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Authors

Malezieux, Meryl
Klein, Alexandra S
Gogolla, Nadine

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Neural Circuits for Emotion

Meryl Malezieux,[1,2,*] Alexandra S. Klein,[1,3,*] and Nadine Gogolla[1,2]

[1]Circuits for Emotion Research Group, Max Planck Institute of Neurobiology, Martinsried, Germany

[2]Current affiliation: Emotion Research Department, Max Planck Institute of Psychiatry, Munich, Germany; email: ngogolla@psych.mpg.de

[3]Current affiliation: Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, California, USA

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*These authors contributed equally to this article

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Abstract

Emotions are fundamental to our experience and behavior, affecting and motivating all aspects of our lives. Scientists of various disciplines have been fascinated by emotions for centuries, yet even today vigorous debates abound about how to define emotions and how to best study their neural underpinnings. Defining emotions from an evolutionary perspective and acknowledging their important functional roles in supporting survival allows the study of emotion states in diverse species. This approach enables taking advantage of modern tools in behavioral, systems, and circuit neurosciences, allowing the precise dissection of neural mechanisms and behavior underlying emotion processes in model organisms. Here we review findings about the neural circuit mechanisms underlying emotion processing across species and try to identify points of convergence as well as important next steps in the pursuit of understanding how emotions emerge from neural activity.

Contents

INTRODUCTION

What is an emotion? Everyone has an intuitive sense of what an emotion is; however, among scientists, the definition of emotions remains vigorously debated (Adolphs 2017; Adolphs & Anderson 2018; Adolphs & Andler 2018; Adolphs et al. 2019; Anderson & Adolphs 2014; Berridge 2018; Bliss-Moreau 2017; de Waal 2011; de Waal & Andrews 2022; Feldman Barrett 2006; James 1884; LeDoux 2012, 2021; LeDoux et al. 2016; Panksepp 2005, 2011a). This controversy may be partly due to attempts at explaining different phenomena. From a human psychological perspective, emotions are often defined as consciously perceived feelings of emotions (LeDoux & Hofmann 2018, Russell 1980). However, emotions can also be defined by their assumed function in supporting survival (Adolphs & Andler 2018, Ekman & Oster 1979, Shariff & Tracy 2011, Zych & Gogolla 2021). In this view, emotions are hidden internal states that can be inferred from knowledge about their causes and consequences and are conserved across species (Adolphs & Andler 2018, Anderson & Adolphs 2014, Darwin 1872, Kryklywy et al. 2020, Panksepp 2005).

In our view, the struggle to define emotions should not prevent scientists across disciplines and with different viewpoints from jointly tackling some of the most burning questions in affective neurosciences: How are different aspects of emotions (conscious experience and functional states) implemented in the brain? How do functional emotion states relate to conscious, subjective feelings? Do animals have emotions, and if so, to what extent do they experience them? Gaining insights into these questions may also inform us about the mechanisms underlying emotional disorders and thus is of clinical relevance.

We want to advocate for collaboration among scientists from multiple disciplines, studying diverse species, as well as for the formulation of specific and testable hypotheses that may help to resolve points of dissent. To that end, we first review a few general insights into the neural circuits underlying selected, discrete functional emotion states, which have been mostly studied in animal models. We then highlight a few emerging principles common to the neuronal circuits underlying these discrete functional emotion states. We further attempt to extract what has been learned from animal studies about the encoding of valence versus discrete emotion states and finally conclude with suggestions for future directions in the field of emotion research.

DEFINING AND INVESTIGATING EMOTIONS ACROSS SPECIES

In this review, we consider emotions as functional states (functional emotion states, or emotion states for short) that are adaptive for the organism and differentiate these functional emotion states from the conscious percepts of emotions (feelings of emotion), which can only be assessed in humans. For now, we remain agnostic about how these two concepts relate, although we believe that they are oftentimes (but likely not always) linked. Indeed, some brain regions have been implicated in both the processing of functional emotion states and the emergence of feelings of emotions (Damasio 1998, Damasio & Carvalho 2013), indicating an intricate relationship between the two phenomena. On the other hand, evidence from human research has shown that subliminal emotional stimuli can elicit unconscious emotional reactions and bias behavior, even in the absence of conscious associated feelings (Berridge 2018), thus providing evidence that emotion states and feeling of emotions can also exist as separate phenomena.

Recognizing emotions as evolutionarily conserved functional states allows us to consider scientific evidence collected from different species, including human and nonhuman animals. Functional emotion states can be conceptualized as central brain states arising from a multitude of external and internal inputs and affecting a multitude of variables in behavior, body, and brain (Adolphs 2017, Adolphs & Anderson 2018, Adolphs & Andler 2018, Anderson & Adolphs 2014, Damasio & Carvalho 2013, Panksepp 2011a). In this view, the presence of an emotion state can be inferred from observations of its causes and consequences, and feelings of emotion may, or may not, accompany it. Furthermore, emotion states have been proposed to be characterized by certain features that may help to distinguish emotion states from other behavioral states or reflexes and to identify these states across diverse species (**Figure 1**) (Adolphs 2017, Adolphs & Anderson 2018, Anderson & Adolphs 2014). These features include the following:

- Global coordination and pleiotropy: Emotion states coordinate multiple (pleiotropic) behavioral, bodily, biochemical (i.e., hormonal, neurochemical), and cognitive changes and thus globally affect the entire organism.
- Valence: Emotion states can usually be characterized as positive or negative (Berridge 2019, Namburi et al. 2015, Tye 2018).
- Intensity: Emotions occur in a graded manner, ranging from weak to strong.
- Priority: Emotion states gain priority over many ongoing processes such as volitional or other ongoing behaviors.
- Generalization: Emotion states may be elicited by stimuli or contexts that were associated with the initial trigger stimulus.
- Persistence: Emotion states usually outlast the initial trigger stimulus.

Emotion states have also been referred to as action programs to underline that they are causing pleiotropic changes and to distinguish them from feelings of emotion (Damasio & Carvalho 2013). It is important to note that the term action programs also implies automaticity. However,

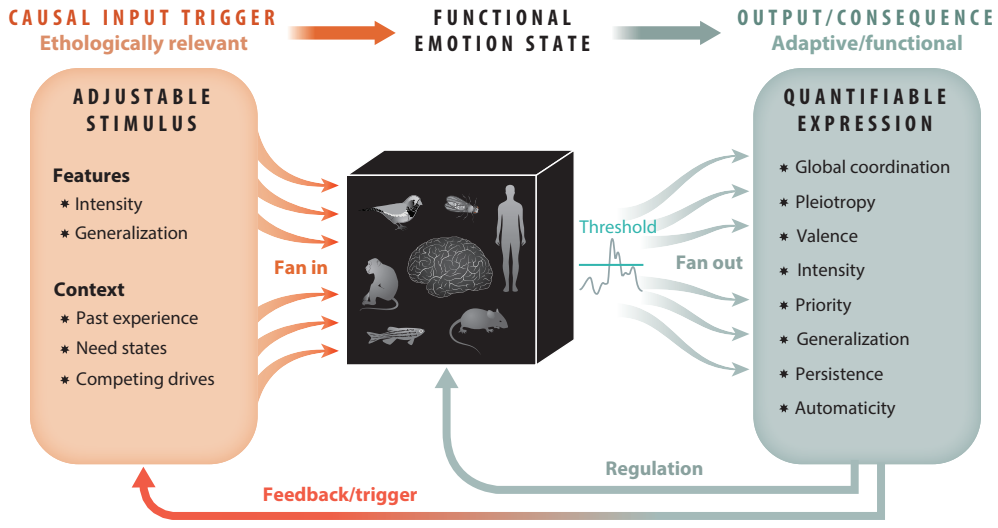

Figure 1

Experimentally inferring emotion states across species. Evolutionary conserved functional emotion states (*black box*) are hidden internal states that can be inferred from knowledge about their causes (input or trigger, *left*) and consequences (emotion expression, *right*). Diverse triggers and contexts can cause similar emotion states (fan in), which can elicit a multitude of organismal changes (fan out). This arrangement allows the researcher to experimentally control and manipulate diverse features and contexts of ethological emotion triggers, quantify the resulting expression of the emotion state, and test whether the expressions adhere to emotion-characteristic features. The relationship between changes in stimulus input and the response of the organism can help to infer the presence of an emotion state.

while emotion states trigger recurrent patterns of coordinated organismal changes, they are also flexible and adapt to the circumstances and nature of the emotion trigger. Emotion expressions can thus be thought of as semiflexible, situated between stereotypic reflexes and volitional behavior (Adolphs & Anderson 2018, Anderson & Adolphs 2014).Taken together, assessing whether behavioral, physiological, and neural activity patterns adhere to at least some of these properties may help to identify them as emotion states across species. Furthermore, dissecting the complexity of emotion states into separable features and studying their underlying neural mechanisms in isolation may yield insights into possibly conserved neural circuit motifs.

NEURAL CIRCUITS UNDERLYING FUNCTIONAL EMOTION STATES

The majority of past research has addressed emotions as distinct states, considering either a clear function (in animal models) or feeling of emotion (in humans). Here we first focus on insights gained from studying emotions as separate states. However, it should be noted that whether emotion states are represented in categories of discrete states or decoded from variables along continuous dimensions remains an unresolved question in affective neurosciences.

Neural Circuits for Fear and Anxiety

Conceptually, fear is elicited by a realistic and acute threat, whereas anxiety is evoked by potential, inferred, or anticipated threat (Blanchard & Blanchard 2008, Davis et al. 2010, Grupe & Nitschke 2013). These closely related concepts are the most studied and currently best understood emotion states for several reasons: Expressions of fear and anxiety are well conserved, easily detected, and quantified across animal species. Similarly, ethologically relevant trigger stimuli are easily

identified and experimentally applied. Consequently, nonhuman animal research has delivered a wealth of mechanistic insights into the neural circuits underlying fear and anxiety. We refer the reader to reviews providing in-depth discussions of the neural underpinnings of fear and anxiety (Calhoon & Tye 2015, Tovote et al. 2015) and focus here on summarizing a few emerging principles.

Fear and anxiety engage overlapping but also distinct circuit mechanisms (Tovote et al. 2015). While fear stimuli are generally sensory and therefore processed through the thalamus as well as primary and associative sensory cortices, anxiety triggers are more difficult to localize to specific input structures but likely emerge through sensory, interoceptive (i.e., related to sensory information derived from the body), and/or cognitive paths (Calhoon & Tye 2015, Tovote et al. 2015). Commonly, coordinated activity in the amygdala, bed nucleus of the stria terminalis (BNST), ventral hippocampus (vHPC), and medial prefrontal cortex (mPFC) is thought to evaluate the presence or absence of threat. These brain regions are strongly and reciprocally interconnected, and thus threat stimuli are evaluated by multiple circuit elements. These macrocircuits include both feedforward and feedback signaling from the amygdala to BNST, mPFC, and vHPC, as well as from mPFC and vHPC toward BNST and amygdala (Calhoon & Tye 2015). Circuit computations underlying fear and anxiety seem to overlap most at this macroscopic level, although only few studies have explicitly addressed the interactions between both states (but see Gründemann et al. 2019, Tovote et al. 2015).

Once a threat is detected and a threshold is passed, pathways to trigger expressions of fear (or anxiety) are recruited. Among these are circuits in the periaqueductal gray (PAG), central amygdala (CeA), hypothalamus, lateral septum (LS), and dorsal vagal complex (Calhoon & Tye 2015, Tovote et al. 2015). Depending on the nature and characteristics of the threat, different adaptive defensive behaviors are elicited (Perusini & Fanselow 2015, Zych & Gogolla 2021). Interestingly, diverse modes of fear and anxiety expressions and their underlying neural correlates are remarkably conserved across species (Blanchard et al. 2001, Fanselow 1994, Roelofs 2017, Roelofs & Dayan 2022, Zych & Gogolla 2021).

Fear and anxiety induce states of different persistence and can occur across multiple timescales. Interestingly, in mice, neurons in the insular cortex exhibit long-lasting activity increases in states of heightened anxiety, and this activity is necessary for the persistence of the defensive state (Gehrlach et al. 2019). Similarly, a neuronal subpopulation in the mouse ventromedial hypothalamus exhibits activity that lasts for many tens of seconds after exposure to predator threat, and this activity is required for persistent defensive behaviors (Kennedy et al. 2020). Similar persistent activity changes related to anxiety are found in the basolateral amygdala (BLA) (Gründemann et al. 2019, Lee et al. 2017).

A recurrent theme emerging from the study of fear and anxiety circuits is that of functional antagonism. Indeed, individual nodes, including but not limited to BLA, CeA, and mPFC, are composed of closely intermingled or neighboring circuit elements that have opposite influences on fear and anxiety (Calhoon & Tye 2015, Tovote et al. 2015). This functional opposition can be mediated in several ways. One implementation involves projection-specific neuronal populations, which originate within the same brain region and are able to interact yet mediate opposite effects. For instance, while selective activation of excitatory axonal projections from the BLA to the CeA is anxiolytic, the activation of BLA projections to the vHPC is anxiogenic (Tovote et al. 2015). Another way to mediate opposition is observed in subregions of single brain structures. In the BNST, two neighboring subregions were shown to either promote or impede anxiety (Kim et al. 2013). Similarly, the two main subregions of the mouse PFC influence fear learning in opposing manners: While the input that the amygdala receives from the prelimbic cortex facilitates threat responses, input from the infralimbic cortex suppresses them (Calhoon & Tye 2015). This close

apposition of functionally antagonistic circuits is not restricted to fear and anxiety and is discussed further below when we extract recurrent schemes in emotion coding.

Another lesson learned from the study of fear and anxiety is that discrete emotion states cannot be explained by the activity in a single brain region or neuronal circuit. For a long time, the amygdala seemed a prime candidate to be both sufficient and necessary to produce fear. Indeed, the famous case study patient S.M. suffering from bilateral amygdala damage showed extreme deficits in processing and experiencing fear triggered by external factors or by observing other people's fearful faces (Feinstein et al. 2011). However, later studies showed that patient S.M., as well as other patients with similar lesions, still experienced fear and even panic when exposed to high concentrations of CO_2 (Feinstein et al. 2013). These data suggest that the amygdala is not an essential neural substrate for the experience of fear. Possible interpretations of these striking findings include that there may be amygdala-dependent but also amygdala-independent states of fear, that the amygdala is only part of the processing stream and may be dispensable for fear triggers originating within the body, or that there are no fixed neural correlates of fear and the subjective experience of fear is constructed through inference from diverse neural signals (Feldman Barrett 2017).

Given that fear and anxiety circuits have been extensively studied, do we know whether neuronal mechanisms underlying fear processing are shared between human and nonhuman animals? A few recent studies have highlighted strong similarities in the processing of fear across species. One human neuroimaging study discovered a human colliculus-pulvinar-amygdala circuit that encodes negative emotions and that is highly similar to a previously described visual threat pathway in rodents (Kragel et al. 2021). Another study by Terburg et al. (2018) identified a conserved circuit mechanism in the BLA to regulate escape behavior in rodents and humans. The identification of conserved circuit motifs fills a critical gap between rapidly emerging data on precise neural circuit mechanisms obtained in model organism and human studies.

Neural Circuits for Anger and Aggression

Anger can be described as a negative functional emotion state triggered by diverse aversive circumstances, such as not receiving an expected reward, not achieving the goal of an action, or actions by others that impact the individual's own goals or needs (Richard et al. 2022). One way to express anger is via aggression; however, it is not clear whether all aggressive behaviors are motivated by anger or a separate aggressive emotion state. Similarly, anger, as any functional emotion state, is expressed in a pleiotropic manner, including bodily, cognitive, and diverse behavioral changes. Strikingly, while anger seems by definition to be a negative state, the valence of aggression can, at least under certain circumstances, be positive. For example, it has been shown that mice exhibit preference for aggressive behaviors via dopaminergic signaling in striatal circuits (Golden et al. 2019, Goodwin et al. 2020, Nelson & Trainor 2007).

Most of our knowledge concerning the neural circuit underlying the potentially related anger and aggressive states comes from animal models, where most of the work has focused on aggressive behavior in social contexts (Anderson 2016, Lischinsky & Lin 2020, Nelson & Trainor 2007, Richard et al. 2022). As has already been seen in the case of fear, current models of the neural basis for aggression involve several processing steps. First, diverse sensory inputs are detected, processed, and evaluated. The threshold to express aggressive actions is modulated by other internal state variables such as stress, reproductive, circadian, or energy status. The necessary processing is thought to occur in what has been referred to as the core aggressive circuit, encompassing several strongly interconnected nuclei such as the medial amygdala, BNST, ventromedial hypothalamus, and ventral part of the premammillary nucleus (Lischinsky & Lin 2020, Nelson & Trainor 2007). Evidence collected across species and phyla, including mice, birds, and primates, has found neural

activity correlates upon aggression in all of these centers, and furthermore, manipulations within these brain regions either support or abolish aggression in mice (for details, see Anderson 2016, Lischinsky & Lin 2020). Finally, as a last step, species-specific aggressive behaviors are exhibited, which are usually scaled in intensity from threat display to overt attack. Aggressive motor output is triggered either through direct projections to the midbrain premotor areas or by indirectly impinging on striatal motor circuits and midbrain neuromodulatory systems (Lischinsky & Lin 2020). One key site for aggressive action is the PAG. For example, the PAG is involved in threatening calls in rodents and primates (Jürgens & Ploog 1970, Tschida et al. 2019), and studies in mice revealed that PAG neurons project to jaw muscles and are necessary for aggressive biting (Falkner et al. 2020).

While processing of aggression is hypothesized to occur mostly in subcortical regions, these circuits are under tight forebrain control. Early experiments by Phillip Bard (1928) reported that cats with removed cerebral hemispheres exhibited spontaneous aggression, or sham rage. Hess & Akert (1955) corroborated these results by direct electrical stimulation of distinct sites in the hypothalamus. Current evidence suggests that the mPFC and the LS in particular tonically suppress the hypothalamus to block aggression. Indeed, humans with lesions in their forebrain exhibit increased aggression levels, and inversely, stimulation of the PFC may reduce aggression (Best et al. 2002, Choy et al. 2018). Optogenetic activation of the mPFC reduces—but its activation promotes—aggressive behavior in mice. However, one discrete subpopulation of mPFC neurons inversely promotes aggressive behavior (Biro et al. 2018, Takahashi et al. 2014). Similarly, evidence from mice, rats, and songbirds suggests that lesions of the LS also result in increased aggression, termed septal rage (Lischinsky & Lin 2020). These results reveal an interesting motif where aggression seems to be tonically promoted and has to be actively inhibited to be contained.

A further striking feature of the circuits involved in aggression is that they are situated in very close proximity to, or even overlap with, circuits mediating sexual behaviors and defensive behaviors elicited by fear (Anderson 2016). This overlap in brain regions and neural circuits involved in different emotions is a recurrent scheme that we discuss below.

Neural Circuits for Pleasure

Animals, including humans, actively seek appetitive stimuli. Upon attainment of appetitive goals (e.g., consumption of food, relief from adversity, or achievement of social goals), a positive emotion state is elicited. This state (or states) of pleasure probably evolved to reinforce behaviors that are beneficial for survival and motivate the individual to pursue rewards and care for themselves and for others (Berridge 2018, Berridge & Kringelbach 2015, Burgdorf & Panksepp 2006).

Positive affective states have been shown to consist of two separable processes: pursuit of and acute exposure to pleasant (hedonic) stimuli. These two processes have been termed wanting and liking, respectively (Berridge & Dayan 2021, Berridge & Kringelbach 2015, Berridge & Robinson 2003, Burgdorf & Panksepp 2006). While wanting and liking often co-occur, their underlying neural correlates are separable and the two processes can be temporarily dissociated (Berridge 2018, Berridge & Kringelbach 2015). The state of wanting is mediated by a large collection of brain areas and usually involves dopamine signaling. While dopamine suppression decreases appetitive seeking (Wise 2006), taste-evoked liking or pleasure reactions are not diminished by the same manipulation (Peciña et al. 1997). This evidence refutes a long-held hypothesis suggesting that the mesolimbic dopamine system is integral to the state of pleasure. Indeed, evidence in rats and humans clearly demonstrates that dopamine is neither necessary nor sufficient for pleasure to be expressed or experienced (Berridge & Robinson 1998, Brauer & De Wit 1997, Liggins et al. 2012, Peciña et al. 2003, Sienkiewicz-Jarosz et al. 2013).

How does one assess liking or the emotion state of pleasure in nonhuman animals? While human studies usually involve conscious, subjective ratings of pleasure, objectively quantifiable hedonic reactions have also been identified across species. Orofacial expressions of liking as well as disliking (or disgust) occur in newborn infants, apes, and monkeys, as well as in rats and mice (Dolensek et al. 2020; Ganchrow et al. 1983; Grill & Norgren 1978a,b; Steiner et al. 2001). While the brainstem controls these behavioral expressions (Grill & Norgren 1978b, Steiner 1973), their initiation and regulation are tightly controlled by forebrain structures.

Indeed, consistent with the notion that orofacial expressions represent expressions of emotion states and not simple reflexes, they are modulated by internal states such as hunger and thirst (Dolensek et al. 2020, Kaplan et al. 2000) and associative learning (Delamater et al. 1986, Dolensek et al. 2020), and they are subject to hedonic enhancement through neurochemicals (Berridge & Kringelbach 2015, Castro & Berridge 2017, Mahler et al. 2007). Further, they exhibit emotion features, including scalability, valence, flexibility, and persistence (Dolensek et al. 2020, Grill & Norgren 1978a). Apart from orofacial movements, vocalizations displayed during prosocial interactions or anticipation of rewards have been characterized as behavioral expressions of positive emotions in primates and rodents (Jürgens 1979, Knutson et al. 2002, Panksepp & Burgdorf 2000).

Using orofacial movements as readouts of pleasure, research in rodents has shown that activation of hedonic hot spots in the brain can enhance the liking reactions to sweetness (Berridge & Kringelbach 2015). These hot spots have been found in rats within the orbitofrontal cortex, insular cortex, medial shell of the nucleus accumbens (NAc), and ventral pallidum (VP) (Berridge 2003, Berridge & Kringelbach 2015, Castro & Berridge 2017). Interestingly, hedonic hot spots are functionally connected so that blocking opioid function in one prevents the liking enhancement in the other (Smith & Berridge 2007).

Intriguingly, while stimulation of the prefrontal cortex and NAc is sufficient to enhance liking, neither of them is necessary; that is, damage does not cause loss of hedonic function (Berridge & Kringelbach 2015). So far only one region has been identified as necessary for liking: the VP. Lesions in this brain area produce reversal from liking to disliking, causing sweetness to elicit excessive disgust reactions (Cromwell & Berridge 1993, 1994).

Finally, even though humans make clear distinctions in their feelings of pleasure, it is currently unknown whether only one or different brain states of pleasure exist. In humans, many diverse rewards, including food, sex, and addictive drugs, activate a largely overlapping set of brain regions that have also been highlighted by studies in animal models. These regions include orbitofrontal, insular, and anterior cingulate cortices, as well as the NAc, VP, and amygdala (Berridge & Kringelbach 2015).

Neural Circuits for Disgust

Disgust is a strong functional emotion state aimed at avoiding potential sources of disease (Chapman & Anderson 2012; Curtis 2011, 2014; Kavaliers et al. 2019; Stevenson et al. 2019). Through human evolution, disgust may have been extended to more abstract stimuli such as social stimuli or moral transgressions (Chapman & Anderson 2012). Disgust evokes characteristic behavioral patterns that are scaled in intensity. Orofacial expressions of disgust such as mouth gapes and headshakes can be triggered by bitter or exuberantly salty tastants in mammals, including humans, rats, and mice (Berridge 2018; Dolensek et al. 2020; Grill & Norgren 1978a,b). While emotion states of disgust and fear are both considered defensive states, the behavioral expressions of these states, as well as their neural correlates, are clearly separable. Indeed, studies in humans suggest that fear and disgust regulate sensory acquisition in opposing directions: When experiencing fear, human subjects cover larger visual fields, exhibit faster eye movements, and increase

the nasal volume and air velocity during breathing, whereas disgust induces opposite changes (Susskind et al. 2008).

The neuronal correlates of disgust only started to emerge recently and were reviewed elsewhere (Berridge 2018, Berridge & Kringelbach 2015). In short, neuroimaging studies found activity in insular cortex and subcortical striatal circuitry to be correlated to the experience of disgust in humans (Chapman & Anderson 2012). Findings in mice demonstrating neuronal activity in insular cortex neurons that correlates with expressions of disgust corroborate these results (Dolensek et al. 2020). Furthermore, mouse facial expressions of disgust can be evoked by optogenetic stimulation of the posterior insula (Dolensek et al. 2020, Wang et al. 2018). Intriguingly, studies from the Berridge lab (Ho & Berridge 2014) have revealed that small lesions in an otherwise hedonic hot spot of the VP can cause sweetness to elicit excessive disgust reactions. Similar observations were made earlier when large ablations of the entire telencephalon, which included the VP and other forebrain structures, were shown to cause disgust and other aversive emotions (Bard 1928, Grill & Norgren 1978b). These surprising findings hint at a disinhibition of a negative-valenced circuitry in the remaining forebrain that resembles the disinhibition of aggressive behavior by forebrain lesions discussed above.

Taken together, while the sensory triggers and behavioral expressions of disgust are clearly distinct from other emotion states such as pleasure or fear, they engage partially overlapping brain areas such as the VP, NAc, and insular cortex.

Neural Circuits for Social Emotions

An important and well-conserved function of emotion is to motivate social behaviors, including mating, pair bonding, coherence of social groups, infant attachment, and prosocial behaviors. Social emotions exhibit emotion features such as scalability, persistence, and valence across species and are strongly modulated by need and context (Anderson 2016, Lee et al. 2021, Lischinsky & Lin 2020, Padilla-Coreano et al. 2022). Whether social emotions represent a distinct category of separable states, can be explained as part of other emotion states (e.g., pleasure, aggression, or disgust), or are defined as continuous variables is not known. While social emotions are often studied as separate phenomena, the brain regions and large-scale circuits of social emotions resemble those underlying self-centered emotions. For instance, aggressive, mating, and parental behaviors are all mediated by distinct circuit elements in the hypothalamus (Anderson 2016, Kohl et al. 2018, Lischinsky & Lin 2020). Studies in mice revealed that observational learning relies on structures such as the anterior cingulate cortex and the amygdala (Allsop et al. 2018). Empathy and prosocial behavior are thought to rely on prefrontal, cingulate, and insular cortices as well as the amygdala across species (de Waal & Preston 2017, Paradiso et al. 2021).

Neural Circuits for Physiological Need States, or Homeostatic Emotions

Bodily alarm and physiological need states such as pain, hunger, thirst, or fatigue have also been referred to as homeostatic emotions (Craig 2003a, Denton 2012). Whether considered as functional emotion states or internal states related to body physiology, they clearly exhibit certain emotion features such as scalability, valence, and global coordination of complex behavioral patterns, oftentimes aimed at restoring homeostasis.

Recent studies in rodents have demonstrated that the neural substrates underlying fear, anger, or pleasure and those serving homeostatic emotions are oftentimes intertwined and sometimes even overlapping. For example, neuronal populations in the mouse insular cortex encode thirst and hunger (Livneh et al. 2020), fear and anxiety (Gehrlach et al. 2019, Klein et al. 2021), pain (Gehrlach et al. 2019), and even precise information about bodily sickness (Koren et al. 2021).

Interestingly, single neurons whose activity strongly correlated to emotion states such as disgust or pleasure (as assessed through facial expressions) were found in the same insular regions that respond to sensory stimuli such as sweet and bitter tastants and pain, but also freezing (Dolensek et al. 2020, Gehrlach et al. 2019). Similarly, human imaging studies have shown that emotions such as pain or disgust perceived in the self or observed in others are encoded nearby and even partially overlappingly in the insular cortex (Singer et al. 2004, Wicker et al. 2003). Similar overlap has been observed in other brain regions. For instance, in the CeA, the same population of genetically identified neurons expressing protein kinase C-δ mediates the influence of anorexigenic signals, gates conditioned fear expression, and amplifies pain responses (Cai et al. 2014, Haubensak et al. 2010, Wilson et al. 2019), while an antagonistic, yet interconnected, cell population expressing serotonin receptor 2a promotes food consumption (Douglass et al. 2017). A similar proximity of emotion and bodily physiology is observed in the hypothalamus, which is implicated in controlling various basic survival functions, including feeding, metabolic control, drinking and excretion, thermoregulation, fever induction, fear and aggression, mating, and maternal care (Saper & Lowell 2014).

The close proximity or overlap of neuronal populations processing classical emotions, social emotions, and homeostatic emotions may be advantageous to compare and align actions in response to diverse simultaneously arising survival needs.

Neural Circuits Linking Interoception and Emotion

Interoception refers to the sensing and experiencing of the physiological state of the body (Chen et al. 2021, Craig 2002), as well as the regulation of bodily functions by the brain (Furman 2021). The links between interoception and emotion constitute the basis of several theories of emotion such as the early theories of James-Lange or Cannon-Bard (Cannon 1927, James 1884, Wallon 1972), as well as more recent emotion theories (Craig 2002, Critchley & Garfinkel 2017, Damasio & Carvalho 2013, Feldman Barrett 2017, Seth & Friston 2016). Feelings of emotion are especially hypothesized to rely strongly on interoception (Feldman Barrett & Simmons 2015, Seth 2013, Seth & Friston 2016).

One of the main routes of information exchange between the body and the brain is the vagus nerve. Signals transmitted via the vagus nerve have been shown to play important roles in motivational and emotional states (Critchley & Garfinkel 2017, Critchley et al. 2013, Mayer 2011). Studies in rodents have revealed multi-synaptic ascending vagal pathways that mediate reward seeking and sugar preference (Bai et al. 2019, Buchanan et al. 2022, Fernandes et al. 2020, Han et al. 2018). Furthermore, interfering with vagal transmission reduces innate anxiety and is associated with lowered noradrenaline levels in the PFC and NAc core (Klarer et al. 2014). A recent study found that freezing-related heart-rate decreases are transmitted to the insular cortex via the vagus nerve and gate fear extinction, suggesting interoceptive modulation of insular cortex activity during freezing as a mechanism to cope with excessive fear (Klein et al. 2021). In humans, cardiovascular signals intensify feelings of fear and anxiety and influence fear processing and emotional learning (Garfinkel & Critchley 2016). A link between interoception, anxiety disorders, and depression, as well as a prominent role for the processing of interoceptive signals in the insular cortex, has been suggested for a long time (Paulus & Stein 2006, 2010; Wiebking et al. 2010). Vagus nerve stimulation has been approved in treatment-resistant depression (Nemeroff et al. 2006), and the potential benefit of vagus nerve stimulation in the treatment of anxiety disorders is currently being considered (McIntyre 2018). Central sensation of breathing, another interoceptive signal, also has a strong influence on fear. Indeed, breathing signals transmitted from the olfactory bulb to the dorsomedial prefrontal cortex are necessary to maintain freezing in mice (Bagur et al. 2021).

Not only do emotion states get influenced by or emerge from bodily sensations, they also prominently elicit changes in the body. Emotion expressions affect all systems and organs of the body, including the gastrointestinal tract, heart, lung, immune system, and vascular system (Ashhad et al. 2022, Critchley & Garfinkel 2017, Critchley et al. 2013, D'Acquisto 2017, Kreibig 2010, Mayer 2011). Indeed, multivariate pattern classification was able to extract emotion-specific changes in simultaneously acquired autonomic nervous system parameters, including measures of cardiovascular, electrodermal, respiratory, thermoregulatory, and gastric activity (Kragel & LaBar 2014).

Thus, bodily signals influence different aspects of emotion such as feelings of emotion, emotion expression, and persistence. Emotion states and feelings in turn adaptively regulate body functions. This circular arrangement allows for an intriguing feedback loop that remains poorly understood.

RECURRENT SCHEMES IN NEURAL CIRCUITS FOR EMOTION

The evidence reviewed above summarizes insights we have gained from studying distinct functional emotion states separately. In the following section, we will highlight a few common schemes that appear in the neural circuits underlying emotion states.

Overlap in Brain Regions Involved in Emotion

It becomes obvious from the evidence reviewed above that diverse functional emotion states engage a largely overlapping set of brain regions. Indeed, there seem to be a few emotion hub regions that play a role in most, if not all, emotion states. Among these are subcortical regions such as the hypothalamus, amygdala, and NAc; cortical regions such as the insular and anterior cingulate cortices and mPFC; and brainstem regions such as the PAG. **Figure 2** highlights how distinct functional emotion states overlappingly engage brain regions across the entire brain.

Hierarchical, Parallel Processing Streams and Feedback Loops

The idea that distinct emotion states engage distributed but overlapping brain regions is not new. Brain-wide circuit models for emotion were proposed eight decades ago by Papez (1937) and MacLean (1949). In more recent years, Panksepp (2011b) proposed that emotion states are processed on three different levels defined by nested anatomical hierarchies. According to Panksepp, primitive features of emotion are processed in deep subcortical structures such as the brainstem, basal ganglia, thalamus, hypothalamus, and amygdala, which are conserved across many species (Cannon 1927, Kryklywy et al. 2020, Panksepp 2005). In support of this view, emotion expressions are exhibited in human and nonhuman animals even in the total absence of neocortex (Bard 1934, Damasio et al. 2013, Panksepp et al. 1994, Shewmon et al. 1999). Furthermore, activity manipulations of specific hypothalamic (and other subcortical) neurons drive diverse emotion expressions across species, including invertebrates (Anderson 2016, Kunwar et al. 2015, Lee et al. 2014). Secondary processes, localized in the limbic system, a brain network comprising the hippocampus, hypothalamus, thalamus, and amygdala, may support emotional learning and the evaluation and integration of multifaceted stimuli (Panksepp 2011a). Indeed, the vast literature on fear conditioning highlights the important role of the limbic system in emotional learning (LeDoux 2000, 2003). Finally, tertiary process, including cognition and the subjective appraisal of feelings, are posited to be mediated by neocortical areas (Panksepp 2011b).

Despite the general plausibility of this hierarchical model, recent evidence suggests that emotions are not processed only along a one-way stream but rather that information flows in multiple feedforward and feedback loops connecting different processing levels with each other (Anderson

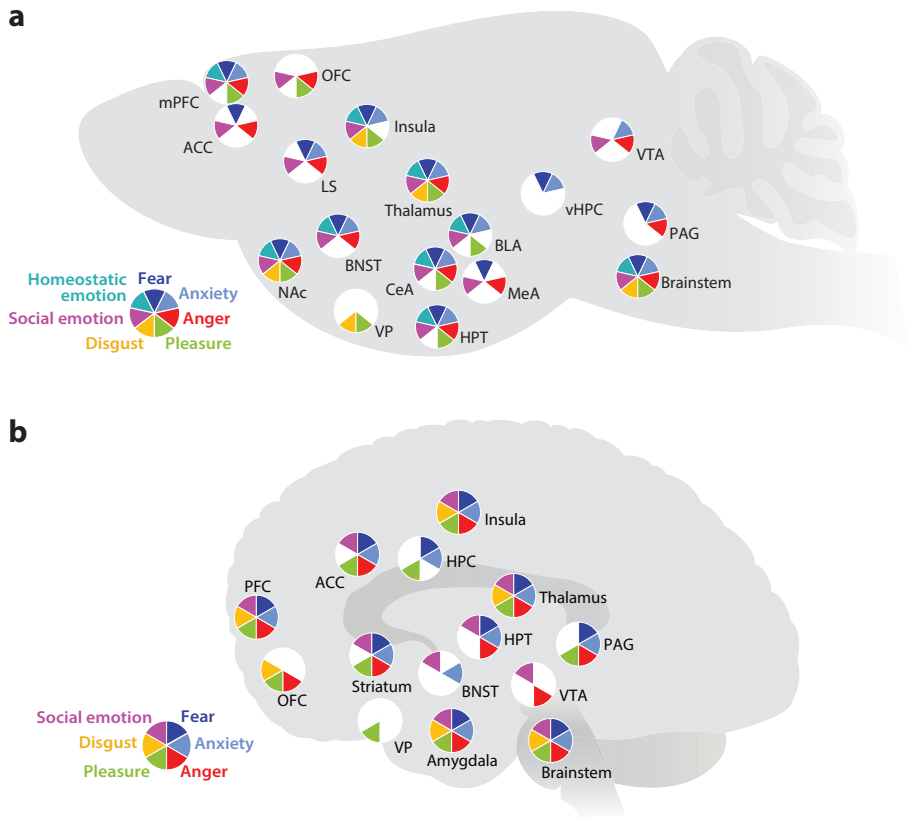

Figure 2

Largely overlapping and conserved brain regions involved in emotions. Recent work in rodents and humans has begun to highlight several conserved brain regions that are implicated in emotion processing across species. Interestingly, many of these regions are implicated in several emotion states of different valences. (*a*) Sagittal view of the rodent brain highlighting regions implicated in emotions. (*b*) Sagittal view of the human brain highlighting regions implicated in emotions. Note the conservation of many of these regions between rodents and humans. For clarity, we chose not to display the anatomical and functional connections between these regions. However, it should be noted that most of these regions are heavily interconnected and form functional networks that are crucial for the emergence and control of emotions. Abbreviations: ACC, anterior cingulate cortex; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; HPC, hippocampus; HPT, hypothalamus; LS, lateral septum; MeA, medial amygdala; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; vHPC, ventral hippocampus; VP, ventral pallidum; VTA, ventral tegmental area.

& Adolphs 2014, Damasio 1998, de Waal 2011, Panksepp 2011a). This complex arrangement may allow for the integration of various sensory, cognitive, bodily, and external information components. It has been suggested that different hierarchical levels may reflect evolutionary history, where primary emotion processes may already have existed in very simple organisms, and the emotion-processing steps diversified with increasing brain complexity.

Neural Circuits for Emotion Are Organized at Multiple Scales

Functional emotion states engage both large-scale and local microcircuits. Large-scale circuits connect different regions across the entire brain and form networks with strong reciprocal

connectivity. Microcircuits act within subnuclei and consist of subpopulations of neurons that are defined by distinct inputs or outputs and have surprisingly distinct roles, oftentimes mediating conflicting emotion states. Microcircuits operate as switch boards to select the next step in a line of decisions toward valence assignment and an appropriate emotion response pattern. We discuss the neural circuit elements decoding valence or driving distinct emotions in the following sections.

Neural Circuits for Valence Decoding

One core computation suggested to underlie functional emotion states is the evaluation of whether something is good or bad (Anderson & Adolphs 2014, Berridge 2019, Tye 2018). Decoding positive versus negative valence may occur via dedicated neuronal subpopulations or projections, also referred to as labeled lines (Tye 2018). For instance, innate valence is attributed to separate sets of touch and taste receptors in the periphery (Craig 2003b, Liljencrantz & Olausson 2014, Marshall et al. 2019), which engage separate information streams toward the insular cortex. Furthermore, innately appetitive or aversive tastants activate topographically distinct subregions of the insular cortex and are transmitted via segregated projections to distinct amygdala subnuclei (Liljencrantz & Olausson 2014, Wang et al. 2018). Distinct projection streams dedicated to valenced versus nonvalenced information exist for all external sensory modalities. Valenced sensory information often bypasses the primary sensory thalamic and cortical areas to directly target higher-order cortical structures such as the ventromedial PFC and insular, orbitofrontal, and anterior cingulate cortices. Thus, it has been hypothesized that supramodal representations of valence may have evolved from modally organized sensory signals in simpler organisms (Kryklywy et al. 2020).

However, such strict separation between opposing valences does not provide flexibility, which is an essential feature of emotion states. Flexibility in valence might be implemented by different circuit motifs that enable valence decisions. One such potential motif was coined divergent paths (Tye 2018). Here, incoming stimuli are evaluated as positive or negative at a switch point, which then activates either appetitive or aversive projections depending on an internal evaluation. Alternatively, via the opposing components motif (Tye 2018), differently valenced inputs arrive at a single neuron, which integrates the information and computes valence from these diverse inputs. Finally, valence may also be attributed through neuromodulatory gain (Tye 2018). This motif is meant as complementary to the other circuit motifs and may act on longer time scales.

Neural Circuits Driving Distinct Emotion States

It remains unknown whether emotions are defined by simple variables such as valence and arousal or whether distinct categories of emotions are laid down in specific neuronal circuits. One way to think about emotion states is to define them as decision processes. In this framework, the brain uses a range of partially preprogrammed algorithms that provide optimal solutions, namely, specific behavioral expression patterns of emotion (Bach & Dayan 2017). These decisions may not be restricted to decoding whether something is positive or negative as seen above but rather may include decisions about valence and category.

Evidence supporting this notion comes from several recent studies. For instance, the rodent insula has been shown to be divided into distinct valence domains (Gehrlach et al. 2019, Wang et al. 2018). When globally activated, subregions of the insular cortex drive either aversive or appetitive behaviors. However, the triggered aversive behaviors are diverse and span fear-, disgust-, and pain-like reactions. Specific efferent projections were found to mediate different aspects of aversive experiences such as promoting fear expressions or inhibiting feeding (Dolensek et al. 2020, Gehrlach et al. 2019). Similar findings were made in the BNST, where distinct subnuclei mediate opposite effects on anxiety, but different features of anxiolysis are implemented by segregated

efferent projections (Kim et al. 2013). Taken together, these findings highlight a hierarchical implementation where valence is assessed in distinct subregions of global brain regions (Berridge & Kringelbach 2015, Gehrlach et al. 2019, Kim et al. 2016, Wang et al. 2018), while fine-tuned decisions regarding emotion-specific action patterns are computed in projection-defined neuronal subpopulations within these subregions.

Finally, in line with the idea of a decision process, it may be advantageous that an intense emotion state gains priority over other competing states. Such a winner-takes-all or attractor model of emotions would be ideally implemented through circuits in which the neural elements processing diverse emotion states are closely intermingled and able to interact, for example, through similar circuit motifs as discussed above for valence attribution.

FUTURE DIRECTIONS

An Inclusive yet Accurate Terminology

We have used words that refer to human emotions throughout this review when addressing findings in all animals. This choice was not made to highlight that nonhuman animals necessarily have conscious feelings that resemble human experiences but to acknowledge that there are links between human and nonhuman emotion. We believe that the conscious perception of emotion is a small aspect of the emotion state underlying it and that there is clear overlap between emotion triggers, adaptive functions, emotion expressions, and their underlying brain correlates in humans and nonhuman animals.

While we advocate for an inclusive usage of the term emotion, we believe that parts of the vigorous debates about the right definition and taxonomy may be helped by more precise language. The evidence reviewed here shows that emotions likely consist of many processing steps that have distinct neural underpinnings. Emotion processes may include events that have to undergo feature extraction (e.g., decoding of valence, proximity, intensity), trigger interpretation (comparison to learned valence and value), contextual evaluation (assessment of competing needs, environmental factors), selection of adaptive expression patterns (bodily, behaviorally, cognitively), and sometimes emotion learning, conscious feelings of emotion, and many more. Studies of emotion could thus be helped by clearer definitions of the actual processing steps under investigation.

A Need for Multidimensional Behavioral and Physiological Readouts of Emotion

Emotion research critically relies on precise readouts of emotion. However, readouts that span multiple emotion states and are sensitive enough to reveal properties of emotion, including intensity, valence, or persistence, are scarce. Interestingly, a recent study using machine vision approaches demonstrated that facial expressions may be a promising avenue to precisely quantify diverse emotion states in mice (Dolensek et al. 2020). Correlating facial expression readouts with high-resolution interrogation of neural circuits may be an exciting future avenue to investigate how different emotion states are represented in the brain of model organisms. Similarly, the field of behavioral tracking and classification has seen a revolution over the past few years (Luxem et al. 2022, Mathis & Mathis 2020). Despite this progress, most recent studies of the neural underpinnings of emotion, whether in human or nonhuman animals, have focused on a very limited set of emotion readouts and stimuli. We believe that in order to fully capture the complexity of emotion states, future studies should assess multiple behavioral, physiological, and neuronal activity measurements in an integrated manner and vary stimuli across intensities and valences. Such approaches would not only improve the classification and measurement of emotion but also

represent an opportunity to address the commonalities and differences of emotion across species and to address long-held questions concerning the dimensionality or categorization of emotions. Furthermore, many physiological and behavioral variables could be assessed in human and nonhuman species and help address the relationship between self-reported and objectively expressed emotions in humans and nonhuman emotion experience.

Toward a Multiscale, Cross-Species Science of Emotion

Emotions are processed in distributed networks across the entire brain. Therefore, whole-brain activity correlates of emotion processes are desirable in addition to investigating the neuronal mechanisms within single brain regions or isolated circuit elements. While many human neuroimaging studies consider activity in the entire brain, invasive activity recordings at greater resolution are not possible in healthy human subjects. In nonhuman animals on the other hand, invasive techniques allow precise circuit dissections, but whole-brain imaging techniques such as functional magnetic resonance imaging are difficult to apply in awake, behaving animals. The recent establishment of functional ultrasound imaging as a whole-brain imaging technique in awake, behaving animals such as rodents, birds, ferrets, and monkeys (Edelman & Macé 2021) may represent an unprecedented opportunity to discover brain-wide emotion processes in real time and pair them with in-depth dissections of neural circuit mechanisms in animal models. Parallel observations between whole-brain activity in human and nonhuman animals may yield extraordinary insights into potential similarities and differences in the encoding of emotions between species.

CONCLUSION

Emotion is a large, complicated, yet fascinating topic. We have tried to provide an overview of some aspects of the neuronal circuits contributing to emotion states. Recent advances in technology to assess neural circuit mechanisms as well as to track and classify behaviors in model organisms have revolutionized our capacity to answer questions about circuit mechanisms underlying emotion states. Finally, we believe that if we can turn the current dissent in defining emotions into testable hypotheses, the entire field of emotions could better align research in human and nonhuman animals and make great strides forward in the attempt to identify the neural basis of emotion.[1]

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[1]Recent work has highlighted a bias in citation practices in neuroscience toward underciting papers from women first and last authors (Dworkin et al. 2020). In the present review, we are citing 11.7% woman/woman, 12.3% man/woman, 17.2% woman/man, and 58.9% man/man, exceeding the expected proportions of woman/woman and man/woman citations in the field of neuroscience.

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