical and brainstem regions are also sent to the pgACC, which also receives inputs regarding autobiographical details, personal concerns, and conceptual knowledge from the default network and lateral PFC. By reprocessing and evaluating interoceptive signals in relation to these broader contextual representations, the pgACC contributes to an appraisal that is related to the capacity to understand and label feelings and may facilitate learning, decision making, and the communication of emotional states to others.

Appraisals of emotional state. Humans may be unique in the amount of time and effort directed at managing emotional responses. Emotion regulation is a complex skill and is intimately tied to adaptive social life. The evidence reviewed here suggests that the lateral PFC may contribute to highly contextualized appraisals that modulate emotional responses. Specifically, the lateral PFC may represent the value of ongoing emotions based on social goals, task context, and other long-term goals. Thus, lateral PFC plays a role in monitoring the emotional output associated with other PFC and subcortical appraisals, and in triggering emotional regulatory strategies when there is a mismatch between desired and actual emotions.

Conclusions and Future Directions

The PFC plays an important role in emotional processing, yet a global theory that provides a clear understanding of the distinct functions of its subregions has remained elusive. We have introduced the appraisal-by-content model to synthesize the diverse range of neuroscientific findings pertaining to this topic and to provide a comprehensive resource for understanding the PFC's role in emotion. This model suggests that every PFC subregion plays a role in valuation, but operates on different inputs, imposed by the constraints of anatomical and functional connectivity. This novel perspective on the PFC's role in emotion provides a novel lens through which existing findings can be integrated and predictions can be made to guide future work.

The presence of somewhat distinct neural substrates underlying each appraisal dimension would allow for the dynamic activation of any combination of appraisals at any given time. In this way, an emotional episode can be simple or complex, depending on the number of currently active appraisal dimensions and the extent to which there is a congruence among them. Our model of PFC contributions to emotion is consistent with the view of emotion as a dynamic, unfolding process (Barrett et al., 2014; Gross, 2015; Lewis, 2005; Scherer, 2001). Furthermore, this framework can be expanded to incorporate all emotion-related brain regions based on the idea of appraisals at various levels of abstractness. The PFC in particular may be involved in appraisals of complex and abstract information, including high-level contextual information accumulated over a long time period (e.g., tens of seconds). In this way, PFC subregions may assign value to specific inputs based on a rich, multidimensional, multilevel model of the internal and external environment. For example, the lateral OFC may use a model of the current context to assign value to external sensory events, whereas the medial OFC may use a model of the current context to assign value to internally generated events (e.g., an episodic memory). Furthermore, damage to any given region would have multiple consequences. For example, damage to the DMPFC would interfere with evaluating others' mental states, and also interfere with the use of mental state information to value sensory objects, as the lateral OFC would no longer have access to this type of contextual information. Thus, while each PFC subregion is preferentially involved in evaluating a specific type of information, these evaluations take into account contextual information from numerous other brain regions.

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The relatively high-level appraisals carried out by PFC subregions may play an important role in modulating subcortical and brainstem functions, enabling broad contextualized representations of the environment to guide valuations and emotion-related behavior. This is consistent with evidence that the PFC plays a key role in emotion regulation. The appraisal-by-content model introduces a more detailed and precise description of PFC's role in emotion in terms of appraisals. The model can also account for PFC's involvement in the generation of emotion. Thus, PFC and subcortical regions may primarily differ in the complexity/abstractness of representations they operate on during appraisal.

Limitations of the Appraisal-By-Content Model

In addition to its strengths, our model has a number of limitations that need to be acknowledged. For example, the evidence for our framework is stronger for some regions than others, because of the lack of appropriate studies, or lack of clear-cut results that favor a single interpretation of function. For example, there is little question that the lateral OFC contributes to the appraisal of external sensory input. On the other hand, there are far fewer studies, especially human studies, that have focused on isolating the function of the sgACC. Thus, the idea that the sgACC contributes to appraisals of endocrine and autonomic signals should be viewed as tentative. Human evidence is needed to corroborate the rodent and macaque work demonstrating a causal link between sgACC function and changes in physiological arousal. The paucity of human data could be the result of signal dropout in fMRI studies, or the use of mildly arousing emotional stimuli (e.g., IAPS pictures) that may not engage the sgACC appraisals that drive changes in the physiological arousal. Additionally, hypothesis-driven studies are needed to examine the idea that sgACC's function can be understood as a type of appraisal. In a similar vein, more hypothesis driven studies are needed to assess the proposed function of the DMPFC. There is little doubt regarding the association of this region and mentalizing and representing person knowledge. However, only recently have links been made between this literature and potential appraisal-related functions. Thus, our contention that the DMPFC plays a role in *assigning value* to other's intentions (as opposed to simply representing those intentions) needs to be empirically tested in future research.

A popular interpretation of medial OFC function is that it supports a common currency value signal, or a value comparison process in an abstract common currency space. However, we have outlined limitations of this interpretation, and have reviewed a number of recent findings that instead suggest a role in evaluating episodic memories and imagined future events. Nevertheless, medial OFC is activated across many different paradigms, rendering anything but a clear picture. While we believe that a role in evaluating internally generated events best captures existing evidence, this idea should be viewed as a hypothesis until studies have provided tests that can favor one theory over another. For example, if a study is able to show that medial OFC activation is more sensitive to evaluations of internally generated events than exteroceptive sensations, then this would provide clear support for the present model over the common currency model. More broadly, strong claims about relative functional specialization require data from studies that orthogonalize distinct appraisal dimensions and demonstrate that PFC subregions are differential sensitive to a particular appraisal. Unfortunately, few studies to date have done this. Thus, although the empirical findings across many different studies provide considerable support for our model, there are currently few studies that have provided the type of clear-cut evidence that would strongly favor our model over alternatives. Differences in experimental design complicate the task of comparing findings across studies; however, we have tried to find the common thread among tasks that are associated with activation of each subregion.

Following Teuber (1972) and others, we believe that it is important to arrive at a global theory of the PFC involvement that specifies the unity and diversity of functions across its subregions. We have proposed that appraisal or valuation is a unifying principle of PFC function in emotion. While it is well accepted that several PFC regions perform valuation-related functions (e.g., OFC), other regions have generally been interpreted through a different lens (e.g., viewing lateral PFC function through the lens of a cognitive control framework). We believe that there is now overwhelming evidence suggesting that lateral PFC is also centrally involved in appraisal processes. However, the similarities and differences between the type of valuation performed by regions such as the OFC versus lateral PFC is currently unknown. We have suggested that differences across PFC subregions are mainly tied to the content or type of input that is evaluated, but also suggested the possibility that lateral PFC valuations may be more abstract (that is, less directly grounded in visceral or exteroceptive experience). This idea is rather speculative at present, and deserves to be investigated in future work. More generally, a global theory of PFC function requires that each PFC subregion is examined from many different angles, so that proper comparisons across regions can be made.

Finally, because of the scope of this review it was not possible to perform an exhaustive review of literature pertaining to each PFC subregion. Thus, it is possible that we may have omitted at least some relevant studies that would further support or possibly contradict our interpretations. However, we hope that our synthesis of the literature and the account offered here of functional unity and diversity across PFC subregions will stimulate new empirical and theoretical developments in our understanding of PFC's contributions to emotion.

Future Research Directions

There are several theoretical and methodological considerations that may be helpful in guiding future research. First, studies could benefit from adopting a neurophenomenological approach (Fazelpour & Thompson, 2015). This would involve use of online experience sampling to acquire precise subjective reports about emotional experience, and then examining patterns of brain activation that are time-locked to these reports. This may be especially relevant for probing areas of the medial PFC that support functions that may or may not be aligned with manipulations of external stimuli (e.g., self-evaluation). Indeed, regions along the medial wall of the PFC may be particularly involved in appraisal processes that may constrain the flow of internally oriented thoughts (Christoff et al., 2016). Some studies have acquired information about subjective preferences, however it would be beneficial to additionally acquire reports on the extent to which an individual's attention is directed toward sensory features, valenced memories,

self-referential thoughts, prospective mental simulations, or inferences about mental states. A neurophenomenological approach will be critical for linking neural activation to different appraisal dimensions.

Second, given that many PFC regions are preferentially activated when attention is directed internally, it may be beneficial for future studies to focus more extensively on tasks that require episodic memory, future simulations, and self-referential processing rather than relying on manipulations of external stimuli. Moreover, it is important to contrast activation in conditions of interest against a resting baseline. If a region exhibits differential activation between two conditions, but an overall *deactivation* relative to a resting baseline, this implies that the region is sensitive to the manipulation, but that its *core function* has not been isolated. This is critical because many PFC regions involved in emotion are part of the default network that exhibits high resting state activity (Raichle et al., 2001; Shulman et al., 1997).

Third, current experimental paradigms for assessing action appraisal are limited in that they often examine simple button press responses. In contrast, psychological theories of emotion have articulated a rich variety of emotion-related action tendencies that *alter one's relationship* to the external environment, including: moving away from (self-protection from something/someone), moving against (opposing something/someone), moving toward (desire for contact with something/someone), acting in command (ability to make use of favorable opportunities or handle difficult situations), and acting in a helpless manner (wanting to do something but not feeling capable; Frijda, Kuipers, & Ter Schure, 1989). Additionally, it is becoming increasingly appreciated that action-value systems evolved in ecological settings that involved foraging behaviors and the precise optimization of biomechanical operations in relation to environmental parameters such as its geometry (Cisek, 2012; Cisek & Kalaska, 2010; Kolling et al., 2012). A complete neurobiological account of action tendencies in the context of emotion (including the function of the aMCC) thus requires the acquisition of neuroscientific data using paradigms informed by psychological and ethological theories of action tendencies. Given the practical technological constraints associated with fMRI scanners, it may be necessary to correlate naturalistic action tendencies measured outside of the fMRI scanner, with brain data collected inside of the scanner.

Fourth, we lack a neurobiological understanding of how different appraisal dimensions interact, and how this relates to the dynamic unfoldment of an emotional episode (Cunningham & Zelazo, 2007; Gross, 2015; Lewis, 2005; Scherer, 2001). Electrophysiological data often reveal that specific neurons increase their activity at different latencies following stimulus onset, suggesting a continuously evolving functional role within a network. One interesting possibility is that the activity and network interactions of neurons (and regions) at different time-points may reflect a continuously updated appraisal dimension. Furthermore, over longer periods of time, experience will shape emotional mechanisms, giving rise to individual differences in emotional functioning. For example, as a result of certain experiences in conjunction with one's genetic predisposition, appraisal mechanisms may become biased toward certain activation patterns (Lewis, 2005), and in turn, this may "pre-tune" perceptual systems such that some categories of stimuli receive preferential processing over others, and will further reinforce the tendency to activate certain appraisal patterns (Todd et al., 2012). The framework provided here, in conjunction with recent advances in network neuroscience (Bassett et al., 2014; Calhoun, Miller, Pearlson, & Adali, 2014; Cole et al., 2016; Davison et al., 2015; Hutchison et al., 2013; Zalesky et al., 2014), may prove helpful in elucidating the dynamic nature of emotion. Additionally, it will be important to link the dynamic interaction among appraisal dimensions to functional accounts of emotion (Farb, Chapman, & Anderson, 2013; Susskind et al., 2008).

Fifth, future work would benefit from employing tasks that orthogonalize different appraisal dimensions to dissociate the roles of PFC subregions (e.g., orthogonalizing the valuation of exteroceptive sensations, self-image, and future events). Such task designs would provide a strong test of functional variation across PFC subregions. As well, it is difficult to isolate a core emotion-related function and rule out all extraneous factors with a single task. Different conditions that appear to differ on a single dimension of interest may also differ along other variables, especially difficulty. Thus, studies that include multiple tasks that vary in surface features but require a similar core process may be critical for identifying brain activation patterns that track a core emotional process and are insensitive to other extraneous task elements. In this way, there can be greater certainty about the aspect of the task that is driving the neural response.

Sixth, it will be critical to converge on a standard PFC parcellation and precise anatomical labels, that are also consistently used across studies when reporting activated brain regions. Given current anatomical and functional data, we suggest that the term "ventromedial prefrontal cortex" is no longer useful and should be discarded in favor of more precise anatomical labels. The distinct cytoarchitecture, connectivity patterns, and functions of the sgACC, pgACC, medial OFC, and RMPFC suggests that these regions should not be subsumed under a single label. Greater anatomical precision will facilitate the integration of findings across studies and promote a more accurate understanding of structure-function relationships.

Seventh, it is well-established that self-evaluations play a critical role in clinical conditions including depression (Beck, 1991). However, the neuroscience of how value is assigned to self-identity is in its infancy, with evidence pointing toward the RMPFC as a key player. There are several important questions to address in future work. For example, what are the key neural substrates involved in assigning value to different aspects of self-identity (e.g., physical attributes, personality variables such as intelligence, possessions, and so on)? And what are the neural mechanisms associated with experience-dependent changes in self-evaluation that may be relevant for understanding clinically significant alterations in emotional functioning (e.g., a shift toward extreme negative self-evaluations and low self-worth in depression)? Although self-evaluations are a central aspect of human emotional life, this territory is largely uncharted in the realm of neuroscientific inquiry. Great strides could be made by combining psychological models of self-identity with advances in reinforcement learning models of decision making. The current framework offers testable predictions about the contributions of different PFC subregions that could be incorporated into such models.

Finally, the theoretical literature has documented numerous appraisal dimensions that were not covered in this review. Studies are needed that map the specific neural substrates underlying these

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additional appraisals. This final point also highlights the crucial need for greater integration between psychological models and neuroscientific studies of emotion.

Conclusions

Emotion plays a central role in human life, propelling changes across multiple systems to facilitate survival and well-being. The dynamic nature of emotion is supported by a widely distributed and complex neural architecture. Tremendous progress has been made in delineating the relative specialization of different brain regions with respect to emotional processes. We have provided a comprehensive review of the emotion-related functions of the PFC, and proposed the appraisal-by-content model, which offers a unified perspective on the distinct contributions of different PFC subregions. The specificity outlined in this model offers novel perspectives on a number of key topics including emotion regulation and value-based decision making. Additionally, the relationships between structure and function proposed here may offer novel insights into the locus of neural dysfunction in clinical conditions. With advances in technologies and experimental paradigms, neuroscientific research is rapidly progressing toward a complete picture of the neurobiological basis of healthy and dysfunctional emotional processing.

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