The Role of the Orbitofrontal Cortex in Anxiety Disorders

MOHAMMED R. MILAD[a] AND SCOTT L. RAUCH[a,b]

[a]*Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA*

[b]*McLean Hospital, Belmont, Massachusetts 02478, USA*

ABSTRACT: Advances in neuroimaging techniques over the past two decades have allowed scientists to investigate the neurocircuitry of anxiety disorders. Such research has implicated the orbitofrontal cortex (OFC). Characterizing the role of OFC in anxiety disorders, however, is principally complicated by two factors–differences in underlying pathophysiology across the anxiety disorders and heterogeneity in function across different OFC sub-territories. Contemporary neurocircuitry models of anxiety disorders have primarily focused on amygdalocortical interactions. The amygdala is implicated in generating fear responses, whereas cortical regions, specifically the medial OFC (mOFC) and the ventromedial prefrontal cortex (vmPFC), are implicated in fear extinction. In contrast to mOFC, anterolateral OFC (lOFC) has been associated with negative affects and obsessions and thus dysfunctional lOFC may underlie different aspects of certain anxiety disorders. Herein, we aim to review the above-mentioned theories and provide a heuristic model for conceptualizing the respective roles of mOFC and lOFC in the pathophysiology and treatment of anxiety disorders. We will also review the role of the OFC in fear extinction and the implications of this role to the pathophysiology of anxiety disorders.

KEYWORDS: amygdala; fear extinction; conditioning; ventromedial prefrontal cortex; neuroimaging

INTRODUCTION

The orbitofrontal cortex (OFC) is implicated in a variety of functions, particularly higher-order executive functions. These executive functions include control and inhibition of inappropriate behavioral and emotional responses, decision making, maintaining behavioral flexibility to switch between different problem solving strategies, and evaluation of contingencies between

Address for correspondence: Mohammed R. Milad, Ph.D., Department of Psychiatry, Massachusetts General Hospital, Bldg 149, 13th Street, 2nd Floor, Charlestown, MA 02129. Voice: 617-724-8533; fax: 617-726-4078.
milad@nmr.mgh.harvard.edu

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different stimuli to guide future behaviors to maximize reward and minimize punishment (for example, see Refs. 1–4). Inappropriate function of the OFC, therefore, could lead to an array of behavioral deficits and psychopathology, ranging from making a wrong financial decision to disabling anxiety. Here, we focus on the role of OFC in anxiety disorders. Specifically, we will address: 1) the pertinent neuroanatomical connections of the OFC, 2) the contribution of different sub-regions of the OFC to specific pertinent functions, and 3) the implications of OFC anatomy and function to anxiety disorders. In this review, we will outline findings from studies relevant to these three points with specific emphasis on the human OFC and its contribution to anxiety disorders.

ANATOMICAL CONNECTIONS OF THE OFC

The detailed inputs and outputs of the OFC have been well characterized in rats, non-human primates, and to some degree in humans.[5–9] Though this material will be covered in greater detail elsewhere in this volume, we will summarize the connections that we believe are most pertinent to anxiety disorders. The OFC is part of the prefrontal cortex and receives projections from the magnocellular division of the mediodorsal nucleus of the thalamus.[10] Based on connections and architectonics of the OFC and parts of the medial prefrontal cortex (mPFC), Price and colleagues[5,6] proposed two functional networks: orbital and medial networks of the orbitomedial prefrontal cortex (OMPFC).

According to this classification, the orbital network is composed of mostly lateral orbitofrontal structures that receive input from all sensory modalities and is proposed to be critical for sensory integration and food intake. Lateral OFC projects to more central and dorsal regions of the striatum[11] that may influence behaviors in response to punishment, as well as automated or ritualized behaviors evolved to escape or otherwise mitigate danger. The medial network of the OMPFC includes parts of the ventral medial prefrontal cortex (vmPFC) and anterior cingulate (including BA 25, and parts of BA 32 and 24), as well as parts of the medial division of the OFC. This medial network has projections to visceromotor structures critical to modulate behavior. For example, medial OFC (mOFC, which is part of the medial network) projects massively to the ventral striatum,[12] and these projections are thought to subserve the modulation of reward-related behaviors. Furthermore, mOFC projects to the amygdala[6,13] as well as to the lateral hypothalamus,[14] the periaqueductal gray,[14] and the hippocampus.[9] These projections are thought to influence emotional expression.[13,15] Thus, the anatomical connections to and from the OFC clearly support its overall function in the integration of different sensory modalities and in using this information along with previous experiences to guide future behavioral outcome with maximum benefit to the organism.

OFC FUNCTIONS RELEVANT TO ANXIETY DISORDERS

Lateral versus Medial OFC Function in Reward and Punishment

The function of the OFC in reward and goal-directed behavior has been extensively studied in rodents and in non-human primates (for reviews, see Refs. 2, 16–18). Herein, we will primarily focus on human neuroimaging studies. Several recent neuroimaging studies have shown that the mOFC increases its activity during the anticipation of reward,[19–22] when evaluating attractive faces,[23–25] and during the consumption of chocolate.[26] On the other hand, anterolateral OFC (lOFC) appears to increase its activity in response to cues signaling the absence of reward,[19,27] unpleasant smell and touch,[28,29] anticipation of viewing aversive pictures,[30] and aversion to eating excessive chocolate.[26] Recall of positive affect preferentially activates the mOFC, whereas negative affects preferentially activate the lOFC.[27] Thus, a theme has emerged emphasizing the role of the mOFC in evaluating and mediating responses to positive affective states, whereas the lOFC appears to play a role in evaluating and mediating responses to negative affective states.[31,32] Several other studies have provided additional support for this dichotomous role of the mOFC and lOFC in valence-specific responses.[33,34] Finally, Kringelbach and Rolls[1] have conducted an extensive meta-analysis in which they reviewed 87 published articles that have examined the role of the OFC in rewards and punishments; the results provided support to this heuristic theme dichotomizing the OFC into medial versus lateral subdivisions, associated with positive versus negative valence, respectively. This is pertinent to models of anxiety disorders, given that such conditions are characterized by imbalance toward negatively valenced cognitions, such as anticipation of adverse of outcomes. Thus one might hypothesize that subjects with anxiety disorders would exhibit excessive lOFC and/or deficient mOFC function.

Medial OFC and Fear Extinction

In addition to the above-mentioned functions of the OFC, several animal studies along with recent human neuroimaging studies also implicate the mOFC and the vmPFC in the extinction of conditioned fear responding.[35–40] Several studies have shown that the rat vmPFC is implicated in the extinction of cued fear conditioning.[41–50] Lesions or inactivation of the vmPFC do not prevent short-term extinction learning, but they do impair recall of extinction after a delay.[45,47,49,51] Furthermore, interfering with NMDA receptors, protein kinases, or protein synthesis in vmPFC impairs consolidation of extinction learning.[52,53] Consistent with extinction-related plasticity in vmPFC, neurons in the infralimbic sub-region of vmPFC increase their activity when rats are recalling extinction, as evidenced by single-unit recording,[54] evoked potential recording,[55,56] and metabolic mapping.[42]

Recent neuroimaging studies have specifically linked the human vmPFC to extinction recall after fear conditioning and extinction training. Specifically, using functional MRI, two recent studies showed that vmPFC activity increased during extinction recall.[57,58] Using structural MRI, we recently demonstrated that thickness of the vmPFC in healthy humans was positively correlated with the magnitude of extinction recall expressed in the first two extinction trials during test.[59] Moreover, consistent with the previous neuroimaging studies, we observed increased vmPFC activity to an extinguished conditioned stimulus during extinction recall that was positively correlated with extinction success (measured by skin conductance response).[60] Thus, these recent human neuroimaging data strongly support the role of the mOFC and adjacent vmPFC in expressing extinction memory and therefore reducing conditioned fear to a previously conditioned stimulus.

Challenges to a Parsimonious Account of OFC in Anxiety Disorders

The data are vast regarding functions of OFC across animals and man. We have chosen two popular heuristics that we believe help to organize data pertinent to the role of OFC in anxiety disorders. Nonetheless, we wish to acknowledge and underscore that substantial data exist that do not fit neatly into these conceptualizations and some even contradict these models. In many instances, lack of clarity regarding the precise regions involved highlights the importance of such details, given these heuristics that posit opposite effects based on fine anatomy within OFC. For example, surgically severing cortical (including OFC)-subcortical connections results in the reduction of anxiety symptoms.[61] In a pediatric population examined after traumatic brain injury, the number of lesions within the OFC inversely correlated with anxiety symptoms and post-traumatic stress disorder (PTSD).[62] In rats, whereas inactivation of the infralimbic region reduced anxiety-like defensive responding, inactivation of the ventromedial orbital region had the opposite effect,[63] suggesting that different sub-regions within the vmPFC may have antagonistic effects on anxiety-like behaviors.

CLINICAL CHARACTERISTICS OF ANXIETY DISORDERS

Anxiety disorders are characterized by exaggerated anxiety and inappropriate fear responses to relatively harmless stimuli. Anxiety disorders include PTSD, panic disorder (PD), phobias including social anxiety disorder (SAD) and specific phobia (SP), and obsessive-compulsive disorder (OCD). The pathogenesis of these anxiety disorders remains unknown, though the etiology of PTSD is nominally defined. In the aftermath of a severe traumatic event, PTSD patients develop a constellation of symptoms including re-experiencing

phenomena, avoidance, and hyperarousal. PD is characterized by recurrent panic episodes that typically occur spontaneously. Panic attacks entail a rapid escalation to extreme anxiety that is accompanied by physical symptoms including rapid breathing, palpitations, sweating, and dizziness. Emotional and cognitive symptoms, such as the feeling that something catastrophic is about to happen, also accompany panic attacks. Individuals with PD often develop anticipatory anxiety, repeated panic episodes, and avoidance of places or situations where they believe panic attacks are more likely to occur.

Phobias are characterized by exaggerated anxiety responses to innocuous stimuli, such as small animals, or social situations, such as public speaking. The critical phenomenological features across the phobias are that: A) the cause of fear reactions are generally circumscribed and specific, and B) the objects of phobias tend to be stimuli that do in fact pose some degree of threat or risk in a particular setting. OCD is characterized by intrusive, unwanted thoughts (i.e., obsessions) and ritualized, repetitive behaviors (i.e., compulsions). The obsessions are commonly accompanied by anxiety that drives the compulsions. The compulsions, therefore, are performed to neutralize and attenuate the obsessions and anxiety.

CURRENT HYPOTHESES AND FINDINGS REGARDING PATHOPHYSIOLOGY OF ANXIETY DISORDERS: SUPPORT FROM NEUROIMAGING STUDIES

In the following section of this review, we will summarize neuroimaging studies pertaining to the pathophysiology of anxiety disorders. Given the massive literature published in this arena, we will focus on findings related to the medial and lateral regions of the OFC.

Post-traumatic Stress Disorder

One of the hypotheses regarding the development of PTSD is that hyperconditionability (forming abnormally strong associations between the trauma-induced emotions and stimuli present during trauma exposure),[64,65] along with failure to extinguish these fear responses, may underlie the emotional perseveration commonly observed in PTSD.[38,66–69] This led investigators to hypothesize that the exaggerated fear and anxiety in PTSD may result from hyper-responsivity within the amygdala to threat-related stimuli, with inadequate top-down governance over the amygdala by the vmPFC and mOFC (for example, see Ref. 35).

Indeed, this hypothesis is supported by a substantial body of neuroimaging data. For example, the majority of studies comparing PTSD to non-PTSD control groups have consistently shown diminished mPFC activation (see FIG. 1). Symptom provocation studies indicate that when exposed to reminders of

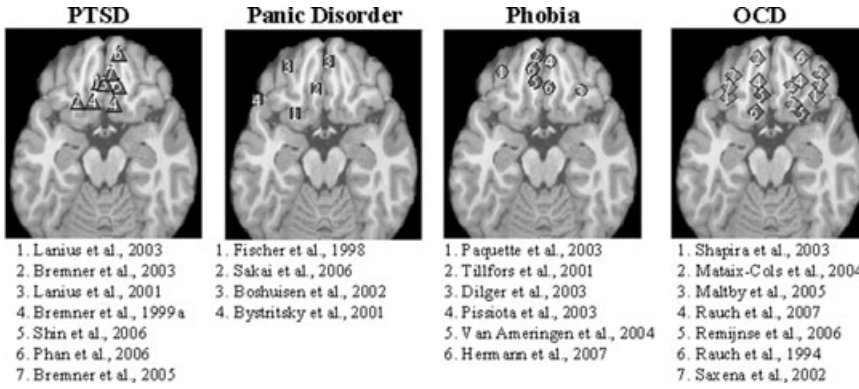

FIGURE 1. Summary of neuroimaging studies across all anxiety disorders showing increases in activity in comparison with controls or associated with anxiety symptoms (illustrated in red across all the anxiety disorders) and decreases in activity in comparison with controls or associated with anxiety symptoms (illustrated in blue across all anxiety disorders).

traumatic events, PTSD patients exhibit attenuated responses within mPFC areas.[70–75] Shin and colleagues[71] observed decreases in mPFC activity that were inversely correlated with increases in amygdala activity in PTSD. Additional support for the involvement of prefrontal areas in PTSD comes from morphometric MRI studies, where PTSD patients showed smaller mPFC volumes in comparison with non-PTSD controls; in some instances, these diminished prefrontal volumes have included mOFC structures. While many of the frontal structural and functional abnormalities in PTSD extend beyond the OFC, several studies have reported such findings that are referable to the mOFC regions as well as adjacent areas. For example, PTSD patients exhibit attenuated mOFC and subcallosal cortical activation during retrieval of emotionally valenced words[76] and during exposure to reminders of traumatic events.[77,78]

Panic Disorder

One hypothesis indicates that panic attacks evolve in the context of what should be minor anxiety episodes because of failures in the systems responsible for limiting such normal responses, similar to the model of PTSD.[38] Alternatively, panic episodes could reflect anxiety responses mediated by structures, such as the amygdala, at the subconscious level. Activation of the amygdala without the awareness of the threat-related stimulus has in fact been documented.[79,80] Thus, this model might characterize PD by fundamental amygdala hyper-responsivity to subtle environmental cues, thereby initiating full-scale threat-related responses in the absence of conscious awareness of the initial triggers. We have previously proposed that the basis for the development of PD

resembles the pathogenesis of PTSD, regardless of the etiology of the initial panic attacks.[81]

Data from neuroimaging studies have indicated dysfunctional mOFC and amygdala activity in PD (for example, see Refs. 82, 83, FIG. 1). Some of these studies used symptom-provocation techniques in which the panic episode was pharmacologically induced. For example, Woods and colleagues[84] employed single photon emission computed tomography and yohimbine infusions and found that PD subjects experienced increased anxiety and exhibited decreased regional cerebral blood flow (rCBF) in bilateral frontal cortex. Fischer and colleagues[85] captured a spontaneous panic attack during positron emission tomography (PET) acquisition in a single case and reported data showing decreased rCBF in right mOFC and anterior cingulate cortex during the acute event. Neutral state studies have found increased OFC activity at rest in PD, whereas, successful treatment with imipramine was accompanied by an attenuation of this OFC hyperactivity.[86] Interestingly, an inverse correlation was observed between OFC resting activity in the treated PD patients and their anxiety levels, suggesting again that OFC may be recruited to dampen anxiety in a compensatory fashion. A recent PET study comparing glucose consumption before and after cognitive behavioral therapy showed that successful treatment was accompanied by increased glucose consumption in medial prefrontal areas.[87]

Phobias

Note that, although specific (animal) phobias and SAD represent discrete disorders, we have summarized them beneath the same heading here. This was done pragmatically, due to the limited body of OFC findings for each condition, as well as the convergence of results and phenomenological similarities between these disorders. In phobias, the offending stimuli are generally more circumscribed and of a stereotypic nature. Thus, it has been previously proposed that the clinical features of phobias may reflect hypersensitivity in the pathways that mediate innate fear, responses to stimuli that evolution has made source for this type of fear, such as snakes and spiders.[88] This would most likely involve exaggerated activity of the amygdala along with dysfunction within the OFC.[89] Further, such dysfunction might only be evident during exposure to specific phobic stimuli. Neuroimaging data have in fact supported this view (see FIG. 1). Specifically, OFC dysfunction has been implicated in SAD as well as SP, and these aberrant responses are observed to occur only in the setting of exposure to the phobic object.[90,91] For example, one PET symptom-provocation study contrasting public versus private speaking conditions found decreases in mOFC in the SAD relative to the non-phobic group.[92] Another PET symptom-provocation study reported deactivation of mOFC in SAD during exposure to phobia-inducing events.[93] A recent fMRI study also reported decreased activity of the mOFC in phobic patients upon exposure to phobia-inducing pictures.[94]

Analogous studies have conversely found increased activation in lOFC regions when spider-phobic subjects viewed phobia-related pictures.[95]

Obsessive-Compulsive Disorder

OCD appears to be distinct from the other anxiety disorders in several respects. In general, pathophysiological models of this disorder have focused on cortico-striato-thalamo-cortical circuitry.[96–101] One hypothesis suggests that the primary pathology is within the striatum, which leads to inefficient gating at the level of the thalamus. This leads to hyperactivity within OFC (corresponding to the intrusive thoughts) and hyperactivity within anterior cingulate cortex (corresponding to anxiety, in a non-specific manner).[89,96,102–104] It is important to note that OCD is a highly heterogeneous condition, such that its subtypes may be characterized by somewhat different pathophysiological profiles.

With respect to neuroimaging data and OCD, hyperactivity in the OFC has been the most consistent finding across many studies using different experimental paradigms (for example, see Refs. 96, 105–107, see FIG. 1). Pre/post-treatment studies have likewise indicated attenuation of abnormal regional brain activity within OFC, anterior cingulate cortex, and caudate nucleus associated with successful treatment.[97,108–110] Moreover, similar changes have been observed for both pharmacological and behavioral therapies.[97,111] Treatment studies have also consistently indicated that the magnitude of OFC activity prior to pharmacotherapy predicts subsequent response to serotonin reuptake inhibitors,[97,111,112] such that lesser magnitude of OFC hyperactivity predicts better response to treatment. Symptom provocation studies using PET[113,114] and fMRI[115,116] have also shown increased OFC activation along with increased activation in other brain regions including the anterior cingulate cortex and caudate nucleus; such increases in activity were associated with the OCD symptomatic state. A recent fMRI study has shown that improvement of OCD symptoms either due to pharmacological or behavioral therapy interventions, reduced symptom-provocation increases in the OFC.[117]

Interestingly, increased activation in the lOFC and caudate appear to be specific to OCD. On the other hand, dysfunctional mOFC activity is generally observed across all anxiety disorders.[67] Note that in a symptom-provocation study, Rauch and colleagues[113] showed that whereas OCD symptom severity was directly correlated with lOFC activation, severity of anxiety in OCD was inversely correlated with posteromedial OFC activity (see FIG. 1). It has also been shown that activity within OFC correlated directly with subsequent response to cognitive behavior therapy,[111] consistent with the concept that magnitude of mOFC function may be associated with the capacity for patients to benefit from an extinction-based therapy.

THE ROLE OF THE OFC IN EXTINCTION: IMPLICATIONS FOR ANXIETY DISORDERS

Cognitive behavioral therapy is considered to be effective for essentially all anxiety disorders. As with fear extinction in rats, during behavioral therapy patients with anxiety disorders are exposed to the anxiety-inducing stimuli in the absence of any negative reinforcement.[118] After several sessions of exposure therapy, the majority of patients learn to inhibit their fear responses.[119] However, some patients with anxiety disorders fail to respond to exposure therapy,[120,121] consistent with the hypothesis that extinction learning may be especially deficient in these treatment-resistant patients.

Despite the direct link between OFC dysfunction in anxiety disorders, the role of OFC in fear extinction, and the fact that extinction forms the basis for exposure therapy used to treat anxiety disorders, the integrity of the OFC in anxiety disorders in the context of fear extinction, and specifically extinction recall, has not been thoroughly examined. Although the neuroimaging studies reviewed above have undoubtedly provided critical information regarding the neurocircuitry of anxiety disorders, most of those studies have employed experimental tools that did not directly assess the functional integrity of the OFC during fear extinction. Understanding the neural mechanisms of fear extinction may be fundamental to elucidating the pathophysiology of anxiety disorders. Such a line of inquiry could also enhance our understanding of the mechanism of action by which extinction-based treatments confer their therapeutic effects (e.g. see Refs. 35, 81).

SUMMARY AND CONCLUSIONS

We have presented a brief review, adopting popular schemes for subdividing OFC into mOFC and lOFC zones. This conceptualization provides a useful heuristic for considering the neurocircuitry pertinent to the pathophysiology and treatment of anxiety disorders. Specifically, we propose that the two extremes of OFC dysfunction are manifested in the anxiety disorders. On the one hand, across the anxiety disorders, hypoactive mOFC is detected where there is a failure to inhibit inappropriate fear and anxiety responses. On the other hand, hyperactive lOFC is most commonly detected when there are prominent anxiety-laden cognitions, such as in OCD. This simplistic model reconciles a large volume of initial neuroimaging findings, which otherwise appear superficially inconsistent, with a broad array of OFC increases and decreases. Further, this theoretical framework leads to straightforward testable hypotheses about regional brain function, severity of symptoms, and predictors of treatment response. Perhaps most importantly, this model suggests new targets for neuromodulatory treatments that might seek to enhance mOFC function in the service of fortifying extinction capacity, or to attenuate excessive lOFC activity to mitigate obsessions and worries.

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REFERENCES

1. KRINGELBACH, M.L. & E.T. ROLLS. 2004. The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. Prog. Neurobiol. **72:** 341–372.
2. SCHOENBAUM, G. & M. ROESCH. 2005. Orbitofrontal cortex, associative learning, and expectancies. Neuron **47:** 633–636.
3. O'DOHERTY, J. 2003. Can't learn without you: predictive value coding in orbitofrontal cortex requires the basolateral amygdala. Neuron **39:** 731–733.
4. IZQUIERDO, A., R.K. SUDA & E.A. MURRAY. 2004. Bilateral orbital prefrontal cortex lesions in rhesus monkeys disrupt choices guided by both reward value and reward contingency. J. Neurosci. **24:** 7540–7548.
5. ONGUR, D., A.T. FERRY & J.L. PRICE. 2003. Architectonic subdivision of the human orbital and medial prefrontal cortex. J. Comp Neurol. **460:** 425–449.
6. ONGUR, D. & J.L. PRICE. 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex **10:** 206–219.
7. CARMICHAEL, S.T. & J.L. PRICE. 1994. Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J. Comp Neurol. **346:** 366–402.
8. BARBAS, H. 2000. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull. **52:** 319–330.
9. CAVADA, C. *et al.* 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb. Cortex **10:** 220–242.
10. FUSTER, J.M. 2001. The prefrontal cortex–an update: Time is of the essence. Neuron **30:** 319–333.
11. FERRY, A.T., X.C. LU & J.L. PRICE. 2000. Effects of excitotoxic lesions in the ventral striatopallidal–thalamocortical pathway on odor reversal learning: Inability to extinguish an incorrect response. Exp. Brain Res. **131:** 320–335.
12. FERRY, A.T. *et al.* 2000. Prefrontal cortical projections to the striatum in macaque monkeys: Evidence for an organization related to prefrontal networks. J. Comp Neurol. **425:** 447–470.
13. BARBAS, H. *et al.* 2003. Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. BMC Neurosci. **4:** 25.
14. FLOYD, N.S. *et al.* 2000. Orbitomedial prefrontal cortical projections to distinct longitudinal columns of the periaqueductal gray in the rat. J. Comp Neurol. **422:** 556–578.
15. GUSNARD, D.A. *et al.* 2003. Persistence and brain circuitry. Proc. Natl. Acad. Sci. USA **100:** 3479–3484.
16. SCHULTZ, W. 2006. Behavioral theories and the neurophysiology of reward. Annu. Rev. Psychol. **57:** 87–115.
17. ROLLS, E.T. 2004. The functions of the orbitofrontal cortex. Brain Cogn. **55:** 11–29.

18. HOLLAND, P.C. & M. GALLAGHER. 2004. Amygdala-frontal interactions and reward expectancy. Curr. Opin. Neurobiol. **14:** 148–155.
19. URSU, S. & C.S. CARTER. 2005. Outcome representations, counterfactual comparisons and the human orbitofrontal cortex: implications for neuroimaging studies of decision-making. Brain Res. Cogn. Brain Res. **23:** 51–60.
20. COX, S.M., A. ANDRADE & I.S. JOHNSRUDE. 2005. Learning to like: a role for human orbitofrontal cortex in conditioned reward. J. Neurosci. **25:** 2733–2740.
21. GALVAN, A. *et al.* 2005. The role of ventral frontostriatal circuitry in reward-based learning in humans. J. Neurosci. **25:** 8650–8656.
22. KIM, H., S. SHIMOJO & J.P. O'DOHERTY. 2006. Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain. PLoS Biol. **4:** e233.
23. O'DOHERTY, J. *et al.* 2003. Beauty in a smile: The role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia **41:** 147–155.
24. WINSTON, J.S. *et al.* 2007. Brain systems for assessing facial attractiveness. Neuropsychologia **45:** 195–206.
25. ISHAI, A. 2007. Sex, beauty and the orbitofrontal cortex. Int. J. Psychophysiol. **63:** 181–185.
26. SMALL, D.M. *et al.* 2003. Dissociation of neural representation of intensity and affective valuation in human gustation. Neuron **39:** 701–711.
27. MARKOWITSCH, H.J. *et al.* 2003. Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. Cortex **39:** 643–665.
28. ROLLS, E.T., M.L. KRINGELBACH & I.E. DE ARAUJO. 2003. Different representations of pleasant and unpleasant odours in the human brain. Eur. J. Neurosci. **18:** 695–703.
29. ROLLS, E.T., J.V. VERHAGEN & M. KADOHISA. 2003. Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness, and capsaicin. J. Neurophysiol. **90:** 3711–3724.
30. NITSCHKE, J.B., I. SARINOPOULOS, K.L. MACKIEWICZ, *et al.* 2006. Functional neuroanatomy of aversion and its anticipation. Neuroimage **29:** 106–116.
31. ELLIOTT, R. *et al.* 2000. Selective attention to emotional stimuli in a verbal go/no-go task: an fMRI study. Neuroreport **11:** 1739–1744.
32. O'DOHERTY, J. *et al.* 2001. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat. Neurosci. **4:** 95–102.
33. BLAIR, R.J. *et al.* 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain **122**(Pt 5): 883–893.
34. ZALD, D.H. & J.V. PARDO. 2000. Functional neuroimaging of the olfactory system in humans. Int. J. Psychophysiol. **36:** 165–181.
35. MILAD, M.R. *et al.* 2006. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol. Psychol. **73:** 61–71.
36. BARAD, M. 2005. Fear extinction in rodents: basic insight to clinical promise. Curr. Opin. Neurobiol. **15:** 710–715.
37. SOTRES-BAYON, F., C.K. CAIN & J.E. LEDOUX. 2006. Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex. Biol. Psychiatry **60:** 329–336.
38. RAUCH, S.L., L.M. SHIN & E.A. PHELPS. 2006. Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research–past, present, and future. Biol. Psychiatry **60:** 376–382.

39. QUIRK, G.J., R. GARCIA & F. GONZALEZ-LIMA. 2006. Prefrontal mechanisms in extinction of conditioned fear. Biol. Psychiatry **60:** 337–343.
40. DAVIS, M. *et al.* 2006. Pharmacological treatments that facilitate extinction of fear: relevance to psychotherapy. NeuroRx. **3:** 82–96.
41. BERRETTA, S. *et al.* 2005. Infralimbic cortex activation increases c-Fos expression in intercalated neurons of the amygdala. Neuroscience **132:** 943–953.
42. BARRETT, D. *et al.* 2003. Metabolic mapping of mouse brain activity after extinction of a conditioned emotional response. J. Neurosci. **23:** 5740–5749.
43. HERRY, C. & N. MONS. 2004. Resistance to extinction is associated with impaired immediate early gene induction in medial prefrontal cortex and amygdala. Eur. J. Neurosci. **20:** 781–790.
44. SIERRA-MERCADO, D. *et al.* 2006. Inactivation of ventromedial prefrontal cortex reduces expression of conditioned fear and impairs subsequent recall of extinction. Eur. J. Neurosci. **24:** 1751–1758.
45. CORCORAN, K.A. & G.J. QUIRK. 2007. Activity in prelimbic cortex is necessary for the expression of learned, but not innate, fears. J. Neurosci. **27:** 840–844.
46. QUIRK, G.J. *et al.* 2000. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J. Neurosci. **20:** 6225–6231.
47. LEBRON, K., M.R. MILAD & G.J. QUIRK. 2004. Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. Learn. Mem. **11:** 544–548.
48. SANTINI, E. *et al.* 2004. Consolidation of fear extinction requires protein synthesis in the medial prefrontal cortex. J. Neurosci. **24:** 5704–5710.
49. MORGAN, M.A., L.M. ROMANSKI & J.E. LEDOUX. 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci. Lett. **163:** 109–113.
50. MILAD, M.R., I. VIDAL-GONZALEZ & G.J. QUIRK. 2004. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behav. Neurosci. **118:** 389–394.
51. SIERRA-MERCADO, D., JR. *et al.* 2006. Inactivation of the ventromedial prefrontal cortex reduces expression of conditioned fear and impairs subsequent recall of extinction. Eur. J. Neurosci. **24:** 1751–1758.
52. HUGUES, S., O. DESCHAUX & R. GARCIA. 2004. Postextinction infusion of a mitogen-activated protein kinase inhibitor into the medial prefrontal cortex impairs memory of the extinction of conditioned fear. Learn. Mem. **11:** 540–543.
53. BURGOS-ROBLES, A. *et al.* 2007. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. Neuron **53:** 871–880.
54. MILAD, M.R. & G.J. QUIRK. 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature **420:** 70–74.
55. HERRY, C. & R. GARCIA. 2002. Prefrontal cortex long-term potentiation, but not long-term depression, is associated with the maintenance of extinction of learned fear in mice. J. Neurosci. **22:** 577–583.
56. FARINELLI, M. *et al.* 2006. Hippocampal train stimulation modulates recall of fear extinction independently of prefrontal cortex synaptic plasticity and lesions. Learn. Mem. **13:** 329–334.
57. KALISCH, R. *et al.* 2006. Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. J. Neurosci. **26:** 9503–9511.

58. PHELPS, E.A. *et al.* 2004. Extinction learning in humans: role of the amygdala and vmPFC. Neuron **43:** 897–905.
59. MILAD, M.R. *et al.* 2005. Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proc. Natl. Acad. Sci. USA **102:** 10706–10711.
60. MILAD, M.R. *et al.* 2007. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol. Psychiatry **62:** 446–454.
61. WEINGARTEN, S. 1999. The Human Frontal Lobes: functions and Disorders. B. Miller & J. Cummings, Eds. Guilford Press. New York.
62. VASA, R.A. *et al.* 2004. Neuroimaging correlates of anxiety after pediatric traumatic brain injury. Biol. Psychiatry **55:** 208–216.
63. WALL, P.M. *et al.* 2004. Differential effects of infralimbic vs. ventromedial orbital PFC lidocaine infusions in CD-1 mice on defensive responding in the mouse defense test battery and rat exposure test. Brain Res **1020:** 73–85.
64. ORR, S.P. *et al.* 2000. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. J. Abnorm. Psychol. **109:** 290–298.
65. ORR, S.P., L.J. METZGER & R.K. PITMAN. 2002. Psychophysiology of posttraumatic stress disorder. Psychiatr. Clin. North Am. **25:** 271–293.
66. LIBERZON, I. & B. MARTIS. 2006. Neuroimaging studies of emotional responses in PTSD. Ann. N. Y. Acad. Sci **1071:** 87–109.
67. RAUCH, S.L. *et al.* 1998. Neuroimaging and the neuroanatomy of PTSD. CNS Spectr. **3:** 30–41.
68. DAVIS, M. *et al.* 2006. Effects of d-cycloserine on extinction: translation from preclinical to clinical work. Biol. Psychiatry **60:** 369–375.
69. PITMAN, R.K., L.M. SHIN & S.L. RAUCH. 2001. Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. J. Clin. Psychiatry **62**(Suppl 17): 47–54.
70. PHAN, K.L. *et al.* 2006. Corticolimbic blood flow during nontraumatic emotional processing in posttraumatic stress disorder. Arch. Gen. Psychiatry **63:** 184–192.
71. SHIN, L.M. *et al.* 2004. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch. Gen. Psychiatry **61:** 168–176.
72. SHIN, L.M. *et al.* 2001. An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biol. Psychiatry **50:** 932–942.
73. SHIN, L.M. *et al.* 1999. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. Am. J. Psychiatry **156:** 575–584.
74. LANIUS, R.A. *et al.* 2002. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. Biol. Psychiatry **52:** 305–311.
75. LIBERZON, I., J.C. BRITTON & K.L. PHAN. 2003. Neural correlates of traumatic recall in posttraumatic stress disorder. Stress **6:** 151–156.
76. BREMNER, J.D. *et al.* 2003. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biol. Psychiatry **53:** 879–889.
77. BREMNER, J.D. *et al.* 1999. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress

disorder: a positron emission tomography study. Biol. Psychiatry **45:** 806–816.
78. BREMNER, J.D. 1999. Alterations in brain structure and function associated with post-traumatic stress disorder. Semin. Clin. Neuropsychiatry **4:** 249–255.
79. MORRIS, J.S., A. OHMAN & R.J. DOLAN. 1998. Conscious and unconscious emotional learning in the human amygdala. Nature **393:** 467–470.
80. WHALEN, P.J. *et al.* 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J. Neurosci. **18:** 411–418.
81. RAUCH, S.L., L.M. SHIN & C.I. WRIGHT. 2003. Neuroimaging studies of amygdala function in anxiety disorders. Ann. N. Y. Acad. Sci. **985:** 389–410.
82. BYSTRITSKY, A. *et al.* 2001. Functional MRI changes during panic anticipation and imagery exposure. Neuroreport **12:** 3953–3957.
83. SAKAI, Y. *et al.* 2005. Cerebral glucose metabolism associated with a fear network in panic disorder. Neuroreport **16:** 927–931.
84. WOODS, S.W. *et al.* 1988. Carbon dioxide-induced anxiety. Behavioral, physiologic, and biochemical effects of carbon dioxide in patients with panic disorders and healthy subjects. Arch. Gen. Psychiatry **45:** 43–52.
85. FISCHER, H. *et al.* 1998. Brain correlates of an unexpected panic attack: a human positron emission tomographic study. Neurosci. Lett. **251:** 137–140.
86. NORDAHL, T.E. *et al.* 1998. Regional cerebral metabolic asymmetries replicated in an independent group of patients with panic disorders. Biol. Psychiatry **44:** 998–1006.
87. SAKAI, Y. *et al.* 2006. Changes in cerebral glucose utilization in patients with panic disorder treated with cognitive-behavioral therapy. Neuroimage **33:** 218–226.
88. OHMAN, A. & S. MINEKA. 2001. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol. Rev. **108:** 483–522.
89. AOUIZERATE, B. *et al.* 2004. Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. Prog. Neurobiol. **72:** 195–221.
90. PISSIOTA, A. *et al.* 2003. Amygdala and anterior cingulate cortex activation during affective startle modulation: a PET study of fear. Eur. J. Neurosci. **18:** 1325–1331.
91. PAQUETTE, V. *et al.* 2003. "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. Neuroimage **18:** 401–409.
92. TILLFORS, M. *et al.* 2001. Cerebral blood flow in subjects with social phobia during stressful speaking tasks: a PET study. Am. J. Psychiatry **158:** 1220–1226.
93. VAN AMERINGEN, M. *et al.* 2004. A PET provocation study of generalized social phobia. Psychiatry Res **132:** 13–18.
94. HERMANN, A. *et al.* 2007. Diminished medial prefrontal cortex activity in blood-injection-injury phobia. Biol. Psychol. **75:** 124–130.
95. DILGER, S. *et al.* 2003. Brain activation to phobia-related pictures in spider phobic humans: an event-related functional magnetic resonance imaging study. Neurosci. Lett. **348:** 29–32.
96. CANNISTRARO, P.A. & S.L. RAUCH. 2003. Neural circuitry of anxiety: evidence from structural and functional neuroimaging studies. Psychopharmacol. Bull. **37:** 8–25.

97. BAXTER, L.R., JR. 1992. Neuroimaging studies of obsessive compulsive disorder. Psychiatr. Clin. North Am. **15:** 871–884.
98. SAXENA, S. & S.L. RAUCH. 2000. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr. Clin. North Am. **23:** 563–586.
99. VAN DEN HEUVEL, O.A. *et al.* 2005. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. Arch. Gen. Psychiatry **62:** 922–933.
100. REMIJNSE, P.L. *et al.* 2006. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. Arch. Gen. Psychiatry **63:** 1225–1236.
101. MALTBY, N. *et al.* 2005. Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. Neuroimage **24:** 495–503.
102. GRAYBIEL, A.M. & S.L. RAUCH. 2000. Toward a neurobiology of obsessive-compulsive disorder. Neuron **28:** 343–347.
103. ZALD, D.H. & S.W. KIM. 1996. Anatomy and function of the orbital frontal cortex, I: anatomy, neurocircuitry; and obsessive-compulsive disorder. J. Neuropsychiatry Clin. Neurosci. **8:** 125–138.
104. ZALD, D.H. & S.W. KIM. 1996. Anatomy and function of the orbital frontal cortex, II: Function and relevance to obsessive-compulsive disorder. J. Neuropsychiatry Clin. Neurosci. **8:** 249–261.
105. SHAPIRA, N.A. *et al.* 2003. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. Biol. Psychiatry **54:** 751–756.
106. MATAIX-COLS, D. *et al.* 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch. Gen. Psychiatry **61:** 564–576.
107. RAUCH, S.L. *et al.* 2007. Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. Biol. Psychiatry **61:** 330–336.
108. HURLEY, R.A. *et al.* 2002. Predicting treatment response in obsessive-compulsive disorder. J. Neuropsychiatry Clin. Neurosci. **14:** 249–253.
109. PERANI, D. *et al.* 1995. [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. Br. J. Psychiatry **166:** 244–250.
110. SWEDO, S.E., H.L. LEONARD & J.L. RAPOPORT. 1992. Childhood-onset obsessive compulsive disorder. Psychiatr. Clin. North Am. **15:** 767–775.
111. BRODY, A.L. *et al.* 1998. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. Psychiatry Res. **84:** 1–6.
112. RAUCH, S.L. *et al.* 2002. Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: A PET symptom provocation study. Neuropsychopharmacology **27:** 782–791.
113. RAUCH, S.L. *et al.* 1994. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch. Gen. Psychiatry **51:** 62–70.
114. MCGUIRE, P.K. *et al.* 1994. Functional anatomy of obsessive-compulsive phenomena. Br. J. Psychiatry **164:** 459–468.
115. ADLER, C.M. *et al.* 2000. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. J. Psychiatr. Res. **34:** 317–324.

116. BREITER, H.C. *et al.* 1996. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch. Gen. Psychiatry **53:** 595–606.
117. NAKAO, T. *et al.* 2005. [Duration effect on neuropsychological function and treatment response of OCD]. Seishin Shinkeigaku Zasshi **107:** 1286–1298.
118. WALD, J. & S. TAYLOR. 2003. Preliminary research on the efficacy of virtual reality exposure therapy to treat driving phobia. Cyberpsychol. Behav. **6:** 459–465.
119. DAVIDSON, J.R. & E.B. FOA. 1991. Refining criteria for posttraumatic stress disorder. Hosp. Community Psychiatry **42:** 259–261.
120. FOA, E.B. 2000. Psychosocial treatment of posttraumatic stress disorder. J. Clin. Psychiatry **61**(Suppl 5): 43–48.
121. VAN MINNEN, A. & M. HAGENAARS. 2002. Fear activation and habituation patterns as early process predictors of response to prolonged exposure treatment in PTSD. J. Trauma Stress **15:** 359–367.