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Chapter 22

Emotional Dysfunction in Psychopathology and Neuropathology: Neural and Genetic Pathways

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EMOTIONAL DYSFUNCTION IN PSYCHOPATHOLOGY AND NEUROPATHOLOGY: NEURAL AND GENETIC PATHWAYS

In our view, emotions are "short-lived psychological-physiological phenomena that represent efficient modes of adaptation to changing environmental demands" (Levenson, 1994). As depicted in Fig. 22.1, emotions are initiated by appraisal processes, often rapid and unconscious but sometimes more protracted and conscious, and produce coordinated changes in disparate physiological systems including facial expression, voice, somatic muscles, and autonomic nervous system (Levenson, 2003). Subjective emotional experience (the "feelings" we have when in the throes of an emotion) arises from interoceptive and proprioceptive processing of visceral and somatic information and sensations that are produced when these physiological systems are activated (Levenson, 2003).

Emotional functioning in humans is incredibly durable. Emotions are generated by phylogenetically ancient, well-conserved neural circuits (Rosen & Levenson, 2009) and can persist even in decorticate brains (Shewmon, Holmes, & Byrne, 1999). Emotions appear early in ontogeny; infant distress cries and smiles provide critical avenues for bidirectional communication and influence between child and caregiver. Emotions are also built for the long haul. Emotional functioning is sustained at high levels at the outreaches of normal aging, long after cognitive and physical abilities have shown

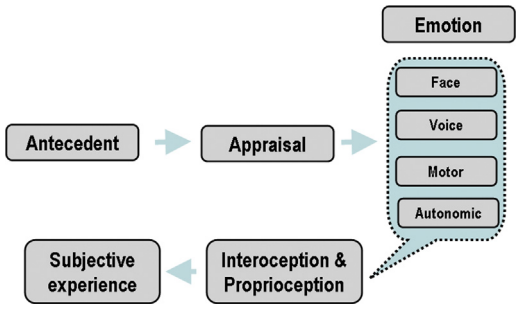

FIGURE 22.1 The emotional system.

Genomics, Circuits, and Pathways in Clinical Neuropsychiatry. http://dx.doi.org/10.1016/B978-0-12-800105-9.00022-6

dramatic declines (Levenson, 2000; Salthouse, 2004). Despite these indicators of durability, human emotion is also extremely vulnerable to dysfunction. In a large number of psychiatric and neurological diseases, emotions change in ways that interfere with daily living, work, and relationships and create enormous problems for patients, loved ones, and society.

In this chapter, we first review the current state of knowledge about neural and genetic influences on three aspects of emotional functioning (emotional reactivity, emotion regulation, and emotional affiliation). Emotional reactivity, regulation, and affiliation are all critical for daily living and maintaining mental and physical health. Importantly, each is highly vulnerable to disruption in psychopathology and neuropathology. In the final part of the chapter, we consider ways in which tools and concepts derived from modern affective science can help elucidate the relationships among neural circuits, genes, emotional functioning, and pathology and provide insights about etiology, diagnosis, and treatment that can be useful in clinical contexts.

EMOTIONS AND EMOTIONAL PROCESSES EMOTIONS: SHORT AND DISCRETE

Before initiating our discussion of neural and genetic pathways related to emotional functioning, it is important to clarify the kinds of emotional phenomena upon which we will be focusing. We have presented a model of emotion and emotional elicitation that would be characterized in the current marketplace of emotion theories as "evolutionary," "functional," and "peripheralist." In addition to theoretical diversity, affective scientists also differ in the temporal aspects of the affective phenomenon of interest. Whereas we might focus on a 5-s burst of sadness, others would focus on longer-lasting sad moods that could last for hours or days, and yet others would focus on even longer-lasting sad traits that could last for years or a lifetime (Ekman, 1984). Thus, the affective phenomena that we will be primarily considering in this chapter are short-lived, typically lasting for a matter of seconds, although they can be reactivated repeatedly over longer periods. In our view, these kinds of elemental, brief emotions are: (1) well-suited for precise study in the laboratory, (2) well-matched in grain of measurement for making functional links with neural circuits and genes, and (3) clinically relevant by virtue of being vulnerable to disruptions in psychopathology and neuropathology.

In addition to temporal considerations, affective scientists differ in their views about how best to parse affective space. In our work, we have followed a "discrete emotions" approach (Ekman, 1992), which proposes that there are particular emotions (eg, fear, anger, sadness, happiness, disgust, contempt) that differ from each other in terms of their associated physiological, expressive, and subjective qualities and that represent generalized evolved solutions (Tooby & Cosmides, 1990) to timeless problems, challenges, and opportunities (eg, sadness for dealing with loss, happiness for dealing with gains). For us, discrete emotions provide a meaningful and highly useful bridge to different forms of psychopathology and neuropathology. For example, a patient with a specific phobia is more likely to have problems with fear than with sadness, whereas the opposite would be true for a patient with depression. Likewise, a patient with amyotrophic lateral sclerosis (ALS) who is experiencing pseudobulbar affect may show expressive displays that resemble sadness and/or happiness but not those that resemble fear or disgust (Olney et al., 2011). There is a different view that eschews discrete, evolved emotions, and instead envisions emotional states as existing in a multidimensional space (eg, a two-dimensioned circumplex based on valence and arousal) and as being largely socially constructed (Russell & Barrett, 1999). In work with clinical syndromes using categorical systems for diagnosing psychopathology such as the *Diagnostic and Statistical Manual* (DSM) (American Psychiatric Association, 1994), historically the discrete emotions view has been more prominent. However, the dimensional view may make greater inroads with the introduction of the Research Domain Criteria (RDoC) (Insel et al., 2010), which views psychopathology in a dimensional rather than categorical manner.

EMOTIONAL PROCESSES

Emotion is often treated as if it were a single entity, a practice that can lead to difficulties when exploring links with particular neural circuits and genes, which arguably are better matched with finer-grained behavioral phenomena. Just as cognition is best considered as consisting of multiple dissociable processes (eg, short-term memory, executive control, computation), emotion needs to be broken down into smaller functional units. In this chapter we focus on three emotional processes that are particularly important when considering normal and pathological emotional functioning: (1) emotional reactivity, (2) emotional regulation, and (3) emotional affiliation.

Emotional Reactivity

Emotional reactivity refers to the capacity to generate emotions in response to salient challenges, threats, and opportunities. In the laboratory, emotional reactivity is typically assessed by exposing individuals to carefully selected sensory stimuli

(eg, films, still images, sounds) that are known to elicit strong emotional reactions in most people. Emotional reactivity is then quantified by measuring the magnitude and duration of the emotional response in behavior, physiology, and subjective experience.

Emotional Regulation

Emotional regulation refers to the capacity to adjust aspects of the emotion response in accordance with personal, interpersonal, and social goals and standards. Most typically this involves downregulating emotion (eg, reducing anger in a dispute with a loved one) but it can also involve amplifying emotion (eg, increasing sadness to communicate distress clearly to another person). In the laboratory, emotional regulation is typically assessed by exposing individuals to emotion-eliciting situations and either giving them explicit regulatory instructions (eg, do not allow your emotions to show) or leaving them free to regulate or not using their own strategies. Emotional regulation is then quantified by measuring the magnitude and duration of emotional response (usually compared with a condition in which regulation is minimized).

Emotional Affiliation

Emotional affiliation refers to the capacity to use emotion to create and maintain social connections. It is a process that reflects the strongly social and interpersonal nature of human emotion (Keltner & Kring, 1998). In the laboratory, emotional affiliation can be assessed by exposing individuals to a social situation in which they have to process emotional information from other people and/or respond to the emotions of others. Emotional affiliation can be quantified by measuring (1) the ability to recognize (Bowers, Blonder, & Heilman, 1991) or track (Goodkind et al., 2012) emotions in others; (2) the emotional reactions that occur in response to the emotions of others (Sze, Gyurak, Goodkind, & Levenson, 2012); and (3) the patterns of emotional reactivity and regulation that occur in interactions with intimate others (Gottman & Levenson, 1986; Levenson, Haase, Bloch, Holley, & Seider, 2013).

EMOTIONAL FUNCTIONING: NEURAL PATHWAYS

In this section, we will discuss the neural circuitry that subserves emotional reactivity, regulation, and affiliation. Studying this circuitry in both normal and clinical populations provides a basis for understanding how the nervous system not only supports these emotional functions but also provides important clues for beginning to understand the basis of individual differences in emotional functioning. These individual differences exist both in the "normal" range (eg, some people are more emotionally reactive than others) and "abnormal" range. The latter are particularly important for understanding the neural pathways that are associated with emotional dysfunctions associated with neuropathology and psychopathology.

EMOTIONAL REACTIVITY

Distributed neural systems initiate the coordinated changes in autonomic nervous system reactivity and facial expression that characterize emotion. Consistent with the schematic of emotional response presented earlier, after appraisal of a salient stimulus, a network of brain regions that includes the anterior cingulate cortex, central nucleus of the amygdala, hypothalamus, and brain stem work with the anterior insula to initiate the emotional response and monitor the cascade of visceral and motor changes that accompany that response. For example, a state of fear might activate a pattern of bodily changes in which heart rate speeds, hands become sweaty, and blood is redirected from the periphery to large-muscle groups (eg, the legs) that can help us escape a predator or intruder. These rapid physiological changes are coupled with action tendencies that make certain behaviors (eg, fleeing) more likely than others. In addition to these intrapersonal changes, emotions also serve important interpersonal functions. The expressive changes that occur (in facial expression, appearance, and vocalizations) alert conspecifics to the dangerous situation and help prepare them to deal effectively with the situation (Levenson, 1999). We turn next to a review of the brain structures that support the initiation of this complex multisystem emotional response.

Anterior Cingulate Cortex

The cingulate gyrus is a band of cortex that surrounds the corpus callosum. The cingulate can be further divided into distinct subregions that are based on cytoarchitectonic, connectivity, and functional divisions (Bush, Luu, & Posner,

2000). The posterior cingulate cortex is a key node in the default mode network that is typically active at rest and during episodic and prospective memory tasks. The midcingulate (or dorsal anterior cingulate cortex) is often engaged during attention and executive control, and the anterior cingulate cortex (which includes pregenual and subgenual subregions) is critical for emotion generation (Buckner, Andrews-Hanna, & Schacter, 2008; Ochsner, Silvers, & Buhle, 2012; Seeley, Zhou, & Kim, 2012; Sturm et al., 2013; Vogt, 2005). The anterior cingulate cortex is reciprocally connected with anterior insula, amygdala, periaqueductal gray, hypothalamus, nucleus accumbens, and orbitofrontal cortex, regions important for salience detection, emotional reactivity, and social regulation (Seeley et al., 2007). Through connections with orbitofrontal cortex, the anterior cingulate cortex is a centrally positioned hub that receives salient information about the environment and triggers visceromotor activity via subcortical structures and the brain stem (Ongur, An, & Price, 1998).

Amygdala

The amygdala is a structure in the medial temporal lobe that has long been implicated in emotion (Davis & Whalen, 2001). Although the amygdala gained notoriety for its role in fear (LeDoux, 1992), it is now known that the amygdala activates in response to a wide range of salient stimuli, including both negative and positive antecedent events (Murray, 2007), and is also essential for the formation of emotional memories (Cahill & McGaugh, 1998). The amygdala is composed of multiple subnuclei that have been largely delineated in nonhuman animals via tract-tracing studies and have been cross-validated in humans using structural and functional imaging parcellation techniques (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; McDonald, 1998). The basolateral amygdala receives sensory information from the thalamus, hippocampus, and cortex, relaying this information to the central nucleus as well as other regions involved in appraisal, memory, and approach or avoidance behavior (Davis & Whalen, 2001). The central nucleus, through direct projections to the hypothalamus and via brain stem nuclei that support autonomic functions such as respiration, heart rate, and sweating, initiates the autonomic cascade that accompanies emotion and alters attention and vigilance through reciprocal connections with orbitofrontal cortex (Ongur & Price, 2000; Price & Amaral, 1981). With direct projections to the trigeminal and facial motor nuclei, the central nucleus also has an integral role in emotional facial expression (Davis & Whalen, 2001).

Hypothalamus

The hypothalamus has a key role in thermoregulation, appetite, sleep, sexual behavior, and emotion. Composed of multiple subnuclei (eg, paraventricular nucleus, dorsomedial nucleus, lateral hypothalamic area), the hypothalamus receives afferent information from multiple regions including medial orbitofrontal cortex, amygdala, and anterior cingulate cortex (Ongur et al., 1998). The hypothalamus has efferent projections to autonomic nuclei in the brain stem including rostral ventrolateral medulla, dorsal motor nucleus of the vagus, and the nucleus of the solitary tract as well as the intermediolateral column of the spinal cord (Guyenet, 2006; Price & Amaral, 1981; Saper, Loewy, Swanson, & Cowan, 1976; Tucker & Saper, 1985). There is evidence that each subregion of the hypothalamus has a distinct role in autonomic reactivity, with some areas increasing and others decreasing cardiovascular arousal (Fontes, Xavier, de Menezes, & Dimicco, 2011). Although stimulation of the hypothalamus can lead to both autonomic and behavioral defense reactions in decerebrate nonhuman animals (Bard, 1934), other studies give greater emphasis to the role the hypothalamus has in generating the autonomic response in emotion rather than a behavioral response (LeDoux, Iwata, Cicchetti, & Reis, 1988).

Brain Stem

The brain stem contains multiple nuclei that have important roles in homeostatic regulation and emotion. The periaqueductal gray is a structure that surrounds the cerebral aqueduct and has a columnar organization (Bandler & Keay, 1996). The lateral column, which receives projections from the central nucleus of the amygdala, has a role in sympathetic nervous system activity, whereas the ventrolateral column has the opposite effect and slows the heart and respiration through inhibitory vagally mediated parasympathetic pathways (Behbehani, 1995). Stimulation of the periaqueductal gray can elicit various behavioral responses including vocalizations, fight, flight, or freezing (Bandler, Keay, Floyd, & Price, 2000) and trigger patterned, coordinated autonomic responses involving multiple organ systems (Carrive & Bandler, 1991; Dampney, Furlong, Horiuchi, & Iigaya, 2013).

Other brain stem regions also have important roles in the coordination of somatic, respiratory, electrodermal, and cardiovascular events. Rostral ventrolateral medulla, which receives afferent projections from the periaqueductal gray, contributes most notably to sympathetic nervous system activity that increases heart rate, blood pressure, and respiration (Fontes et al., 2011; Menezes & Fontes, 2007). The nucleus of the solitary tract has a role in efferent visceromotor pattern generation in addition to being a central afferent way station for incoming sensory information from the body (Andresen & Kunze, 1994). The nucleus of the solitary tract and the parabrachial nucleus, a region that also receives substantial afferent viscerosensory inputs, integrates incoming interoceptive information regarding the physiological state of the viscera. This continuous stream of sensory information arrives at the brain stem via the lamina I spinothalamocortical pathway and vagal afferents and is then relayed on to the thalamus and insula, where it undergoes more comprehensive processing (Benarroch, 2006; Craig, 2002).

Whereas sympathetic nerves emerging from the intermediolateral column of the spinal cord support sympathetic functioning, parasympathetic nervous system activity is primarily governed by the activity of the vagus (cranial nerve X). The vagus originates in two nuclei in the medulla: the dorsal motor nucleus and the nucleus ambiguus. Whereas the branch of the vagus that originates in the dorsal motor nucleus predominantly supports autonomic functions below the diaphragm (eg, intestines), there is a phylogenetically newer branch of the vagus that arises from the nucleus ambiguus, which has the central role of slowing the heart from the pace that is set by the sinoatrial node (Dergacheva, Griffioen, Neff, & Mendelowitz, 2010; Porges, 2001).

This newer branch of the vagus is myelinated and is important for respiratory sinus arrhythmia, a modulation of heart rate that is linked to the respiratory cycle. Levels of respiratory sinus arrhythmia have been linked to individual differences in empathy and prosocial behavior (Kogan et al., 2014). Through its close connections with other cranial nerves that support facial expression, the branch of the vagus that emerges from the nucleus ambiguus is considered to be essential for fostering a calm physiological state in mammals that is necessary for socioemotional attunement and communication (Porges, 2001).

Insula

The insula, a structure located deep in the Sylvian fissure, has a key role in numerous cognitive and affective processes. The insula can be divided into several subregions (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Through its projections to somatosensory and motor cortex, the midposterior insula is a key hub for sensorimotor processing and has an important role in sensing physical cues from the body and motor acts. The dorsal anterior insula, which has connections to ventrolateral prefrontal cortex, supplementary motor area, striatum, and subthalamic nucleus, has a predominant role in executive control, an ability that requires attention, working memory, response inhibition, and task-set maintenance (Aron, 2007). The ventral midinsula is integral for processing olfactory and gustatory stimuli, and the ventral anterior insula (or "frontoinsula") has strong connections with the anterior cingulate cortex, amygdala, hypothalamus, and brain stem and is a key node in social behavior, empathy, and emotion (Seeley et al., 2008). Although the insula and anterior cingulate cortex are often coactive during functional neuroimaging tasks of emotion and empathy, there is accumulating evidence that the primary role of the anterior cingulate cortex is initiation of motor behavior whereas that of the insula is sensing the body's internal milieu (Craig, 2009; Seeley et al., 2012).

The anterior insula is theorized to be one of the final sites for integrating visceral information from the body with homeostatic, hedonic, and motivational factors (Craig, 2009). The anterior insula is thus considered to be a primary center for assembling the subjective feeling states that accompany emotion. The insula maintains an online representation of the body's internal states through a pathway dedicated to interoception (Craig, 2002; Critchley & Harrison, 2013). The lamina I spinothalamocortical tract is a pathway through which information about the internal organs is relayed via small-fiber sympathetic afferents to brain stem centers including the nucleus of the solitary tract and parabrachial nucleus. From there, this information is shuttled to the ventroposterior medial nucleus of the thalamus and then to the posterior dorsal insula, midinsula, and finally, to the anterior insula. Parasympathetic afferent information is relayed via a similar pathway, but it is sent directly from the periphery to the brain stem via vagal afferents. Whereas sympathetic afferents may be more heavily represented in the right anterior insula, parasympathetic afferents may be more heavily represented in the left anterior insula (Craig, 2005). Patients who have lesions of the anterior insula (such as those with behavioral variant frontotemporal dementia) exhibit profound deficits in empathy and emotion (Seeley et al., 2008), which is likely because these patients are unable to access internal cues that typically promote understanding of and responsiveness to the emotions of others.

EMOTION REGULATION

Humans regulate emotions by choosing the situations they encounter, altering these situations, attending to certain aspects of the environment and ignoring others, changing the ways they appraise a situation, and modifying their overexpression of emotion (Gross, 1998). Regulation strategies that occur early in the cascade of emotion (eg, attentional deployment and reappraisal) can effectively attenuate emotion generation and decrease emotional experience, whereas regulatory strategies that occur later in the emotional cascade (eg, suppression) can actually accentuate emotional experience and autonomic reactivity (Gross & Levenson, 1993).

Most research on the neural systems that support emotion regulation has focused on conscious (ie, explicit) emotion regulation strategies, and these studies most often have examined the neural correlates of reappraisal (Ochsner et al., 2012). By contrast, an emerging literature on more automatic (ie, implicit) emotion regulation suggests that both kinds of emotion regulation recruit overlapping distributed neural systems. Functional neuroimaging studies of reappraisal typically find that prefrontal cortex is important for both cognitive control and emotion regulation. When participants engage prefrontal regions during reappraisal tasks that are aimed at lowering negative emotion, they exhibit lower activity in subcortical brain regions such as the amygdala when they are presented with emotional stimuli (McRae et al., 2010; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Here we will provide more details about brain regions that are pertinent for emotion regulation.

Ventrolateral Prefrontal Cortex

Ventrolateral prefrontal cortex is a region of the frontal lobes that is typically associated with response inhibition and goal-appropriate response selection (Aron, Robbins, & Poldrack, 2004). This region is often recruited during reappraisal tasks in which participants alter their interpretation of a negative stimulus to minimize its emotional impact. Reappraisal studies that invoke reinterpretation of a stimulus typically engage ventrolateral prefrontal cortex in conjunction with other regions (Goldin, McRae, Ramel, & Gross, 2008; McRae et al., 2010). Suppression, a form of response modulation in which participants are instructed to clamp down on their emotions, has also been linked to ventrolateral prefrontal cortex activity as well as activity in dorsal anterior insula (Hayes et al., 2010). As described previously (see the "Insula" section), the dorsal anterior insula is a key hub in the "stop signal" network that enforces behavioral control and response inhibition. Implicit emotion regulation, which can be measured simply by having participants label their affective states, also engages the ventrolateral prefrontal cortex. Whereas suppression may not attenuate activity effectively in emotional reactivity networks, implicit emotion regulation strategies can diminish activity in emotion generators such as the amygdala (Lieberman, 2007; Payer, Baicy, Lieberman, & London, 2012). Consistent with its role in emotional control, atrophy in ventrolateral prefrontal cortex has been linked to emotion dysregulation in patients with frontotemporal dementia, which suggests that volume loss in this region may unleash affective responsiveness (Sturm et al., 2014).

Dorsolateral Prefrontal Cortex

Dorsolateral prefrontal cortex, together with ventrolateral prefrontal cortex and dorsomedial prefrontal cortex (see the subsequent Affiliation section for more details about this region), can also be recruited during emotion regulation (Silvers, Wager, Weber, & Ochsner, 2015; Staudinger, Erk, & Walter, 2011). The dorsolateral prefrontal cortex is a region of the frontal lobes that is most typically associated with executive functions including working memory and selective attention (Curtis & D'Esposito, 2003). Through connections with parietal cortex, dorsolateral prefrontal cortex is a key node in dorsal attention networks that support basic cognitive selection of sensory information and response (Corbetta & Shulman, 2002). Although this region does not project directly to emotion generators, it may influence emotional reactivity by altering higher-order perceptual attention systems (Ochsner et al., 2012).

Anterior Midcingulate Cortex

The anterior midcingulate cortex has strong connections with lateral prefrontal cortex, parietal cortex, premotor cortex, and supplementary motor area (Bush et al., 2000) and has an important role in conflict detection, attention, and cognitive control (Seeley et al., 2007). This region is typically activated during demanding cognitive tasks that engage executive functions including working memory, response selection and inhibition, competition monitoring, and error detection (Botvinick, Cohen, & Carter, 2004; Carter et al., 1998). Often active during reappraisal, the dorsal anterior cingulate may

promote performance monitoring by detecting mismatches between one's intended and actual emotional states, thus fueling further emotional downregulation.

Inferior Parietal Lobe

The inferior parietal lobule is a posterior region of the brain that is most well-known for its role in visuospatial processing. Parietal cortex is also involved in other, nonspatial processes including perspective-taking and judgment of social closeness between people (Parkinson, Liu, & Wheatley, 2014; Yamazaki, Hashimoto, & Iriki, 2009).

Distancing, a form of reappraisal in which individuals create more psychological space between themselves and an emotional stimulus, seems to rely relatively more upon parietal cortex than other forms of emotion regulation (Koenigsberg et al., 2010). It is possible that distancing requires participants to alter their spatiotemporal perspective to decrease their feelings of connection with the stimulus (Ochsner et al., 2012). This region has also been found to be important for overcoming our own emotions to take the perspective of another, an ability that may also depend on a separation of self from other through distancing (Silani, Lamm, Ruff, & Singer, 2013).

EMOTIONAL AFFILIATION

Humans possess the neural circuitry necessary to support the formation and maintenance of meaningful, enduring social relationships (Baumeister & Leary, 1995; Beckes & Coan, 2011). Social contact, which promotes a sense of calm in the brain and autonomic nervous system, is essential to health and longevity (Beckes & Coan, 2011; Porges, 2001). Social support attenuates neural activity in regions that detect and respond to threat and danger (Coan, Schaefer, & Davidson, 2006; Zaki, Schirmer, & Mitchell, 2011) and increases activity in autonomic and neuroendocrine systems that support positive emotions, bonding, and empathy (Carter, Williams, Witt, & Insel, 1992; Porges, 2001; Stellar, Cohen, Oveis, & Keltner, 2015).

As noted earlier, emotional affiliation is a broad construct that encompasses a number of different subprocesses. In this section we will focus on two aspects of emotional affiliation: (1) emotion recognition (the ability to recognize the emotions of others), and (2) emotions that occur in intimate relationships (focusing on nurturant love and compassion, two emotions that promote social relationships and prosociality). Responding emotionally to the emotions of others (sometimes called "emotional empathy"), another important aspect of emotional affiliation, will not be included in this section. Not surprisingly, research has shown that the neural systems that support emotional empathy largely overlap with those involved in emotion generation (Engen & Singer, 2013). These circuits were reviewed in the section on emotional reactivity presented earlier.

Superior Temporal Sulcus

The superior temporal sulcus, and often the temporoparietal junction, is a brain region that is important for numerous aspects of social cognition. This region is typically active during tasks of cognitive empathy and perspective-taking (Frith & Frith, 2006; Saxe & Kanwisher, 2003). The superior temporal sulcus is also important for the detection of social cues including prosody, faces, trustworthiness, and intention (Ethofer et al., 2006; Sabatinelli et al., 2011; Winston, Strange, O'Doherty, & Dolan, 2002). Activity in this region has also been linked to altruism and higher levels of prosocial behaviors including fairness and generosity, which suggests that being able to understand the minds of others may promote an other-oriented focus and feelings of selflessness (Morishima, Schunk, Bruhin, Ruff, & Fehr, 2012; Takagishi, Kameshima, Schug, Koizumi, & Yamagishi, 2010).

Dorsomedial Prefrontal Cortex

The medial prefrontal cortex is a midline frontal region typically associated with self-processing and other-processing. The medial prefrontal cortex can be parcellated into dorsal and ventral parts, with the dorsomedial prefrontal cortex responding more to stimuli about other people and the ventromedial prefrontal cortex responding more to stimuli that are self-related (Denny, Kober, Wager, & Ochsner, 2012). Dorsomedial prefrontal cortex, working with other structures (eg, posterior cingulate cortex, posterior superior temporal sulcus, and medial temporal lobes), is considered to be a necessary node in the default mode network that enables humans to project themselves outside the present moment and focus on things other than the self in the here-and-now (Buckner & Carroll, 2007; Mitchell, 2009). Consistent with this idea, dorsomedial prefrontal cortex is often active during tasks in which participants must focus on the perspectives and

feelings of other people (Abu-Akel & Shamay-Tsoory, 2011; Iacoboni et al., 2004; Mitchell, 2009). The dorsomedial prefrontal cortex is also active during certain types of emotion regulation (eg, reappraisal), which may reflect the fact that reappraisal requires people to reconsider the perspectives of others and the significance of emotional situations (Silvers et al., 2015).

Ventral Striatum

The ventral striatum has a prominent role in reward processing. With strong connections with other emotion generators, this region (and especially the nucleus accumbens) is active during the anticipation and receipt of monetary and social rewards (Izuma, Saito, & Sadato, 2008; Knutson, Adams, Fong, & Hommer, 2001). Positive emotional stimuli, such as positive faces and pleasant scenes, also activate the ventral striatum (Wager et al., 2008), as do feelings of social connection, interpersonal warmth, and feeling understood (Inagaki & Eisenberger, 2012, 2013; Morelli, Torre, & Eisenberger, 2014). Studies of attachment and nurturant love find higher activity in ventral striatum (as well as other emotion-relevant regions including the anterior insula, anterior cingulate cortex, and periaqueductal gray) when participants view photographs of people for whom they have strong feelings of love and connection, compared with when they view people with whom they are less close (Acevedo, Aron, Fisher, & Brown, 2012; Bartels & Zeki, 2004).

Interestingly, individuals who have undergone compassion training exhibit increased activity in the ventral striatum in response to distressing photographs, which suggests that an other-oriented compassionate focus promotes prosocial helping feelings rather than self-oriented feelings of personal distress (Klimecki, Leiberg, Ricard, & Singer, 2014).

Medial Orbitofrontal Cortex

The orbitofrontal cortex is a ventral region of the frontal lobes that is important for the detection and tracking the value of a stimulus (Rolls, 2000). Whereas the lateral orbitofrontal cortex is essential for monitoring information that is relevant for tracking potential punishments, the medial orbitofrontal cortex is integral for processing reward-related cues (Kringelbach & Rolls, 2004). Via projections to ventral striatum and emotion-generating systems, the medial orbitofrontal cortex facilitates online decoding and monitoring a stimulus's reward value.

This region is integral in evaluating the meaning of primary rewards, such as odors, and social rewards, such as observing others acting prosocially (Fehr & Camerer, 2007; Rolls, 2008). The medial orbitofrontal cortex is active not only when people themselves receive a reward but also when they view others receiving rewards, which suggests that this region enables us to experience reward for ourselves and it also facilitates our ability to share the positive experiences of others vicariously (Hare, Camerer, Knoepfle, & Rangel, 2010; Morelli, Sacchet, & Zaki, 2014).

Septal Area

The septal area is a subcortical region that has strong projections to emotion-generating areas and has a key role in feelings of social connectedness and bonding. In rats, oxytocin binding in the septal area has been associated with maternal behaviors that promote kinship bonds (Francis, Champagne, & Meaney, 2000). In humans, the septal area is active when an individual has positive feelings toward others, including experiences of unconditional trust, empathy, and social connection. Activity in this region during a scanner-based empathy task predicts real-world prosocial helping behavior (Krueger et al., 2007; Morelli, Rameson, & Lieberman, 2014). Consistent with its strong role in affiliative behavior, atrophy in the septal area has been linked to a decline in prosocial feelings in patients with frontotemporal dementia (Moll et al., 2011).

EMOTION FUNCTIONING: GENETIC PATHWAYS

Researchers have used a number of different strategies to study the genetic bases of emotional functioning in humans, including (1) adoption and twin studies, (2) genome-wide association studies (GWAS), and (3) studies of common genetic polymorphisms. Adoption and twin studies seek to apportion variance in emotion-relevant factors between genetic and environmental sources. GWAS examine large parts of the human genome (often assaying up to a million

single-nucleotide polymorphisms [SNPs] in thousands of individuals)[1] and have studied the genetic architecture of emotion-relevant personality traits and psychopathologies, such as neuroticism (de Moor et al., 2012) and affective disorders (Liu et al., 2011). Studies of common genetic variants or polymorphisms (ie, those present in greater than 1% of the population) often follow a hypothesis-driven approach and study links between variations in candidate genes and distal emotion-related traits or psychopathologies such as neuroticism (Lesch et al., 1996) or depression (Caspi et al., 2003), or more proximal emotion processes such as emotional reactivity (Gyurak et al., 2013).

Research linking genes with emotional processes of reactivity, regulation, and affiliation, the focus of the current chapter, have largely come from the candidate gene tradition[2] and thus will be the focus of our review. However, there is ongoing debate over the validity and usefulness of the different strategies for studying genetic pathways, and the candidate gene approach has received significant criticism (Flint & Munafò, 2013; Manolio et al., 2009).

MODEL OF THE GENETIC PATHWAY

In our view, the pathway that links candidate genes, emotion processes, and health outcomes in humans starts with genes that regulate neurotransmitter or hormone systems (eg, serotonin, dopamine, oxytocin) that influence the neural systems described earlier in this chapter (eg, amygdala, prefrontal cortex) that are critical for emotional processes such as reactivity, regulation, and affiliation. Polymorphisms in these genes create slight "biases" in these emotional functions (eg, greater capacity for emotion downregulation, tendency to respond to particular kinds of environmental events with larger-magnitude emotional responses). Because these biases are slight, they require well-designed laboratory studies with tightly controlled stimuli, precise measurement of emotional responding, thoughtful participant sampling, control for other contributing genetic influences, and careful replication to afford confidence in findings.

Such studies can reveal the "proximal" effects of genetic polymorphisms on emotional functioning. It is likely that these biases contribute to the individual differences in emotional functioning that appear in trait measures (eg, neuroticism) and in more casual observations about individual differences (eg, one person being seen as more emotionally labile than another). These biases also have effects as they interact with different kinds of environments (eg, abusive versus supportive parenting, high-stress versus low-stress lives) over the life course, contributing to more "distal" outcomes related to health and wellness (eg, depression, attention-related disorders, cardiovascular disease).

In the realm of candidate gene studies, many studies have demonstrated pathways from genetic polymorphisms to distal outcomes with moderation by environmental factors (eg, polymorphisms of the serotonin transporter (5-HTT) gene linked to depression, moderated by life stress) (Caspi et al., 2003). A number of studies have also demonstrated pathways from genetic polymorphisms to more proximal effects on emotional functioning (Gyurak et al., 2013). Studies that incorporate both the proximal and distal parts of this genetic pathway in humans would have significant advantages but are extremely challenging to mount. Such studies would require careful longitudinal assessments of genes, emotional functioning, environments, and disease processes and would need to deal with other complexities as well. At every point along any putative pathway linking a particular genetic polymorphism with a particular outcome as moderated by a particular environment, other genes and environmental factors exert influences (Manuck & McCaffery, 2014). For example, epigenetic work has shown that environmental factors (eg, maternal care) can modulate genetic effects by altering DNA methylation and gene expression (Weaver et al., 2004).

Consistent with the focus of this chapter on emotional reactivity, regulation, and affiliation, we will review the literature that has explored the proximal effects of common genetic polymorphisms involved in regulating serotonergic, dopaminergic, and oxytocinergic systems on these aspects of emotional functioning.

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1. GWAS approaches typically examine SNPs but not other kinds of genetic structural variations (eg, repeat polymorphisms such as 5-HTTLPR). Some have proposed that studying these structural variations could help explain some of the "missing heritability" produced by SNP-based GWAS (Manolio et al., 2009).

2. An important exception includes a series of SNP-based GWAS (Iacono, Malone, Vaidyanathan, & Vrieze, 2014) that examined the genetic architecture of a number of psychophysiological phenomena (ie, antisaccade eye-tracking performance, resting-state EEG, P3 event-related potential amplitude, electrodermal habituation) in a large sample of twins who were assessed at age 17 or 20 years. Notably, the authors also examined the genetic architecture of startle eye blink modulation, an aspect of spontaneous emotion regulation, using a GWAS approach and found "little evidence of heritability in either biometric or molecular genetic analyses" (Vaidyanathan, Malone, Miller, McGue, & Iacono, 2014).

EMOTIONAL REACTIVITY

Serotonin-Related Genes

Serotonin is a neurotransmitter that is centrally involved in emotional reactivity (Carver, Johnson, & Joormann, 2008). A key regulator of serotonergic functioning is the 5-HTT protein, which removes serotonin released into the synaptic cleft. The serotonin transporter protein is encoded by a single gene (*SLC6A4*) on chromosome 17. Transcriptional activity of the *SLC6A4* gene is modulated by several common variants, including variations in the serotonin transporter–linked polymorphic region (5-HTTLPR). 5-HTTLPR is a repeat-length polymorphism with two primary variants. The short allele variant is associated with lower 5-HTT expression and thus with less uptake of serotonin from the synaptic cleft. The long allele variant is associated with higher transporter expression and thus with greater uptake of serotonin from the synaptic cleft (for a review, see Canli and Lesch (2007) and Lesch et al. (1996)).

There is growing evidence that the short allele of 5-HTTLPR amplifies emotional reactivity in positive (eg, amusement), negative (eg, fear), and self-conscious (eg, embarrassment) emotions. Numerous studies document a link between the short allele of 5-HTTLPR and heightened amygdala reactivity (Hariri et al., 2002 but see Bastiaansen et al., 2014), cortisol reactivity (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2013), startle reactivity (Brocke et al., 2006), and subjective, behavioral, and physiological reactivity (eg, Gyurak et al. (2013), Study 1) to different kinds of negative emotional stimuli. Evidence for heightened stress reactivity associated with the short allele is further corroborated by a number of nonhuman animal studies with rhesus monkeys, mice, and rats (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). Several studies (Way & Taylor, 2010) have shown a link between the short allele of 5-HTTLPR and heightened reactivity in social-evaluative situations that often elicit self-conscious emotions powerfully (Tracy & Robins, 2007). We (Gyurak et al. (2013), Study 2) also have found evidence that the short allele is linked to heightened self-conscious emotional reactivity (ie, heightened embarrassment-related emotional reactions when watching oneself singing in a karaoke task). Research has also shown that the short allele is linked to positive emotional reactivity (Haase et al., 2013), heightened attention to positive images (Beevers et al., 2011), heightened self-reported positive affect in response to positive spousal affect (Schoebi, Way, Karney, & Bradbury, 2012), and heightened positive emotional expressions in response to positive and ambiguous stimuli (Haase et al., 2015). Enhanced reactivity to positive environmental conditions associated with reduced 5-HTT expression has also been demonstrated in 5-HTT knockout mice (Kästner et al., 2015). Besides 5-HTTLPR, other genes that involved in serotonergic functioning have emerged as important sources of individual differences in emotional reactivity (eg, monoamine oxidase-A gene and reactivity to negative socioemotional experiences) (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007).

Other Genes

Genes involved in oxytocinergic functioning have also been implicated in emotion reactivity. Variations in the oxytocin-receptor gene have been linked to structural differences in brain regions implicated in emotion reactivity (eg, amygdala, hypothalamus) (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011) and to individual differences in stress reactivity (Rodrigues, Saslow, Garcia, John, & Keltner, 2009).

EMOTION REGULATION

Dopamine-Related Genes

Dopamine is a neurotransmitter that plays an important role in emotion regulation. The protein catechol-*O*-methyltransferase (COMT) is a key regulator of dopamine in the prefrontal cortex (Meyer-Lindenberg et al., 2005). This polymorphism has two allele variants, the valine (val) allele and the methionine (met) allele, which are linked to sizeable variations in COMT enzyme activity (Lachman et al., 1996). Compared to the val allele, the met allele is associated with decreased COMT enzymatic activity and thus greater extracellular prefrontal dopamine (Tunbridge, Bannerman, Sharp, & Harrison, 2004).

Most studies that have examined COMT's role in prefrontal functioning have done so in the context of cognitive tasks, including executive functioning, working memory, fluid intelligence, and attentional control (Dickinson & Elvevag, 2009). These studies show that, overall, the met allele tends to confer a cognitive advantage in healthy populations.

The role of the COMT gene in emotional functioning in general and emotion regulation in particular is less clear. The COMT gene has been implicated in distal outcomes of psychopathology related to emotional dysregulation, but findings have not been consistent (Caspi et al., 2008) (for a review, see, for example, Witte and Floel (2012)). In terms of proximal outcomes, some studies have found that the met allele leads to reduced emotion regulation and lower top-down neural regulatory control (Bishop, Cohen, Fossella, Casey, & Farah, 2006) (for a review, see Canli, Ferri, and Duman (2009)). In a related vein, meta-analytic results from functional MRI studies have been interpreted as indicating that the met allele confers a cognitive advantage but an emotion-processing disadvantage (Mier, Kirsch, & Meyer-Lindenberg, 2010). In contrast, another set of studies reached the opposite conclusion: namely, that the met allele enhances emotion regulation (Canli et al., 2009). For example the met allele has also been found to predict higher self-reported emotion regulation (eg, "It is easy for me to get over a disappointing experience") (Weiss et al., 2014) and lower self-reported personal distress in emotional situations (eg, "Being in a tense emotional situation scares me") (Poletti et al., 2013).

To date, few studies have examined the effect of COMT on emotion regulation using laboratory paradigms derived from modern affective science. In two studies, we (Sapozhnikova et al., in preparation) have found that individuals with the met allele show greater emotion regulation abilities (ie, indexed by greater downregulation of emotional experience and emotional behavior) in several well-established emotion regulation tasks (ie, anticipated acoustic startle; instructed suppression; instructed cognitive reappraisal). Moreover, other studies by our group (Gyurak, Goodkind, Kramer, Miller, & Levenson, 2011; Gyurak et al., 2009) have found close links between emotion-regulating abilities and aspects of cognitive functioning (eg, executive functioning) that have been found to be enhanced in met allele carriers.

Other Genes

Emotion regulation is thought to be a function of bidirectional activity of both emotion-generating and emotion-regulating neural circuits. Thus, key candidate genes involved in emotion reactivity have also been implicated in emotion regulation (for reviews, see Canli et al. (2009) and Pezawas et al. (2005)).

EMOTIONAL AFFILIATION

Oxytocin-Related Genes

Oxytocin functions as a neurotransmitter and is thought to be centrally involved in affiliative behaviors associated with the caregiving-attachment system (Taylor et al., 2000). Oxytocinergic functioning depends on the availability of oxytocin receptors (OXTR). The OXTR is encoded by a single gene which is located on chromosome 3p25. It contains several dozen SNPs whose functionality is not yet fully understood. Among those, a common SNP (rs53576) in the OXTR gene has received particularly widespread attention.

Studies have shown that genetic variations in OXTR are implicated in a wide variety of affiliative behaviors, including maternal sensitivity (Bakermans-Kranenburg & van Ijzendoorn, 2008), prosocial temperament (Tost et al., 2010), prosocial behavioral cues (Kogan et al., 2011), seeking support under distress (Kim et al., 2010), loneliness (Lucht et al., 2009), altruistic behavior in economic tasks (Israel et al., 2009), and real-world prosocial behavior under threat (eg, volunteer work, charitable activities) (Poulin, Holman, & Buffone, 2012). However, a meta-analysis (which did not differentiate among different aspects of social behavior) failed to find support for an association between two commonly studied OXTR SNPs (including rs53576) and social behavior (Bakermans-Kranenburg & van Ijzendoorn, 2014).

It is possible that the link between OXTR and affiliation is more specific. Early nonhuman animal studies (examining knockout mice) suggested that OXTR has a crucial role in social recognition (Ferguson et al., 2000). Experimental studies in which oxytocin was administered intranasally likewise pointed to a role in boosting social cognition and cognitive empathy (but see Bartz et al. (2010), and Domes, Heinrichs, Michel, Berger, and Herpertz (2007)). Consistent with this, Rodrigues et al. (2009) showed that individuals with the GG variant of OXTR rs53576 had higher cognitive empathy, as measured by the "Reading the Mind in the Eyes" test and an other-oriented empathy scale. In a similar vein, individuals with the GG variant of rs53576 were found to have higher emotional empathy, indicated by increased levels of sympathetic and subjective arousal when perceiving harm to others (Smith, Porges, Norman, Connelly, & Decety, 2014).

A variety of other OXTR SNPs have been implicated in self-reported emotional and cognitive empathy (Wu, Li, & Su, 2012), but results have not always been consistent (Skuse et al., 2014). Studies linking OXTR genetic polymorphisms to objective, performance-based measures of cognitive empathy (Goodkind et al., 2012) or emotional empathy (Sze et al., 2012) have been rare. Yet, nonhuman animal studies point to a pivotal role of OXTR in social behavior and social recognition (Ferguson et al., 2000; Sala et al., 2013). It is hoped that future research will clarify OXTR's role in cognitive and emotional empathy in humans using more objective measures.

Other Genes and Affiliation

There is also evidence that polymorphisms associated with the vasopressin system are implicated in affiliative behaviors (Walum et al., 2008). This is consistent with the well-documented role that oxytocin and vasopressin have in social behaviors (for a review, see Meyer-Lindenberg et al. (2011)).

NEURAL AND GENETIC PATHWAYS: CLINICAL IMPLICATIONS

Thus far in this chapter, we have focused on the neural and genetic pathways that influence three key emotional processes: emotional reactivity, emotion regulation, and emotional affiliation. We now turn to a consideration of how these processes are disrupted in psychopathology and neuropathology.

EMOTIONAL DYSFUNCTION IN PSYCHOPATHOLOGY AND NEUROPATHOLOGY

Emotional Reactivity

Abnormalities in emotional reactivity are found in emotion magnitude (emotions that are too large or too small), duration (emotions that are too long-lasting or too short-lasting), and onset (emotions that are too slow or too quick to onset). Problems in emotional reactivity can manifest in a particular emotion (eg, overly large fear response in phobias) or in multiple emotions (eg, diminished reactivity in numerous emotions in frontotemporal dementia) (Eckart, Sturm, Miller, & Levenson, 2012; Sturm, Ascher, Miller, & Levenson, 2008). Dysfunction can also manifest in a lack of coherence among different aspects of the emotional response. Thus, for example, in schizophrenia expressive behavior can be profoundly blunted whereas subjective emotional experience remains strong (Kring & Neale, 1996). The inverse is seen in patients with ALS who have pseudobulbar affect, in which expressive behavior and physiological responses can be large whereas subjective experience is much smaller (Olney et al., 2011). Low coherence among aspects of the emotional response can be confusing and uncomfortable for patients and can interfere greatly with others' ability to understand the patient's emotional state and respond appropriately.

Emotion Regulation

Abnormalities in emotion regulation occur when emotions are either underregulated or overregulated. These problems may occur with particular emotions or with multiple emotions. The intimate connection between emotional reactivity and emotion regulation (Ochsner et al., 2004) can make it difficult to apportion responsibility for a particular symptom to different processes. Thus, for example, a patient with obsessive-compulsive disorder who reacts with inordinately high levels of disgust in response to lack of cleanliness likely reflects some combination of high levels of emotional reactivity and low levels of emotion regulation. In neurological patients, dissociations are sometimes found between instructed and spontaneous regulation. For example, patients with frontotemporal dementia do well at downregulating emotional responses when they are told exactly what to do but show markedly less downregulation when placed in a situation in which downregulation is the norm and they are not told what to do (Goodkind, Gyurak, McCarthy, Miller, & Levenson, 2010).

Emotional Affiliation

Abnormalities in emotional affiliation take a number of different forms, including poor recognition of emotions in others, lack of emotional response to the emotions of others, difficulty sustaining emotional interactions with intimate others, and overenmeshment with the emotions of others. These problems are major contributors to disruptions in social relationships that are found in many kinds of psychopathology (Ware, Hopper, Tugenberg, Dickey, & Fisher, 2007). Dissociations

among different aspects of emotional affiliation are often hallmark features of pathology. For example, individuals with antisocial personality disorder may be good at recognizing the emotion that another person is experiencing but may have abnormal emotional responses to that person's emotion (eg, recognizing that another person is sad, not feeling sympathy, and then using the emotional information in exploitative ways).

EMOTION IN DIAGNOSIS

Psychopathology: *Diagnostic and Statistical Manual*

In the DSM-IV (American Psychiatric Association, 1994), alternations in emotional functioning are part of the descriptions of most Axis I and many Axis II disorders. Unfortunately, these descriptions are general and do not take advantage of the more differentiated constructs used in modern affective science. For example, among Axis I disorders in the DSM, emotional dysfunctions are described as follows (with italics added):

- Schizophrenia: "… may display *inappropriate affect* (eg, smiling, laughing, or a silly facial expression in the absence of an appropriate stimulus)"
- Autistic disorder: "*abnormalities of mood or affect* (eg, giggling or weeping for no apparent reason …)"
- Major depressive episode: "*depressed mood* most of the day, nearly every day"
- Manic episode: "a distinct period of abnormally and persistently elevated, expansive, or irritable mood …"
- Posttraumatic stress disorder: "*restricted range of affect* (eg, unable to have loving feelings)"
- Bulimia nervosa: "Binge eating is typically triggered by *dysphoric mood* states …"
- Dissociative identity disorder: "Particular identities may emerge in specific circumstances and may differ in reported age and gender, vocabulary, general knowledge, or *predominant affect*."

Psychopathology: Research Domain Criteria

Longstanding problems with the DSM (eg, intradiagnostic heterogeneity, interdiagnostic comorbidity, arbitrary cutoffs, too many syndromes) stimulated the development of the RDoC (Insel et al., 2010), a more dimensional, construct-based system of diagnosis designed for research use that is grounded in neurobiology and genetics rather than clinical observation. RDoC replaces syndromes with a set of five domains (negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems). Within each domain are a set of constructs (eg, acute threat in the negative valence domain) which must have a plausible associated neural circuitry and which span a range of normal to abnormal functioning. RDoC constructs were generated from a set of meetings of scientists and refined by the oversight committee with the door left open for future changes, additions, and deletions. Because of these origins, it is unsurprising that the initial set of constructs is more a snapshot of the current state of neuroscience than of the current state of clinical symptomatology. We believe that the RDoC approach holds great promise for producing meaningful, clinically relevant research in the coming years and for ultimately leading to a different kind of nosology for diagnosis and treatment.

RDoC has not yet fully elaborated its constructs in terms of its "units of analysis" (which include behavior, self-reports, and physiology, the critical trio for emotion) and measurement paradigms, but it certainly seems amenable to the ideas and organizational scheme presented in the current chapter. Emotional reactivity fits into the Negative and Positive valence systems domains (although RDoC seems to be more focused on "fear" than on other emotions). Emotion regulation fits into the arousal/regulatory systems domain (which currently has fewer constructs than the other domains and thus may expand in later versions). Emotional affiliation fits into the systems for social processes domain (which has "affiliation/separation" as one of its constructs).

Neuropathology

In neurology and neuropsychology, historically there has been much greater focus on the measurement and precise description of cognitive, language, and motor deficits than on emotional deficits. This is understandable given that many lesions and neurodegenerative disorders produce dramatic impairments in cognitive, language, and motor domains. However, these disorders often produce significant alternations in emotional functioning as well. When emotional functioning has been considered in neuropathology, it has often been conceptualized in general terms akin to those found in the DSM. For example, in the original consensus diagnostic criteria for frontotemporal dementia (Neary et al., 1998), a disorder that has profound effects on emotional functioning (Levenson & Miller, 2007), "early emotional blunting" is one

of five core diagnostic features, the dominant features of the disorder are said to be "character change and disordered social conduct," and emotion is not mentioned in any of 15 supportive diagnostic features or any of the supportive neuropsychological test results.

EMOTION IN TREATMENT

Most of the major treatments for clinical disorders, whether biological, pharmacological, or psychotherapeutic, implicitly or explicitly target emotional functioning. Biological treatments such as deep brain stimulation and transcranial magnetic stimulation (George et al., 1996; Holtzheimer et al., 2012) are directed toward influencing the activity of the key neural circuits described earlier in the context of neural pathways. Pharmacological treatments target key neurotransmitter systems, including those discussed earlier in the context of genetic pathways. Psychotherapy has long focused on influencing emotional processes. This began with catharsis in psychoanalysis (Freud, 1910) and has continued with modern cognitive therapies (Beck, 1976), which target appraisal processes involved in both emotional reactivity and emotional regulation. A focus on emotional affiliation is seen in many therapies for couples (Johnson, Hunsley, Greenberg, & Schindler, 1999).

Arguably, one of the greatest challenges for the effective treatment of emotional dysfunction is lack of precision and specificity. As noted earlier, DSM clinical disorders are extremely complex and replete with heterogeneity and comorbidity, and define emotional dysfunctions in general ways. Most existing treatments are similarly imprecise. Thus, it is extremely difficult to isolate and reach certain circuits with biological treatments and to target particular neurotransmitters in particular brain regions with pharmacological treatments. It has similarly been difficult to isolate specific active ingredients in different psychotherapies that are effective with particular disease mechanisms.

There appears to be a clear movement in the treatment arena toward targeting more specific mechanisms (eg, RDoC) and toward developing treatments that ameliorate particular symptoms across a wide range of disorders (Harvey, Watkins, Mansell, & Shafran, 2004). This points to the need for better and more precise characterization of treatment targets. In the realm of emotional functioning, such precision has long been the concern of affective scientists studying emotional processes such as reactivity, regulation, and affiliation. Ironically, the insights and tools derived from laboratory studies of emotion have been slow to find their way into clinical practice. Nonetheless, we believe that building bridges that connect the laboratory to the bedside (and the bedside to the laboratory) will provide valuable clues that will be useful in understanding the etiology of emotional dysfunctions that are found in neurological, psychological, and psychiatric disorders and in identifying promising neural, genetic, and behavioral targets for future treatments.

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