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From Basic Processes to Real-World Problems: How Research on Emotion and Emotion Regulation Can Inform Understanding of Psychopathology, and Vice Versa

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Abstract

Research on emotion and emotion regulation is expected to improve our understanding of psychopathology. However, achieving this understanding requires overcoming several obstacles, including the paucity of objective markers of specific emotions or psychiatric diagnoses, and the fact that emotion regulation is a concept that can be difficult to operationalize. We review affective neuroscience research that has addressed these issues by focusing on psychological and neural mechanisms implicated in approach and avoidance behaviors, as revealed by studies of fear, anxiety, and reward processing. Dysfunction in these mechanisms may serve as risk markers for psychopathology, while emotion regulation research demonstrates that some of them are susceptible to volitional control. The conclusion acknowledges limitations of affective neuroscience and highlights goals for future work.

Keywords

emotion; emotion regulation; psychopathology; affective neuroscience; fear; reward

This is an opportune time to consider research on emotion, emotion regulation (ER), and psychopathology. Upcoming revisions to the DSM-IV and ICD-10 have drawn attention to concerns about how mental illness is defined, studied, and treated (Hyman, 2010). While psychiatric diagnoses are framed categorically in the DSM-IV, they are not “natural kinds” that exist independent of human norms (Hyman, 2010). Instead, they reflect a combination of harmful dysfunction in psychological and neural mechanisms plus violation of social values (Wakefield, 1992). While social values will always be subject to change, there is optimism that understanding of psychology and neuroscience will yield a firmer foundation for work on mental illness (Hyman, 2010). Given the role of emotion dysregulation in psychopathology (American Psychiatric Association, 2000), this translates into hope that studies of emotion and ER will lead to improvements in diagnosis and treatment.

In this context, it is disconcerting to realize that specific emotions implicated in mental illness, such as fear and sadness, are subject to the same critique as psychiatric diagnoses namely, that they are not natural kinds (Barrett, 2006). In other words, while emotion labels

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such as “fear” are useful tools for social interaction, they may not correspond to distinct patterns of brain activity. Although there is debate over the accuracy of this point (e.g., Izard, 2007), the controversy suggests that a simple neuroscientific explanation of psychopathology in terms of excessive fear or sadness will not be forthcoming.

Understanding psychopathology in terms of faulty ER mechanisms requires meeting another challenge, namely that the term “emotion regulation” is overly broad (Cole, Martin, & Dennis, 2004). For example, ER could refer to situations in which emotions modulate other psychological processes, such as when arousing stimuli grab attention, as well as situations in which emotions are targeted for regulation, such as when one tries to remain calm in the face of growing anger. Interest in the latter phenomenon reflects the role of emotion dysregulation in many forms of psychological distress (Kring & Sloan, 2010). Focusing on this form of ER helps delimit the topic, but the innumerable ways in which emotional responses could be regulated raise questions: Is there a way to organize these strategies? How can ER be distinguished from effects of emotion?

In short, research on emotion, ER, and psychopathology is timely but challenging. Addressing the challenges will require a multidisciplinary approach. With that proviso in mind, this review provides examples of progress in affective neuroscience[1] with a focus on how research in emotion, ER, and psychopathology is mutually informative. In the first section we outline a conceptual framework that has guided affective neuroscience research on these topics. The second and third sections review investigations of basic mechanisms implicated in fear, anxiety, and reward processing. In the conclusion we discuss limitations of affective neuroscience and highlight promising future directions.

Keep it Simple: A Basic Mechanisms Approach

Researchers in emotion and psychopathology face a common problem: the phenomena of interest may not have an independent existence that can be discovered. This problem is especially obvious with respect to psychiatric diagnoses, which are defined by self-reported symptoms rather than pathophysiology (Hyman, 2010). For example, to meet DSM-IV criteria for Major Depressive Disorder (MDD), an individual must exhibit five of nine symptoms for two weeks (American Psychiatric Association, 2000). Consequently, two individuals with MDD could have only a single common symptom. This heterogeneity frustrates searches for psychological and biological correlates of MDD, as convergence on a core set of relevant mechanisms is difficult. Searches for neural signatures of specific emotions can also prove frustrating (Barrett, 2006; but see Izard, 2007), because similar phenomena (e.g., increased heart rate) are characteristic of multiple specific emotions.

Affective neuroscience research has made progress by taking a different tack. This research program acknowledges that emotions involve changes in subjective experience, behavior, and physiology (Lang, 1995). However, in order to leverage research in non-human animals, emphasis is placed on behavior and physiology (Davis, 1992; LeDoux, 2000). Furthermore, this program emphasizes that emotional responses can be organized along the broad motivational dimensions of approach and avoidance (Bradley, Codispoti, Cuthbert, & Lang, 2001). Studying psychological and neural mechanisms that support approach and avoidance

[1]For ease of exposition, we use the term “affective neuroscience” to refer to work in multiple fields of inquiry, including behavioral, clinical, cognitive, and social neuroscience as well as physiological psychology.

behaviors[2] avoids challenges associated with identifying signatures of specific emotions while providing insight into emotions that might be considered categorically distinct.

This research program is directly relevant to psychopathology. If psychiatric diagnoses partly reflect harmful dysfunction in psychological and neural mechanisms (Wakefield, 1992), then accurately defining dysfunction is critical. Affective neuroscience speaks to this issue by highlighting mechanisms that support emotional well-being and may be dysfunctional in psychopathology (LeDoux, 2000). For example, heightened resting amygdala activity might serve as a risk marker for anxiety disorders (Etkin & Wager, 2007), much as high blood pressure is a risk marker for cardiovascular disease (Hyman, 2010).

Affective neuroscience can also uncover mechanisms that support ER, but it is first necessary to unpack this term. A process model has done this by using temporal criteria to sort ER strategies into two categories, antecedent- and response-focused (Gross, 1998). Antecedent-focused strategies alter which emotional responses are elicited in a given context and include situation selection, situation modification, attentional deployment, and use of cognitive strategies such as reappraisal (Lazarus, 1991) to alter the meaning of an emotionally eliciting stimulus. By contrast, response-focused strategies (e.g., expressive suppression) are used to modulate emotional responses once they arise.

This model has guided affective neuroscience research by delineating ER strategies of interest. Reappraisal has been particularly well-studied (Deveney & Pizzagalli, 2008; Dillon & LaBar, 2005; Jackson, Malmstadt, Larson, & Davidson, 2000; Ochsner et al., 2004; Urry, 2010). Reappraisal studies have identified components of emotional responses that are susceptible to modulation and investigated how modulation occurs (see below). Furthermore, ER research underscores the point that interpretations of emotional stimuli affect behavior and physiology. This is a given in cognitive approaches to emotion (Frijda, 1993), but it can be under-appreciated in affective neuroscience because of the emphasis on work in non-human animals.

To substantiate the claims made in this section, the next two sections review work related to fear, anxiety, and reward processing. Both sections identify mechanisms that are implicated in emotion generation, modulated by ER, and dysfunctional in psychopathology.

Uncovering Basic Mechanisms by Studying Fear and Anxiety

When threatened with a pain-inducing stimulus, mammals exhibit behaviors (e.g., freezing) and physiological changes (e.g., release of stress hormones) that have been operationally defined as fear responses (Davis, 1992; LeDoux, 2000). Fear responses have been well-studied, and below we discuss relevant findings. Given space limitations, we focus on studies of potentiated startle, which have mapped the neural systems linked to fear responses (Davis, Walker, Miles, & Grillon, 2010); startle has also been used to investigate psychopathology (Vaidyanathan, Patrick, & Cuthbert, 2009) and ER (Jackson et al., 2000). The wealth of useful data from startle studies underscores the value of focusing on mechanisms that implement simple approach or avoidance behaviors.

[2]Practically speaking, in the laboratory it is easier to elicit full-blown approach and avoidance behaviors in non-human animals than in human participants. However, it is hypothesized that the same neural systems that implement actual approach and avoidance also implement conceptually related changes in ratings of subjective experience, measures of central and peripheral nervous system activity, and various circumscribed measures of behavior (Bradley et al., 2001).

Startle As a Measure of Emotion

Pavlovian conditioning is often used to study startle in rodents (Davis, 1992). When a neutral conditioned stimulus (CS) (e.g., a tone) is repeatedly paired with an aversive unconditioned stimulus (US) (e.g., a shock), its presentation will eventually elicit behavioral signs of fear (LeDoux, 2000). Fear-potentiated startle refers to increased startle amplitude during presentation of a fear-conditioned CS relative to baseline or presentation of non-conditioned neutral stimuli (Brown, Kalish, & Farber, 1951). Fear is thus operationally defined by increased startle amplitude (Davis, 1992).

Extensive evidence supports a critical role for the amygdala in potentiated startle (Davis, 1992). With respect to conditioned fear, the basolateral amygdala (BLA) and the central amygdala (CeA) can be considered the amygdala's input and output systems, respectively (Davis et al., 2010). Briefly, the BLA receives sensory input about the CS and US, supports the formation of CS-US associations, and sends projections to the CeA. In turn, the CeA projects to brain regions that orchestrate behavioral signs of fear, including a brainstem nucleus critical to the startle response.

Multiple findings support this model. First, lesions of the BLA made before fear conditioning block fear-potentiated startle, presumably by preventing the formation of CS-US associations, but lesions made after conditioning do not have this effect, presumably because CS-US associations have already been established (Sananes & Davis, 1992). By contrast, lesions of the CeA made directly before testing (24–48 hours after fear conditioning), do block fear-potentiated startle, presumably by disconnecting the BLA from the brainstem (Hitchcock & Davis, 1986). Second, electrical stimulation of the amygdala reliably increases startle amplitude (Koch & Ebert, 1992). Third, anxiolytic drugs reduce fear-potentiated startle (Davis et al., 2010). In short, investigations of fear-potentiated startle have revealed neurobiological systems that support the acquisition and expression of fear responses.

Potentiated startle has also proven useful for identifying brain regions differentially involved in a phenomenon conceptually related to fear: anxiety. In rodents these constructs are defined by their time-course (fear responses are shorter) and the eliciting stimuli (fear is elicited by discrete cues, anxiety by more diffuse cues). For example, while conditioned fear cues elicit brief but intense signs of fear, exposure to light evokes signs of sustained apprehension in rats (including potentiated startle; Walker & Davis, 1997a), which is sensible given that rats are nocturnal and at greater risk of predation during daylight.

Walker and Davis (1997b) provided evidence that two brain regions, the CeA and the bed nucleus of the stria terminalis (BNST), make dissociable contributions to fear and anxiety. The BNST is a part of the "extended amygdala" and receives projections from the BLA. These authors demonstrated that inactivation of the CeA disrupted cue-potentiated startle but left light-potentiated startle intact, while inactivation of the BNST disrupted light-potentiated startle but left cue-potentiated startle intact. Inactivation of the BLA blocked both forms of potentiated startle, consistent with the hypothesis that it sends information about CS-US associations to the CeA and BNST. Thus, the CeA and BNST support phasic fear and sustained fear (i.e., anxiety), respectively, with the BLA contributing to both.

This work is translational, as most of the phenomena described above have been observed in humans. First, startle amplitude is increased in the presence of a fear-conditioned CS (e.g., Hamm, Greenwald, Bradley, & Lang, 1993). Second, consistent with our diurnal nature, darkness (rather than light) enhances startle in humans (e.g., Melzig et al., 2007). Third, mirroring findings in non-human animals (Richardson & Elsayed, 1998), startle research has shown that contextual fear conditioning occurs when discrete cues are poor predictors of US

delivery (Grillon & Davis, 1997). Fourth, fear-potentiation of startle is reduced in patients with amygdala damage (e.g., Funayama, Grillon, Davis, & Phelps, 2001), although the precise contributions of the BLA, BNST, and CeA to fear-potentiated startle in humans remain poorly understood.

In summary, studies of potentiated startle have identified basic neural mechanisms that support fear and anxiety. It is important to recognize, however, that the amygdala is not specialized for negative emotion, *per se* (Whalen, 1998), as several neuroimaging studies document amygdala responses to positive stimuli (e.g., Anderson et al., 2003). Furthermore, in addition to abolishing fear-potentiated startle, lesions of the CeA disrupt attentional orienting to cues that predict food rewards (Holland & Gallagher, 1999). This finding comes from a large literature on amygdala contributions to reward processing (Baxter & Murray, 2002; Holland & Gallagher, 1999). Thus, rather than being the neural locus of fear or anxiety, the amygdala appears to subserve more basic processes, including attentional vigilance, learning motivationally relevant cue-outcome associations, and modulating activity in other brain regions involved in representing value, encoding memories, and initiating approach or avoidance (Davis & Whalen, 2001; Holland & Gallagher, 1999; LeDoux, 2000). These conclusions are relevant to mental illness, as reviewed next.

Startle in Anxiety

Apprehension and associative learning in panic disorder—Panic disorder (PD) is characterized by panic attacks (brief periods of physiological hyperarousal) and anticipatory anxiety concerning their onset (American Psychiatric Association, 2000). Given the similar intensity of panic attacks and conditioned fear responses, it might be hypothesized that PD involves increased potentiated startle to conditioned fear cues. However, multiple studies reveal normative cued-fear responses in patients with PD (Grillon, Ameli, Goddard, Woods, & Davis, 1994; Grillon et al., 2008; Lissek et al., 2010). Instead, PD is marked by heightened vigilance and overly general associative learning.

Evidence for heightened vigilance comes from studies manipulating the predictability of aversive stimuli. A first experiment established that unpredictability and a suitable level of aversive stimulation are necessary to elicit contextual startle potentiation in healthy controls (Grillon, Baas, Lissek, Smith, & Milstein, 2004). Participants viewed cues that signaled no possibility of aversive stimulation, predictable aversive stimulation (aversive stimulation while the cue was visible), and unpredictable aversive stimulation (aversive stimulation not synchronized to cue presentation). For one group the aversive stimulation was electric shock, whereas for another a less aversive airblast to the larynx was the US. Startle probes were delivered while the cues were visible and during inter-trial intervals (ITI). Two key findings emerged. First, the predictable condition elicited fear-potentiated startle in both groups, demonstrating that the shock and airblast were sufficient to elicit fear in response to discrete cues. Second, only the shock group showed a linear increase in ITI startle amplitude across the no stimulation, predictable stimulation, and unpredictable stimulation conditions. This pattern suggests increased apprehension in anticipation of an unpredictable stimulus that was not evident in controls exposed to the weaker aversive stimulus (the airblast).

By contrast, a similar study revealed that unpredictable delivery of weakly aversive stimuli (unpleasant sounds) is sufficient to elicit contextual conditioning in PD (Grillon et al., 2008). Unlike healthy controls, participants with PD showed a linear increase in ITI startle amplitude across the no stimulation, predictable stimulation, and unpredictable stimulation conditions. In other words, a weak (unpredictable) threat elicited anxious apprehension in participants with PD, whereas a more aversive threat was needed to elicit a similar pattern in controls.

The ease with which contextual fear was elicited in PD suggests dysfunction in associational learning mechanisms. Direct evidence for such dysfunction emerged from an investigation of fear generalization (Lissek et al., 2010), in which participants underwent a fear conditioning protocol that used visually presented rings of different sizes as conditioned stimuli. One stimulus was never paired with electrical shock (CS−), while another was repeatedly paired with shock (CS+). Critically, the CS− and CS+ defined the endpoints of a size continuum, and in a subsequent generalization test, startle responses were measured as participants viewed stimuli distributed across four classes of intermediate size. Both groups showed normal fear-conditioning, evident in increased startle to the CS+ versus the CS−. The key finding came from the generalization test. Controls generated similar startle responses to the CS+ and to stimuli one size class removed. By contrast, the panic group demonstrated similar startle responses to the CS+ and stimuli up to three size classes removed. This overgeneralization of fear may reflect insufficiently specific learning about the predictive nature of the CS+ and CS− in PD.

D-cycloserine augmentation of extinction learning—In addition to identifying specific mechanisms that may contribute to psychological distress, affective neuroscience can point toward new treatments. Startle research has helped stimulate a new approach to psychopharmacological treatment for fear and anxiety. Specifically, animal work indicating that extinction of fear-potentiated startle is facilitated by intra-amygdala infusions of the partial *N*-methyl-D-aspartate agonist d-cycloserine (DCS; Walker, Ressler, Lu, & Davis, 2002) led researchers to investigate whether DCS augments exposure treatments for anxiety (Deveney, McHugh, Tolin, Pollack, & Otto, 2009). This work is based on the premise that extinction and exposure both involve learning that fear-conditioned stimuli are no longer reinforced.

DCS was first used to augment exposure-based treatment for height phobia (Ressler et al., 2004). Briefly, relative to patients receiving placebo, those administered DCS before exposures reported less distress in a virtual reality elevator at a second session, as well as less distress and weaker physiological responses in the elevator, reduced phobic symptoms, and increased exposures to heights in daily life 3 months later. The post-treatment measures were obtained while patients were drug-free, consistent with facilitated extinction learning rather than a direct effect on anxiety. Similar results have been obtained in social anxiety disorder (Hofmann et al., 2006) and obsessive compulsive disorder (e.g., Kushner et al., 2007), and a meta-analysis reported a consistent benefit of DCS on extinction learning (Norberg, Krystal, & Tolin, 2008).

Startle and Amygdala Activity as Measures of ER

To date, most neuroscientifc studies of ER have investigated instructed ER, in which participants are explicitly directed to modulate their emotional responses. Startle methodology is useful in this context because it is resistant to experimenter demand (as a reflex, it is not under conscious control) and sensitive to short-lived emotional states. Thus, startle probes can provide insight into “affective chronometry” (Davidson, 1998), which refers to attempts to track the wax and wane of emotional states.[3]

The first startle study of instructed ER involved a paradigm that has become widely used (Jackson et al., 2000). Participants viewed negative and neutral pictures, and several seconds into the picture-viewing period they heard an ER cue: either “enhance”, “maintain”, or “suppress” (only the maintain cue was presented on neutral trials). The cues instructed

[3]Our focus here is on studies of instructed, volitional ER, but ER processes are thought to lie on a continuum ranging from automatic to highly controlled (Davidson, 1998). The same features that make startle attractive in studies of volitional ER make it a useful tool for investigation of more automatic forms of ER that do not require conscious awareness.

participants to cognitively increase, sustain, or decrease their emotional responses to the negative pictures. Startle probes were presented prior to the regulation cues and at three time points afterwards. Two key findings emerged. First, startle amplitude evoked before cue onset was larger on negative than neutral trials, confirming induction of negative emotion. Second, startle amplitude to probes presented after the cues decreased in the expected order —enhance > maintain > suppress—indicating that participants could modulate negative emotions evoked by the pictures. These findings established that startle can distinguish between effects of emotion and ER.

The results also raise important questions. First, given that the amygdala supports potentiated startle, does cognitive ER influence amygdala activity? Several fMRI studies have addressed this question, and the answer is yes (Eippert et al., 2007; Ochsner et al., 2004; Schaefer et al., 2002). When participants cognitively increase, decrease, or maintain the emotional impact of negative pictures, amygdala activity is usually enhanced, reduced, or sustained, respectively, relative to passive viewing (but see Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007).

Second, are these findings valence-specific? A valence-specific hypothesis predicts that if participants are asked to cognitively increase and decrease their emotional responses to positive and negative pictures, opposite patterns of startle modulation should emerge (negative trials: increase > maintain > decrease; positive trials: increase < maintain < decrease), reflecting the fact that, during passive viewing, startle amplitude is typically potentiated when avoidance motivation is primed but reduced when approach motivation is primed (Lang, 1995). By contrast, an arousal-based hypothesis proposes that the same pattern of startle modulation by cognitive regulation (i.e., increase > maintain > decrease) should emerge regardless of picture valence.

Results from two startle studies support the arousal hypothesis (Dillon & LaBar, 2005; Driscoll, Tranel, & Anderson, 2009). In both studies, the same pattern of startle modulation was observed across negative and positive picture trials (e.g., enhance > maintain > suppress in Dillon & LaBar, 2005). This is consistent with fMRI results indicating that regulation of positive and negative emotions has similar effects on amygdala activity (Beauregard, Levesque, & Bourgouin, 2001; Kim & Hamann, 2007). Thus, at least with respect to startle and amygdala activity, cognitive regulation appears to modulate arousal rather than valence.

Third, what mechanisms implement these effects? At the neural level, one mechanism has just been described: arousal-based modulation of amygdala activity. This appears to reflect the influence of various aspects of the prefrontal cortex (PFC) and anterior cingulate cortex. These regions are recruited during attempts to increase or decrease negative emotions, and reappraisal success as indexed by self-report often correlates with activity in PFC structures (e.g., Eippert et al., 2007; see also Urry, van Reekum, Johnstone, & Davidson, 2009).

At the psychological level, researchers are isolating component processes that support regulation strategies. For example, an fMRI study of reappraisal (van Reekum et al., 2007) found that shifts in eye gaze accounted for substantial variance in brain activity that would otherwise have been attributed to reappraisal (e.g., participants looked away from arousing picture elements when decreasing emotion). Consequently, a subsequent study directed participants' gaze to arousing and non-arousing elements of the pictures to control for attentional contributions to reappraisal (Urry, 2010). Encouragingly, reappraisal goal (increase, view, decrease) did not interact with gaze direction for ratings of emotional intensity and peripheral psychophysiological responses, suggesting that reappraisal effects do not simply reflect shifts in externally-directed attention.

Finally, are these ER effects sensitive to psychopathology? Initial research on this topic is yielding promising results. For example, in an fMRI study featuring sad film clips, depressed adults reported greater difficulty regulating sadness than controls, and difficulty regulating sadness was correlated with the intensity of depressive symptoms and left amygdala activation in depression (Beauregard, Paquette, & Levesque, 2006). Another study found an inverse correlation between activity in the ventromedial PFC and amygdala during down-regulation of negative emotion in controls, but found the reverse relationship in depressed participants (Johnstone et al., 2007). Encouraging findings have also been reported for other disorders (e.g., social anxiety: Goldin, Manber, Hakimi, Canli, & Gross, 2009), thus this line of research appears promising.

Reward

Although "reward processing" is not an emotion, the fact that all mammals consistently expend effort to approach and obtain appetitive stimuli suggests that studying reward processing may provide insight into basic mechanisms relevant to positive emotions and ER (Berridge & Kringelbach, 2008; Burgdorf & Panksepp, 2006). Furthermore, work on reward has applied value because anhedonia, which refers to loss of pleasure, is an important symptom of depression, schizophrenia, and substance abuse (American Psychiatric Association, 2000). To date, most research on anhedonia has relied on self-report measures. While valuable, these cannot provide information on hedonic processes that are inaccessible to introspection (Berridge & Kringelbach, 2008; Pizzagalli, in press). Because affective neuroscience can shed light on such processes, it may prove helpful in this context.

Reward Anticipation, Consummation, and Learning

Reward processing can be divided into three psychological components: anticipation ("wanting"), consummation ("liking"), and learning about relationships between cues and rewarding outcomes (Berridge & Kringelbach, 2008). Neurally, these components are instantiated in a network that extends from the midbrain, through the amygdala and striatum, and into various cortical regions, including the orbitofrontal cortex (OFC). Evidence from non-human animals suggests that "liking" may largely depend on opioid and cannabanoid receptors in two aspects of the ventral striatum, namely, the nucleus accumbens (NAcc) and ventral pallidum, whereas "wanting" appears to depend largely on dopaminergic (DA) neurons that originate in the midbrain and project to the striatum (Berridge, 2007).

Work in non-human primates reveals that reward-related learning is reflected in the firing patterns of midbrain DA neurons (Schultz, 1998), although whether these neurons play a causal role in learning is unclear (Berridge, 2007). Relevant data come from studies of appetitive conditioning in which a CS predicts an appetitive US (e.g., food). In early stages of CS-US learning, when US delivery is still unpredictable, DA neurons respond strongly to the US. Because the US is unexpected (and rewarding), these DA bursts are assumed to code a "positive prediction error". As the CS-US relationship is learned, DA neurons cease responding to the US and instead begin responding to the CS. Notably, once the CS-US contingency is learned, omission of an expected reward will yield a "dip" in the firing rate of DA neurons. This signals a "negative prediction error", as the outcome is worse than expected. The ability of DA neurons to track CS-US contingencies is thought to support behavioral flexibility in pursuit of desired outcomes (Montague, Hyman, & Cohen, 2004; Schultz, 1998).

These findings have translated well to humans. With respect to subjective experience, anticipation and consummation are dissociable: anticipation is associated with reward responsiveness and mental imagery, whereas consummation is associated with openness to experience and appreciation of a range of positive outcomes (Gard, Germans Gard, Kring, &

John, 2006). Meanwhile, neuroimaging (D'Ardenne, McClure, Nystrom, & Cohen, 2008) and intracranial recordings (Zaghloul et al., 2009) confirm that the human midbrain responds to unexpected rewards with increased activity, coding positive prediction errors. The same ventral striatal regions implicated in "wanting" in non-human animals respond to reward-predicting cues in human MRI studies (Dillon et al., 2008; Knutson & Cooper, 2005). Finally, mirroring non-human data, receipt of rewards elicits activity in PFC (Dillon et al., 2008; Knutson & Cooper, 2005), and OFC and anterior cingulate regions have been implicated in stimulus-reward and action-reward learning, respectively (Berridge & Kringelbach, 2008; Rushworth, Behrens, Rudebeck, & Walton, 2007).

Reward Processing in Psychopathology

This work is valuable to investigations of psychopathology because it suggests three routes to anhedonia: dysfunction in the anticipatory or consummatory phases, or deficits in cue-reward contingency learning. Because these components are psychologically and neurobiologically more homogenous than psychiatric diagnoses, studying them could pave the way for precise therapeutic interventions with broad applicability.

Along these lines, we used fMRI to examine anticipatory and consummatory phases of reward processing in MDD (Pizzagalli et al., 2009; see also Knutson et al., 2008). Trials featured cues predicting monetary gains, penalties, or "no change" feedback. Cues were followed by a target (to which participants responded by pressing a button) and then feedback. Relative to controls, MDD participants displayed weaker responses to monetary gains, but not penalties or neutral feedback, in the left NAcc and the bilateral dorsal caudate (a component of the dorsal striatum). Although additional studies are needed, the group difference in the nucleus accumbens suggests a deficit in hedonic responses to reward in MDD, while the caudate finding may reflect weaker action-reward associations in depression (Pizzagalli et al., 2009). However, our design could not rule out group differences in cue-reward learning, and an elegant neuroimaging study provided evidence for this type of dysfunction in depression (Kumar et al., 2008). It is important to recognize that dysfunctions in various components of reward processing are not mutually exclusive. Moreover, given the clinical heterogeneity of MDD, a one-to-one correspondence between depression and dysfunction in specific reward components should not be expected.

Similar approaches have been used successfully in schizophrenia. Parsing reward into anticipatory and consummatory phases has suggested the answer to a major puzzle (Gold, Waltz, Prentice, Morris, & Heerey, 2008; Pizzagalli, in press): why do individuals with schizophrenia consistently report symptoms of anhedonia while demonstrating normative responses to pleasurable stimuli? Both neuroimaging (Juckel et al., 2006) and experience sampling (Gard, Kring, Germans Gard, Horan, & Green, 2007) indicate that schizophrenia is characterized by a deficit in anticipatory but not consummatory pleasure. For example, a series of behavioral studies found that, relative to controls, individuals with schizophrenia showed few deficits in immediate responses to positive stimuli (Gold et al., 2008). However, patients displayed difficulty representing rewarded information in working memory, selecting between immediate and future rewards, and tracking rapidly shifting stimulus-reward contingencies. These findings suggest that anhedonia in schizophrenia may reflect impaired ability to envision future positive outcomes, although in-the-moment responses appear intact (Gard et al., 2007; Gold et al., 2008).

Deep brain stimulation for anhedonia—Understanding of the reward network has led to a new treatment for treatment-resistant depression: deep brain stimulation targeting the ventral striatum. This approach is preliminary and considered only when all other treatments have failed, but results have been encouraging. In initial studies, stimulation of the NAcc

resulted in reduced anhedonic symptoms and immediate mood improvement that disappeared as soon as stimulation stopped (Bewernick et al., 2010; Schlaepfer et al., 2007). In a sample of treatment-resistant patients, stimulation of the ventral capsule/ventral striatum had beneficial effects on multiple measures of depression and general functioning that were evident over one year later (Malone et al., 2009). More studies are needed, but these results highlight the potential for targeted interventions, based on pre-clinical reward research, to lead to improvement in positive emotional experience.

Regulation of Positive Emotional Responses

It is clear that people can cognitively regulate positive emotional responses, and studies mentioned above provide corroborating evidence via reductions in startle amplitude (Dillon & LaBar, 2005; Driscoll et al., 2009) and amygdala activity (Beauregard et al., 2001; Kim & Hamann, 2007). However, while the amygdala makes important contributions to reward processing, neuroimaging studies of reward emphasize the contributions of the dorsal and especially ventral striatum. Are these regions susceptible to top-down modulation? The answer appears to be yes.

Initial evidence comes from Kim and Hamann (2007), who demonstrated that, relative to passive viewing, cognitively increasing positive emotions elicited by pictures yielded increased activity in the ventral striatum. More direct evidence with respect to reward comes from Delgado, Gillis, and Phelps (2008), who implemented a design in which two different colored squares served as conditioned stimuli for delivery of monetary gains. One conditioned stimulus was consistently rewarded (CS+), whereas the other was not (CS−). Critically, presentation of the CS was preceded by instructions to either simply attend or cognitively regulate emotional arousal elicited by the CS. Skin conductance responses revealed that the CS+ elicited greater peripheral physiological activity than the CS− following the attend instruction, but not following the regulate instruction. Similarly, the ventral striatum responded more strongly to the CS+ versus the CS− in the attend condition, but not in the regulate condition. These regulation effects, which presumably reflect top-down signals from PFC regions, demonstrate that striatal reward signals are sensitive to cognitive modulation.

These data suggest that while anhedonia might reflect a deficit in reward anticipation, consummation, or learning, it could also stem from an inability to cognitively sustain positive emotional responses once they arise. Support for this hypothesis comes from an fMRI study that examined NAcc activity as controls and MDD participants attempted to cognitively regulate positive emotions elicited by pictures (Heller et al., 2009). The key result was that, relative to controls, participants with MDD could not cognitively sustain a heightened NAcc response to positive pictures. In addition, among patients, a greater decrease in NAcc activation over time correlated with lower levels of positive affect, highlighting important convergence between neural responses and subjective experience. The group difference in sustained NAcc activation was linked to a weaker functional connection between the NAcc and the left middle frontal gyrus in depression. This is notable because a similar PFC region was identified by Delgado et al. (2008) in their study of positive emotion regulation. Collectively, these findings indicate that PFC-striatal connections support cognitive regulation of positive emotion.

Conclusions

The current, selective review highlights how investigations of emotion, ER, and psychopathology can be mutually informative. By focusing on approach and avoidance behaviors that are conserved across species, affective neuroscience has provided insight into basic psychological and neural mechanisms that support emotional responses (LeDoux,

2000; Schultz, 1998). Findings from this research program serve as a foundation for many subsequent investigations in ER and psychopathology. In turn, work in these areas can inform understanding of emotion. For example, ER research serves as a reminder that the way in which emotional stimuli are interpreted influences behavior and physiology, and it can identify which components of an emotional response are susceptible to modulation. Along these lines, demonstrations of reappraisal effects on amygdala activity suggest the need to revise the hypothesis that the amygdala is a cognitively impenetrable fear module (Ohman & Mineka, 2001).

However, affective neuroscience has limitations worth noting. First, emphasizing behavior and physiology over subjective experience entails a trade-off. This approach avoids challenges associated with pinning down conscious experience and has facilitated experimental progress (LeDoux, 2000), but a different strategy may be needed to develop an affective neuroscience of feelings (Barrett, Mesquita, Ochsner, & Gross, 2007). Second, affective neuroscience cannot yet speak to highly contextualized individual differences in emotional experience. These limitations are clinically relevant. Individuals who seek psychological treatment usually complain of problems at the level of conscious experience, but because of the limitations just mentioned, affective neuroscience is not yet suited to address those complaints. Instead, they may be best understood in the context of well-elaborated theories of conscious experience, such as those that support cognitive behavioral therapy (Beck, 1976) or mindfulness-based interventions (Kabat-Zinn, 1990). However, affective neuroscience can support these interventions by illuminating mechanisms of change (e.g., Goldapple et al., 2004).

Going forward, imaging genomics is expected to be a particularly exciting area of research. To date this work has uncovered relationships between genetic variation, individual differences in trait measures of emotion, and important but fairly blunt measures from affective neuroscience, such as amygdala reactivity to blocked presentation of fearful faces (Hariri, 2009). These studies suggest that investigation of more complex relationships between genes and neural circuitry may reshape our understanding of individual differences in emotional lability, capacity for emotion regulation, and symptoms of psychopathology (Hariri, 2009). Indeed, continued cross-talk between scientists working on emotion, ER, and psychopathology can be expected to drive progress in each of these domains.

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