IS THERE AN "EMOTIONAL BRAIN"?

Recent empirical findings provide evidence that brain measures sensitively and specifically relate to particular categories of emotion, but they involve systems distributed across the brain, which probably serve basic information-processing functions that are not dedicated or evolved for emotion per se. Thus, there are many routes to (and many brain systems involved in) emotion, and which shades of experience and sub-processes are rooted in which brain systems remains largely unknown. There may be many neurophysiological varieties of different "shades" of common emotions like anger, sadness, and joy, with different brain representations; and there is not one type of negative affect, but many. This "view from the brain" challenges us to think about whether traditional, psychological models of affect grounded in phenomenology (including both basic emotion and dimensional models of affect) really carve the emotional brain at its joints.

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5.7 THE BRAIN IS ORGANIZED TO EMOTE

Andrew S. Fox

Emotions are not organized in the brain; the brain is organized to emote. The biology of emotion has been embedded in the brain throughout evolution, because emotions are critical to survival and reproduction. Behaviors elicited by reward and punishment can be seen across phylogeny in flies, fish, rodents, and monkeys, as well as in humans. Although the full experience of feeling "fear" presumably differs across species (LeDoux, 2016), even aplysia and zebrafish share with humans the ability to flee from a potential threat (Blaser, Chadwick, & McGinnis, 2010; Carew, Hawkins, & Kandel, 1983; Carew, Pinsker, & Kandel, 1972; Xu, Scott-Scheiern, Kempker, & Simons, 2007). Here, I argue that emotions are organized across neural systems that were developed, conserved, coopted, and elaborated throughout evolution.

The genes, molecules, regions, and circuits that contribute to emotionally relevant brain function are embedded within evolutionarily old as well as more recently evolved regions of our genome, and, as a result, our brains. The human brain contains emotionally relevant systems that have been maintained through evolution. These older systems are intermingled with more recently evolved primate-specific systems. Many of the molecular and hormonal bases of emotion are conserved across species that diverged from humans hundreds of millions of years ago. As more recent neural systems evolved, emotions continued to guide adaptive decision-making and survival. Therefore, even primate-specific cortical systems that emerged in the last 50 million years remain emotionally relevant. Using examples drawn from research into the neural substrates of fear and anxiety, I will discuss how human emotion is instantiated within distributed networks that incorporate evolutionarily old and recently evolved substrates.

EMOTIONS ARE, IN PART, ORGANIZED ACROSS DISTRIBUTED MOLECULAR SYSTEMS

Many models of brain evolution have focused on the development of circuits and systems, rather than the molecular underpinnings of brain function. For example, the highly influential, though no longer popular, "triune brain" model of the brain was based on studies of shared neuroanatomy between species, and suggested that human cortex evolved to overcome the emotional impulses initiated by our "reptilian brain" (MacLean, 1990). More recently, researchers have demonstrated that the basic components of emotionally relevant brain circuits were in place long before even reptiles roamed the earth.

A great illustration of this importance of shared molecular circuits comes from the Nobel prize–winning work of Dr. Eric Kandel, who uncovered the basic molecular basis for long-term potentiation (LTP) in the sea slug (*Aplysia californica*) (Carew et al., 1983, 1972; Hawkins, Abrams, Carew, & Kandel, 1983; Kandel, 2001). These mechanisms are now understood to be evolutionarily conserved as mediators of defensive behavior, as LTP strengthens relevant synapses in the amygdala that allow conditioned stimuli to elicit avoidance behavior in rodents, and probably in humans (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Rogan, Stäubli, & LeDoux, 1997). Clearly, this is not the sole function of LTP, but it nicely illustrates the role of evolutionarily conserved processes in the experience of emotion in humans. This shared mechanism has implications for the mechanism of emotional learning.

The evolutionarily conserved biological bases of emotions extend far beyond associative learning

circuits in the amygdala. Although common fruit flies (*Drosophila melanogaster*) presumably do not experience feelings of "fear," it is clear that they detect and actively avoid a range of threats (Gibson et al., 2015; Jonsson, Kravitz, & Heinrich, 2011; Suh et al., 2004). For example, drosophila, like humans, innately engage in avoidance of high CO_2 concentrations, as well as the odorants released by stressed flies (Ai et al., 2010; Garner, Attwood, Baldwin, James, & Munafò, 2011; Lejuez, O'Donnell, Wirth, Zvolensky, & Eifert, 1998; Marshall-Berenz, Gonzalez, Leyro, & Zvolensky, 2011; Prehn, Ohrt, Sojka, Ferstl, & Pause, 2006; Suh et al., 2004). In fruit flies, CO_2 avoidance at low concentrations (~2%) relies on a single type of acid-sensing olfactory sensory neurons, which can affect behavior through multiple internal pathways (Suh et al., 2004). As I will outline later, critical molecular features of this olfactory sensory neuron may be conserved in humans, where CO_2 inhalation can induce air hunger and panic attacks.

The neurobiological bases of CO_2-induced panic in humans remain unknown, but unlike many other fears, the emotional consequences of CO_2 inhalation appear to be triggered by neurons outside the amygdala, as humans with bilateral amygdala damage can experience panic after CO_2 inhalation (Feinstein et al., 2013; Feinstein, Adolphs, Damasio, & Tranel, 2011). In rodents, there is some evidence to suggest that CO_2 inhalation–induced panic is mediated by the periaqueductal gray (PAG) (Schimitel et al., 2012).

CO_2-induced panic in humans has been suggested to be initiated by acid-sensing (proton-gated) ion channels, which are similar to those that play a role in CO_2 avoidance in fruit flies (Ziemann et al., 2009). Acid-sensing channels are expressed throughout the brain, in regions that include the PAG (see: http://mouse.brain-map.org/). Moreover, these receptors are largely evolutionarily conserved across fish and mammals, and seem to have been elaborated from the genes required for CO_2 avoidance in the ancestry we share with flies (see: https://www.ncbi.nlm.nih.gov/gene/). Together, these data provide an example of an evolutionarily conserved sensation that leads to avoidance behavior. These data suggest that over the course of evolution, CO_2-avoidance has been elaborated from its initial olfactory-sensory mechanism, to be incorporated into a distributed neural circuit in the human brain that can trigger the subjective experience of panic. This suggests that emotional brain systems are, in part, instantiated in sensory molecules that represent conserved needs for survival.

Panic upon CO_2 detection is not the only example of evolutionarily conserved molecular function relevant to emotion. The molecular bases of unconditioned fear and anxiety are also at least partially shared across many species. One of the most effective anti-anxiety medications in humans is diazepam, first marketed as *Valium*. Diazepam functions to decrease anxiety-like behavior in monkeys (Kalin & Shelton, 1989), mice (Crawley & Davis, 1982; Davis, 1992), and even zebrafish (Bencan, Sledge, & Levin, 2009). Based on studies in non-human animals, we know that diazepam works by facilitating GABA-ergic (gamma-aminobutyric acid–ergic) transmission at specific GABA-receptor complexes (e.g. Rowlett, Platt, Lelas, Atack, & Dawson, 2005; Rudolph et al., 1999). This is particularly interesting because it suggests that endogenous ligands that activate benzodiazepine-sensitive GABA-receptor sites may serve an evolutionarily conserved function to decrease anxiety. Importantly, in the human brain, the expression of GABA-ergic receptor complexes that bind benzodiazepines is not limited to brain regions that humans share with zebrafish, nor are they uniformly distributed throughout the brain (see: http://human.brain-map.org/). Rather, it seems that these receptor complexes are preferentially, but not uniquely, expressed throughout fear and anxiety–relevant brainstem, limbic, and cortical brain regions, including the central nucleus of the amygdala. Again, this suggests that evolution has effectively taken an emotionally relevant molecular mechanism and incorporated it into our brain throughout evolution.

The hypothalamic-pituitary-adrenal (HPA) axis provides another excellent example of evolutionarily conserved molecular pathways relevant to understanding emotion. In the HPA axis, corticotrophin-releasing hormone (CRH) is released by hypothalamic neurons, promoting the release of adrenocorticotrophin hormone (ACTH) from the anterior pituitary, which, in turn, promotes the release of cortisol from the adrenal glands (Herman & Cullinan, 1997). Interestingly, all vertebrates make corticosteroids, and the genes that encode CRH, ACTH, and corticotrophin are conserved in species even further back in our evolutionary tree (Nesse, Bhatnagar, & Young, 2007). These days, the HPA axis is primarily discussed in relation to the experience of potential threat, and, in humans, it has been specifically linked to social threat (Dickerson & Kemeny, 2004), but this has not always been the case. Corticosteroids are thought to have been involved in preparing the body to respond to threat, and to alter non-specific

immunity. However, at each level of HPA function, molecules have been co-opted (i.e., exapted) for other aspects of threat-responding. CRH can trigger locus coeruleus activity to alter attention processes (Berridge & Waterhouse, 2003); ACTH can be cleaved from the same polypeptide family (Proopiomelanocortin) as the beta-endorphins that can temporarily suppress pain (Harris, Dijkstra, & Hofmann, 2014); and corticosteroids can alter gene expression to alter memory formation (de Quervain, Roozendaal, & McGaugh, 1998; Kim & Diamond, 2002). Thus, much like emotions themselves, the molecular bases of emotions have co-evolved with the body they live in. In primate species, stress can alter corticosteroid gene expression in cortical brain regions that do not exist in the common ancestors with whom we share corticosteroids (Patel, Katz, Karssen, & Lyons, 2008). Together, these data highlight the multifunction role of emotion-relevant molecules, and provide numerous examples in which molecular underpinnings of emotion have been evolutionarily conserved and incorporated into the evermore-complex and more recently evolved brain systems.

In summary, many of the molecular building blocks of emotion are conserved across species, and, in human brains, these molecules have been built upon and repurposed to provide additional context and quality to the experience of emotion.

EMOTIONS ARE, IN PART, ORGANIZED ACROSS DISTRIBUTED BRAIN CIRCUITS

We have established that many emotionally relevant functions were established hundreds of millions of years ago as our ancestors diverged from the ancestors of flies, fish, and slugs over the course of evolution. These molecules are now incorporated into the brains of mammalian species, and through regulation of their expression and their incorporation into emotion-related brain regions, they have continued to expand their functional role in the experience of emotion. This process, by which our brains have elaborated upon emotion-relevant systems, has continued through the more recent evolution of mammals, including primates.

Throughout mammalian evolution, natural selection has favored the brain systems that support adaptive behavior. Because many behaviors have remained adaptive, it is unsurprising that the neural substrates that underlie these behaviors have been conserved. For example, in rodents, it has been well established that freezing behavior to avoid detection by an inescapable potential predator relies on the periaqueductal gray (Bandler & Shipley, 1994; Tovote et al., 2016). Freezing behavior remains adaptive in humans in response to many inescapable potential threats, and the corresponding macrostructure of the PAG remains remarkably similar (see: http://atlas.brain-map.org/; Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012). Moreover, fMRI studies suggest the PAG is involved in responding to threats in the MRI scanner (Satpute et al., 2013), and invasive studies suggest stimulation of the periaqueductal gray can induce feelings of fear and panic (Nashold, Wilson, & Slaughter, 1969). Although less is known about our aquatic ancestors, the homologous region of the zebrafish brain (griseum centrale), seems to play a similarly crucial role in triggering threat-elicited freezing (Agetsuma et al., 2010). In mammals, however, the brain network surrounding the PAG is highly complex. PAG function can be modulated directly via direct projections from both subcortical regions, like the central nucleus of the amygdala (Ce), and cortical regions, including the subgenual anterior cingulate (An, Bandler, Ongür, & Price, 1998; Bandler, Keay, Floyd, & Price, 2000; Davis & Whalen, 2001; Tovote et al., 2016). Many other regions are poised to influence PAG function indirectly, via connections to PAG-projecting neurons in the Ce (Davis & Whalen, 2001). This circuitry highlights the multiple mechanisms by which the prefrontal cortex can alter emotion-relevant behavior, and it highlights how evolutionarily conserved regions can be incorporated into a more complex network of brain regions.

Brain regions do not remain static throughout evolution. Although the basic divisions of the amygdala are conserved between rodents and humans, substantial changes have occurred over 75 million years of evolutionary divergence (Fox, Oler, Tromp, Fudge, & Kalin, 2015; Gibbs et al., 2007). In comparison to rodents, non-human primates have relatively enlarged basal and lateral amygdala regions. These regions are expanded even further in humans and are thought to correspond to an increasing reliance on emotional learning via visual information (Chareyron, Banta Lavenex, Amaral, & Lavenex, 2011; Pitkänen & Amaral, 1998; Turner, Mishkin, & Knapp, 1980). Thus, even brain regions that are largely homologous

across species continue to be elaborated to fit the specialized needs of humans and other species during the course of evolution.

Just as evolution can co-opt emotion-relevant molecules and brain regions, those brain regions can also be incorporated into larger networks of brain connectivity. This process provides a mechanism for recently evolved brain regions to elaborate and refine evolutionarily old functions. This is one way that recently evolutionarily diverged prefrontal cortex (PFC) regions continue to be implicated in emotion-relevant processing. Perhaps the most famous demonstration of prefrontal cortical involvement is the story of Phineas Gage (Macmillan, 2002), but many studies in humans, nonhuman primates, and rodents have demonstrated that damage to the prefrontal cortex leads to pervasive alterations in threat processing. In rodents, projections from part of the prefrontal cortex, the infralimbic cortex (IL), to the amygdala play a role in extinguishing threat-related memories (Milad & Quirk, 2002, 2012). In nonhuman primates, orbitofrontal cortical amygdala interactions are critical for guiding behavior in response to alterations in how an animal predicts to be rewarded or punished (e.g., value-guided decision-making) (e.g., Baxter, Parker, Lindner, Izquierdo, & Murray, 2000; Murray & Izquierdo, 2007). In humans, fMRI studies in neurologically intact individuals suggest that emotion regulatory processes rely on the prefrontal cortex (Buhle et al., 2013). In addition, the previously mentioned divergence in amygdala volume is accompanied by increased connectivity with the well-developed primate prefrontal cortex. It is, at least in part, through these bidirectional amygdala-prefrontal connections, which course through the uncinate fasciculus, that recently evolved prefrontal cortical regions can play a critical role in the processing of emotion. This proposed role of prefrontal regulation of amygdala function suggests that amygdala function may not be strictly comparable across species, and it provides a plausible mechanism by which emotionally relevant information can be transmitted from prefrontal cortex to the evolutionarily older effector systems, for better (extinction and reappraisal) or worse (rumination, anxious apprehension).

Together, these data demonstrate that as some brain regions continue to diverge further and further from the evolutionarily-conserved emotion-related circuitry that we share with other species, these recently evolved brain regions continue to serve our emotional needs.

CONCLUSION

Emotions are not organized in any way that is amenable to a single method (or "level" of analysis). It is clear that specific molecules, the neurons they are expressed in, and the way those neurons are connected to each other all play an important role in giving rise to more complex emotional states, traits, and disorders. The study of brain evolution can help guide our understanding of how emotions are organized in the brain.

The principles discussed here apply to all functional emotional systems. Many of the known molecular substrates associated with alterations of human emotion have been largely conserved across the genomes of flies, fish, mice, monkeys, and humans for hundreds of millions of years. The genes that code for the dopamine and serotonin systems are highly homologous to their ancestral counterparts (e.g., Peroutka & Howell, 1994; Strausfeld & Hirth, 2013). Each of these molecules can have widespread influences on multiple aspects of emotion (i.e., experience, behavior, and physiology), and is hypothesized to be critical to emotional processing (Berger, Gray, & Roth, 2009; Canli & Lesch, 2007; Haber & Knutson, 2010; Wise & Rompre, 1989).

The building blocks of emotion developed over hundreds of millions of years and are continuously revised to meet the needs of our species. Our brains are not like Russian nesting dolls, wherein we have grown complex cortical controllers for our "reptilian brains"; the true organization of the brain is very much more complex (and is likely to extend outside of the central nervous system; see Rosenkranz's response to Question 11). Evolution has resulted in bidirectional connections between the evolutionarily old and new, has altered the molecular composition and regulation of conserved regions, and has inserted evolutionarily old molecules into more recently evolved brain regions. Our brains are organized to emote. Much like the understanding emotion itself, a full understanding of the biology that gives rise to emotion will require a coordinated cross-species systems biology approach.

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