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Neural Circuit Motifs in Valence Processing

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How do our brains determine whether something is good or bad? How is this computational goal implemented in biological systems? Given the critical importance of valence processing for survival, the brain has evolved multiple strategies to solve this problem at different levels. The psychological concept of "emotional valence" is now beginning to find grounding in neuroscience. This review aims to bridge the gap between psychology and neuroscience on the topic of emotional valence processing. Here, I highlight a subset of studies that exemplify circuit motifs that repeatedly appear as implementational systems in valence processing. The motifs I identify as being important in valence processing include (1) Labeled Lines, (2) Divergent Paths, (3) Opposing Components, and (4) Neuromodulatory Gain. Importantly, the functionality of neural substrates in valence processing is dynamic, context-dependent, and changing across short and long timescales due to synaptic plasticity, competing mechanisms, and homeostatic need.

Overview

When we experience the world around us, we are bombarded with a barrage of sensory information. Somehow, we are able to filter out the unimportant information and rapidly respond to our dynamic surroundings in an adaptive manner.

Hedonic "valence" refers to the degree to which something is pleasurable (positive valence) or aversive (negative valence). The concept of valence processing emerged from psychology over a century ago and has more recently been projected onto specific neural substrates throughout the corticolimbic system.

Perhaps the most comprehensively studied circuit node in valence processing is the amygdala, but the circuits involving the prefrontal cortex, striatum, lateral hypothalamus, habenula, and neuromodulatory systems have been well placed in the valence processing framework as well. In this review, I provide a perspective wherein I work from the bottom up through David Marr's three levels of analysis, suggesting that we can indeed learn from the implementational level to infer algorithmic, and perhaps even computational, features of the system (Marr and Poggio, 1976).

Terminology

To address the lack of consensus on the definition of relevant terms, I will state the operational definitions at the outset of this review.

Here, I operationally define "emotion" as a subjective internal state and "motivated behaviors" as quantifiable readouts that serve as a proxy for the intangible "emotion" (Figure 1). In the simplest terms, motivated behaviors fall into two classes: seeking pleasure and avoiding pain (Berridge, 1999; Elliot, 2006; Elliot and Covington, 2001; Solomon, 1980).

Operationally, emotional "valence" refers to the "sign" of the internal state, either positive (supporting approach behavior) or negative (supporting avoidance behavior) (Frijda, 1986; Lang, 1995; Russell, 1980). In contrast, "value" refers to the relative inferred worth of a stimulus along a continuous spectrum. Projecting the psychological concepts onto the language of mathematics: value may refer to any integer along a continuous spectrum, whereas *valence refers only to the sign of that integer*—working in a binary code (Figure 1).

Some environmental stimuli have innate valence, such that no prior experience is required to have emotional responses to them. Other stimuli are initially neutral and require learning to form associations between these "conditioned stimuli" and their motivationally significant outcomes (Pavlov, 2010; Rescorla and Wagner, 1972).

Disclaimer of Subjectivity

Although I may use the term emotion throughout this review, I fully acknowledge that—even in humans—we do not have a way to reliably measure the subjective experience of emotion, which is an internal state (Figure 1). Instead, I will discuss studies based on measures of self-report or other quantifiable behavioral outputs as proxies to estimate these intangible internal states.

Theories of Emotion

Open Questions of Emotion

From Charles Darwin's pioneering "evolutionary theory of emotion," which proposes that emotions have evolved along with the rest of our brains and bodies, lies the implication that the emotions that aid survival the most are likely to be most well conserved (Adolphs and Anderson, 2018; Darwin, 1872). Indeed, the simplest possible reduction of "emotion primitives" are those that spark us to escape from threats and seek out rewards (Anderson and Adolphs, 2014).

There are two unresolved (and perhaps unresolvable) controversies within the field of emotion theory: (1) whether emotions are discrete or continuous (Adolphs and Anderson, 2018; Ekman, 1992; Ekman and Davidson, 1994; Ekman et al., 1983; Lang, 1995; Russell, 1980), and (2) whether emotions are experienced in the same way by humans and other animals (Adolphs and Anderson, 2018; Anderson and Adolphs, 2014; Darwin, 1872; Fanselow and Pennington,

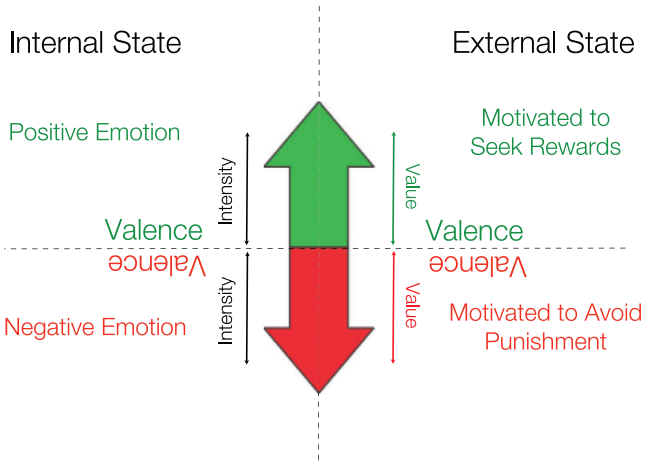


Figure 1. Defining Concepts with Terminology
Schematic differentiating related, but distinct, terms in emotion research. Green represents positive valence, while red represents negative valence. Valence refers to the "sign" of the state, with positive representing rewarding states and negative representing aversive ones. Value tracks the worth of external stimuli on a continuum analogous to integers that can be positive or negative. Intensity indicates the absolute value of the strength of an internal state.

2017; LeDoux, 2017; LeDoux and Pine, 2016; Panksepp, 2004, 2005). Perhaps these questions may never be definitively answered, but the neural circuit mechanisms of emotional processing across species may offer new clues toward both of them.

The uncertainty of philosophical or semantic debates dissuade many from what may well be the most important (and addressable) questions in neuroscience:

What lies between the stimulus and the response?
What are the processes that define our individuality?
How do we subjectively experience the world around us?

This review will focus on many pieces of work that begin to form cohesive motifs that will be the building blocks of answers to these questions.

Before I dive into describing circuit-level investigations that cluster around particular motifs, I will briefly highlight a few key pieces of evidence from psychology that greatly influenced the crystallization of this conceptual framework. I include only the simplest of well-supported models as these are the most likely to be consistent across species.

The Two-Factor Theory of Emotion

The idea that the subjective experience of emotion is accompanied by "bodily changes" was first posited by William James in 1884. James further asserted that physiological arousal contributed to our interpretation of salient events in our environment (James, 1884, 1890). Walter Cannon criticized James for the notion that autonomic arousal defined emotional states due to the relative lack of diversity in physiological states as compared to subjectively perceived emotional states (Cannon, 1927, 1929a; James, 1890; Lang, 1994; Lange and James, 1922, 1922).

The two-factor theory of emotion suggests an order of operations wherein the processing of importance precedes the evaluation of valence. The two-factor theory of emotion was supported by Schachter and Singer's seminal experiments (Schachter and Singer, 1962; Schachter and Wheeler, 1962) as well as the work of Dutton and Aron (Dutton and Aron, 1974), both suggesting that emotion is a response following physiological arousal and the selection of a cognitive label (Schachter and Singer, 1962). In Schachter and Singer's experiments, subjects were given an injection of a substance that was in actuality either epinephrine or placebo, and told to expect (1) physiological arousal, (2) nothing, or (3) side effects different to those one would expect from epinephrine. Then, each group was presented with a "stooge" (confederate experimenter to present defined behavior as a stimulus) who behaved in either a manner indicating positive emotional valence ("euphorically") or a manner indicating negative emotional valence ("angrily"). The result of this study was that if the subject was ignorant to (or misinformed about) the side effects of the injection, they self-reported a significantly stronger emotional state consistent with that of the "stooge" (true for both euphoria and rage conditions) than if they were informed of the physiological arousal effects they should expect from the injection or if they received a placebo injection (Schachter and Singer, 1962).

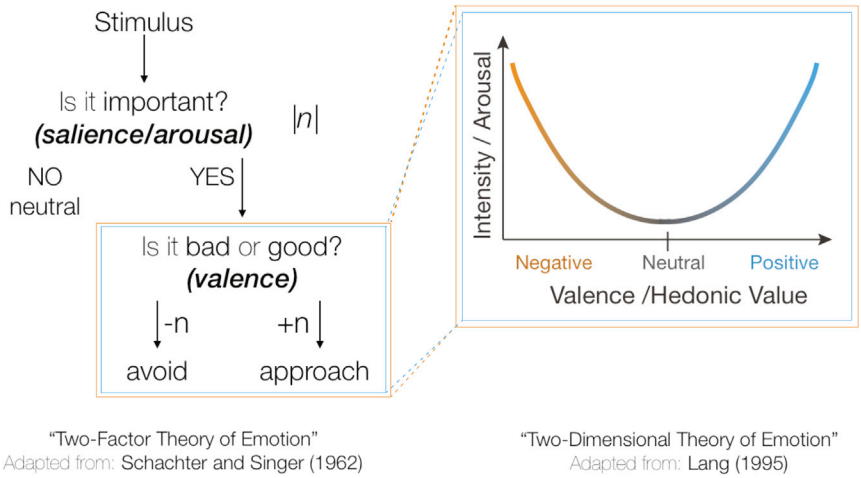
The order of operations suggested by this phenomenon was even further demonstrated in the (in)famous "misattribution of arousal" study wherein male subjects considered a female experimenter more attractive after walking across a high bridge (thought to induce heightened arousal) than after walking across a low bridge (Dutton and Aron, 1974). This distinction has been additionally supported by cognitive studies using fMRI in humans (Kensinger and Corkin, 2004).

An important implication of the two-factor framework is that the recognition of a salient or arousing stimulus is a distinct process that occurs *before* valence processing (Figure 2). The immediate logical extension of this framework may be that the encoding of "absolute value" (|n|) or intensity of the response to the stimulus is upstream of the neural representation of "valence" (+n or –n; Figure 2). Indeed, studies using modern neuroscience approaches to dissect neural circuits in rodent models have found that circuits controlling physiological arousal and behaviors related to internal emotional state are separable (Kim et al., 2013; see below for further discussion).

The Two-Dimensional Theory of Emotion

While the number of dimensions in emotion has been debated, the simplest framework includes two scalars: (1) arousal or intensity (relating to the salience of a given stimulus) and (2) valence or hedonic value (Figure 2; adapted from Lang, 1995). One implication of this depiction of the two-dimensional theory of emotion is that emotions at the most extreme ends of the spectrum for positive and negative valence yield the highest levels of arousal. Another implication is that if stimuli are neutral, and have neither positive nor negative valence, then the arousal level produced by that emotion will be very low. Finally, an indirect implication of this conceptual framework is that emotions can be plotted along a continuum.

The concept that emotions are analog rather than digital is quite controversial—as prominent emotion researchers such as Ekman and Russell have framed emotions as being discrete. While I remain agnostic on this issue, a benefit of conceptualizing



"Two-Factor Theory of Emotion"
Adapted from: Schachter and Singer (1962)

"Two-Dimensional Theory of Emotion"
Adapted from: Lang (1995)

Figure 2. Key Theories of Emotional Processing
In both theories, valence is conceptualized distinctly from arousal level. In one framework it is a subsequent step; in another it is on a distinct axis.

emotion along a continuum is that within any "discrete" emotion, there might be combinations of emotions, and that within any discrete emotion (e.g., fear) there may be varying levels of intensity.

Yet another distinction in Lang's two-dimensional framework is that the poles of positive and negative emotion are fundamentally opposites. This is in contrast to Russell's circumplex model, which suggests that high arousal emotions may be more similar than they are different. For example, one of the primary emotions identified by Ekman is "surprise"—an emotion that is of high arousal but of neither positive nor negative valence per se. Yet one could also make the argument that the initial process of experiencing surprise will be followed by a cognitive reappraisal of that emotion (Dutton and Aron, 1974; Lazarus, 1991; McRae et al., 2010; Ochsner et al., 2002), which comes along with an eventual valence assignment.

Which one of these psychological theories is correct? What would qualify as evidence for or against a proposed process for the subjective experience of emotion? These controversies live on because they are difficult or impossible to directly test.

For the purposes of this review, I refrain from choosing a single model, but rather look to the neuroscience behind emotional processing in an effort to marry new insights from neural circuit mechanisms of emotion and motivation to classic emotion theories. Indeed, as I will briefly outline, the neurobiological motifs are as varied as the theories that they may embody.

Biological Substrates for Emotional Processing

Neuroscience and psychology are often considered distinct disciplines, despite the iterative relationship that they have shared. The psychological concept of valence as an aspect of emotion long preceded the neuroscientific conceptualization of the computational goal of valence processing. Although valence processing is thought to be a distributed process, as suggested by whole-brain *in situ* hybridization (Xiu et al., 2014) and multi-site transcriptional profiling (Mukherjee et al., 2018), I will spotlight a subset of critical circuit nodes.

From the inceptive research of Brown and Schafer—over a century ago—temporal lobectomies left rhesus macaques with many cognitive and motor functions intact but with the inability to assign motivational significance to various environmental stimuli (Brown and Schäfer, 1888). Kluver and Bucy then termed this condition "psychic blindness" (Klüver and Bucy, 1937). Later, Weiskrantz specifically localized this function to the amygdala (Weiskrantz, 1956).

The amygdala has long been identified as a critical hub important for emotional processing, and its importance in emotional processing for both positive and negative emotion was known (Brown and Schäfer, 1888; Fuster and Uyeda, 1971; Klüver and Bucy, 1937; Weiskrantz, 1956) long before it was largely forgotten during a period of hyperfocus on its role in fear (Adolphs et al., 1995; Ciocchi et al., 2010; Davis, 1992; Duvarci and Pare, 2014; Ehrlich et al., 2009; Fanselow and Gale, 2003; Fanselow and Pennington, 2017; Haubensak et al., 2010; Herry and Johansen, 2014; LaBar et al., 1998; LeDoux, 1995, 2017; LeDoux and Pine, 2016; Maren, 2005; Maren and Quirk, 2004; Paré et al., 2004), and then more recently remembered (Janak and Tye, 2015; Paton et al., 2006; Shabel and Janak, 2009). Causal manipulations of valence-encoding cell populations targeting immediate early genes (Gore et al., 2015; Redondo et al., 2014) or transcription factors (Han et al., 2009; Hsiang et al., 2014) are consistent with the indelible nature of valence-encoding neurons within the lateral and basolateral amygdala.

The focus of neuroscience research on the role of the amygdala as a "fear center" stemmed from the identification of classical fear conditioning as one of the most robust, reproducible (and hence popular) behavioral tasks used in the study of learning and memory (Fanselow and LeDoux, 1999; Maren, 2001; Rescorla, 1966). The Pavlovian auditory fear conditioning paradigm came to be defined under very specific parameters, and this strict parametrization accelerated the progress of research on this biological process by clamping the variability of the task. Through this, the anatomical inputs to the basolateral amygdala complex (BLA; which includes the lateral, basolateral, and basal amygdala nuclei) were identified as an important site of convergence and of Hebbian plasticity for associations of both negative and positive associations (Clem and Huganir, 2010; McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997; Rumpel et al., 2005; Tye et al., 2008).

Recent reports provide empirical evidence in support for Schachter and Singer's two-factor theory of emotion. The famous case study patient, S.M., who suffered from bilateral amygdala damage, has taken center stage in providing insights toward the importance of the amygdala in generating emotional responses such as fear to stimuli, in recognizing emotion in other

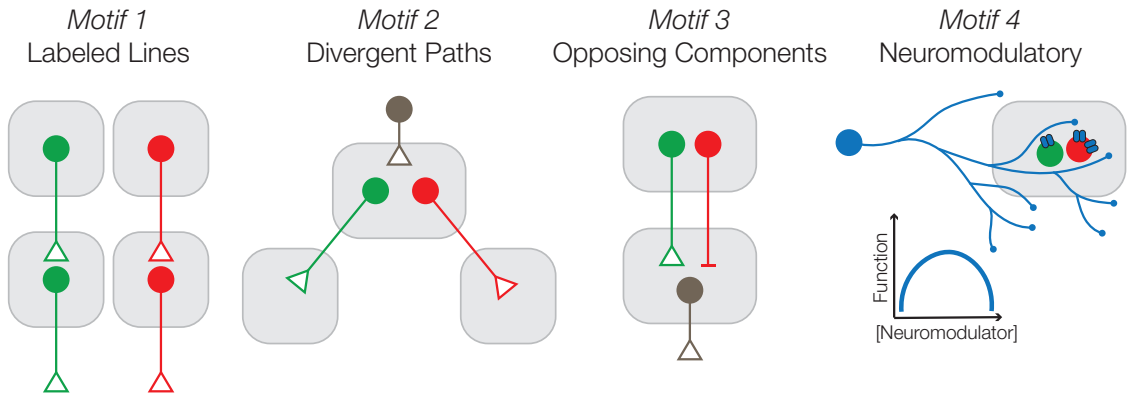


Figure 3. Motifs in the Neural Circuit Mechanisms of Valence Processing

Four motifs are depicted on an implementational level. Motif 1: Labeled Lines represents a circuit with parallel sensorimotor paths for positive and negative stimuli that directly relay to downstream circuits driving approach and avoidance that do not interact or influence each other, which lends the algorithmic advantage of speed and robustness. Motif 2: Divergent Paths represents a circuit that receives the same sensory input but diverges to distinct downstream targets steered by synaptic weights and offers the advantages of associative plasticity, flexibility, and reversal. Motif 3: Opposing Components represents a circuit that, within an anatomically defined projection, contains neurons of diverse functionality that can serve to coordinate, regulate, and weigh different inputs. Motif 4: Neuromodulatory Gain represents a circuit wherein concentration-dependent activation of metabatropic receptors can extend plasticity timescales to allow for single-trial learning, state dependency, and context switching.

people's faces, and in learning emotional associations (Adolphs et al., 1995, 1999, 2005; but see Hamann and Adolphs, 1999). More recently, a study demonstrated that upon hypoxic suffocation, patient S.M. was capable of producing the autonomic arousal associated with panic—even with bilateral amygdala damage (Feinstein et al., 2013). A more detailed dissection of the neural circuits in the mouse demonstrated that distinct circuit components within the extended amygdala mediated the autonomic and behavioral components of anxiety (Kim et al., 2013).

Circuit Motifs in Valence Processing

Although the amygdala had been implicated in emotional processing, the introduction of modern neuroscience approaches that enabled more precise dissection based on anatomical or genetic features at single-cell resolution was pivotal in determining whether the amygdala encoded salience or valence. In this review, instead of providing an exhaustive survey of the impossibly rich and distributed literature on this topic, I will attempt to curate a selection of studies that best exemplify what I identify as important, recurring neural circuit mechanism "motifs" in processing emotional or motivational valence (Figure 3).

There are numerous studies that examine valence assignment based on subregion differences. For example, within the nucleus accumbens (NAc), finer granularity in the subregion definition appears to be essential, as slight movements along the rostral-caudal gradient (Reynolds and Berridge, 2002, 2003), the dorsal-ventral axis (Al-Hasani et al., 2015), or medial-lateral aspect (Yang et al., 2018) can change pharmacological or optogenetic activation from signaling positive to negative valence, or vice versa. Additionally, there are a large number of examples wherein neurons within one region show diversity in valence encoding as measured by either electrophysiology or activity-dependent tagging (Gore et al., 2015; Kim et al., 2016; Paton et al., 2006; Redondo et al., 2014; Shabel and Janak, 2009). There are many such examples throughout the brain (regional or cellular diversity), but I will not focus on them in this review because we lack the accompanying anatomical, genetic, cellular-resolution recording evidence to meet our operational definition of valence (Beyeler et al., 2018; Namburi et al., 2016), which requires that we can determine whether a neuron displayed excitatory, inhibitory, or no responses to stimuli of both positive and negative valence. The lack of anatomical or genetic information overlaid with cellular-resolution recordings also precludes our ability to determine whether this is due to differences in the circuits they belong to (supporting the Labeled Lines model), where they project (supporting the Divergent Paths model), what they release and converge upon (supporting the Opposing Components model), or how they are differentially modulated by G protein-coupled receptors (motif 4: Neuromodulatory Gain). For a review of this literature, see Namburi et al. (2016).

The circuit motifs described in Figure 3 represent some of the most frequently seen biological substrates for valence processing, and each lend themselves to distinct algorithmic models.

Motif 1: Labeled Lines

The computational goal of the "Labeled Lines" motif is to keep streams of communication relaying rewarding stimuli to motor systems that drive approach separate from those detecting punishing stimuli that would plug into motor systems that drive avoidance. The algorithmic advantages of this motif are that it is fast and robust. The algorithmic disadvantages are that without crosstalk, it provides limited flexibility and does not allow for valence switching, or comparison (and relative weighting) of competing motivational drives.

If at the most primordial level we define emotional processing as what occurs between the stimulus and response, then applying biological motifs from sensory systems might be a logical first step. There are environmental stimuli that are innately aversive, as such stimuli predict threats to our survival with some reliability (angry faces that may predict attack, bitter tastants that may predict poison, visual patterns that predict predators,

painful stimuli that may reflect tissue damage, extreme temperature, etc.). There are others that are innately appetitive, as such stimuli reliably predict rewards that may aid in our survival or that we have evolved to find rewarding (stimuli associated with a potential mate, sweet tastes that indicate transiently available calorically dense foods, stimuli associated with safety, etc.). In terms of information flow through the brain, the Labeled Lines model suggests that each set of aversive or appetitive stimuli should plug into distinct circuits that exist in parallel to then drive distinct motor patterns.

Toward the logic that valence processing would be most adaptive if performed rapidly, minimal processing (and thus minimal time) would be required in a Labeled Lines model. This is particularly true in the case of innate valence processing or instinctual behaviors, which are so critical to survival that a bias toward an innate system is evolutionarily advantageous (Adolphs and Anderson, 2018; Robinson and Barron, 2017).

Some examples of the Labeled Lines motif come from olfactory (Root et al., 2014) and gustatory cues (Wang et al., 2018). Valence in these sensory modalities have been articulated in terms of "delicious versus disgusting." A recent study examining the processing of sweet and bitter tastants showed strikingly separable anatomical connectivity leading from the insular cortex to the BLA and the central nucleus of the amygdala (CeA), respectively (Wang et al., 2018).

Another such example comes from the mesolimbic system, showing that different inputs to midbrain dopamine neurons in the ventral tegmental area (VTA) project onto distinct projection-defined subpopulations (Lammel et al., 2012; Lodge and Grace, 2006; Stamatakis and Stuber, 2012). Specifically, these studies show that the lateral dorsal tegmentum projects to the NAc-projecting VTA dopamine neurons known to primarily mediate reward, while lateral habenula (LHb) neurons primarily synapse onto VTA dopamine neurons that project to the prefrontal cortex (PFC), which have been reported to mediate aversion (Gunaydin et al., 2014; Lammel et al., 2011; but see Ellwood et al., 2017).

One potential limitation of this motif might be the flexibility of this function, particularly in the case of Hebbian plasticity. Although any visual or auditory stimulus could be paired with either a punishment or a reward, it is even plausible that a Labeled Lines model could underlie the "strong" input associated with the unconditioned stimulus that drives plasticity at the "weak" input carrying information about the conditioned stimulus.

Yet the Labeled Lines model is too simple on its own, and most often is observed in conjunction with another motif. Even some of the best examples of parsing valence in spatially segregated compartments within the mushroom body of *Drosophila* also involve neuromodulatory contributions (see Cohn et al., 2015, a hybrid of motifs 1 and 4).

Several counterexamples undermine this motif's suitability as a mechanistic explanation for all functions of valence processing. First, the ability to rapidly or permanently reverse responses to discrete stimuli depending on context is poorly explained by the Labeled Lines model; for example, (1) changes in the perception of salt as appetitive or aversive based on the homeostatic need state of the animal; (2) the cliché example of getting a 10 in blackjack—depending on the other card(s) you hold, this could give you blackjack or bust you; and (3) the ability to reverse innate valences (acquired tastes to coffee or alcohol as well as conditioned taste aversion).

Indeed, the Labeled Lines motif offers no opportunities for crosstalk, in contrast to the "Divergent Paths" motif, which provides a common input and divergent outputs, or the "Opposing Components" motif, which provides a convergence point allowing for a comparison between different inputs (Figure 3). Each of these motifs offers opportunities for crosstalk and therefore for a "winner-take-all" computation.

Motif 2: Divergent Paths

The computational goal of the "Divergent Paths" circuit motif is to facilitate associative learning of either valence to initially neutral stimuli and the potential for "valence switching." Algorithmically, this process is mediated by the sorting of signals following learning-induced plasticity to downstream sites that can then select from distinct motor programs with the additional input of information regarding a situation (e.g., a threatening condition could signal to select from motor programs such as freeze, escape, or attack).

Using an analogy popularized in the prefrontal cortex (Miller and Cohen, 2001), one model for how valence is assigned is to liken incoming information to a train coming in on a railroad where one set of rails leads it to avoidance and another drives approach behavior. In this "Divergent Paths" model, the railroad forks at certain brain regions such as the amygdala and local computations serve to act as the "switch operator." This motif is most likely to appear in regions that have similar types of projection neurons, but diverse projections, such as amygdala, hippocampus, thalamus, and cortex.

Enabled by nascent technologies such as optogenetic-mediated projection-specific manipulation (Tye and Deisseroth, 2012; Tye et al., 2011), the Divergent Paths motif has witnessed a proliferation of support. Perhaps biased by the original demonstration of this technique in the amygdala (Tye et al., 2011), which demonstrated that a "minority population" of projection-defined neurons could display the opposite behavioral phenotype from the structure as a whole, the amygdala has proven to be fertile ground for examples of this motif.

For examples of innate valence, the initial application of optogenetic-mediated projection-specific manipulation identified the BLA-CeA projection as anxiolytic (Tye et al., 2011), specifically biased toward the lateral aspect of the CeA (CeL), which in turn produced feedforward inhibition on neurons in the medial aspect of the CeA (CeM), consistent with reports identifying functionally distinct and mutually inhibitory microcircuitry within the CeA (Ciocchi et al., 2010; Haubensak et al., 2010). In contrast, projections from the BLA to the ventral hippocampus (vHPC) were shown to be anxiogenic (Felix-Ortiz et al., 2013). BLA-PFC projections also show a negative valence bias, to a lesser degree, in both learned associations (Burgos-Robles et al., 2017) and innate expression (Felix-Ortiz et al., 2016).

In terms of associative learning, BLA projections to the NAc (medial to the anterior commissure) have been repeatedly shown to mediate positive valence and support positive reinforcement (Beyeler et al., 2016; Britt et al., 2012; Namburi et al., 2015; Ramirez et al., 2015; Stuber et al., 2011). In contrast, BLA-CeM projections predominantly encode negative valence and

optogenetic activation of BLA-CeM produces avoidance (Beyeler et al., 2016; Namburi et al., 2015). This example provides strong support for the Divergent Paths model due to the multilevel support for the functionality differences coming from (1) opposing changes in synaptic strength onto BLA-NAc and BLA-CeM neurons following fear or reward conditioning (Namburi et al., 2015); (2) opposing effects of optogenetic manipulation (Britt et al., 2012; Namburi et al., 2015; Ramirez et al., 2015; Stuber et al., 2011); (3) distinct population encoding of positive or negative valence as revealed by projection-identified large-scale single-unit recordings during discrimination tasks (Beyeler et al., 2016); and (4) evidence of crosstalk and interaction between positive and negative valence-encoding populations (Beyeler et al., 2018; Calhoon et al., 2018), thereby differentiating it from the Labeled Lines model.

The PFC, which shares many of the sensory inputs and striatal and brainstem outputs of the BLA, is also emerging as a fertile ground for Divergent Paths motifs. Although PFC projections to the NAc have been implicated in reward-related processes (Britt et al., 2012; Kalivas and McFarland, 2003; Murugan et al., 2017; Otis et al., 2017), Vander Weele and colleagues have demonstrated that PFC neurons projecting to the periaqueductal gray (PAG) drive avoidance and are modulated by dopamine to display amplified responses to aversive stimuli (Vander Weele et al., 2018), which suggests that motif 4 may serve to execute switching in motif 2. Notably, it is yet unclear whether the context-dependent function or "mixed selectivity" of PFC neurons (Rigotti et al., 2013) is a universal feature of PFC neurons or if there are any subpopulations that show an indelible, "hard-wired" function.

Another such example may be the divergence of outputs from the striatum. Relatively intermingled populations of D1 and D2 dopamine receptor subtype-expressing medium spiny neurons (MSNs) have been shown to mediate very different signals. In the dorsal striatum, D1 MSNs have been shown to mediate increased locomotor activity (Kravitz et al., 2010) and to signal positive reinforcement (Kravitz et al., 2012), while D2 MSNs have been shown to mediate reduction in movement and punishment (Kravitz et al., 2010, 2012). In many ways, these studies highlight the dichotomy of neurons in the same region that have been shown to project to distinct targets (Smith et al., 1998), but given that the divergent paths of the striatum may have partially nonoverlapping inputs (Flaherty and Graybiel, 1994; Friedman et al., 2015), the basal ganglia may fit into both the Labeled Lines and Divergent Paths motifs.

However, the Divergent Paths motif is also unlikely to account for all brain mechanisms of valence encoding. One piece of evidence that suggests this model is too simple is the heterogeneity within each projection-defined population (Beyeler et al., 2016; Burgos-Robles et al., 2017; Nieh et al., 2015), even in cases where the optogenetic manipulation induces behavioral changes consistent with a positive or negative valence signal.

A possible explanation of these data that could still be consistent with the Divergent Paths model is that we have not yet achieved the technology to enable the practical access to the level of granularity required—specifically, we are currently able to target projections to different brain regions, but we are not yet able (with high yield) to access neurons that project to specific cell types within those downstream targets. Other problems that may be impossible to experimentally address in a manner consistent with this model include cases of promiscuous collateralization, mixed selectivity (Rigotti et al., 2013), and state dependence (Calhoon et al., 2018). However, the existence of an integration site allows for the opportunity for multiple sites of plasticity, both at the divergence site and in downstream targets. More often than not, the neurons that diverge from a given region may locally interact and therefore show coordinated activation during natural behaviors (Beyeler et al., 2018; Calhoon et al., 2018; Cui et al., 2013).

The Divergent Paths model has several limitations and does not apply to cases when (1) neurons of distinct projections are functionally similar in terms of valence coding (Betley et al., 2013; Jennings et al., 2013; Stamatakis et al., 2016), and (2) functionally opposing cell types within the same projection exist, especially when shown that they synapse on similar targets downstream (Nieh et al., 2015). However, from a functional perspective, the Divergent Paths motif is complementary to the Opposing Components motif, and each may serve to orchestrate competing mechanisms by either distributing or converging information to ultimately lead to a "winner-take-all" computation before action selection.

Motif 3: Opposing Components

In this case, opposing signals that may arrive from a given target synapse onto the same downstream effector cells. The computational goal in the "Opposing Components" motif is to integrate diverse signals in a convergent algorithm. The advantages of this implementation include flexibility, balanced regulation, and coordination, as well as an integrated readout for competing valence signals.

Although there are many examples of functionally distinct cell types, this motif is not to be confused with just any genetic marker, as some genetic markers may be directly related to the inputs and outputs of a cell. This motif speaks to what the neurons are actually releasing and how they are affecting their downstream target neurons—assuming similar connectivity and structure. This motif is often seen in subcortical regions that carry much heterogeneity, including hypothalamic and extended amygdala circuits (Felix-Ortiz et al., 2013; Haubensak et al., 2010; Tan et al., 2012; Tye et al., 2011; van Zessen et al., 2012). While there are many such examples, this motif is best displayed by regions where opposing components share similar connectivity features (projections, synaptic output).

One prototypical example is that of the lateral hypothalamus (LH) and its projections to the midbrain. While the LH can claim one of the most diverse collections of cell types, I will focus on glutamatergic and GABAergic neurons since their functions are so emblematic of opposition.

The LH contains both glutamatergic and GABAergic neurons, and early studies examining the LH projection to the VTA identified its robustly positive reinforcing properties (Olds and Milner, 1954), and these effects were attributed to the direct glutamatergic input onto VTA dopamine neurons (Kempadoo et al., 2013). This projection indeed exists; however, subsequent studies have demonstrated that LH:GABA neurons (Jennings et al., 2013, 2015; Nieh et al., 2015), and not LH:glutamate neurons (Stamatakis et al., 2016), mediate positive reinforcement.

A recent study used photoidentification of LH→VTA neurons to reveal that a subset of this projection-defined population encoded the learned action of reward-seeking or "conditioned reinforcement" (Nieh et al., 2015). Consistent with the logic from addiction literature that reward-seeking actions, when repeated many times, can become habits that evolve into compulsive reward-seeking behavior (Everitt and Robbins, 2005), activation of LH→VTA neurons increased compulsive reward-seeking and positive reinforcement (Barbano et al., 2016; Nieh et al., 2015). Yet the specific mechanisms underlying this behavioral manipulation were unclear. The LH→VTA projection included both GABAergic and glutamatergic neurons, and both of these opposing components synapse promiscuously on both GABA and dopamine neurons within the VTA (Nieh et al., 2015). Despite the existence of monosynaptic connectivity for both LH→VTA:GABA and LH→VTA:glutamate, these distinct components served opposite functions by mediating positive and negative valence, respectively (Barbano et al., 2016; Nieh et al., 2016; Stamatakis et al., 2016). Indeed, LH→VTA:GABA activation mediated positive reinforcement, motivational salience, and disinhibition of VTA dopamine neurons via local VTA GABA neurons (Nieh et al., 2016)—in contrast to the previous model that LH→VTA:glutamate directly excited VTA dopamine neurons (Kempadoo et al., 2013).

Another important example includes the projection from the LH to the PAG, which has been known to be important for coordinating distinct strategies for responding to pain, stressors, and environmental threats (Bandler and Shipley, 1994). A recent study demonstrated that the LH:GABA→PAG projection facilitated predatory attack, while the LH:glutamate→PAG projection mediated evasion (Li et al., 2018). Thus far, this evidence is consistent with an Opposing Components motif, but does not yet demonstrate that LH:GABA and LH:glutamate inputs synapse onto the same cell types within the PAG. Indeed, the PAG itself contains both excitatory and inhibitory neurons that disinhibit the excitatory projection neurons (Tovote et al., 2016), akin to the disinhibitory microcircuit seen locally in the VTA (Cohen et al., 2012; Morales and Margolis, 2017; Nieh et al., 2015, 2016; Tan et al., 2012; van Zessen et al., 2012). Finally, another such example of opposing components is seen upstream of the LH, for inputs arriving from the BNST that drive opposing valences (Giardino et al., 2018).

The Opposing Components motif is highly complementary to the Divergent Paths motif, and these two models are not mutually exclusive (as the Labeled Lines and Divergent Paths implicitly are). Many of the same pitfalls for the above motif come up again here. Dispersed connectivity to multiple downstream cell types appears to be a sub-motif in itself, with direct monosynaptic excitation and feedforward inhibition presenting itself repeatedly (Felix-Ortiz et al., 2013; Haubensak et al., 2010; Nieh et al., 2016; Tan et al., 2012; Tovote et al., 2016; Tye et al., 2011; van Zessen et al., 2012), though this is beyond the scope of this review. The distributed signaling through multiple parallel channels on a local level here could offer more abundant sites for plasticity in the short- and long-term. However, each of the aforementioned motifs falls short of explaining how cognitive flexibility or single-trial learning are implemented.

Motif 4: Neuromodulatory Gain

One potential computational goal of this motif is to provide a feedback signal with a slower temporal scale that can then guide plasticity within the other circuit motifs. Perhaps the most versatile, and yet elusive, motif for valence coding is that of neuromodulatory or neuropeptidergic influence on the other circuit motifs (Figure 3). Indeed, this motif could work in combination with any of the aforementioned circuit mechanisms. However, empirical examination of this motif presents a substantially greater level of technical difficulty, yet in theory could account for the credit assignment problem (the challenge of how a given outcome would be associated with a stimulus when many stimuli preceded it), initial learning on behaviorally relevant timescales, and flexible changes in behavioral states—which is largely beyond the scope of this review. Here, I will focus on the role of neuromodulatory gain in valence processing, which I distinguish from "fast neurotransmitter systems" by their action on G protein-coupled receptors and second messengers, which thereby allow for an amplified signal that can exert its effects for extended periods of time to allow for plasticity on behaviorally relevant timescales (Bittner et al., 2017).

Broadly speaking, neuromodulators were once conceptualized as "broadcast signals" that would amplify a signal to shift the brain into a distinct state. Systemic administration (or ingestion) of drugs that primarily targeted certain neuromodulatory systems would promote certain behavioral states, and this widespread knowledge may have propagated this concept. For example, drugs that increased dopamine release or dopaminergic signaling, or prevented dopamine uptake generally induced subjective states of heightened motivation or positive hedonic value (Breiter et al., 1997; Gawin and Ellinwood, 1988; Goldman-Rakic, 1997; Koob, 1992; Phillips et al., 2008; Wise, 1998, 2004). Another contrasting example may be the effects of drugs involved in serotonin release, serotonin signaling, or the very popular selective serotonin reuptake inhibitors (SSRIs), which generally induced subjective states of pleasure, well-being, and relaxation (Arango et al., 2002; Caspi et al., 2003; Eisner et al., 1989; Lucki, 1998; Owens and Nemeroff, 1994; Sánchez and Meier, 1997; Wurtman and Wurtman, 1995). Unsurprisingly, the mechanisms of action of various neuromodulatory systems on diverse targets throughout the brain are much more complicated than initially thought.

Because exploring each neuromodulatory or neuropeptidergic system—or even an in-depth exploration of one such system—is beyond the scope of this review, I will again highlight a few examples that help to exemplify the "Neuromodulatory Gain" motif.

Starting from the classic examples that birthed the notion of separating arousal and valence, the catecholamines have raised the notion of an inverted-U-shaped curve with a vast array of functions. Amy Arnsten has described this in the context of dopamine and norepinephrine in the PFC, wherein low levels of catecholamines produce low arousal along with lower executive function (distracted, disorganized, forgetful, disinhibited), whereas moderate catecholaminergic innervation produces optimal arousal and higher cognitive function (focused, responsible, organized), but then with higher-than-optimal levels of catecholaminergic tone in the PFC, we returned to lower

executive function (Arnsten, 1997, 2009). The contribution of dopamine and serotoin have also been reviewed in depth by Hailan Hu (Hu, 2016).

Many have conceptualized catecholamine release as a proxy for stress (Abercrombie et al., 1989; Arnsten, 2009; Cabib and Puglisi-Allegra, 1996; Morilak et al., 2005). In so doing, this model can be extended to other functions, including social behavior (Shansky and Lipps, 2013; Wichmann et al., 2017) and even valence processing (Lemos et al., 2012). The relationship between stressors of different types, severities, and durations and VTA dopamine activity has led to a confusing literature regarding valence and hedonic signaling, best explained by a model wherein either too much or too little dopamine can lead to depression-like symptoms (Chang and Grace, 2014; Chaudhury et al., 2013; Lammel et al., 2014; Moore et al., 2001; Tye et al., 2013; Valenti et al., 2011). Although dopamine may have had phases in its history when it was thought to mediate reward, its role is not so simple. First, dopamine gates plasticity in the amygdala that is necessary for both fear conditioning (Bissière et al., 2003) and reward-related learning (Tye et al., 2010a). Second, as described in more detail above, dopamine can mediate positive valence in the ventral striatum (Phillips et al., 2003; Tsai et al., 2009; Witten et al., 2011), but negative valence in the prefrontal cortex (Gunaydin et al., 2014; Lammel et al., 2011, 2012). In *Drosophila*, dopamine also displays a "switch operator" role in valence processing (Cohn et al., 2015).

Norepinephrine has also had an ambiguous role in valence processing. Like dopamine, norepinephrine is released in response to stressors (Valentino et al., 1983) and other salient stimuli, independent of valence (Berridge and Waterhouse, 2003). Norepinephrine arising from the locus coeruleus has primarily been implicated in vigilance, wakefulness, and arousal (Aston-Jones and Cohen, 2005; Aston-Jones et al., 1994; Carter et al., 2010, 2013; Jones et al., 1977). Yet Berridge and Waterhouse have speculated toward the positively reinforcing nature of stimulants targeting the norepinephrine system (Berridge and Waterhouse, 2003). Photostimulation of the norepinephrinergic neurons and terminals in the amygdala has been shown to be aversive and anxiogenic (McCall et al., 2015, 2017).

These findings fit well into the framework first established by Schachter and Singer (Schachter and Singer, 1962), described above, and may well be influenced by gain or context. Importantly, Arnsten proposes that this inverted-U-shaped curve is mediated by the signaling of specific receptor subtypes in the brain for both dopamine and norepinephrine (Arnsten, 2009).

One of the greatest mysteries of this field is how valence is first assigned. In the case of one trial learning (fear conditioning, conditioned taste aversion, copulation), there is the challenge of the temporal credit assignment problem (Sutton, 1984): how does the brain determine when the event or behavior deserves the credit for the outcome? Particularly in the case of the Divergent Paths motif, how does the metaphorical switch operator "know" which way to switch the tracks? What is the neural substrate for the signal telling the switch operator to guide information down one path or another?

I speculate that one possible mechanism is that neuropeptidergic or neuromodulatory signals targeting diverse receptor subtypes, or even receptor expression levels, can increase or decrease the relative gain on signals traveling down various paths. This is not likely to be a globally uniform mechanism. For example, dopamine signaling in certain subregions of the striatum may signal reward, while signaling aversion or salience in other regions of the brain.

Even more likely is the yet-unappreciated role of the dozens (or even hundreds) of yet-uncharacterized neuropeptides that can play such modulatory roles. To spotlight one understudied neuropeptide of interest, consider neurotensin. Neurotensin is found in many different brain regions and circuits, and was initially implicated in reward processing, particularly with respect to midbrain dopamine neurons (Binder et al., 2001; Cador et al., 1986; Glimcher et al., 1984, 1987; Palacios and Kuhar, 1981). Indeed, photostimulation of LH neurotensin neuron terminals in the VTA robustly supported positive reinforcement (Kempadoo et al., 2013). In contrast, neurotensin has also been linked to fear conditioning (Amano et al., 2008). Neurotensin is thought to play a role in modulating glutamatergic transmission (Ferraro et al., 2008). Fascinatingly, neurotensin has been shown to either facilitate or suppress glutamatergic signaling in the VTA depending on the concentration of neurotensin applied (Kempadoo et al., 2013). Recently, in projection-defined populations of amygdala neurons that have been shown to mediate positive or negative valence in terms of differential synaptic plasticity following fear or reward conditioning, optogenetic manipulation, and routing of valence-related information *in vivo* (Beyeler et al., 2016, 2018; Namburi et al., 2015), these BLA-NAc and BLA-CeM neurons show a significantly different level of neurotensin-1 receptor expression (Namburi et al., 2015). Therefore, I speculate that neuropeptides such as neurotensin may have the ability to contribute to the mechanism signaling the "switch operator" to actively guide information down one projection or another. This specific hypothesis, and this motif in general, beg further investigation. This line of inquiry will be challenging, demanding new technological approaches and pushing the limits of what we can manipulate and measure, but I predict will be well worth the effort.

Complications in Existing Models of Valence Encoding

Although there may be some neurons in the brain that are hardwired to signal for rewards or punishments, there are many more that are likely to be dependent on (1) homeostatic need state, (2) context, (3) prior experience, and (4) competing mechanisms. Further, given the many factors that contribute to the ultimate selection of an appropriate behavioral response to environmental stimuli, there may be a "winner-take-all" mechanism. How the winner is computed from the diversity of signals integrated is yet unclear, but is evolving with recent evidence.

Importantly, recent studies that produce apparently contradictory results may have not carefully taken these caveats into consideration. For example, somatostatin-positive (SOM+) neurons in the CeA have been manipulated using similar approaches (mouse lines and optogenetic tools) to reach very different results. Specifically, some investigators have reported that photostimulation of SOM+ CeA neurons produces defensive behavior (e.g., freezing, escape) (Fadok et al., 2017; Li et al., 2013; Penzo et al., 2014, 2015; Yu et al., 2016). Yet others targeting this same

population have found that photostimulation of SOM+ CeA neurons drives appetitive behaviors (Han et al., 2017; Kim et al., 2017). One explanation that satisfactorily reconciles this seemingly contradictory work is that the CeA serves to actively gate and scale output, taking into account state, context, and prior experience (Fadok et al., 2018). To even begin to empirically evaluate this new perspective, we must first begin by carefully documenting the dependent variables listed above in detail.

Changes in circuit function related to state changes, short-term or long-term synaptic potentiation, and real-time input regarding context all have the potential to alter the function of valence-encoding circuits. State changes induced by homeostatic need, stress, or arousal level can alter the function of all four of the circuit motifs described above. Short-term plasticity induced by recent experiences could prime synaptic function to alter subsequent activity. Long-term synaptic plasticity is often a consideration that is overlooked and could result from a "natural" event wherein experiencing a stimulus in a given context could introduce a bias in subsequent behavior. Long-term synaptic plasticity could also be induced by "experimental" events such as photostimulation of a certain population of neurons repeatedly across weeks of behavioral testing, which could cause profound changes in circuit function. One such example may be seen in the case where LH:GABA→VTA projections were stimulated in the context of food consumption, and then photostimulation of the same neurons in an empty chamber produced feeding-related motor sequences (Nieh et al., 2015)—but when naive animals were photostimulated, the motivated behaviors could be directed at objects, social agents, and non-food stimuli to elicit a variety of context-dependent motor sequences (Nieh et al., 2016).

Homeostatic Need State Influences Emotion and Decision-Making

The brilliant thought leader Walter Cannon pioneered the connection between homeostatic need state and emotional processes (Cannon, 1927, 1929a, 1929b, 1932). Cannon defined the term "homeostasis" (from the Greek words for "same" and "steady") as any process that organisms use to actively maintain stable conditions necessary for survival (Cannon, 1932). This can relate to thermoregulation, osmoregulation, energy balance, and sleep homeostasis.

Sometimes the emotional valuation of a given stimulus is directly tied to homeostatic need state, for example, in the case of salt appetite: the same concentration of sodium solution can be either aversive or appetitive, depending on the physiological salt appetite state of the animal as determined by both behavioral and neural correlates (Chang et al., 2017; Tindell et al., 2006).

Cannon's classic study, wherein it was difficult or impossible to detect the physiological difference between hunger and rage (Cannon, 1929a), a notion popularized by modern media as the "hangry" phenomenon, exactly revisits this concept (MacCormack and Lindquist, 2018). A startling realization of this was described in the highly controversial observation of 1,000+ judges hearing parole decisions in Israel—the decisions at the beginning of the day started ~65% positive, steadily plummeting to less than 10% right before a meal break, only to jump back up to ~65% after the meal (Danziger et al., 2011). Yet these observations carry a number of caveats that are difficult to address.

While we are still at the early stages of understanding the neural mechanisms that link homeostatic need to emotional valence processing, modern neuroscience technologies have catapulted us forward in our understanding by providing well-controlled experiments and biologically based evidence. Neural responses to food-associated stimuli are heightened when animals are hungry (Burgess et al., 2016; Livneh et al., 2017). Neurons thought to signal hunger and thirst rapidly change firing when animals anticipate immediate access to water or food (Chen et al., 2015; Gizowski and Bourque, 2018; Zimmerman et al., 2016; Burton et al., 1976). Further, circuits that mediate positive or negative valence in the amygdala undergo synaptic plasticity of the inputs and local connections when animals are acutely hungry (Calhoon et al., 2018; Namburi et al., 2015).

Prior Experience and Context Dependency on Valence Processing

From pathological cases ranging from post-traumatic stress disorder (PTSD) to drug addiction, context can induce powerful changes in the interpretation of cues depending on associations formed with those contexts during prior experiences. The neural substrates for these may differ in some cases; for example, the NAc is only important for context-induced reinstatement of reward-related processes (Chaudhri et al., 2008; Cruz et al., 2014; Kalivas and McFarland, 2003), whereas other regions such as the dentate gyrus of the hippocampus are important for context-induced reinstatement, independent of valence (Redondo et al., 2014).

Context may influence the set of stimuli we anticipate or expect. The same stimulus could be positive, negative, or neutral, depending on the context. For example, a small reward may be interpreted as positive if no reward was expected, but as a punishment if a larger reward was expected. No stimulus at all might be neutral or negative, depending on the expectation. These initial predictions and pioneering observations were termed "reward-prediction error" as coded by dopamine neurons in the VTA (Cohen et al., 2012; Rescorla and Wagner, 1972; Schultz et al., 1997), and remain one of the most well-studied models in behavioral neuroscience. These examples also influence other limbic structures, as evidence of reward-prediction error signals is found throughout the brain, including similar signals in the LH (Nieh et al., 2015) and inverted signals in the LHb (Bromberg-Martin and Hikosaka, 2011; Matsumoto and Hikosaka, 2007). The complex manner in which these reward-prediction error signals are constructed has been revealed by technically challenging recordings in neurons that provide monosynaptic input to VTA dopamine neurons (Tian et al., 2016).

Further, both thalamic input to the amygdala (Do-Monte et al., 2017) and the activity of a subpopulation of amygdala neurons (Tye et al., 2010b) can signal a "frustration-like" state (operationally defined as a negative valence mediated increase in vigor of responding) when an expected reward is unexpectedly omitted.

Cognitive Influences on Valence Processing

Importantly, context is but one of the "top-down" mechanisms by which cognitive reappraisal may influence emotional

Box 1. Important Methodological Parameters to Report

Currently, many publications fail to include details that could alter results and their interpretation. For example, knowing if an animal had previously been exposed to food in a given context could alter the behavior of the animal even if food is absent on the next test. Previous manipulation to the brain, as well as the actions or cues paired with manipulation, could induce dramatic changes to subsequent behavior and neural activity following experience-dependent plasticity. To provide a more cohesive foundation for our field, I would urge researchers studying valence processing to record the following details for animal experiments:

1. Species, strain, and genotype
2. Age and sex (and estrus cycle if appropriate)
3. Current housing conditions
    a. Cage size and shape
    b. Number of cage mates
    c. Social rank if known
    d. Body weight
    e. Food content (nutrient breakdown, source, and lot number)
    f. Feeding schedule
    g. Light/dark schedule
    h. Maternal exposure
    i. Water schedule
    j. Potential stressor exposure(s)
    k. Noise and disruption level
    l. Antibiotics and other drugs
    m. Environmental enrichment
    n. Ventilation type
4. Housing condition history (each of the measures above for the animal's history, to the best knowledge of the experimenter, including shipping history)
5. Testing conditions
    a. Time of testing
    b. Habituation type and duration
    c. Handling experience
    d. Size, illumination, and temperature of testing room
    e. Other uses of testing room, particularly those that could leave residual odors
    f. Experimenter(s) details and schedule
    g. Prior exposure to stimuli (tones, sucrose, shocks, social agents, etc.)
    h. History and context of prior exposure to testing room or apparatus
    i. Testing apparatus dimensions and material
    j. Cleaning agents and cleaning schedule
    k. Experimenter present or detectable during test?
6. Previous testing history
    a. Order/schedule of behavioral testing
    b. Spacing of testing schedule (consecutive days? Weekends off?)
    c. Duration and timing of current session and previous sessions
    d. Multiple experiments? If so, were groups shuffled?
    e. Same experimenter or different?
    f. Did manipulation of brain activity occur? Details of total manipulations performed are necessary.
    g. Previous state during testing (was animal previously deprived or stressed in this testing arena?)
7. Data collection details
8. Controls in data collection and analysis for order effects

evaluation (Ochsner et al., 2002). Further along these lines, context can be abstracted to stimulus-action-outcome probabilities based on prior experiences, and likely serves to influence the evaluation of discrete stimuli via the interaction of cortico-amygdala interactions in non-human primates (Saez et al., 2015; Salzman and Fusi, 2010). The tension between "top-down" and "bottom-up" interactions between cognitive and emotional processing is on display throughout human development, during which the structural and functional connectivity of the amygdala and cortex is dynamic (Casey et al., 2008; Saygin et al., 2015; Somerville et al., 2010). "Bottom-up" processes can be amplified by manipulating amygdalar projections to the prefrontal cortex when animals are in situations of ambiguous (Felix-Ortiz et al., 2016) or conflicting valence signals (Burgos-Robles et al., 2017), and in both of these cases serves to bias animals toward negative valence processes.

Another important and well-conserved function in the brain is social or observational learning. Learning the action-outcome associations through observation, particularly in the case of potential threats, can provide an evolutionary advantage—evidenced by the conservation of this ability across species from flies and rodents, to primates, including humans (Bruchey et al., 2010; Jeon et al., 2010; Kavaliers et al., 2001; Mineka et al., 1984; Olsson et al., 2007; Sokolowski, 2010). From Albert Bandura's classic "bobo doll" study emerged social learning theory—to learn from others, we must observe, imitate, and create a model for the world based on this information (Bandura, 1978; Bandura et al., 1961, 1966).

Observational learning relies on the anterior cingulate cortex (ACC) and the BLA (Jeon et al., 2010; Olsson et al., 2007). Indeed, the ACC detects changes in behavioral state of social agents and relays this information to the BLA, where associations can be formed about environmental stimuli (Allsop et al., 2018). In humans, "theory of mind" centers in the cortex interact with the amygdala in conscious control of empathy for emotional pain (Bruneau et al., 2015; Saxe and Kanwisher, 2003). Taken together, when higher cognitive input (of multiple kinds) is required to evaluate the valence of stimuli, real-time cortical input to the amygdala appears to be necessary.

These studies that have emerged in the recent decade finally allow us to provide a mechanistic explanation of the original concepts put forth by the pioneering psychologists that developed theories of emotion such as Schachter and Singer, Lazarus, and others (Lazarus, 1991; Schachter and Singer, 1962; Schachter and Wheeler, 1962), bridging the gaps between psychology, cognitive science, and neuroscience.

Orchestration of Competing Drives and a Winner-Take-All Model

Although in the laboratory, experiments often present animals with very few salient stimuli predicting outcomes with high contingencies that are rewards or punishments, these are not the conditions in which brains have evolved. In nature, many rewards come at an energy cost, with some probability function for success, and some risk of a threat upon survival. Instead, the world is brimming with stimulation for our senses and wrought with conflicting information invoking competing motivational drives.

Throughout evolution, reward-seeking almost invariably increases our vulnerability to environmental threats. As primitive humans, we could stay in the safety of our caves, or go out to forage or hunt—facing the risks of life-threatening weather or predation. Visiting places with universally valuable commodities (e.g., waterhole) would increase the likelihood that we could be ambushed from behind while drinking, or from the water by a reptilian predator. Amygdala recordings during a foraging task show distinct responses during foraging ventures and retreats to the nest, relating the encoding properties of amygdala neurons to extend beyond stimulus representations to action selection (Amir et al., 2015). Indeed, amygdala neurons that projected to the prefrontal cortex allowed for more accurate decoding of responses in the face of conflicting cues that predicted reward or punishment when they were co-presented (Burgos-Robles et al., 2017).

How do we choose when to approach and when to avoid? What are the computations that are rapidly performed to help us evaluate our environment and select an appropriate response as quickly as possible?

Recent evidence about how the amygdala computes valence suggests there may be some imbalances, with circuits mediating fear and disgust dominating over circuits predominantly important for reward-seeking. Specifically, the BLA-CeM projection that is predominantly encoding negative valence (Beyeler et al., 2016; Namburi et al., 2015), has greater influence over neighboring amygdala neurons (Beyeler et al., 2018) and is more capable of suppressing BLA-NAc neurons (Calhoon et al., 2018) than the converse. Rather than a "majority vote" mechanism, as we previously proposed in 2015 (Janak and Tye, 2015), I would now revise this to include the possibility that some "votes" count more than others—some neurons have the ability to suppress or excite more neighboring neurons and are therefore "more influential"—much like an electoral college.

Why might the brain work this way? An evolutionary reason is that predatory threats may incur immediate death, while the postponement of reward-seeking is far less likely to do so. A computational reason is that asymmetric weights of distributed algorithms (akin to synaptic weights on distributed circuits) will converge faster than symmetric ones (Xiao and Boyd, 2004). A few hundred milliseconds across trillions of reactions could mean the difference between propagation of a species or eventual extinction.

Outlook

We work in an exciting era wherein psychological theories from generations past are not only being tested, but are also grounded in biology to the level of cells and synapses serving to connect generations of researchers spanning centuries and fields of research (Cannon, 1927; Darwin, 1872; Schachter and Singer, 1962).

Yet many important questions remain unanswered. To continue forward, we as a field must be more meticulous in recording the details of our methodology to allow readers to determine whether the states, prior experiences, and contextual conditions could confound the interpretation of our results (Box 1).

We must also begin to examine a more integrative model, wherein each model contains multiple motifs—extending beyond the basic ones described here. Finally, we must continue to tackle the important, yet elusive and technically challenging, fundamental principles of the brain. After all, we have yet to answer the simplest question: how do we tell if something is good or bad? If we succeed in understanding the algorithmic and implementational levels of valence processing, then the development of circuit-based treatments (or perhaps even cures) using strategies such as neural circuit reprogramming (Tye, 2014) becomes more feasible.

Above all, the dissemination of information to a broader audience, and the cross-pollination between disparate fields of basic science such as neuroscience, psychology, engineering, computer science, genetics, plant biology, chemistry, and nanoscience to facilitate true integration will be the key to accelerating our understanding of our own minds.

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