

# Mood disorders and abnormal cingulate cortex

Ray J. Dolan

**M**ood disorders, in their diverse manifestations, are prevalent sources of social morbidity. An important goal in clinical neuroscience is to provide a neurobiological account of these and other related psychiatric disorders. Therefore, the recent report of a focal deficit of the subgenual cingulate cortex in patients with mood disorder is of considerable interest and importance<sup>1</sup>. In considering these findings, it is important to be aware of conceptual difficulties relating to the interpretation of neurobiological findings in psychiatric populations.

One difficulty is the specification of the very object of study. Nosological entities, such as major depression, are derived largely from descriptive psychopathology and, characteristically, they present with a highly variable repertoire of symptoms. The likelihood that such an arbitrarily defined entity will have a unique neurobiology is open to serious question. Nevertheless, this assumption is implicit in much of the research in the field. Clearly, Drevets *et al.* were aware of this difficulty and restricted their study to patients with either bipolar disorder (that is, patients with episodes of mania and depression) or patients with unipolar depression with a strong family history. In other words, the potentially confounding effect of biological heterogeneity was reduced by limiting the study to rigorously defined patient groups.

Even when adopting rigorous selection criteria, there is still the possibility that it is symptoms or symptom clusters, and the abnormal psychological processing that they reflect, that will relate best to underlying neurobiology. Using a symptom-based approach, distinct profiles of neural activity have been described in association with the common patterns of symptom expression in both depression and schizophrenia<sup>2,3</sup>. It would be intriguing to know whether the patients in the study of Drevets *et al.* shared common symptom profiles. This could provide a clue to the psychological processes mediated by the focal abnormality described in their patients. Symptoms are, in principle, susceptible to a cognitive analysis that can point to the relevant underlying processes. As an example, hallucinations are proposed to represent a failure of normal self-monitoring<sup>4</sup>.

However, an approach to complex disorders based on symptoms does not totally rule out the possibility that a core neurobiological deficit with variable anatomical expression may account for distinct symptom profiles.

Psychological theory provides a framework for explaining symptoms and disease processes. In the study of memory the impact of theory, where memory has been fractionated with respect to conscious access, temporal duration and functional role, is self evident. Emotion has proved more impenetrable both from the perspective of psychological theory and neurobiology. Emotional regulation is usually ascribed to the limbic system. This conceptualization is now seen as having fostered an unnecessary dichotomy between cognition and emotion. At a more fundamental level, no consensus exists as to the core anatomical structures that constitute the limbic system. Many researchers now argue that the concept of emotion is too general and suggest an analysis akin to that developed in the understanding of memory function. A notable effort to fractionate emotion can be found in the work of LeDoux, who has elaborated a neurobiological model of fear processing involving structures such as the thalamus and amygdala<sup>5</sup>. Therefore, an emerging perspective suggests a focus on discrete emotions.

The precise deficit highlighted by Drevets *et al.* was a functional and morphometric abnormality, localized to a region of the anterior cingulate cortex just below the genu of the corpus callosum in patients with distinct types of mood disorder<sup>1</sup>. The deficit involved decreased resting state measures of blood flow and glucose metabolism in addition to decreased cortical volume in the same region. A small sample of bipolar patients had increased glucose metabolism in this region while in a manic phase of their illness. What makes these findings compelling is that they were replicated over a number of different subject groups.

These findings are both important and exciting and add to other evidence indicating abnormal cingulate function in mood disorders. A central role for the cingulate in mediating emotional experience was first postulated on anatomical grounds by Papez<sup>6</sup>. A more

dorsal cingulate region has been highlighted in earlier functional neuroimaging studies of mood disorder<sup>7</sup>. Drevets and colleagues note that this region has extensive anatomical connections with other structures implicated in emotional behaviour, including the amygdala, as well as with the sites of origin of brainstem ascending neuromodulatory systems. As already indicated, the question left unanswered is what psychological processes are mediated by this region. Some clues are provided by recent neuropsychological and functional neuroimaging studies.

Damasio, and colleagues have shown that a ventromedial prefrontal region, which overlaps the subgenual cingulate, is important in evaluative aspects of behaviour, particularly with respect to future outcomes of current behavioural repertoires<sup>8</sup>. Rolls *et al.* have highlighted the role of a similar region in emotional learning mechanisms<sup>9</sup>. Elliott and colleagues, in recent functional neuroimaging experiments, have shown that a similar region is activated when subjects monitor performance feedback<sup>10</sup>. The suggestion from these studies is that this region has an evaluative role with respect to whether present or future behaviour will lead to reward or punishment. If this is the case, the question raised is whether these findings can be reconciled with pathology of this region in mood disorders? While speculative, a deficit in evaluative processing could lead to an absence of behavioural incentive as well as the apathy and anhedonia which are core features of mood disorders.

The message from the study of Drevets *et al.* is that this and related cingulate regions may be critical in emotion control and, as a consequence, should be an important target for complementary forms of research, such as histopathological and neurochemical assessments. A functional analysis of its role in normal cognition is clearly of equal importance. For many years psychiatric research existed in a vacuum with respect to the rest of neuroscience. It is now clear that progress in understanding mental illness is critically dependent upon on-going interactions with neuroscience. It is equally clear that, more than any other investigative modality, functional neuroimaging has

*R.J. Dolan is at the Wellcome Department of Cognitive Neurology, Queen Square, London, UK WC1N 3BG.*

tel: +44 171 833 7472  
fax: +44 171 813 1420  
e-mail: rdolan@fil.ion.ucl.ac.uk

contributed to fostering and sustaining these interactions.

References

1 Drevets, W.C. et al. (1997) Subgenual prefrontal cortex abnormalities in mood disorders *Nature* 386, 824-827  
 2 Liddle, P. et al. (1992) Patterns of cerebral blood flow in schizophrenia *Br. J. Psychiatry* 160, 179-186  
 3 Bench, C.J. et al. (1993) Regional cerebral blood flow (rCBF) in depression measured by

positron emission tomography (PET): the relationship with clinical dimensions *Psychol. Med.* 23, 579-590

4 Frith, C.D. (1987) The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action *Psychol. Med.* 17, 631-648  
 5 LeDoux, J. (1996) *The Emotional Brain*, Simon & Schuster  
 6 Papez, J.W. (1937) A proposed mechanism of emotion *Arch. Neurol. Psychiatry* 79, 217-224  
 7 Bench, C.J. et al. (1992) The anatomy of melancholia. Abnormalities of regional

cerebral blood flow in major depression *Psychol. Med.* 22, 607-615

8 Damasio, A.R. (1995) *Descartes' Error: Emotion, Reason and the Human Brain* Macmillan Press  
 9 Rolls, E.T. et al. (1994) Emotion related learning in patients with social and emotional changes associated with frontal lobe damage *J. Neurol. Neurosurg. Psychiatry* 57, 1518-1524  
 10 Elliott, R., Frith, C.D. and Dolan, R.J. Differential neural response to positive and negative feedback in planning and guessing tasks *Neuropsychologia* (in press)

## Response from Drevets

Clinical neuroscience investigations into the biology of mood disorders struggle with the limitation that psychiatric nosology remains at a syndromic level, in which behavioral signs and symptoms, rather than pathophysiology, define diagnostic entities. Consequently, specific links between syndrome and pathophysiology may not exist, and syndromes such as major depressive disorder are expected to encompass etiopathologically heterogeneous groups of disorders<sup>1</sup>. Addressing this limitation in research aimed at elucidating the neuroimaging correlates of psychiatric syndromes and the cognitive-behavioral correlates of neuroimaging abnormalities is the subject of Dolan's insightful and eloquent commentary<sup>2</sup>.

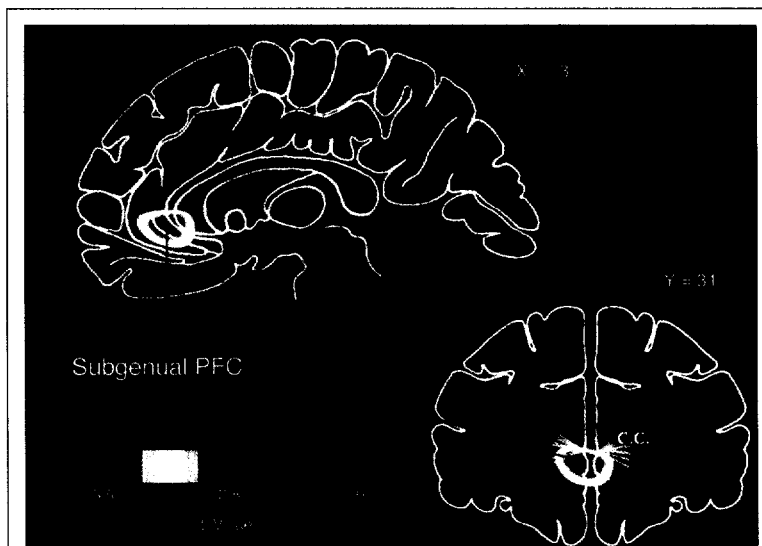
As summarized by Dolan, we recently reported that positron emission tomographic (PET) measures of regional blood flow and glucose metabolism and magnetic resonance imaging (MRI)-based measures of gray matter volume are abnormally reduced in the subgenual prefrontal cortex (PFC) in depressed subjects with familial major depressive disorder ('unipolar depression') and bipolar disorder ('manic-depressive illness')<sup>3</sup> (Fig. 1). This cortex is situated on the anterior cingulate gyrus lying ventral to the genu of the corpus callosum and, as such, may also be described as the subgenual or subcallosal anterior cingulate cortex. These data complement other evidence implicating anterior cingulate function in normal and pathological emotional states<sup>2</sup>.

In considering approaches for further characterizing the nature of these neuroimaging abnormalities, Dolan proposes that the neurobiological deficits that they reflect may correlate more closely with a symptom cluster than with a discrete clinical category. Application of this 'symptom-based approach' is exemplified by a seminal study in which he and his colleagues linked the abnormal blood flow reduction found in the dorsolateral PFC in both major depression and schizophrenia to ratings of impoverished speech

(presumably reflecting psychomotor slowing and psychomotor impoverishment in the depressed and schizophrenic samples, respectively)<sup>4</sup>. Dolan queries whether the mood disordered groups we studied may also have common symptom profiles that correlate with the anatomical abnormality in the subgenual PFC.

Dolan further proposes that, based upon evidence that this region plays an

evaluative role in normal cognitive processing, dysfunction within the subgenual PFC may be associated specifically with a 'deficit in evaluative processing' that leads to the pathological emotional features of mood disorders. The results of lesion analyses, electrophysiological studies and other functional imaging data (including studies performed by Dolan and his colleagues) converge to suggest that the subgenual PFC is part of a ventromedial prefrontal cortical system for evaluating the outcome of behavior in terms of punishment and reward<sup>5-7</sup>. Damasio hypothesized that this evaluative process



**Fig. 1** Decreased blood flow in the prefrontal cortex of depressed subjects. The area of reduced glucose metabolism in the subgenual portion of the anterior cingulate gyrus (subgenual PFC) is illustrated in an image composed of voxel t-values comparing depressives and controls. The image was produced by a voxel-by-voxel computation of the unpaired t-statistic to identify inherent differences in metabolism between a sample of familial bipolar and unipolar depressives (n = 17) and a sample of healthy control subjects (n = 12). This t-image was generated *post hoc* to provide optimal localization of the metabolic abnormality identified using other techniques (which included comparisons involving independent subject samples). The negative t-values, shown in a coronal section at 31 mm anterior to the anterior commissure (Y = 31 mm) and a sagittal section at 3 mm left of the midline (X = -3 mm), correspond to areas where metabolism is decreased in the depressive subjects relative to controls. The area of reduced metabolism in the subgenual PFC is at least partly accounted for by a corresponding reduction in cortex, as MRI-based morphometric measures in the same subjects showed that the left subgenual PFC grey matter volume is reduced in both bipolar disordered and unipolar depressed groups relative to the control group. The primary PET images from which the t-image was generated were stereotaxically transformed into the coordinate system of Talairach and Tournoux<sup>18</sup>, from which the corresponding atlas outlines are shown. Anterior is to the left and dorsal is towards the top of the page. Reproduced, with permission, from Ref. 3.

W.C. Drevets is at  
the University of  
Pittsburgh Medical  
Center, PET Center,  
B-938 PUH,  
200 Lothrop Street,  
Pittsburgh,  
PA 15213, USA.

tel: +1 412 647 0736  
 fax: +1 412 647 0700  
 e-mail: drevets@pet.  
 upmc.edu