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The emotional brain: Combining insights from patients and basic science

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Emotional functioning has been a relatively neglected aspect of neurological disease in the modern era. With few exceptions [e.g. Damasio and Van Hoesen 1983; Robinson, Kubos et al. *1984*; Robinson, Parikh et al. 1993; Damasio 1999) (LaBar, LeDoux et al. 1995; Young, Aggleton et al. 1995) (Sprengelmeyer, Young et al. 1996) (Adolphs, Damasio et al. 1996; Rapcsak, Galper et al. 2000) (Calder, Keane et al. 2000) (Tranel, Bechara et al. 2002) (Anderson and Phelps 2002; Hornak, Bramham et al. 2003)], most research in neurological illness has focused on its impact upon motor, sensory and cognitive abilities. Yet, as amply illustrated by the articles included in this issue, neurological diseases, ranging from focal lesions, to epilepsy to neurodegenerative disease influence emotional functioning, resulting in a wide-variety of symptoms ranging from depression, anxiety, loss of motivation, loss of empathy, and loss of emotional control. As with sensory or motor deficits, these changes in emotion have profound effects on work and social functioning. The case descriptions in this special issue illustrate the challenges we face in trying to understand the origins of these deficits, but also highlight the opportunity we have to improve our understanding of emotional functions by studying them in patients with neurological diseases. These articles stimulate a variety of questions including: How should we approach the study of emotional functioning in neurological disease? What methods should be used to quantify emotion, and how can these measures be tied to dysfunction in daily life? The cases included in this issue demonstrate some of the novel approaches that are available to researchers, and also illustrate the complexity of the emotional problems in these diseases while pointing the way toward new approaches that will need to be taken in the future.

A thorough understanding of impaired emotion in neurological disease will need to take into account different aspects of emotional functioning, and different types of emotions, while considering the roles of several brain regions. Models of emotional processing that identify the psychological and neuroanatomical components of the emotional system have been developed and should be useful in guiding future studies. Thus, in this overview, we will provide a brief discussion of the relevant aspects of emotional functioning and their putative neuroanatomical basis. We will then address how the articles included in this issue of

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Neurocase help to move us toward an understanding of the ways in which emotional systems are disturbed with brain injury.

Emotional functioning: Key processes

We cannot hope to understand the roles of various brain regions in emotion unless our model of emotional functioning includes major aspects of the behavioral manifestations and experience of emotion. The complexity of the brain's system for emotional processing is suggested by the following definition of emotion, which stresses the role of emotion as an adaptive function:

> "Emotions are short-lived psychological-physiological phenomena that represent efficient modes of adaptation to changing environmental demands. Psychologically, emotions alter attention, shift certain behaviors upward in response hierarchies, and activate relevant associative networks in memory. Physiologically, emotions rapidly organize the responses of disparate biological systems including facial expression, somatic muscular tonus, voice tone, autonomic nervous system activity, and endocrine activity to produce a bodily milieu that is optimal for effective response. Emotions serve to establish our position vis-à-vis our environment, pulling us toward certain people, objects, actions and ideas, and pushing us away from others. Emotions also serve as a repository for innate and learned influences, possessing certain invariant features, and others that show considerable variation across individuals, groups, and cultures" (Levenson 1994).

While this definition of emotion is only one of many, its value for this discussion is in illustrating the organizing functions of emotion, and reflecting that emotions are multifaceted responses involving thoughts, visceral sensations and facial and bodily reactions. When strong, these reactions can occur very quickly, and in a coordinated, stereotypical fashion. This allows emotions to be implemented efficiently in response to situations that are critical for well-being (e.g. encountering the iconic saber-toothed tiger). When weaker, they may be implemented only partially. The definition also stresses that some aspects of emotion are innate, and some are more variable across individuals.

This description of emotion focuses primarily on emotion as a reaction. However, to account fully for emotional processing, it is necessary to understand the chain of events that leads up to this reaction, beginning with appraisal mechanisms that include processing and interpreting external (visual, auditory or other types of perception) and internal (thought) stimuli. Appraisal can be quick and automatic, residing outside of conscious awareness (Kunst-Wilson and Zajonc 1980; Murphy and Zajonc 1993; Ohman and Soares 1993) or may incorporate extensive processing of the identity of a stimulus and its context. For example, one's emotional reaction to seeing a steak could depend on whether you like steak, whether you are seeing a picture of a steak or visualizing a real steak, and how hungry you feel.

Another important aspect of emotion that goes beyond emotional reaction is emotional understanding, which refers to our ability to recognize emotions in ourselves and in others. This process of recognizing emotions, in addition to the ability to respond emotionally to the emotions of others, and to act in prosocial, sympathetic ways are all part of the broader construct of empathy (Levenson and Ruef 1992).

A model of emotional functioning must also account for the fact that emotional reactions are typically adjusted to match situational demands, a process referred to as emotion regulation. Depending on the situation, we modify our subjective feelings about a stimulus, for instance by reexamining its meaning (e.g., recognizing that the saber-toothed tiger in the museum is

just a model). This example of emotion regulation has been referred to as reappraisal. We can also choose to alter emotional reactions by down-regulating them, for example by taking deep breaths or controlling our facial expressions, which has been referred to as suppression. These processes, and other types of regulation, are another important component of the brain's emotional processing systems, and may be particularly relevant to human emotional processing.

Importantly for the purposes of this special section of Neurocase, alterations in all of these aspects of emotional functioning, including emotional reactions, emotion regulation, appraisal, emotional understanding, and empathy, are found in a number of neurological diseases. Thus, studies of neurological disease and of the neural substrates of emotional functioning would be well served to consider the full range of emotional functioning.

In keeping with this suggestion, in the discussion that follows, we briefly review and discuss the brain regions most closely associated with some of the major aspects of emotional functioning, including: appraisal, reactivity, regulation and understanding. This review is by no means exhaustive, nor should it be taken as suggesting that each region is linked with only one of these functions. The boundaries between the various aspects of emotional functioning can be blurry and the interactions among them are complex. Moreover, key brain regions are likely participate in multiple aspects of emotional functioning. Nevertheless, even this brief review conveys the important point that emotional functioning appears to be subserved by interactions between the brainstem, the diencephalon, and several frontal and anterior temporal regions.

Neuroanatomy of emotion

Appraisal

Of all aspects of emotional processing, appraisal is the one about which we have the most detailed neuroanatomical information from both animal and human studies. It is well-accepted that the amygdala is an important component of the appraisal system. The amygdala is necessary for acquisition of conditioned responses to stimuli predicting potential harm (LeDoux 1992; Bechara, Tranel et al. 1995; LaBar, LeDoux et al. 1995; LeDoux 1996), and is also important for recognition of facial expressions of emotions, in particular those with negative valence (Adolphs, Tranel et al. 1994; Scott, Young et al. 1997; Adolphs, Tranel et al. 1999; Anderson, Spencer et al. 2000; Davis and Whalen 2001; Gorno-Tempini, Pradelli et al. 2001; Phan, Wager et al. 2002; Rosen, Perry et al. 2002; Adolphs and Tranel 2004; Williams, McGlone et al. 2005{Adolphs, 2005 #4728). Direct connections from sensory processing regions in the thalamus (such as the medial and lateral geniculate nuclei) as well as regions specialized for more elaborate sensory processing in the cerebral cortex allow the amygdala access to incoming sensory information (Doron and LeDoux 1999). The existence of multiple pathways by which sensory information can reach the amygdala has led to the hypothesis that the subcortical route allows relatively crude processing of emotional stimuli, while pathways through the cortex allow for more detailed assessment (Armony and LeDoux 1997).

Emotional content may also be represented earlier in the sensory processing stream. For instance, functional MRI studies have shown that extrastriate visual processing regions in the fusiform and inferolateral temporal regions modify their activity during face viewing depending on the emotion depicted (Winston, Henson et al. 2004). Anatomical studies of tissue loss in patients with dementia have linked failure to recognize emotions with tissue loss in temporal regions likely linked to visual processing (Rosen, Wilson et al. 2006).

Beyond the amygdala, other brain regions have been implicated in emotional appraisal. In particular, the medial and orbital portions of the frontal lobes appear to play an important role in modifying previously established associations. For instance, in fear conditioning, extinction of previously learned associations between neutral cues and aversive outcomes is prevented by lesions to the medial frontal cortex (Sotres-Bayon, Cain et al. 2006). These data are consistent with studies showing that neurons in the medial portions of the orbital frontal cortex track the current reward value of a given stimulus (Rolls 2004). Thus, while amygdala neurons help to identify cues with emotional significance in the environment, orbitofrontal neurons update the significance of these cues based on current information about the environment and the state of the organism.

The medial frontal regions, especially the anterior cingulate cortex, also play a role in emotion. Similar to the amygdala, these regions are active during viewing of emotional faces in fMRI studies (Phan, Wager et al. 2002), and during tasks where decisions are in part mediated by the emotional content of the stimulus (Bush, Luu et al. 2000). Researchers often distinguish between the more dorsal portion the anterior cingulate cortex, which is thought to play an important role in monitoring of cognitive processing, and the more ventral anterior cingulate, which appears to subserve monitoring of internal sensations related to emotional functions (Vogt, Berger et al. 2003). Lesions to ventral and medial frontal regions impair recognition of emotions (Hornak, Bramham et al. 2003). As will be discussed below, the anterior cingulate also plays an important role in mediating reactions to emotional stimuli.

Reactivity

Animal studies suggest that the expression of complex, organized somatic and visceromotor activity associated with emotion can be generated by subcortical regions, including hypothalamic and brainstem structures such as the periaqueductal gray matter, without the modulation of higher cortical input (Bard 1928; Hess 1954; Panksepp 1998). Other subcortical structures may play an important role in modulating behavior in response to the presentation of potentially rewarding stimuli, including the striatum (the nucleus accumbens and parts of the caudate nucleus). The striatum is heavily connected with the medial and orbital frontal regions (Tekin and Cummings 2002) and several amygdaloid nuclei (Zahm 2000; Cardinal, Parkinson et al. 2002), and appears to participate with these structures in choosing the appropriate response to a stimulus given its association with primary rewards (e.g. food, or other pleasurable outcomes) and the current state of the organism vis-à-vis these rewards (Cardinal, Parkinson et al. 2002).

Higher cortical regions also play an important role in control of emotional reactivity. The insula mediates autonomic function (Augustine 1996; Cheung and Hachinski 2000). Similarly, stimulation of cingulate structures affects autonomic function and elicits behavioral responses such as species-specific distress calls in animals, and vocalizations in humans (Devinsky, Morrell et al. 1995). In the amygdala, the central nucleus appears to organize behavioral and autonomic emotional reactions in the context of emotional learning (Armony and LeDoux 1997). All of these cortical regions appear to mediate their behavioral effects via connections to diencephalic and brainstem structures (LeDoux, Iwata et al. 1988).

Regulation

The voluntary aspects of emotion regulation are least amenable to study in animals, and research investigating these processes in humans has only recently begun. Studies examining the neuroanatomy of emotional regulation in humans via reappraisal have demonstrated increased activation in dorsolateral and ventrolateral frontal structures, with decreased activation in the hypothalamus and amygdala during reappraisal compared with

unregulated emotion. These early studies suggest that voluntary regulation in accomplished through interactions between frontal regions and lower structures involved in appraisal and reactivity (Ochsner and Gross 2005; Goldin, McRae et al. 2008). In contrast, studies of emotional suppression have shown increased activation in the amygdala (Goldin, McRae et al. 2008), which is consistent with the fact that, although outward reactions are masked, the stimulus is being appraised in the same way. Psychophysiological studies indicate that visceral reactivity is heightened with suppression (Gross and Levenson 1993; Gross and Levenson 1997; Hagemann, Levenson et al. 2006).

Emotional Understanding

Given that processing of incoming sensory information is an important component of understanding other people's emotions, it is likely that structures such as the amygdala and other regions important for appraisal are key. Amygdala damage has been shown to cause deficits in identifying emotion in others as well as in feeling emotions (Adolphs, Tranel et al. 1994). As underscored in the earlier discussion, feeling others emotions is an important aspect of emotional empathy. Many fMRI studies examining the neuroanatomy of empathy have studied reactions to seeing others in pain, and have shown activation of the same structures that are activated when one is experiencing pain, including the somatosensory cortex, anterior insula and anterior cingulate cortex (Hein and Singer 2008). Similarly, the anterior insula is activated when seeing someone else experience disgust (Jabbi, Swart et al. 2007). Lastly, many researchers highlight the importance of cognitive processes in empathy, such as the ability to take the perspective of another, and the ability to regulate our emotions based on context. These researchers have implicated other structures as playing a role in empathy, including the parietal lobes, the dorsolateral prefrontal cortex, the ventrolateral prefrontal cortex and the ventromedial prefrontal cortex (Decety and Jackson 2004). A recent study of loss of empathy in patients with neurodegenerative disease linked it with tissue loss in the right temporal pole, right fusiform gyrus, and right subcallosal gyrus, as well as the right caudate nucleus, thus, highlighting regions involved in appraisal and regulation (Rankin, Gorno-Tempini et al. 2006).

Articles in this special issue of Neurocase on the neurology of emotion

The articles in this issue of Neurocase cover a very broad range of issues relevant to emotion. Several describe patients with frontotemporal dementia (FTD). Patients with FTD are important for researchers interested in the study of emotion, because their behavior suggests that they have major deficiencies in emotional processing. Typically they demonstrate profound apathy, losing interest in previously enjoyed activities, and they frequently manifest severe loss of empathy (Liu, Miller et al. 2004) (Rankin, Kramer et al. 2005). Their personality changes have large influences on social function, causing them to fail at work, while alienating them from friends and family. Several prior studies have documented impaired emotional processing in FTD using pictures of facial affect (Levanu, Pasquier et al. 1999) (Keane, Calder et al. 2002) (Rosen, Pace-Savitsky et al. 2004), and more recently, deficits in more complex, self-conscious emotions have been identified (Sturm, Rosen et al. 2006) (Sturm, Ascher et al. 2008). As illustrated in two of the cases in this issue, FTD clearly affects many of the brain regions involved in emotional processing, as do other neurological conditions including epilepsy, infectious and metabolic disorders, stroke and brain tumors. Ultimately, a thorough understanding of emotions in the brain will benefit not only from more detailed study of emotion within each of the disorders, but also from comparison of the different disorders with each other.

The articles in this issue touch on two general themes: The first set of articles (Kipps et al., Narvid et al., Tranel et al., Hixson et al.) directly discuss the effects of neurological diseases on social and emotional processing, and illustrate the complexity of the problems and the

multiple approaches that will be necessary to understand them. The second set of articles (Liu et al., Chang et al., Matthews et al.) highlight preservation of some emotional responses despite profound neurological disease, as illustrated by patients' production and appreciation of art. In contrast to the first set of articles, these illustrate that emotional expression is not all-or-none. Rather, a deterioration of emotional function in the social domain can be accompanied by enhanced emotional expression in other domains, in this case artistic. These cases also illustrate the distinction between the inner experience of emotion and the social aspects of emotion. They suggest that while successful function in the social environment is dependent on the ability to process sensory and emotional signals, the internal experience of emotion can survive despite these impairments, and that art has a unique ability to tap into this internal emotional landscape.

Emotional deficits in neurological injury

Kipps et al discuss the relationship between emotion recognition, behavioral problems, and daily function in neurodegenerative disease using a task that assesses emotion recognition with static pictures of facial affect. They studied patients with FTD and Alzheimer's disease (AD). Impaired emotion recognition may lead FTD patients to misunderstand emotional cues, and thus these perceptual deficits may underlie some of their behavioral difficulties. Kipps et al have taken a step beyond previous work by asking how well deficits in emotion recognition explain the behavioral and functional disturbances. They found a strong relationship between emotion recognition abilities and mood, as measured by a behavioral inventory, however they did not find a strong relationship between emotion recognition and other aspects behavior, or any aspects of daily function. In light of the discussion above, which stresses the various aspects of emotional functioning (appraisal, reactivity, regulation) that are distributed across several frontal and temporal regions, Kipps' results make sense. It seems unlikely that all behavioral and functional problems would be explained by a single deficit in one aspect of emotional understanding. Thus, this result highlights the importance of multimodal assessment of emotion in neurological disease. It also suggests that assessments of behavior may need to be tailored to the specific question. For instance, would emotion recognition be better correlated with a measure of empathy in daily life, rather than measures of behavior such as apathy and disinhibition, which may be based on other emotional or cognitive impairments?

Narvid et al have provided a classical description of a case of FTD with disinhibiton, eating disorders, loss of concern for others, and poor judgment. This case highlights the multiplicity of problems in the emotional system in FTD. Extensive behavioral testing demonstrated impairments in many tasks related to social cognition and emotional understanding, including emotion recognition, theory of mind including visual perspective taking, complex social inference, and imputation of complex intentional biological movement. The imaging provides an excellent example of the how FTD affects many portions of the emotional processing system including the orbitofrontal cortex, medial frontal cortex including the anterior cingulate region, and the insula. The relative sparing of the amygdala underscores the role of non-amygdala regions in emotional understanding. The case also highlights the importance of functions at the border between emotional and other types of processing. For instance, while impairments in perspective-taking and imputation of biological movement could make important contributions to social deficits, are these emotional in nature? Do they have components that are emotional and others that are not? Do the functions of regions putatively involved in tasks like theory-of-mind, such as the orbitofrontal cortex, span both emotional and non-emotional abilities, or are there elemental processes carried out by these regions important for emotional and non-emotional processing? While a single case report cannot be used to link specific cognitive mechanisms to specific impairments in FTD, this case points the way toward the extensive multi-domain

assessment that will be necessary to explain the behavioral abnormalities in FTD. This article also highlights the relationship between FTD and a gene involved in abnormal bone formation, Ext2. Whether this gene has some role in emotional processing, per se, remains to be seen.

Hixson and Kirsch have contributed two cases of patients with epilepsy with significant mood and anxiety problems. While such relationships could be dismissed as coincidental, their accompanying review reveals that affective disorders are quite common in epilepsy. Because epilepsy so often emanates from the amygdala and hippocampus, most studies have used tasks such as fear conditioning and emotion recognition, in which the amygdala is known to be involved. These studies have clearly revealed appraisal deficits, which in some studies correlate with the degree of amygdala damage in epilepsy, particularly in the right hemisphere. Their review also highlights some of the deficits in our current approach to emotion in epilepsy. Similar to FTD, it appears that amygdala damage does not always account for appraisal deficits. Moreover, one suspects that appraisal deficits are insufficient to account for the complex affective disorder seen in patients with epilepsy, as shown in FTD by Kipps et al. This raises the issue of how epilepsy originating in the medial temporal lobes affects the other parts of the emotional processing network. While the work done thus far has been sufficient to reveal a deficit in epilepsy, very little if any work has gone beyond appraisal to look at impairments in reactivity and regulation, and these efforts are sorely needed.

The article by Tranel and Bechara provides another excellent example of the effects of epilepsy on mood and anxiety, and also illustrates the impact on daily function (financial security, employment status, interpersonal functioning in terms of sustaining normal relationships, peers' judgment of social function). In this case they are discussing the effects of amygdala removal for control of epilepsy. They also build on previous work using a gambling paradigm to illustrate the effects of the amygdala damage on decision-making. In their series, the patients with emotional and social changes failed to demonstrate anticipatory skin responses to cues that signaled negative outcomes. They have added a new twist. While much prior work has suggested that social and emotional deficits are more likely with right hemisphere damage (Ross 1985; Ross 1997; Tranel, Bechara et al. 2002), this case series indicates that this may interact with sex. Among their cases, social and emotional problems were associated with right hemisphere damage in men, but with left hemisphere damage in women. They point out that the issue of how sex affects the impact of brain lesions on emotion is frequently ignored, and they propose that these functions may be more tied to verbal processing in women, because of needs required by caring and teaching of offspring. In contrast, they posit that men depend on visuospatial function for hunting and food procurement, and so may have social skills tied to right hemisphere/visuospatial processing.

Emotion and art in brain disease

Liu et al describe a case similar in many ways to the one described by Narvid et al., the difference being the development of a tremendous drive to create art. In their description of VW Liu et al explore the relationship between emotion and artistic pursuit. While VWs ability to appreciate and depict normal emotional features in the world was deteriorating, the reward he received from expressing himself artistically grew and persisted, even at the point where he could barely hold a paintbrush. The authors describe VW as maintaining an inner emotional life, mostly connected to personally relevant events from his past. Several recent articles have focused on abnormalities in the basal ganglia, including the ventral striatum, in FTD (Whitwell, Jack et al. 2006; Kim, Rabinovici et al. 2007). Given the importance of these structures in signaling reward, it is difficult to imagine that these regions were no longer working in VW, although their function could have changed so that the goals that he wished to pursue had shifted.

Chang et al report on a patient with semantic dementia, the temporal variant of FTD, who developed newfound interest in songwriting and painting as illness developed. Although much of the work discussing emotional changes in neurological illness focuses on anatomical changes, this case highlights the importance of neurochemistry. With treatment, this patient's manic and disinhibited behavior improved. His compulsion to paint continued, but his paintings showed less creativity, less detail and less color. As pointed out by the authors, this case builds on an existing literature discussing the relationship between mood and creativity. It suggests that the artistic process depends on several aspects of emotional processing, including motivation, which did not appear to be impaired with treatment of his mania, and creativity, which suffered when he was treated.

Lastly, Matthews et al describe a case of auditory agnosia from progressive neurological impairment, possibly mitochondrial in origin. This patient had a preserved ability to enjoy listening to music from previously loved genres, despite being unable to identify them in any way, or to identify or produce any familiar tunes or to associate musical properties with affect, although he can identify the onset of music. This case highlights the dissociation between perception of music and affective appreciation of music. The authors hypothesize that intact functioning in subcortical systems normally associated with reward may allow enjoyment of the music based only on rudimentary processing, or possibly based on musical illusions. The preservation of subcortical processing of reward represents a common thread with the other articles on art in this issue, all of which discuss patients whose perceptive abilities (for emotion in the first two cases, and for music in this case) have been lost, but who still derive pleasure from art, highlighting the dissociation between appraisal processes and emotional reactivity.

Taken together, the articles included in this special section of Neurocase illustrate the tremendous breadth of issues revolving around emotional dysfunction in neurological diseases. These papers underscore the profound impact of certain neurological dieseases on emotional functioning and point to the high level of sophistication in emotion theory and research that will be needed to understand the specific areas of dysfunction. We hope that these cases will spur an expansion of creative research examining the ways that emotional functioning is impacted across the range of neurological disease, and will stimulate thinking about the value of these approaches for realizing a fuller understanding of the neural structures that subserve the full range of emotional functioning.

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