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The emotional brain: *Fundamental questions and strategies for future research*

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ABSTRACT

Emotions play a central role in human experience. Over time, methods for manipulating emotion have become increasingly refined and techniques for making sense of the underlying neurobiology have become ever more powerful and precise, enabling new insights into the organization of emotions in the brain. Yet recent years have witnessed a remarkably vigorous debate about the nature and origins of emotion, with leading scientists raising compelling concerns about the canon of facts and principles that has inspired and guided the field for the past quarter century. Here, we consider ways in which recent neuroimaging research informs this dialogue. By focusing attention on the most important outstanding questions about the nature of emotion and the architecture of the emotional brain, we hope to stimulate the kinds of work that will be required to move the field forward. Addressing these questions is critical, not just for understanding the mind, but also for elucidating the root causes of many of its disorders.

Emotions play a central role in human experience and there is an abiding interest—among scientists, clinicians, and the public at large—in determining their nature, understanding their origins, and clarifying their implications for health and disease. Methods for eliciting, assessing, and analyzing emotion have become increasingly refined (e.g., [24,27]) and techniques for making sense of the underlying neurobiology have become more powerful and precise (e.g., [52,68,133,139]). The 10 reviews that make up our Special Issue on *Functional Neuroimaging of the Emotional Brain* embody these exciting developments and illustrate the tremendous progress that has been made using brain imaging approaches. Yet recent years have witnessed a remarkably vigorous debate about the nature of emotion, with leading scientists challenging the canon of facts and shared assumptions that has inspired and guided the field for the past quarter-century [10,101,11,13,2,23,26,28,3,4,43,8,81–83,9]. As Adolphs and Anderson recently wrote,

> *"Emotions are one of the most apparent and important aspects of our lives, yet have remained one of the most enigmatic to explain scientifically. On the one hand, nothing seems more obvious than that we and many other animals have emotions…On the other hand, the scientific study of emotions is a piecemeal and confused discipline, with some… advocating that we get rid of the word emotion altogether." ([4], p. xi).*

Here we consider ways in which the Special Issue informs this scientific dialogue, focusing on what we see as some of the most fundamental questions:

- *What is an emotion?*
- *Are emotions natural kinds waiting to be discovered and catalogued (like stars) or human concepts (like constellations)?*
- *Are particular emotions, such as fear, associated with distinct facial expressions and patterns of physiology, or what we might think of as biological 'fingerprints'?*
- *Should we think of emotions as discrete clusters or families of 'basic' emotions—as exemplified in the popular Disney movie "Inside Out"* (http://atlasofemotions.org; [4,36,85,95])…
- *…As points in a smooth, low dimensional space* [105,140,77,90]…
- *…Or some hybrid of these two extremes* [27]?
- *What develops in emotional development?*
- *How are emotions regulated?*
- *How are emotions embodied in the social world?*
- *Do animals have emotions?*

It has been written that "science best progresses through multiple and mutually critical attempts to understand the same problem" ([66], p. 32), and we believe that highlighting key points of consensus and disagreement among our contributors provides a useful opportunity for sharpening constructs, articulating unspoken assumptions, and identifying soft spots in the literature. In focusing attention on these key questions, and juxtaposing clear theoretical goals against the state of the science, we hope to stimulate the kinds of thoughtful discussion and creative research that will be required to understand the nature of emotion and the organization of the emotional brain. At the end of each section, we highlight some of the most important challenges for future research and some strategies for addressing them.

1. The Nature of Emotion

Nummenmaa and Saarimäki tell us that basic emotions—anger, disgust, fear, happiness, sadness, and surprise—exist and are associated with categorically distinct feelings, facial expressions, and patterns of autonomic activity (Nummenmaa & Saarimäki, *this issue*). Barrett and Satpute reject these claims (Barrett & Satpute, *this issue*), arguing that there is little evidence of specificity. Instead, they emphasize the marked differences in behavior and autonomic activity across instances of particular emotions (i.e., intra-emotion variation) and the

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considerable overlap across emotions (e.g., [125]). The two camps seem to agree that emotions reflect broadly distributed neural circuits, noting that there is little evidence of consistent one-to-one mappings between particular emotions and isolated brain regions, such as the amygdala. But they radically differ in their interpretation of those circuits. Nummenmaa and Saarimäki tell us that basic emotions are associated with specific patterns of neural activity (e.g., [108]). But Barrett and Satpute argue that the neural fingerprints revealed by machine-learning approaches markedly differ across studies, laboratories, induction techniques, and even across participants [12]—echoing other recent commentaries [136,72]. Building on these observations, Barrett and Satpute tell us that emotions are not natural kinds and do not reflect invariant biological substrates, that they have no fingerprints in the brain or body. From their perspective, emotions are constructed from domain-general building blocks—cells, regions, circuits, and patterns of autonomic activity—that are not specific to any particular emotion, or even to emotion itself. The configuration of those components is held to be *dynamic*, exquisitely sensitive to momentary fluctuations in the external environment and the internal milieu, and *causally distributed*, with none of the individual components necessary or sufficient for experiencing particular emotions.

So, where do we go from here? It is clear that the last several years have witnessed important advances in our understanding of how emotions are organized in the human brain. At the level of resolution afforded by conventional brain imaging techniques, these new data make it clear that emotions arise from networks, not isolated brain centers (for related perspectives, see Casey et al., *this issue*; Baratta & Maier, *this issue*; Fox & Shackman, *this issue*). Activation in particular brain regions, like the amygdala, explain small amounts of the variance in emotional states (e.g., as indexed by ratings) [21] and emotional disorders [115]. Individual voxels, regions, and functional connections often contribute to multiple mental states and processes, some more emotional, others more cognitive, a one-to-many mapping sometimes dubbed 'multiplexing' [116,119,98]. This work also showcases the utility of machine learning techniques for discovering neural fingerprints and quantifying the degree to which they predict specific emotions, a reverse inference not licensed by traditional 'massively univariate' brain-mapping approaches ([71]; Brooks & Freeman, this issue; Lamm et al., this issue; Spunt & Adolphs, this issue; [72,139]).

Still, it is clear that considerable work remains. It would be premature to draw any strong conclusions about the neural organization of emotion or the prospects of discovering emotion-specific fingerprints based on this first generation of machine-learning studies [72]. A key challenge for the future will be to create more generalizable emotion fingerprints; predictive models that are derived from multiple induction techniques, grounded in parametric variation in one or more read-outs, and tested on independent samples (e.g., ratings, peripheral physiology, behavior) (Lamm et al., this issue; [70,139]). Establishing the construct validity—the sensitivity and specificity—of these models will require comparison with a broad range of comparison tasks and stimuli [141], including a range of emotions [4]. Doing so promises a clearer understanding of how emotions are encoded in the human brain.

Nummenmaa and Saarimäki also remind us that imaging alone cannot address the necessity or sufficiency of the regions or connections embedded within these global patterns of activation—a point made by a number of other contributors (Lamm et al., *this issue*; Spunt & Adolphs, this issue; Baratta & Maier, *this issue*; Fox & Shackman, *this issue*). Addressing this important concern will require a greater focus on biological (e.g., pharmaceuticals, transcranial magnetic stimulation) and psychosocial interventions (e.g., emotion regulation, mindfulness, placebo) in humans (e.g., [35,60,96,135,143]) and a greater emphasis on developing more integrative models in monkeys and rodents ([63,64]; Baratta & Maier, this issue; Fox & Shackman, this issue; [89]). Studies of neuropsychological patients with circumscribed insults are also likely to be fruitful [1,110,34,41,86,92].

2. The Nature of Arousal

Arousal plays a central role in most models of emotion [80], but the underlying neurobiology has remained enigmatic. Satpute and colleagues tell us that this lack of progress reflects two barriers: one conceptual, the other empirical (Satpute et al., *this issue*). Conceptually, arousal encompasses a variety of systems, including those underlying the transition from sleep and sedation to alert wakefulness, those involved in activating the autonomic nervous system (e.g., racing heart), and those underlying the subjective intensity of emotional feelings. All these disparate phenomena are typically lumped under the undifferentiated rubric of 'arousal,' obscuring potentially important differences in neurobiology—an endemic problem in the affective sciences (Lamm et al., this issue; [44]). Satpute and colleagues describe an integrative framework for beginning to organize this complexity. They argue that wakefulness, autonomic arousal, and affective arousal are not categorically distinct phenomena. Instead, they seem to reflect massively overlapping substrates that are "separable in terms of their weighted contributions and functional interactions (i.e., their recipes)."

From an empirical perspective, Satpute and colleagues highlight the challenges of imaging the small brainstem, thalamic, and hypothalamic nuclei thought to be involved in orchestrating different flavors of arousal. They emphasize that "the brainstem is slightly larger than a human thumb" and contains more than 150 distinct nuclei; of these, less than 10% have been successfully identified in humans using *in vivo* imaging techniques. They tell us that several recently developed and emerging approaches—7 T fMRI, multiband imaging sequences, and multi-modal contrast techniques—open to door to imaging many of these regions for the first time. Satpute and colleagues make it clear that these kinds of imaging approaches will be important for understanding whether the mechanisms inferred from animal studies of arousal are conserved in humans. More broadly, when used to survey the entire brain, they also provide critical opportunities for understanding the role of small subcortical nuclei—nuclei nested within the extended amygdala, the thalamus, the hypothalamus, the periaqueductal gray, and so on—in governing the function of distal regions and circuits in ways that we normally experience as alertness (or fatigue), somatomotor activation, and emotion, and—when they go awry—that likely contribute to a range of mental and neurological disorders.

3. The Development of the Emotional Brain

Emotions have their roots early in development and there is widespread agreement that nearly every aspect of emotion continues to change and mature across the lifespan [124,126,54,79,84]. Yet, the nature of these changes and their underlying neurobiology remain poorly understood. Here, Casey and colleagues focus on adolescence, an important and comparatively understudied chapter of life that often marks the first emergence of psychopathology and other burdens on public health and safety (e.g., injury due to risky behaviors) (Casey et al., *this issue*). Adolescents are prone to more intense and labile feelings, and Casey and colleagues suggest that this reflects the asynchronous tuning of different neural circuits, beginning with the maturation of subcortical-subcortical connections early in childhood and culminating in bi-directional cortico-subcortical and cortico-cortical connections in mid and late adolescence. Ultimately, they tell us, this neural asynchrony biases feelings and behavior toward immediate threats and rewards Enhanced connectivity between the amygdala and ventral striatum early in development, for example, is hypothesized to promote rash decisions and impulsive actions in the face of emotionally salient cues.

Identifying the neural mechanisms underlying the development of emotion is exceedingly important, but difficult. Aside from the practical and technical difficulties of imaging youth, it is challenging to disentangle developmental changes in neural connectivity from co-occurring changes in hormones, cognitive control, and experience, including profound changes in stress and autonomy, as children transition to new schools, new jobs, and new kinds of social roles and networks [44]. A growing body of large, richly phenotyped, and publicly available pediatric imaging datasets promises new opportunities for dissecting the contribution of these factors to early-life emotion [107,132], with important implications for identifying modifiable targets and developing more effective interventions for individuals in whom emotion development has gone awry (for related perspectives, see [33,91]).

4. The Regulation of Emotion

We humans frequently regulate our emotions, and we do so using a variety of increasingly well understood strategies [118,123,18,33,56,57]. Like emotional reactivity, emotion regulation can be viewed as both a transient state and a more enduring trait. Trait-like individual differences in emotion regulation are thought to play a critical role in childhood temperament, adult personality, and mental illness [123,25,38]. Silvers and Moreira extend this conceptual framework, emphasizing the distinction between individual differences in the capacity to regulate emotion and in the tendency to use particular regulatory strategies (Silvers & Moreira, *this issue*). Recent meta-analyses suggest that regulatory capacity reflects biasing signals directed from frontoparietal regions to the amygdala and other subcortical structures that play a more proximal role in orchestrating emotional states [19]. Silvers and Moreira highlight emerging evidence that patients with mood and anxiety disorders show intact regulatory capacity in the laboratory—indexed by the ability to voluntarily recruit these frontoparietal regulatory regions—and impaired performance in their daily lives, as indexed by the tendency to choose maladaptive regulatory strategies. Developing a deeper understanding of the nature of regulatory capacity and choice is a fruitful avenue for future research, with implications for more effectively treating emotional disorders and for more efficiently matching patients to the most beneficial psychosocial treatments ('stratified medicine') [115,61].

5. Emotion and the Social World

Social cues, interactions, and relationships dominate the landscape of emotion in contemporary human society. The association between the social and the emotional is complex and recursive: emotional signals can elicit changes in the social environment, which in turn can influence how the sender perceives, experiences, or expresses emotion [47,78]. Emotional experiences are routinely shared and dissected with close companions [104] who, in turn, play an important role in buffering stress, promoting positive affect, and repairing mood [103,122,142]. Maladaptive expressions of negative affect increase the likelihood of adverse social outcomes, including conflict, rejection, and relationship dissolution [121]. In short, human emotion is profoundly social. As part of the Special Issue, several contributors considered ways in which emotions dynamically reverberate between individuals and their social environment.

From Darwin's time on, the face has played an outsized role in in scientific models of emotion [31]. Often, the perception of the facial displays of emotion is conceptualized as an automatic 'readout' of specific cues (e.g., widened eyes, furrowed brow), a purely 'bottom-up' decoding process. Brooks and Freeman tell us about a growing body of work demonstrating that emotion perception is, in fact, often actively shaped by 'top-down' processes (Brooks & Freeman, this issue; [48]). In this way, pre-existing expectations—including prior knowledge, stereotypes, and contextual information—can influence the construction of perceptual representations of emotional and socially relevant signals (e.g., gender, race, and personality) in the ventral visual processing stream. Put simply, our pre-existing thoughts, feelings, and attitudes can literally change how we see others, bias our evaluation of them, and change how we behave. As detailed elsewhere, this line of research is particularly exciting because it is grounded in behavior and because it harnesses machine learning to understand how seemingly 'low-level' perceptual representations can be influenced by expectations [127,128,49].

Spunt and Adolphs stake out a broadly similar position (Spunt & Adolphs, *this issue*), telling us that the processes involved in *detecting* (e.g., widened eyes), *categorizing* (e.g., fear), and *inferring* the likely cause of emotion signals (e.g., imminent crash) occur in parallel [99] and can influence one another in ways that dovetail with predictive coding architectures and Bayesian models of perception (Barrett & Satpute, this issue; [50]). They highlight lesion and machine learning evidence suggesting that categorizing emotion signals (affect 'labeling') is an 'embodied' cognitive process, one that is influenced by changes in the perceiver's momentary interoceptive state evoked by the sender's emotional signals.

Lamm, Rütgen and Wagner focus on empathy, compassion, and other emotions that promote prosocial behavior (Lamm et al., *this issue*). Building on recent work in this area (e.g., [37,141]), they emphasize the importance of neural systems involved in vicarious or shared emotional experiences—a neural analogue to 'embodied' models of emotion decoding. For example, they review evidence that placebo analgesia manipulations not only reduce one's own pain, they can also reduce empathy for the pain of others. These behavioral effects are accompanied by reduced activation in pain-related brain regions and are blocked by opioid antagonists, reinforcing the possibility of shared substrates for own- and other-directed (i.e., egocentric and allocentric) emotions. Lamm and colleagues highlight the challenges of identifying generalizable compassion circuits, patterns of neural activation that are not specific to particular techniques for eliciting or cultivating feelings of compassion. Although their focus is on compassion, it is worth emphasizing that this is a general issue for efforts to understand how particular psychological processes—pain, negative affect, cognitive control, and so on—are organized in the brain [70]. Discerning whether a pattern of activation reflects these kinds of latent constructs is exceedingly difficult—*Is it working memory or visuospatial change detection? Cognitive control or Eriksen flanker? Anxiety or threat-of-shock?*—but can be overcome by examining multiple assays or induction techniques, either meta-analytically or, better still, within individual samples.

6. Animal Models of Emotion (and Beyond)

Darwin emphasized the shared origins and essential continuity of the emotions in humans and animals [31]. Although the nature and interpretation of animal emotion remains contentious, there is widespread consensus that some—though certainly not all—features of emotion can be modeled in animals [101,106,39,4,40,45,81–83,9,95]. This opens the door to addressing questions such as, *Which neural systems are necessary for particular emotional responses? Which are sufficient?* (e.g., [14,15,20,73,75,114,130]). Two sets of contributors to the Special Issue focused on animal models of emotion and both teams highlight issues that are likely to be of interest to all students of emotion, regardless of their species of interest.

Baratta and Maier focus on a rodent model of stress resilience (Baratta & Maier, *this issue*). Stress plays an important role in precipitating a variety of psychiatric illnesses (e.g., [117,121]). Everyone experiences stress from time-to-time and most individuals will experience at least one major trauma in their lifetime [62,67]. Yet the vast majority of individuals exposed to adversity, stressors, or trauma never develop psychopathology. These observations underscore the importance of developing a deeper understanding of the neural mechanisms that confer resilience. Baratta and Maier tell us that instrumental control—the opportunity to avoid shock—has profound consequences for stress reactivity, consistent with work in humans [111,112]. Exposure to shock that is uncontrollable (i.e., unavoidable) produces a constellation of behaviors and physiological signs reminiscent of mood and anxiety disorders. These deleterious effects appear to be mediated by serotonergic cells in the dorsal raphe. The provision of instrumental control blunts these consequences and, remarkably, can even 'immunize' animals during future encounters with uncontrollable stress. Baratta and Maier describe on-going work to pinpoint the circuits underlying these kinds of stress buffering effects. This new evidence suggests that incoming information about the world and the body is routed through prefrontal circuits, with some involved in detecting stressor controllability and others responsible for using that information to appropriately regulate the stress response. Interestingly, this work highlights the critical *functional* significance of a minor *anatomical* projection (< 5% neurons) coursing from the dorsal raphe to the prefrontal cortex. This observation underscores the hazard of over-interpreting semi-quantitative neuroanatomical tracing studies (e.g., + + + vs. +) and prematurely dismissing the importance of 'weak' or 'modest' projections, such as those linking the amygdala to the dorsolateral prefrontal cortex (cf. [16,87]).

Fox and Shackman review the role of the central extended amygdala (EAc) in fear and anxiety (Fox & Shackman, *this issue*). They tell us that the EAc—an anatomical concept encompassing the central nucleus of the amygdala (Ce) and bed nucleus of the stria terminalis (BST)—is an evolutionarily conserved, functionally coherent hub; one that it is anatomically poised to use information about threat, context, and internal states to initiate a range of defensive responses and assemble states of fear and anxiety. They highlight recent imaging studies in monkeys—some including nearly 600 individuals—demonstrating that elevated metabolism in the Ce and BST is associated with heightened signs of fear and anxiety in response to novelty and potential threat. This approach, which integrates naturalistic behavioral, endocrine, and neural responses (18-fluorodeoxyglucose-positron emission tomography; FDG-PET) to ethologically relevant threats, merits comment. The vast majority of human imaging studies have focused on highly artificial manipulations—static faces, sounds, images, small monetary rewards, and so on—presented under unnatural conditions. These manipulations are much less arousing and engaging than the kinds of challenges routinely encountered in daily life ([120,4,82,85,86].[1] As Nummenmaa and Saarimäki note earlier in the Special Issue (Nummenmaa & Saarimäki, *this issue*), there are several strategies for addressing this challenge in the laboratory, including greater use of FDG-PET and a greater focus on more intense, ecologically relevant stimuli (e.g., thermal pain). An alternative approach is to integrate assays of brain function and behavior collected in the scanner—including differences in 'resting-state' function [46]—with measures of emotion and motivated behavior assessed under more naturalistic conditions in the laboratory (e.g., during semi-structured interactions or using commercially available virtual reality techniques; [30,74,76,97,100,129]) or in the field [6]. Recent work combining fMRI with experience-sampling techniques underscores the potential of this approach for identifying the neural systems associated with naturalistic variation in emotion and motivated behavior [42,59,88].

From a conceptual perspective, Fox and Shackman remind us that the words scientists use to describe emotion have the power to illuminate or to obfuscate [102,113]. Here, the problem is that lay people, scholars in other areas, clinicians, psychometricians, and even domain experts often use 'fear' and 'anxiety' in interchangeable or inconsistent ways [137,27,5,51,69]. This problem is not specific to fear and anxiety. Our words for emotion—anger, fear, disgust, joy, sadness and so on—and even more recently coined phrases, like 'uncertain threat,' can, and often do, refer to multiple phenomena [121,136,65,9]. While there will always be a place for verbal shorthand, we urge emotion researchers to be more mindful of nomenclature and the potential for misunderstanding.

Fox and Shackman make it clear that the Ce and the BST are functionally and anatomically complex (for related perspectives, see Satpute et al., *this issue*; Baratta & Maier, *this issue*). Like the nucleus accumbens, periaqueductal gray, and other subcortical structures involved in emotion and motivation, they can be partitioned into multiple subregions, each containing intermingled cell types with distinct, even opposing functional roles (e.g., anxiolytic vs anxiogenic). As a consequence, research that relies on lesions, pharmacological inactivation approaches (e.g., muscimol microinjections), or conventional brain imaging techniques will necessarily reflect a mixture of cells or signals. Baratta and Maier and Fox and Shackman describe how recently developed opto- and chemogenetic tools provide new opportunities for deciphering this complexity and discovering the specific circuit components that control responses to threat and reward. While unfamiliar to many imagers, developing a basic understanding of these methods is a key step to dissolving the kinds of artificial academic silos that separate researchers focused on human and animal emotion.

Fox and Shackman suggest that the tantalizing discoveries afforded by opto- and chemogenetic techniques pose a critical challenge for affective neuroscience. Are the mechanisms conserved across species? Which molecules and micro-circuits underlie differences in fMRI measures of activation? How do they influence the kinds of distributed networks that have been linked to adaptive and maladaptive emotion in humans? *"Reconciling these two levels of analysis—one global, the other local—is mandatory, if we are to develop a complete and clinically useful understanding of"* emotion (Fox & Shackman, *this issue*). Addressing this challenge is difficult, but can be potentially overcome by combining focal perturbations with whole-brain imaging in rodents or monkeys.

7. Conclusions

Understanding how emotions emerge from the brain is a major challenge. Throughout this review, we have outlined some strategies and directions for future research. Among these, several stand out:

- The importance of developing robust and generalizable (i.e., assay- and induction-general) neural models of emotion perception, expression, and experience. Models that are firmly grounded in variation in emotional behavior or experience are likely to be especially fruitful [71].
- The importance of testing whether these models predict real-world emotion.
- The importance of understanding how such models evolve across the lifespan and how they can be implicitly and explicitly regulated by the self and others.
- The importance of testing the necessity and sufficiency of the regions, circuits, and patterns implicated in models of emotion derived from neuroimaging research.
- The importance of bridging the gap separating the mechanistic insights afforded by animal models (i.e., molecules, cell types, and micro-circuits) from human imaging research (i.e., regional activation and inter-regional connectivity).

Understanding the nature and organizational principles of the emotional brain will require substantial time and resources, new kinds of multi-disciplinary collaborations, and new kinds of training models [134,44]. Addressing this challenge is important. Some of the most common, costly, and intractable illnesses—anxiety, depression, schizophrenia, substance abuse, autism, chronic pain, and so on—involve prominent emotional disturbances. Collectively, these debilitating disorders impose a staggering burden on global public health and the economy and existing treatments are far from curative [109,17,22,29,32,53,55,58,94,131,138], underscoring the importance of accelerating efforts to understand the basic neuroscience of emotion.

[1] For example, the vast majority of imaging studies that employ noxious shock allow subjects to self-select the maximal intensity, instructing them to pick the highest level that is 'uncomfortable or unpleasant but *not* actually painful' [7,74,93].

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Author Contributions

TDW envisioned the Special Issue. TDW and AJS served as Guest Editors of the Special Issue. AJS drafted the paper. Both authors edited the paper and approved the final version. Dr. Stephen Waxman served as action editor for this article.

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