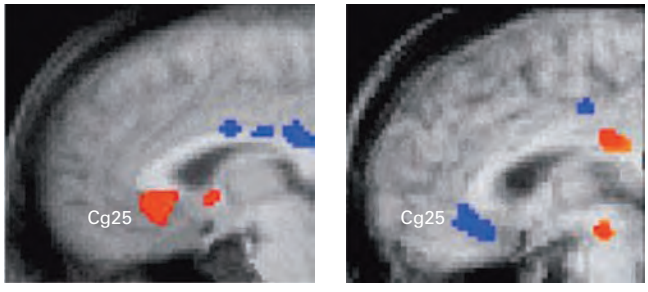
have shown abnormal functioning of the rostral and ventral subdivisions of the anterior cingulate cortex (ACC), a region of prefrontal cortex that participates in the emotional salience network. The rostral and ventral ACC have extensive connections with the hippocampus, amygdala, orbital prefrontal cortex, anterior insula, and nucleus accumbens and are involved in the integration of emotion, cognition, and autonomic nervous system function. The caudal subdivision of the ACC is involved in cognitive processes involved in control of behavior; it has connections with dorsal regions of the prefrontal cortex, secondary motor cortex, and posterior cingulate cortex.

Although abnormal function in both subdivisions of the ACC has been observed in depressive episodes, the most consistent abnormality observed in major depression and in the depressed phase of bipolar disorder is increased activity in the rostral and ventral subdivisions, especially in the subgenual region ventral to the genu (or "knee") of the corpus callosum. In a study using positron emission tomography, effective treatment of major depression with selective serotonin reuptake inhibitor antidepressants was correlated with decreased activity in the rostral ACC, whereas self-induced sadness in healthy subjects increased activity (Figure 61–4). Based on such studies, the rostral anterior (subgenual) cingulate cortex has been used as a target for electrode placement in deep brain stimulation for treatment-resistant major depression, which is operationally defined as depressive illness that has been unresponsive to antidepressant medication and psychotherapy.

Functional abnormalities of brain reward circuitry may also play a role in the symptoms of mood disorders. The reward circuitry comprises the dopaminergic projections from the ventral tegmental area of the midbrain to forebrain targets, including the nucleus accumbens, habenula, prefrontal cortex, hippocampus, and amygdala (Chapter 43). Under normal conditions, these pathways are involved in the valuation of rewards (eg, palatable food, sexual activity, and social interactions) and in motivating the necessary behavior to obtain them. Reward processing appears to be abnormal in depression, based on such symptoms as decreased interest in previously pleasurable activities, decreased motivation, and, when depression is severe, the inability to experience pleasure (anhedonia). Although less well studied, reward processing is also likely abnormal in mania, which is characterized by excessive engagement in goal-directed behaviors, even when they are maladaptive, such as uncontrolled spending, dangerous drug use, and promiscuous sexual activity.

In a recent analysis of resting-state fMRI, data showed that patients with major depression could be stratified based on connectivity patterns that correlated with their degree of anhedonia and anxiety. However, although modulation of the reward circuitry has been considered as a possible treatment for major depression, it has proven difficult in practice. For example, drugs known to activate this circuitry by



Induced sadness in healthy subjects | Depression recovery with SSRI

Figure 61–4 Activity in the rostral anterior (subgenual) cingulate cortex is increased by sadness and decreased by successful treatment of major depression with an antidepressant. (Reproduced, with permission, from Mayberg et al. 1997.)

Left. Healthy volunteers provided a script of their saddest memory that was later used to generate transient sadness while undergoing positron emission tomography (PET). The rostral anterior cingulate cortex was activated (**red** pseudo-color in the sagittal section of the human brain) was activated when the sad story was read. Cg25 is an alternative nomenclature for the cingulate gyrus, Brodmann area 25. The PET ligand was oxygen-15–labeled water, used to measure cerebral blood flow as a proxy for brain activity.

Right. Elevated metabolism in the rostral anterior cingulate cortex was confirmed in subjects with major depression. Following successful treatment with a selective serotonin reuptake inhibitor (SSRI) antidepressant, brain activity in Cg25 decreased (**blue** pseudo-color in the sagittal section of the human brain). The PET ligand was 2-deoxyglucose, used to measure cerebral metabolism as a proxy for brain activity.