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Emotion, mood & anxiety disorders

Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic

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Recent decades have witnessed tremendous advances in the neuroscience of emotion, learning and memory, and in animal models for understanding depression and anxiety. This review focuses on new rationally designed psychiatric treatments derived from preclinical human and animal studies. Nonpharmacological treatments that affect disrupted emotion circuits include vagal nerve stimulation, rapid transcranial magnetic stimulation and deep brain stimulation, all borrowed from neurological interventions that attempt to target known pathological foci. Other approaches include drugs that are given in relation to specific learning events to enhance or disrupt endogenous emotional learning processes. Imaging data suggest that common regions of brain activation are targeted with pharmacological and somatic treatments as well as with the emotional learning in psychotherapy. Although many of these approaches are experimental, the rapidly developing understanding of emotional circuit regulation is likely to provide exciting and powerful future treatments for debilitating mood and anxiety disorders.

Major depressive disorder (MDD) is the most common of all psychiatric disorders. MDD ranks among the top causes of worldwide disease burden and disability, with lifetime risk of 7–12% in men and 20–25% in women1. Although good treatments such as selective serotonin reuptake inhibitors (SSRIs) are effective and available, up to 20% of patients completely fail to respond to standard interventions and nearly 60% may not achieve adequate response2. The different anxiety disorders, including panic disorder, post-traumatic stress disorder (PTSD) and phobias, are also extremely common, with a combined lifetime prevalence of over 28%, and with a similar societal cost-burden to that of MDD3. Anxiety disorders can be extremely debilitating and, overall, have rates of failure to respond similar to those of MDD.

In this review, mood and anxiety disorders will be considered together for several reasons: (i) comorbidity between anxiety and depression is the rule and not the exception, with up to 90% of patients with anxiety disorders experiencing clinical depression at some point in their lifetime4; (ii) there is a significant problem of diagnostic classification, with highly overlapping symptom criteria; (iii) from a neuroimaging perspective the circuits involved in both sets of disorders can be difficult to distinguish; and (iv) the most powerful treatments for both disorders are the same, including antidepressants such as SSRIs and cognitive behavioral therapy (CBT). It is not that biologically meaningful subclassifications do not exist within the broad categories of emotional disorders, rather that the current clinical descriptions are probably not identifying the phenotypic clusters of disorders that may be most useful from a neurobiological and treatment perspective.

Several lines of evidence suggest that there are specific neural circuits within the limbic-cortical

system that mediate stress-responsiveness, mood and emotional regulation. Disorders of mood and anxiety represent brain-based disorders that lead to dysregulation of these circuits. Traditional psychiatric medication, psychotherapy and somatic therapies converge in bringing homeostasis to these disrupted circuits. New neurostimulatory therapies based on progress in understanding emotion circuitry and new pharmacological therapies based on understanding emotional learning are likely to provide more rapid and robust methodologies for treating these debilitating and complex disorders.

Abnormal circuit modulation in mood and anxiety disorders

Human imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have examined differences in brain regional activation in depressed and anxious subjects relative to controls and in patients before and after treatment. This review focuses on components of depression such as sad or dysphoric affect, negative emotions, impaired cognition and anxiety-related symptoms. Many brain areas may underlie some of the different symptom clusters of depression5. In contrast to the brain regions that bring about the negative emotional components of depression, the nucleus accumbens, along with other areas involved in reward processing, are also likely to be involved in the anhedonic components of depression6, 7, 8, 9, 10. Some of these areas may be equally important in the circuitry of depression, but will not be examined here due to space constraints.

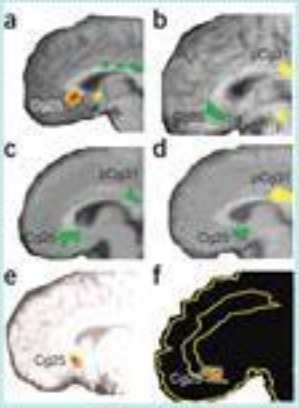
The areas most reproducibly found to be dysregulated in common emotional disorders are the prefrontal cortex (PFC) and subgenual cingulate cortex (Cg25), which seem to be involved in emotion experience and processing, as well as the subcortical hippocampus and amygdala, which are involved in emotional memory formation and memory retrieval5, 11, 12, 13, 14.

For the purposes of illustration, this review will focus primarily on data related to the role of Cg25 in emotion regulation and processing, and the role of the amygdala in emotional memory formation and expression. Cg25 is involved in the production of sad emotions and in antidepressant treatment response. It is activated during transient sadness, and after recovery from depression its activity is decreased compared with baseline after recovery from depression12 (Fig. 1a). Cg25 decreases in activity are seen in response to chronic fluoxetine treatment for MDD (Fig. 1b), as well as during recovery from depression related to Parkinson's disease after chronic fluoxetine treatment (Fig. 1c). Interestingly, subjects who are randomized

to placebo but show a natural recovery from symptoms of depression also have decreased activity in Cg25 from baseline (Fig. 1d). Activity in Cg25 before treatment predicts treatment response with CBT15 (Fig. 1e). Additionally, a response to CBT for social phobia is accompanied by decreases in Cg25 activity, and responders have greater decreases in Cg25 activity than do nonresponders16 (Fig. 1f).

Figure 1.

Figure 1. Subgenual cingulate cortex activation across studies.



(**a**) Transient sadness in healthy volunteers increases activity (red) in Cg25 (arrow) measured with positron emission tomography (PET) (from ref. 12. Reprinted with permission from the *American Journal of Psychiatry*, copyright 1999, American Psychiatric Association.). (**b**) Decreased Cg25 activity (green) with chronic fluoxetine treatment for depression. (**c**) Cg25 decrease (green) in recovery with chronic fluoxetine from Parkinson's disease–related depression. (**d**) Natural recovery with decreased Cg25 activity (green) in patients treated with placebo. Panels **b**–**d** reprinted from ref. 11 by permission of Oxford University Press. (**e**) Predictors of response in subjects responding to CBT for depression included low pretreatment Cg25 activity (red) (from ref. 15. Reprinted with permission from the *American Journal of Psychiatry*, copyright 1999, American Psychiatric Association.). (**f**) Subgenual cortical decreased activity (red) was common in responders compared with nonresponders for those responding both to citalopram and to CBT for social phobia (from ref. 16. Reprinted from *Archives of General Psychiatry*, copyright 2002, American Medical Association. All rights reserved.).

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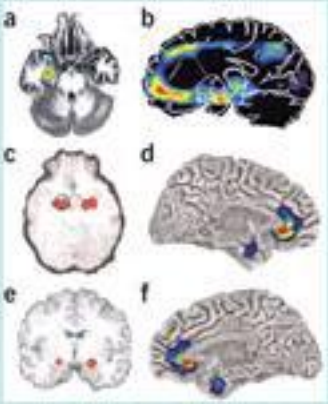
Overactivation of the amygdala is also implicated in depression and anxiety17 (Fig. 2). Amygdala activation decreases with recovery from mood symptoms. Studies that implicate Cg25 also find significant amygdala decreases with response to CBT treatment for social phobia16 (Fig. 2a) and report that sustained amygdala activity before treatment predicts antidepressant response to CBT15 (Fig. 2c).

Figure 2.

Figure 2. Amygdala activation across studies.



(**a**) Responders compared with nonresponders showed greater decreases (red to blue indicates greatest to least decrease) in anxiety-induced amygdala activation in both citalopram and CBT treatment for social phobia (ref. 16. Reprinted from *Archives of General Psychiatry*, copyright 2002, American Medical Association. All rights reserved.). (**b**) In familial MDD, areas of abnormally increased cerebral blood flow (red) compared with that in controls include the amygdala (from ref. 17. Reprinted from *Biological Psychiatry*, copyright 2000, with permission from Elsevier.). (**c**) Predictors of response in subjects responding to CBT for depression included high sustained emotion-induced amygdala activity (circled; red indicates increased regional cerebral blood flow in response to negative words) (from ref. 15. Reprinted with permission from the *American Journal of Psychiatry*, copyright 1999, American Psychiatric Association.). (**d**–**f**) Left (**d**) and right (**f**) hemispheres showing that subgenual cingulate and amygdala show reductions in gray matter volume (red to blue indicates most to least volume decrease) in *5-HTTLPR* high-risk short-allele carriers compared with homozygous long-allele genotypes (Reprinted by permission from Macmillan Publishers, Ltd.: *Nature Neuroscience*, ref. 19, copyright 2005.). Lorazepam, a benzodiazepine used for anxiety treatment, dose dependently attenuates the amygdata activation induced by emotional face viewing (**e**; red indicates greatest decrease in regional cerebral blood flow compared with placebo) (from ref. 99. Reprinted from *Archives of General Psychiatry*, copyright 2005, American Medical Association. All rights reserved.).

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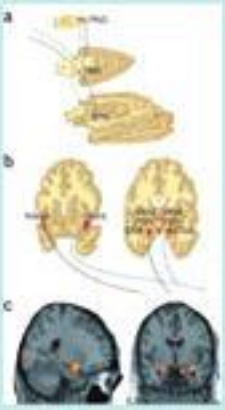
Figure 3. Ascending projections from vagus–nucleus solitarius pathways with VNS.



(**a**) Brainstem view of ascending bilateral pathways of the central autonomic, reticular activating and limbic systems receiving afferent input from the vagus nerve. Vagal–bilateral NTS projections, through synapses in the parabrachial nuclei, project to more rostral and cortical regions. (**b**) Projections of NTS and parabrachial nucleus provide dense innervation of autonomic, reticular and limbic forebrain structures (from ref. 26. Reprinted from *Neurology*, by permission of Lippincott Williams & Wilkins.). NTS, nucleus of the tractus solitarius; PBN, parabrachial nucleus; PAG, periaqueductal gray matter; CNA, central nucleus of the amygdala; PVN, periventricular nucleus of the hypothalamus; VPM, ventral posteromedial nucleus of the thalamus. (**c**) Changes in amygdala and hippocampal regional cerebral blood flow by therapeutic vagus nerve stimulation after 4 weeks of VNS for depression (red-yellow represent areas of greatest decrease in regional cerebral blood flow relative to pretreatment values). Panels **a** and **b** reprinted from *Psychiatry Research*: ref. 29, copyright 2005, with permission from Elsevier.

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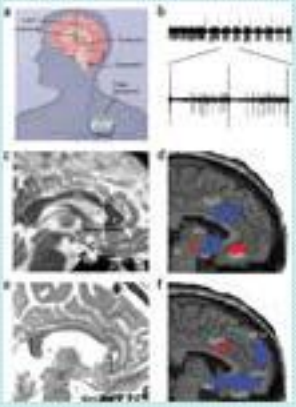
Figure 4. Deep brain stimulation.



(**a**) Schematic of DBS used for Parkinson's patients (modified from WebMD, http://www.medicinenet.com/deep_brain_stimulation/article.htm). (**b**) One possible mechanism of action of DBS-induced inhibition: recordings from a globus pallidus internus (GPi) high-frequency-discharge neuron showing inhibitory periods after each stimulus pulse (50 μA) (from ref. 100. Copyright 2000 by American Physiological Society. Reproduced with permission of American Physiological Society via Copyright Clearance Center.). (**c**) Preoperative MRI target localization for DBS for refractory depression. White dot, location of the sgCg white matter targeted for electrode placement in the DBS depression study, shown in a single subject; white arrow, sgCg gyrus; dotted line, anterior-posterior location of the electrode along the line (black) between anterior commissure and genu of the corpus callosum. (**d**) Baseline PET-derived blood flow: depressed patients show increased activity (red) in Cg25 compared with healthy controls. (**e**) Postoperative MRI in a single DBS patient showing the electrode tip in the sgCg white matter. (**f**) At 3 months, regions of blood flow change measured with PET in treatment responders show decreased activity (blue) compared with pretreatment. Panels **c**–**f** reprinted by permission from an article published in *Neuron*, ref. 58, copyright Elsevier 2005. CC, corpus callosum; ac, anterior commissure; g, genu of the corpus callosum; sgCg, subgenual cingulate; Cg24, cingulate area 24; sn, substantia nigra; hth, hypothalamus; mF10, medial frontal area 10; oF11, orbito-frontal area 11.

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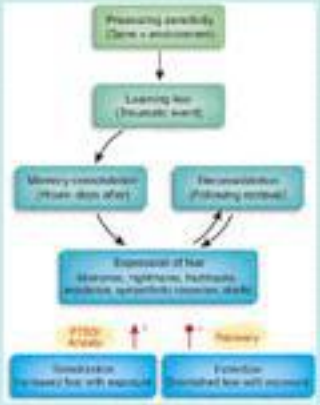
Figure 5. Emotional learning processes related to fear.



The strength and regulation of emotional memories is affected by many factors both before and after the traumatic or fearful event occurs. Genetic heritability comprises up to ~40% of the risk for both depression and PTSD, and early childhood abuse is a very strong risk factor for all mood and anxiety disorders. Memories are not permanent at the time of the trauma, rather they undergo a period of consolidation in which they shift from a labile state to a more permanent state. Some evidence, at least for relatively recent memories, indicates that even after memories become consolidated, they become labile again when recalled—a process known as reconsolidation. The expression of traumatic memories, which can be the source of many symptoms in fear-related disorders, is diminished by the process of extinction, when repeated therapeutic exposures to the fear-related cues reduces or inhibits the fear memories over time. In contrast, there is some evidence that in those who develop PTSD and other pathology, a combination of avoidance of sufficient exposure with intrusive and uncontrollable memories leads to sensitization of the fear response. Arrowhead (+), sensitization increases expression of fear; filled circle (-), extinction decreases expression.

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