

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 depression^{6–10}. 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 retrieval^{5,11–14}.

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

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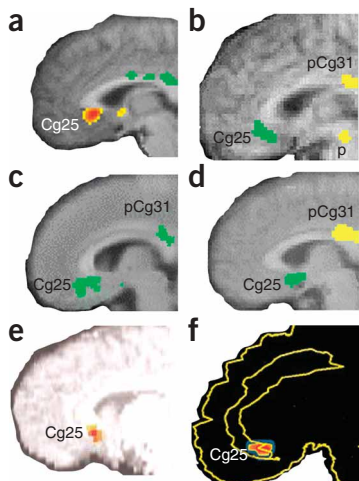


Figure 1 Subgenual cingulate cortex activation across studies. (a) Transient sadness in healthy volunteers increases activity (red) in Cg25 (arrow) measured with positron emission tomography (PET) (from ref. 12. Reprinted with permission from the *American Journal of Psychiatry*, copyright 1999, American 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.).

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).

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).

A genetic polymorphism has repeatedly been implicated in gene by environment interactions for disorders of emotional dysregulation: the serotonin promoter polymorphism 5-HTTLPR (see review by Canli and Lesch¹⁸ in this issue). Carriers of the risk-conferring 5-HTTLPR polymorphism have reduced gray matter volume in the perigenulate region surrounding Cg25 as well as in the amygdala¹⁹ (Fig. 2d,f). Additionally, these areas are tightly coupled with the processing of negative affect in long-allele carriers, whereas they are functionally

uncoupled in the at-risk short-allele carriers. Together these data indicate that prefrontal-limbic circuits, the Cg25 and amygdala areas in particular, may be critically involved in emotional processing and regulation in mood and anxiety disorders.

Neurostimulation therapies modulate dysregulated circuits

Several somatic therapies, available or under investigation, may modulate this disrupted circuit activity. Vagus nerve stimulation therapy (VNS) is approved by the FDA for treatment of medication-resistant depression and was approved earlier for the treatment of epilepsy²⁰. Although the approach seems to be tolerable for long-term use in patients, and relatively few patients have relapsed in the early depression trials, long-term efficacy in refractory patients still remains to be demonstrated.

The initial reasoning behind the use of VNS followed from its apparent effects of elevating mood in patients with epilepsy²⁰, combined with evidence that VNS affects limbic activity in neuroimaging studies²¹. Furthermore, VNS alters concentrations of serotonin, norepinephrine, GABA and glutamate within the brain^{22–24}, suggesting that VNS may help correct dysfunctional neurotransmitter modulatory circuits in patients with depression.

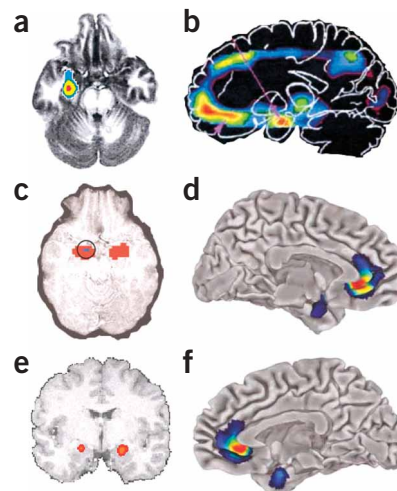


Figure 2 Amygdala activation across studies. (a) Responders compared with nonresponders showed greater decreases (red to blue indicates greatest to least decrease) in anxiety-induced amygdala activation in both citalopram and CBT treatment for social phobia (ref. 16. Reprinted from *Archives of General 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 amygdala 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.).

