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Well-being and affective style: neural substrates and biobehavioural correlates

Richard J. Davidson

Laboratory for Affective Neuroscience, W. M. Keck Laboratory for Functional Brain Imaging and Behavior, University of Wisconsin-Madison, 1202 West Johnson Street, Madison, WI 53706, USA (*rjdavids@wisc.edu*)

One of the most salient features of emotion is the pronounced variability among individuals in their reactions to emotional incentives and in their dispositional mood. Collectively, these individual differences have been described as affective style. Recent research has begun to dissect the constituents of affective style. The search for these components is guided by the neural systems that instantiate emotion and emotion regulation. In this article, this body of research and theory is applied specifically to positive affect and well-being. The central substrates and peripheral biological correlates of well-being are described. A resilient affective style is associated with high levels of left prefrontal activation, effective modulation of activation in the amygdala and fast recovery in response to negative and stressful events. In peripheral biology, these central patterns are associated with lower levels of basal cortisol and with higher levels of antibody titres to influenza vaccine. The article concludes with a consideration of whether these patterns of central and peripheral biology can be modified by training and shifted toward a more salubrious direction.

Keywords: affective neuroscience; resilience; prefrontal cortex; brain asymmetry; emotion regulation; affective style

1. INTRODUCTION

One of the most salient characteristics of emotion is the extraordinary heterogeneity in how different individuals respond to the same emotionally provocative challenge. Such differences in patterns of emotional reactivity play a crucial role in shaping variations in well-being. Although individual differences in emotion processing can be found at many levels of phylogeny, they are particularly pronounced in primates and probably are most extreme in humans. A number of evolutionary theorists have speculated on the adaptive significance of such individual differences (Wilson 1994). Although these arguments have never been applied to the domain of emotion and affective style, it is not difficult to develop hypotheses about how such differences might provide advantages to individuals living in groups. However, rather than focus on the distal causes of such individual differences which are so difficult to subject to rigorous test, I wish only to call attention to the possibility that variability in characteristics such as 'fearfulness' or 'cheerfulness' might provide some adaptive benefit to individuals living together in groups. Instead, this article examines the proximal mechanisms that underlie such individual differences, with a focus on well-being. The central substrates of individual differences in components of well-being will be described. The possible influence of the central circuitry of emotion on peripheral biological indices that are relevant to physical health and illness will also be considered. It is helpful to contrast well-being with specific types of psychopathology that involve dysfunctions in the circuitry of adaptive emotional responding. Accordingly, some mention of recent work on the neurobiology of mood and anxiety disorders will be made. Finally, plasticity in the underlying brain circuitry that instantiates affective style will be described and its role in promoting resilience will be considered.

Affective style refers to consistent individual differences in emotional reactivity and regulation (see Davidson 1998*a*; Davidson *et al*. 2000*a*,*b*). It is a phrase that is meant to capture a broad array of processes that, either singly or in combination, modulate an individual's response to emotional challenges, dispositional mood and affect-relevant cognitive processes. Affective style can refer to valence-specific features of emotional reactivity or mood, or it can refer to discrete emotion-specific features. Both levels of analysis are equally valid and the choice of level should be dictated by the question posed.

Rapid developments in our understanding of emotion, mood and affective style have come from the study of the neural substrates of these phenomena. The identification of the brain circuitry responsible for different aspects of affective processing has helped to parse the domain of emotion into more elementary constituents in a manner similar to that found in cognitive neuroscience, where an appeal to the brain has facilitated the rapid development of theory and data on the subcomponents of various cognitive processes (e.g. Kosslyn & Koenig 1992).

This article will highlight some of the advances that have been made in our understanding of the brain mechanisms that underlie affective style. These advances have emerged from three major sources: studies of patients with discrete lesions of the brain; neuroimaging studies of normal indivi-

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duals; and studies of pathologies of brain function in patients with various psychiatric and neurological disorders that involve abnormalities in emotion. I will use the material on pathology to help to identify the neural circuitry crucial to certain forms of positive affect so that we can begin to place well-being squarely within a neurobiological framework.

Both lesion and neuroimaging studies provide information primarily on the 'where' question; that is, where in the brain are computations related to specific aspects of affective processing occurring. It is important at the outset to consider both the utility of knowing 'where' and how such information can provide insight into the 'how' question; that is, how might a particular part of the brain instantiate a specific process that is essential to affective style. The brain sciences are now replete with information on the essential nature of specific types of information processing in different regions of the brain. For example, there is evidence to suggest that the DLPFC is important for maintaining a representation of information online in the absence of immediate cues. The neurophysiological basis of this type of information processing has been actively studied in the animal laboratory (e.g. Goldman-Rakic 1996, 2000). If this region of the brain is activated at certain times in the stream of affective information processing, we can develop hypotheses on the basis of extant work about what this territory of PFC might be doing during the affective behaviour and how it might be doing it. A related consideration is the network of anatomical connectivity to and from a particular brain region. From a consideration of connectivity, insights may be gleaned as to how a particular brain region might react during a particular form of emotional processing. For example, we know that regions of the amygdala have extensive connectivity with cortical territories that can become activated following activation of the amygdala. In this way, the amygdala can issue a cortical call for further processing in response to potentially threatening stimuli, which must be processed further to assess danger. Other regions of the amygdala have extensive connections to limbic and brainstem circuits that can modulate behavioural and autonomic outflow. Adjustments in autonomic responses and action tendencies are typical components of emotion.

2. CONCEPTUAL AND METHODOLOGICAL CONSIDERATIONS IN THE STUDY OF AFFECTIVE STYLE

Current research on well-being is based largely on the use of self-report measures to make inferences about variation among individuals in type and magnitude of well-being. One important component of neurobiological research on well-being is to begin to dissect well-being into more specific constituents that may underlie the coarse phenomenological descriptions provided by subjects. In addition, research on the neural correlates of well-being may provide an independent biological measure sensitive to variations in well-being that are not subject to the kinds of reporting and judgemental biases commonly found in the self-report measures. For example, researchers have found that questions that precede items asking about well-being can influence a subject's report of well-being. Variations in the weather can similarly affect such reports. These examples illustrate the fact that when subjects are queried about global well-being, they frequently use convenient heuristics to answer such questions and typically do not engage in a systematic integration of utility values over time. It may be that certain parameters of brain function are better repositories of the cumulative experiences that inevitably shape well-being. At the present point in the development of this science, these are mere speculations in search of evidence but the time is ripe for such evidence to be gathered.

The status of research on well-being is now at a point occupied about a decade ago or more by research on mood and anxiety disorders, though it continues to suffer from some of the same problems. Mood and anxiety disorders are generally conceptualized as being caused, or at least accompanied by, dysfunctions of emotion. However, what specific affective process is dysfunctional is rarely, if ever, delineated, and nosological schemes for categorizing these disorders do not rely upon the specific nature of the affective dysfunction in question, but rather are based upon phenomenological description. Research in my laboratory over the past 15 years has been predicated on the view that more meaningful and rapid progress in understanding the brain bases of mood and anxiety disorders can be achieved if we move to an intermediate level of description that penetrates below the categorical, phenomenologically based classifications of the diagnostic and statistical manual (DSM) and seeks to characterize the specific nature of the affective styles that are associated with vulnerability to these forms of psychopathology.

Many of the parameters of affective style, such as the threshold to respond, magnitude of response, latency to peak of response and recovery function, are features that are often opaque to conscious report, though they may influence the subjective experience of emotion. These parameters of responding can be measured in many different response systems including both central and peripheral systems. For example, magnitude of response can be measured in a peripheral measure such as the emotion-modulated startle (Lang 1995) or in a central measure such as activation in the amygdala assessed with fMRI. The extent to which coherence across response systems in these parameters is present has not yet been systematically addressed. In previous work, we have argued that variations in some of these parameters in particular response systems are especially relevant to vulnerability to mood, anxiety and other disorders and also to resilience (e.g. Davidson 2000*a*,*b*). One of the important developments in emotion research in general, and in affective neuroscience in particular, is the capacity to objectively measure these parameters of responding. For example, in several studies we have used the emotion-modulated startle to capture the time-course of valence-specific emotion responding (Larson *et al.* 1998; Jackson *et al.* 2000). The startle reflex is controlled by a brainstem circuit that is influenced by activity in forebrain structures. Davis (1992) elegantly dissected the circuitry through which the magnitude of this reflex is modulated during the arousal of fear in rodents. He demonstrated that it is via a descending pathway from the central nucleus of the amygdala to the nucleus pontine reticularis in the brainstem that the magnitude of startle is enhanced in response to a conditioned fear cue. Lesions of the central nucleus of the amygdala abolish the fear potentiation of the startle but do not affect the magnitude

of the baseline startle. Lang and his colleagues (Vrana *et al.* 1988) were the first to show systematically that in humans, the same basic phenomenon can be produced. They took advantage of the fact that brief acoustic noise bursts produce the eyeblink component of the startle and little else, thus enabling their presentation as innocuous stimuli in the background. By measuring electromyographic activity from the orbicularis oculi muscle with two miniature electrodes under one eye, they were able to quantify the strength of the blink response and show that the magnitude of the blink was greater when subjects were presented with unpleasant pictures in the foreground, compared with the presentation of neutral pictures. Moreover, when subjects were exposed to positive stimuli, the magnitude of startle was actually attenuated relative to a neutral condition (Vrana *et al.* 1988). This same basic effect has now been reported with many different types of foreground stimuli in several modalities (see Lang (1995) for a review).

We have exploited the emotion-modulated startle to begin to characterize the time-course of affective responding, or what I have referred to as affective chronometry (Davidson 1998*a*). By inserting acoustic noise probes at different latencies before and after a critical emotional stimulus is presented, both the anticipatory limb and the recovery limb of the response can be measured. By using paradigms in the MRI scanner that were first studied in the psychophysiology laboratory, the neural circuitry underlying the different phases of affective processing can be interrogated with fMRI. Our current work in this area has emphasized the importance of the recovery function following negative events for vulnerability to certain forms of psychopathology as well as for resilience. We have argued that the failure to recover rapidly following a negative event can be a crucial ingredient of vulnerability to both anxiety and mood disorders, particularly when such a style is combined with frequent exposure to negative events over a sustained period of time. The failure to recover adequately would result in sustained elevations in multiple systems that are activated in response to negative events. By contrast, the capacity for rapid recovery following negative events may define an important ingredient of resilience. We have defined resilience as the maintenance of high levels of positive affect and well-being in the face of significant adversity. It is not that resilient individuals never experience negative affect, but rather that the negative affect does not persist. Such individuals are able to profit from the information provided by the negative affect and their capacity for 'meaning making' in response to such events may be part and parcel of their ability to show rapid decrements in various biological systems following exposure to a negative or stressful event (see Giese-Davis & Spiegel 2003).

3. NEURAL SUBSTRATES OF EMOTION AND AFFECTIVE STYLE

In the following three sections, a brief overview is provided of core components of the circuitry that instantiates some important aspects of emotion and affective style, with an emphasis on PFC and the amygdala. It is not meant to be an exhaustive review, but rather will present selected highlights to illustrate some of the key advances that have been made in the recent past.

Emotion and affective style are governed by a circuit that includes the following structures, and probably also others: DLPFC, vmPFC, OFC, amygdala, hippocampus, ACC and insular cortex. It is argued that different subprocesses are instantiated in each of these structures, and that they normally work together to process, generate and regulate emotional information and emotional behaviour.

4. PREFRONTAL CORTEX

A large corpus of data at both the animal and human levels implicate various sectors of the PFC in emotion. The PFC is not a homogeneous zone of tissue but, rather, has been differentiated on the basis of both cytoarchitectonic and functional considerations. The three subdivisions of the primate PFC that have been consistently distinguished include the DLPFC, vmPFC and OFC. In addition, there appear to be important functional differences between the left and right sides within some of these sectors.

The case for the differential importance of left and right PFC sectors for emotional processing was first made systematically in a series of studies on patients with unilateral cortical damage (Gainotti 1972; Sackeim *et al.* 1982; Robinson *et al.* 1984). Each of these studies compared the mood of patients with unilateral left- or right-sided brain damage and found a greater incidence of depressive symptoms following left-sided damage. In most cases, the damage was fairly substantial, and probably included more than one sector of PFC and often also included other brain regions. The general interpretation that has been placed upon these studies is that depressive symptoms are increased following left-sided anterior PFC damage because this brain territory participates in certain forms of positive affect and when damaged leads to deficits in the capacity to experience positive affect, a hallmark feature of depression (Watson *et al.* 1995). It should be noted that not all studies support this conclusion. In a recent meta-analysis of lesion studies, Carson *et al.* (2000) failed to find support for this hypothesis. Davidson (1993) has previously reviewed many of these studies and has addressed a number of critical methodological and conceptual concerns in this literature. The most important of these issues is that according to the diathesis-stress model of anterior activation asymmetry proposed by Davidson (1995, 1998*b*) and colleagues (Henriques & Davidson 1991), individual differences in anterior activation asymmetry, whether lesion-induced or functional, represent a diathesis. As such, they alter the probability that specific forms of emotional reactions will occur in response to the requisite environmental challenge. In the absence of such a challenge, the pattern of asymmetric activation will simply reflect a propensity but will not necessarily culminate in differences in mood or symptoms. In a study with the largest sample size to date ($n = 193$) for a study of mood sequelae in patients with unilateral lesions, Morris *et al.* (1996) found that among stroke patients, it was only in those with small lesions that the relation between left PFC damage and depressive symptoms was observed. It is likely that larger lesions intrude on other brain territories and mask the relation between left PFC damage and depression.

A growing corpus of evidence in normal intact humans is consistent with the findings derived from the lesion evi-

dence. Davidson and his colleagues have reported that induced positive and negative affective states shift the asymmetry in prefrontal brain electrical activity in lawful ways. For example, film-induced negative affect increases relative right-sided prefrontal and anterior temporal activation (Davidson *et al.* 1990) whereas induced positive affect elicits an opposite pattern of asymmetric activation. Similar findings have been obtained by others (e.g. Ahern & Schwartz 1985; Jones & Fox 1992).

Using a cued reaction time paradigm with monetary incentives, Sobotka *et al.* (1992) first reported that in the anticipatory interval between the cue and the response, EEG differences were observed between reward and punishment trials with greater left-sided frontal activation observed in response to the former compared with the latter trial type. In a more recent study, Miller & Tomarken (2001) replicated and extended this basic effect and, very recently, we (Shackman *et al.* 2003) replicated the Miller and Tomarken effect, showing that reward trials produced significantly greater left prefrontal activation in the anticipatory interval compared with no-incentive trials. Moreover, subjects in this study also participated in a functional MRI study using the identical paradigm and we found that those subjects who showed a robust EEG difference between reward and no-incentive trials also showed a significant difference in asymmetric prefrontal signal change in response to these conditions, with greater left-sided PFC activation in the reward compared with the no-incentive condition. In addition to these studies that manipulated phasic emotion, we will review in § 7 a body of evidence that supports the conclusion that individual differences in baseline levels of asymmetric activation in these brain regions are lawfully related to variations in dispositional affective style. Using an extended picture presentation paradigm designed to evoke longer-duration changes in mood (Sutton *et al.* 1997*a*), we measured regional glucose metabolism with PET to ascertain whether similar patterns of anterior asymmetry would be present using this very different and more precise method to assess regional brain activity (Sutton *et al.* 1997*b*). During the production of negative affect, we observed right-sided increases in metabolic rate in anterior orbital, inferior frontal, middle and superior frontal gyri, whereas the production of positive affect was associated with a pattern of predominantly left-sided metabolic increases in the pre- and post-central gyri. Using PET to measure regional cerebral blood flow, Hugdahl and his colleagues (Hugdahl *et al.* 1995; Hugdahl 1998) reported a widespread zone of increased blood flow in the right PFC including the orbitofrontal and dorsolateral cortices and inferior and superior cortices during the extinction phase after aversive learning had occurred compared with the habituation phase, before the presentation of the experimental contingencies.

Other investigators have used clinical groups to induce a stronger form of negative affect in the laboratory than is possible with normal controls. One common strategy for evoking anxiety among anxious patients in the laboratory is to present them with specific types of stimuli that are known to provoke their anxiety (e.g. pictures of spiders for spider phobics; making a public speech for social phobics). Davidson *et al.* (2000*c*), in a study using brain electrical activity measures, have recently found that when social phobics anticipate making a public speech, they show large increases in right-sided anterior activation. Pooling across data from three separate anxiety disordered groups that were studied with positron emission tomography, Rauch *et al.* (1997) found two regions of the PFC that were consistently activated across groups: the right inferior PFC and right medial orbital PFC.

The vmPFC has been implicated in the anticipation of future positive and negative affective consequences. Bechara *et al.* (1994) have reported that patients with bilateral lesions of the vmPFC have difficulty in anticipating future positive or negative consequences, although immediately available rewards and punishments do influence their behaviour. Such patients show decreased levels of electrodermal activity in anticipation of a risky choice compared with controls, while controls exhibit such autonomic change before they explicitly know that it is a risky choice (Bechara *et al.* 1996, 1997, 1999).

The findings from the lesion method when effects of small unilateral lesions are examined, and from neuroimaging studies in normal subjects and patients with anxiety disorders, converge on the conclusion that increases in right-sided activation in various sectors of the PFC are associated with increased negative affect. Less evidence is available for the domain of positive affect, in part because positive affect is much harder to elicit in the laboratory and because of the negativity bias (see Taylor 1991; Cacioppo & Gardner 1999). This latter phenomenon refers to the general tendency of organisms to react more strongly to negative compared with positive stimuli, perhaps as a consequence of evolutionary pressures to avoid harm. The findings from Bechara *et al*. on the effects of vmPFC lesions on the anticipation of future positive *and* negative affective consequences are based upon studies of patients with bilateral lesions. It will be of great interest in the future to examine patients with unilateral ventromedial lesions to ascertain whether valence-dependent asymmetric effects are also present for this sector of PFC.

Systematic studies designed to disentangle the specific role played by various sectors of the PFC in emotion are lacking. Many theoretical accounts of emotion assign it an important role in guiding action and organizing behaviour towards the acquisition of motivationally significant goals (e.g. Frijda 1994; Levenson 1994). This process requires that the organism have some means of representing affect in the absence of immediately present rewards and punishments and other affective incentives. Such a process may be conceptualized as a form of affective working memory. It is probable that the PFC plays a key role in this process (see Watanabe 1996). Damage to certain sectors of the PFC impair an individual's capacity to anticipate future affective outcomes and consequently result in an inability to guide behaviour in an adaptive fashion. Such damage is unlikely to disrupt an individual's response to immediate cues for reward and punishment, only the anticipation before and maintenance after an affective cue is presented. This proposal can be tested using current neuroimaging methods (e.g. fMRI) but has not yet been rigorously evaluated. With regard to the different functional roles of the dorsolateral, orbitofrontal and ventromedial sectors of the PFC, Davidson & Irwin (1999) suggested, on the basis of considering both human and animal studies, that the ventromedial sector is most probably involved in the representation of elementary positive and negative affective

states in the absence of immediately present incentives. The orbitofrontal sector has most firmly been linked to rapid learning and unlearning of stimulus–incentive associations and has been particularly implicated in reversal learning (Rolls 1999). As such, the orbitofrontal sector is probably key to understanding aspects of emotion regulation (see Davidson *et al.* 2000*d*). One critical component of emotion regulation is the relearning of stimulus–incentive associations that might have been previously maladaptive, a process probably requiring the OFC. The dorsolateral sector is most directly involved in the representation of goal states toward which more elementary positive and negative states are directed.

5. AMYGDALA

A large corpus of research at both the animal and human levels has established the importance of the amygdala for emotional processes (Aggleton 1993; LeDoux 1996; Cahill & McGaugh 1998; Davis & Whalen 2001). Since many reviews of the animal literature have appeared recently, a detailed description of these studies will not be presented here. LeDoux and his colleagues have marshalled a large corpus of compelling evidence to suggest that the amygdala is necessary for the establishment of conditioned fear. Whether the amygdala is necessary for the expression of that fear following learning, and whether the amygdala is the actual locus of where the learned information is stored, is still a matter of some controversy (see Cahill *et al*. 1999; Fanselow & LeDoux 1999). The classic view of amygdala damage in non-human primates resulting in major affective disturbances as expressed in the Kluver–Bucy syndrome, where the animal exhibits abnormal approach, hyperorality and sexuality, and little fear, is now thought to be a function of damage elsewhere in the medial temporal lobe. When very selective excitotoxic lesions of the amygdala are made that preserve fibres of passage, nothing resembling the Kluver–Bucy syndrome is observed (Kalin *et al.* 2001). The upshot of this diverse array of findings is to suggest a more limited role for the amygdala in certain forms of emotional learning, though the human data imply a more heterogeneous contribution.

Although the number of patients with discrete lesions of the amygdala is small, they have provided unique information on the role of this structure in emotional processing. Several studies have now reported specific impairments in the recognition of facial expressions of fear in patients with restricted amygdala damage (Adolphs *et al.* 1995, 1996; Calder *et al.* 1996; Broks *et al.* 1998). Recognition of facial signs of other emotions was found to be intact. In a study that required subjects to make judgements of trustworthiness and approachability of unfamiliar adults from facial photographs, patients with bilateral amygdala damage judged the unfamiliar individuals to be more approachable and trustworthy than did control subjects (Adolphs *et al.* 1998). Recognition of vocal signs of fear and anger was found to be impaired in a patient with bilateral amygdala damage (Scott *et al.* 1997), suggesting that this deficit is not restricted to facial expressions. Other researchers (Bechara *et al.* 1995) have demonstrated that aversive autonomic conditioning is impaired in a patient with amygdala damage despite the fact that the patient showed normal declarative knowledge of the conditioning contingencies. Collectively, these findings from patients with selective bilateral destruction of the amygdala suggest specific impairments on tasks that tap aspects of negative emotion processing. Most of the studies have focused on the perceptual side, where the data clearly show the amygdala to be important for the recognition of cues of threat or danger. The conditioning data also indicate that the amygdala may be necessary for acquiring new implicit autonomic learning of stimulus–punishment contingencies. In one of the few studies to examine the role of the amygdala in the expression of already learned emotional responses, Angrilli *et al.* (1996) reported on a patient with a benign tumour of the right amygdala in a study that used startle magnitude in response to an acoustic probe measured from orbicularis oculi. Among control subjects, they observed the well-known effect of startle potentiation during the presentation of aversive stimuli. In the patient with right amygdala damage, no startle potentiation was observed in response to aversive versus neutral stimuli. These findings suggest that the amygdala might be necessary for the expression of already learned negative affect.

Since 1995, a growing number of studies using PET and fMRI to investigate the role of the amygdala in emotional processes have begun to appear. Many studies have reported activation of the amygdala detected with either PET or fMRI when anxiety-disordered patients have been exposed to their specific anxiety-provoking stimuli compared with control stimuli (e.g. Breiter *et al*. 1996*b*; Rauch *et al.* 1996). When social phobics were exposed to neutral faces, they showed activation of the amygdala comparable to what was observed in both the phobics and controls in response to aversive compared with neutral odours (Birbaumer *et al.* 1998). Consistent with the human lesion data, several studies have now reported activation of the amygdala in response to facial expressions of fear compared with neutral, happy or disgust control faces (Morris *et al.* 1996; Phillips *et al.* 1997). In the Breiter *et al*. fMRI study (Brieter *et al*. 1996*a*), they observed rapid habituation of the amygdala response, which may provide an important clue to the time-limited function of the amygdala in the stream of affective information processing. Whalen *et al.* (1998) observed activation of the amygdala in response to masked fear faces that were not consciously perceived. Unpleasant compared with neutral and pleasant pictures have also been found to activate the amygdala (Irwin *et al.* 1996). Finally, several studies have reported activation of the amygdala during the early phases of aversive conditioning (Buchel *et al.* 1998; LaBar *et al.* 1998). Amygdala activation in response to several other experimental procedures for inducing negative affect has been reported, including unsolvable anagrams of the sort used to induce learned helplessness (Schneider *et al.* 1996), aversive olfactory cues (Zald & Pardo 1997) and aversive gustatory stimuli (Zald *et al.* 1998). Other data on individual differences in amygdala activation and their relation to affective style will be treated in the next section. The issues of whether the amygdala responds preferentially to aversive versus appetitive stimuli, is functionally asymmetric, and is required for both the initial learning and subsequent expression of negative emotional associations, have not yet been adequately resolved and are considered in detail elsewhere (Davidson & Irwin 1999), though some data clearly suggest that the amygdala does activate in response to appetitive stimuli

(Hamann *et al.* 2002). It should be noted that one recent fMRI study (Zalla *et al.* 2000) found differential activation of the left and right amygdala to winning and losing money, with the left amygdala showing increased activation to winning more money, while the right amygdala showed increased activation in response to the parametric manipulation of losing money. Systematic examination of asymmetries in amygdala activation and function in appetitive and aversive contexts should be performed in light of these data. In several recent reviews, Whalen (Davis & Whalen 2001) has argued that a major function of the amygdala is the detection of ambiguity and the issuing of a call for further processing when ambiguous information is presented. I will return to this claim later in the article when the issue of individual differences is addressed.

These findings raise the question concerning the 'optimal' pattern of amygdala function for well-being. Based upon evidence reviewed in § 7 in the context of individual differences, we will argue that low basal levels of amygdala activation, in conjunction with situationally appropriate responding, effective top-down regulation and rapid recovery, characterize a pattern that is consistent with high levels of well-being.

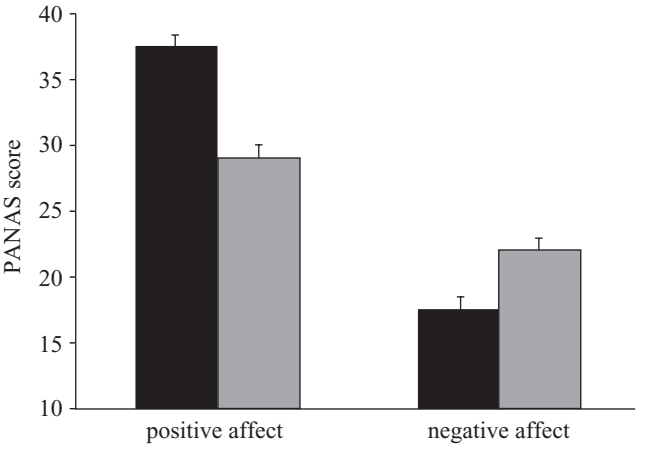

Figure 1. Dispositional positive affect (from scores on the PANAS-General Positive Affect Scale) in subjects who were classified as extreme and stable left-frontally active (black bars; $n = 14$) and extreme and stable right-frontally active (grey bars; $n = 13$) on the basis of electrophysiological measures of baseline activation asymmetries on two occasions separated by three weeks. Error bars denote standard error of the mean. (From Tomarken *et al.* (1992).)

6. HIPPOCAMPUS AND ACC

In this section, brief mention will be made of the contributions of hippocampus and ACC to emotion. More extensive discussion of the contributions of this circuit to emotional processing is contained in several recent reviews (Davidson & Irwin 1999; Bush *et al.* 2000; Davidson *et al.* 2002).

The hippocampus has been implicated in various aspects of memory (see Zola & Squire 2000), particularly declarative memory of the sort we experience when we consciously recall an earlier occurring episode. Its role in emotion and affective style has only recently begun to be gleaned from the available corpus of animal studies on the role of the hippocampus in context-dependent memory (Fanselow 2000). This literature has generally supported a role for the hippocampus in the learning of context. For example, when an animal is exposed to a cue-conditioning procedure where a discrete cue is paired with an aversive outcome, in addition to learning the specific cue–punishment contingency, the animal also learns to associate the context in which the learning occurs with the aversive outcome. Lesions to the hippocampus will abolish this context-dependent form of memory but will have no effect on the learning of the cue–punishment contingency. The fact that the hippocampus is a site in the brain with a very high density of glucocorticoid receptors and participates in the feedback regulation of the hypothalamic–pituitary adrenal axis is particularly germane to the importance of this structure for emotion regulation. Basic research at the animal level has demonstrated the powerful impact of glucocorticoids on hippocampal neurons (Cahill & McGaugh 1998; McEwen 1998). There are data that indicate that exogenous administration of hydrocortisone to humans impairs explicit memory that is presumably hippocampally dependent (e.g. Kirschbaum *et al.* 1996), though there are other data that suggest that in more moderate amounts, cortisol may facilitate memory (e.g. Abercrombie 2000). Several investigators have reported, using MRI-based measures, that hippocampal volume is significantly decreased in patients with several stress-related disorders including PTSD (e.g. Bremner 1999) and depression (e.g. Sheline *et al.* 1996; Bremner *et al.* 2000), though there have also been several failures to replicate (e.g. Vakili *et al.* 2000; Rusch *et al.* 2001). In the studies where hippocampal atrophy has been found, the implication is that excessively high levels of cortisol associated with the stress-related disorder cause hippocampal cell death and result in hippocampal atrophy as seen on MRI. Although virtually all of these studies have focused on the implications of hippocampal changes for cognitive function, particularly declarative memory, we (Davidson *et al.* 2000*a*) have proposed that the hippocampus plays a key role in the context-modulation of emotional behaviour. Moreover, we have suggested that it is in the affective realm where the impact of hippocampal involvement in psychopathology may be most apparent. We suggested that in individuals with compromised hippocampal function, the normal context-regulatory role of this brain region would be impaired and individuals would consequently display emotional behaviour in inappropriate contexts. This argument holds that what may be particularly abnormal in disorders such as PTSD and depression is not the display of 'abnormal emotion' but rather the display of perfectly normal emotion in inappropriate contexts. For example, in the case of the PTSD, the extreme fear and anxiety is probably very adaptive in the original traumatic context. This extreme emotional response probably plays an important role in facilitating the organism's withdrawal from a threatening situation. However, in PTSD, this response is elicited in inappropriate situations. The patient with PTSD behaves similarly to the animal with a hippocampal lesion in failing to modulate emotional responses in a context-appropriate manner. These suggestions are only inferential at the present time. Neuroimaging studies are needed to document the role of the hippocampus in this process in normal and disordered populations. In addition, more attention is needed to understand how and why the

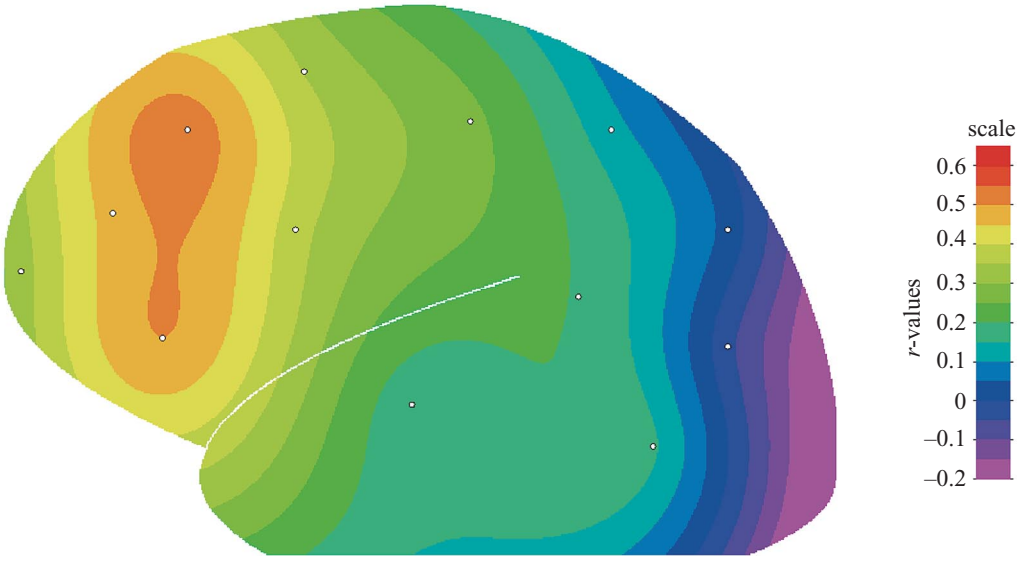

Figure 2. Relations between electrophysiological measures of asymmetry and the difference between the standardized score on the BIS/BAS (Carver & White 1994), $n = 46$. Electrophysiological data were recorded from each subject on two separate occasions separated by six weeks. The BIS/BAS were also administered on these two occasions. Data were averaged across the two time periods before performing correlations. The topographic map displays the correlations between alpha power asymmetry (log-right minus log-left alpha power; higher values denote greater relative left-sided activation) and the difference score between the standardized BAS minus BIS. After correlations were performed for each homologous region, a spline-interpolated map was created. The orange and red values of the scale denote positive correlations. The figure indicates that the correlation between the BAS–BIS difference score and the electrophysiology asymmetry score is highly positive in prefrontal scalp regions, denoting that subjects with greater relative left-sided activation report more relative behavioural activation compared with behavioural inhibition tendencies. The relation between asymmetric activation and the BAS–BIS difference is highly specific to the anterior scalp regions, as the correlation decreases rapidly more posteriorly. The correlation in the prefrontal region is significantly larger than the correlation in the parieto-occipital region. (From Sutton & Davidson (1997).)

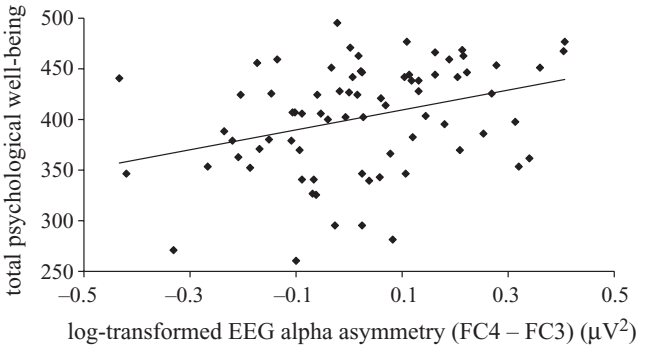

Figure 3. Scatter plot depicting the correlation between frontal EEG asymmetry (FC4–FC3) and total psychological well-being. Relative left-frontal asymmetry (denoted by positive values on the abscissa) is associated with higher levels of well-being; $r(74) = 0.33$; $p = 0.002$. (From Urry *et al.* (2004).)

hippocampus may preferentially extract and process information about context. Finally, some research (e.g. Davis & Lee 1998) indicates that other structures with direct connections to the hippocampus (for example, the bed nucleus of the stria terminalis) also play a role similar to the hippocampus. More work is needed to understand the differential contributions of the different components of this circuitry.

The findings on the role of hippocampal pathology in disease provide us with insights into the role of this structure for adaptive function and well-being. We suggest that effective context-modulation of emotional behaviour is a hallmark sign of well-being and promotes adaptive emotion regulation.

Many studies that have used neuroimaging methods to probe patterns of brain activation during the arousal of emotion have reported that the ACC activates in response to emotion. Several investigators (Whalen *et al.* 1998; Bush *et al.* 2000) have distinguished between cognitive and affective subdivisions of the ACC based upon where activations lie in response to tasks that are purely cognitive versus those that include aspects of emotion. For example, in response the classical colour–word Stroop task (subjects are required to name the colour of colour words that are inconsistent with the colour in which they are printed, for example, the word 'red' printed in blue), ACC activation is found consistently more dorsal to the locus of activation observed in response to an emotional Stroop task with emotional words. However, the question of just what role the more ventral portions of the ACC might be playing in emotion has not been systematically addressed. On the basis of Cohen's model of the role of ACC in conflict monitoring in the cognitive domain (Carter *et al.* 1999), we have proposed that the affective subdivision of the ACC might play a similar role in emotion. When emotion is elicited in the laboratory, this itself presents something of a conflict since social norms dictate certain rules for participant behaviour that do not usually include the display of strong emotion. Thus, the very process of activating

emotion in the unfamiliar context of a laboratory environment might activate ACC. Cohen has suggested that ACC activation results in a call for further processing by other brain circuits to address the conflict that has been detected. In most individuals, automatic mechanisms of emotion regulation are probably invoked to dampen strong emotion that may be activated in the laboratory. The initial call for the processes of emotional regulation may result from ACC activation.

Again, considering the possible role of ACC function in well-being, we will argue on the basis of data we present in § 8 that high levels of ACC activation in situations requiring emotional regulation will be associated with more effective regulatory skill and thus facilitate well-being. In § 7, attention is turned to individual differences in the key components of the circuitry we describe, with a focus on the pattern of individual differences that form the basis for well-being.

7. WHAT ARE INDIVIDUAL DIFFERENCES IN PFC AND AMYGDALA ACTIVATIONS ASSOCIATED WITH?

In both infants (Davidson & Fox 1989) and adults (Davidson & Tomarken 1989) there are large individual differences in baseline electrophysiological measures of prefrontal activation, and such individual variation is associated with differences in aspects of affective reactivity. In infants, Davidson & Fox (1989) reported that 10-month-old babies who cried in response to maternal separation were more likely to have less left- and greater right-sided prefrontal activation during a preceding resting baseline compared with those infants who did not cry in response to this challenge. In adults, we first noted that the phasic influence of positive and negative emotion elicitors (e.g. film clips) on measures of prefrontal activation asymmetry appeared to be superimposed upon more tonic individual differences in the direction and absolute magnitude of asymmetry (Davidson & Tomarken 1989).

During our initial explorations of this phenomenon, we needed to determine if baseline electrophysiological measures of prefrontal asymmetry were reliable and stable over time and thus could be used as a trait-like measure. Tomarken *et al.* (1992) recorded baseline brain electrical activity from 90 normal subjects on two occasions separately by approximately three weeks. At each testing session, brain activity was recorded during eight 1 min trials, four eyes open and four eyes closed, presented in counterbalanced order. The data were visually scored to remove artefacts and then Fourier-transformed. Our focus was on power in the alpha band (8–13 Hz), though we extracted power in all frequency bands (see Davidson *et al.* 1990, 2000*b* for methodological discussion). We computed coefficient alpha as a measure of internal consistency reliability from the data within each session. The coefficient alphas were quite high, with all values exceeding 0.85, indicating that the electrophysiological measures of asymmetric activation indeed showed excellent internal consistency reliability. The test–retest reliability was adequate, with intraclass correlations ranging from 0.65 to 0.75 depending upon the specific sites and methods of analysis. The major conclusion from this study was the demonstration that measures of activation asymmetry based upon power in the alpha band from prefrontal scalp electrodes showed both high internal consistency reliability and acceptable test–retest reliability to be considered a trait-like index.

On the basis of our prior data and theory, we reasoned that extreme left- and extreme right-frontally activated subjects would show systematic differences in dispositional positive and negative affect. We administered the trait version of PANAS (Watson *et al.* 1988) to examine this question and found that the left-frontally activated subjects reported more positive and less negative affect than their right-frontally activated counterparts (Tomarken *et al.* 1992; figure 1). More recently (Sutton & Davidson 1997) we showed that scores on a self-report measure designed to operationalize Gray's concepts of the BIS/BAS scales (Carver & White 1994) were even more strongly predicted by electrophysiological measures of prefrontal asymmetry than were scores on the PANAS (see figure 2). Subjects with greater left-sided prefrontal activation reported more relative BAS to BIS activity compared with subjects exhibiting more right-sided prefrontal activation.

In a very recent study, we extended these early findings and found that baseline measures of asymmetric prefrontal activation predicted reports of well-being among individuals in their late 50s (Urry *et al.* 2004; figure 3). Moreover, this association was present even when the association between prefrontal activation asymmetry and dispositional positive affect was statistically removed. These findings indicate that prefrontal activation asymmetry accounts for variance in well-being over and above that which is accounted for by positive affect.

We also suggested that our measures of prefrontal asymmetry would predict reactivity to experimental elicitors of emotion. The model that we have developed over recent years (see Davidson 1992, 1994, 1995, 1998*a*,*b* for background) features individual differences in prefrontal activation asymmetry as a reflection of a diathesis that modulates reactivity to emotionally significant events. According to this model, individuals who differ in prefrontal asymmetry should respond differently to an elicitor of positive or negative emotion, even when baseline mood is partialled out. We (Wheeler *et al.* 1993; see also Tomarken *et al.* 1990) performed an experiment to examine this question. We presented short film clips designed to elicit positive or negative emotion. Brain electrical activity was recorded before the presentation of the film clips. Immediately after the clips were presented, subjects were asked to rate their emotional experience during the preceding film clip. In addition, subjects completed scales that were designed to reflect their mood at baseline. We found that individual differences in prefrontal asymmetry predicted the emotional response to the films even after measures of baseline mood were statistically removed. Those individuals with more left-sided prefrontal activation at baseline reported more positive affect to the positive film clips and those with more right-sided prefrontal activation reported more negative affect to the negative film clips. These findings support the idea that individual differences in electrophysiological measures of prefrontal activation asymmetry mark some aspect of vulnerability to positive and negative emotion elicitors. The fact that such relations were obtained following the statistical removal of baseline mood indicates that any difference between left- and right-frontally activated PFC in baseline mood cannot account

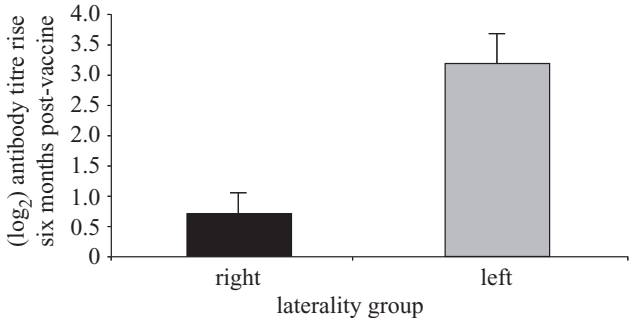

Figure 4. Bar graph of the mean antibody titre rise ($\log_2$) to influenza vaccine six months post-vaccine for extreme groups comprising individuals (average age 58 years) in the top and bottom 25th centiles of activation asymmetry at the lateral frontal (F7/8) site. Error bars denote s.e.m. The difference between groups was highly significant ($t(22) = 3.81$, $p < 0.001$). (From Rosenkranz *et al.* (2003).)

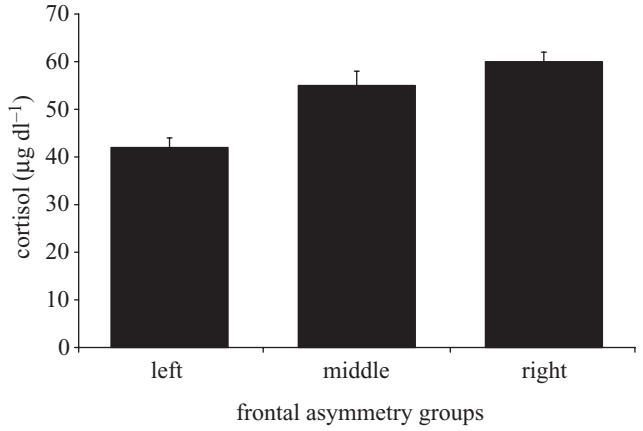

Figure 5. Basal morning plasma cortisol from 1-year-old rhesus monkeys classified as left- ($n = 12$), middle- ($n = 16$) or right- ($n = 11$) frontally activated based upon electrophysiological measurements. Error bars denote s.e.m. (From Kalin *et al.* (1998).)

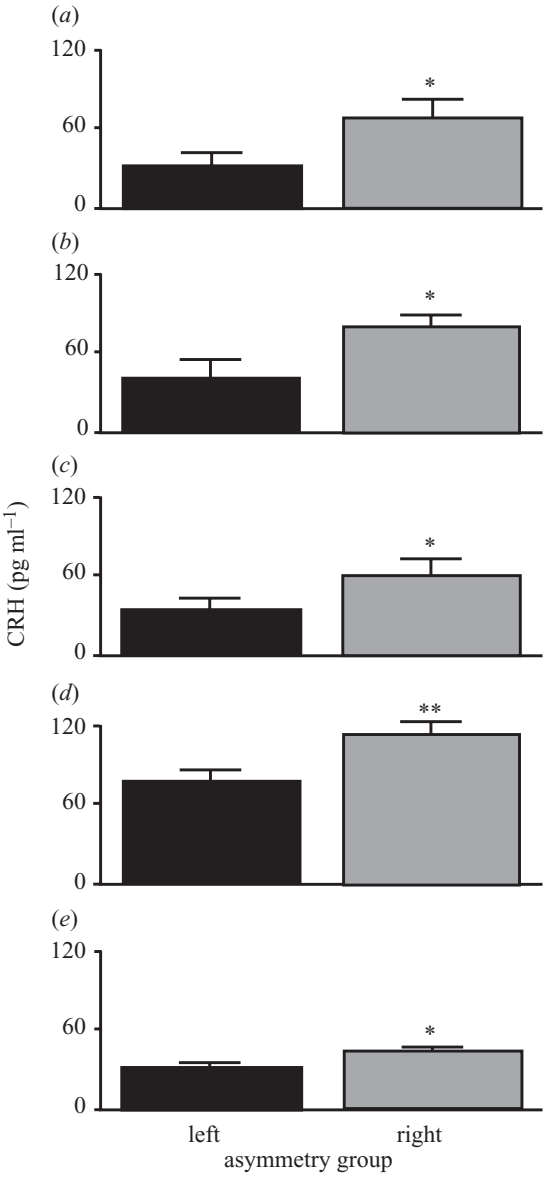

Figure 6. Differences between right- ($n = 9$) and left-prefrontally ($n = 10$) activated animals in cerebrospinal fluid measures of CRH at five different ages: (*a*) four months; (*b*) eight months; (*c*) 14 months; (*d*) 40 months; (*e*) 52 months. Error bars denote s.e.m. The original classification of the animals as extreme right- or left-activated was performed on the basis of brain electrical activity data collected when the animals were 13 months of age. (From Kalin *et al.* (2000).)

for the prediction of the film-elicited emotion effects that were observed. What has not yet been answered by these studies that use baseline measures of brain electrical activity to predict emotional reactivity is what other components of affective circuitry are upregulated and downregulated in response to affective challenges in subjects who differ on measures of baseline prefrontal activation asymmetry. This is a question that must be pursued using a combination of electrophysiological and neuroimaging measures.

Depression is clearly a heterogeneous disorder. In a recent review of the depression literature from the perspective of affective neuroscience (Davidson *et al.* 2002), we suggested that there was a subtype that was associated with deficits in approach-related positive affect, whose proximal cause was predicted to be hypoactivation in certain left prefrontal regions that we have previously implicated in approach-related positive affect. The relation between individual differences in brain electrical measures of prefrontal activation asymmetry and depression is a topic that has received extensive treatment in several recent articles. There has been a failure to replicate (Reid *et al.* 1998) our initial findings of decreased left prefrontal activation in depression (Schaffer *et al.* 1983; Henriques & Davidson 1990, 1991), though there have also been several published independent replications or conceptual replications (e.g. Allen *et al.* 1993; Field *et al.* 1995). Moreover, using PET, Drevets *et al.* (1997) have reported decreased activation in the left subgenual PFC in patients with depression. We interpreted the decrease in left-sided prefrontal activation as a diathesis related to deficits in the approach system and in reward-related responding (Henriques *et al.* 1994; Henriques & Davidson 2000). We also argued that this pattern of left prefrontal hypoactivation would be found only in certain subgroups of mood disordered patients in light of the heterogeneity of the disorder (see Davidson 1998*b* for an extended discussion). Most importantly, we have suggested that it is crucial to move beyond descriptive

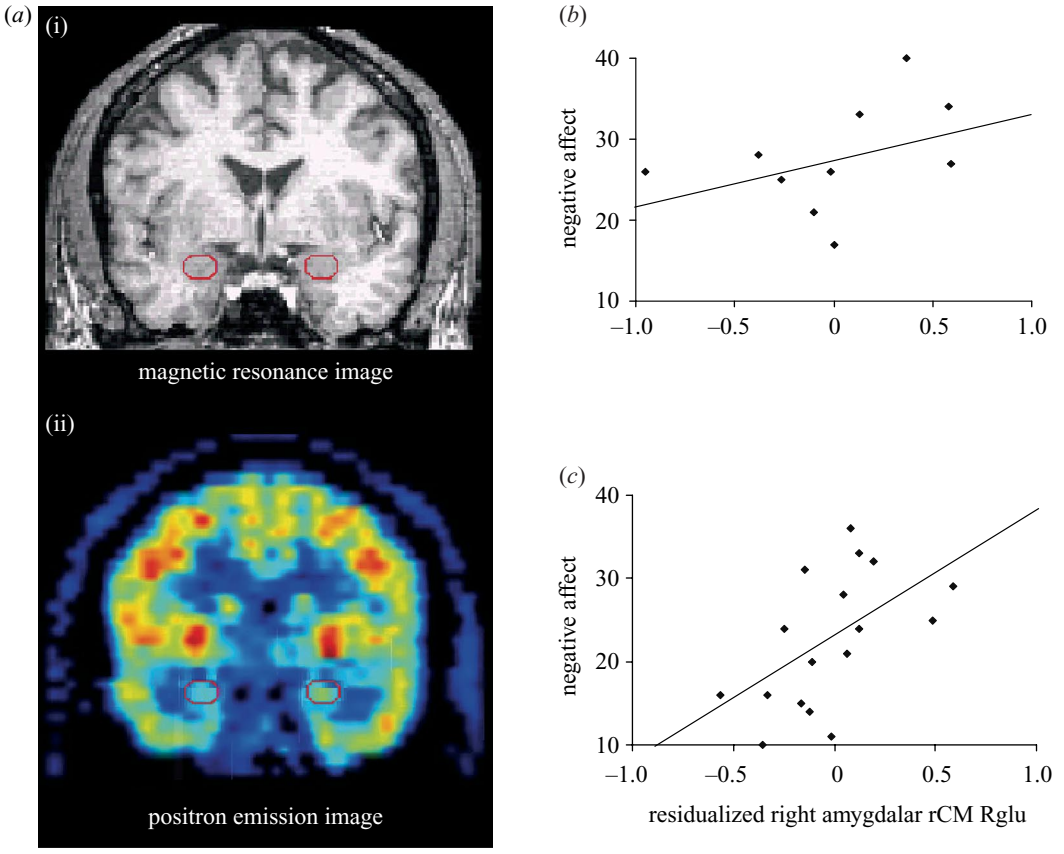

Figure 7. (*a*) Images indicate (i) the MR and (ii) the corresponding PET image from one subject to illustrate our method of MRI-co-registered ROIs around the amygdala. ROIs were individually drawn for each subject around the amygdala, and glucose metabolism was then extracted from the PET image in (ii). (*b*,*c*) Scatter plots display the relation between glucose metabolic rate (residualized for variations in whole brain metabolism) in the right amygdala and dispositional negative affect assessed with the PANAS for two independent samples of depressed patients tested on two different PET scanners ((*b*) sample 1; $r = 0.41$; (*c*) sample 2; $r = 0.56$). Metabolic rate in the left amygdale did not predict PANAS negative affect. The scanner used for the data in (*c*) had better spatial resolution (GE Advance). (From Abercrombie *et al.* (1998).)

phenomenology and to examine with objective laboratory methods variations in reactivity to emotion elicitors in individuals with this proposed diathesis. We have suggested that individuals who display left prefrontal hypoactivation will show specific deficits in reactivity to reward, though the need to consider other components of the circuitry with which the PFC is interconnected must be underscored in any effort to understand the neural bases of emotion and its disorders.

In addition to the studies described above using self-report and psychophysiological measures of emotion, we have examined relations between individual differences in electrophysiological measures of prefrontal asymmetry and other biological indices that, in turn, have been related to differential reactivity to stressful events. Three recent examples from our laboratory include measures of immune function, cortisol and corticotropin-releasing hormone. The latter two measures represent key molecules in the activation of a coordinated response to stressful events. Our strategy in each case was to examine relations between individual differences in measures of prefrontal activation asymmetry and these other biological indices. In two separate studies (Kang *et al.* 1991; Davidson *et al.* 1999) we examined relations between the prefrontal activation indices and NK activity since declines in NK activity have been reported in response to stressful, negative events (Kiecolt-Glaser & Glaser 1981). We predicted that subjects with greater left-sided prefrontal activation would exhibit higher NK activity than their right-activated counterparts because the former type of subject has been found to report more dispositional positive affect, to show higher relative BAS activity and to respond more intensely to positive emotional stimuli. In each of the two studies conducted with independent samples, we found that left-frontally activated subjects indeed had higher levels of NK activity than their right-frontally activated counterparts (Kang *et al.* 1991; Davidson *et al.* 1999). We also examined the magnitude of change in NK activity in response to stress and found that subjects with greater baseline levels of left prefrontal activation showed the smallest magnitude decline in NK activity in response to stress compared with other subjects (Davidson *et al.* 1999).

One of the concerns with the studies that examine NK function is the fact that this is an *in vitro* assay and its significance for immunocompetence is unclear. To address this concern, we recently completed a study examining relations between prefrontal activation asymmetry and antibody responses to influenza vaccine (Rosenkranz *et al.* 2003) in a sample of 52 middle-aged subjects with an average age of 58 years (evenly divided by sex). In this study, we recorded brain electrical measures in the same way as previously described. We compared individuals in the top

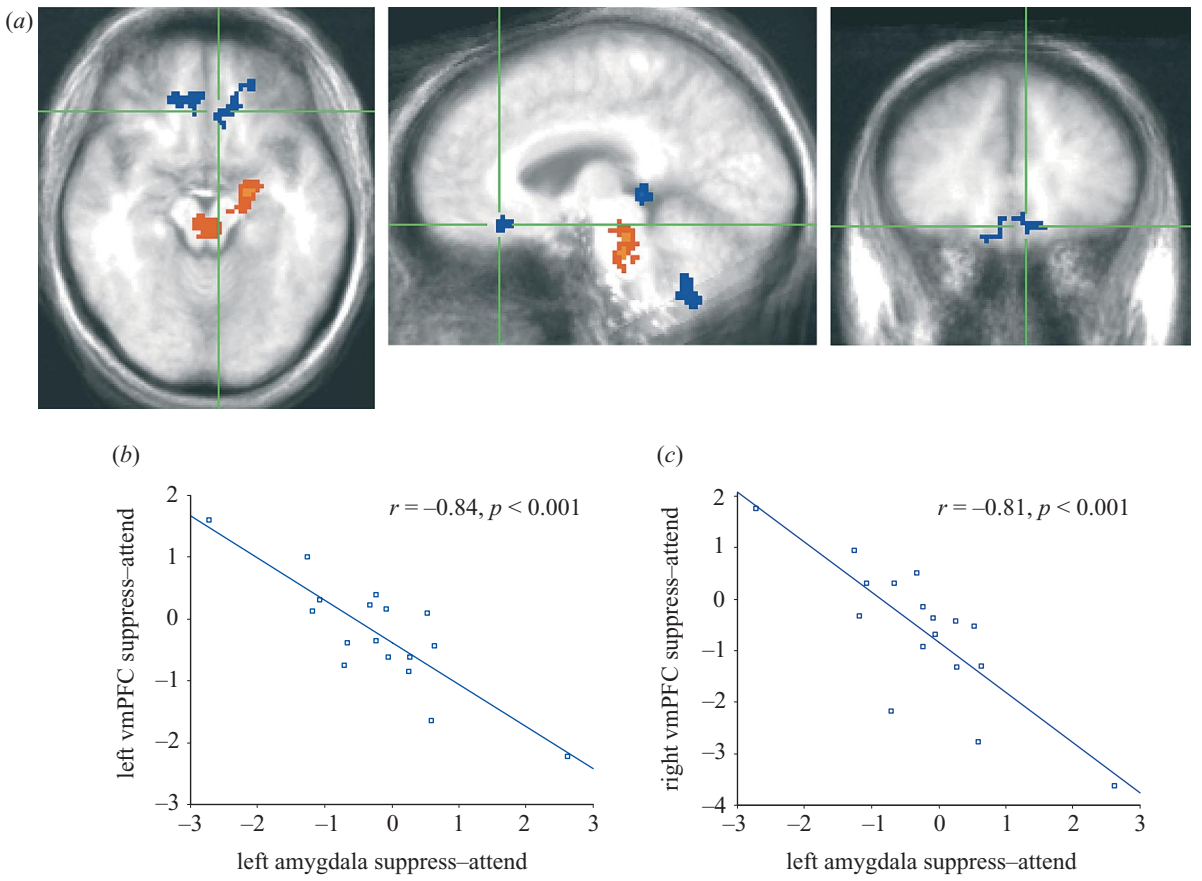

Figure 8. (*a*) Images display of the associations between activation in the amygdale bilaterally and other regions of the brain. Blue areas denote inverse correlations whereas red areas denote positive correlations. The data reveal an inverse association between activation in vmPFC and signal change in the amygdala following aversive pictures in response to instructions to suppress (downregulate) negative affect, compared with a condition during which subjects were instructed to attend to the stimuli. ($n = 17$; from Urry *et al.* 2003). (*b*) Left vmPFC cluster (including subgenual ACC) with left amygdala, $r = -0.84$, $p < 0.001$; (*c*) right vmPFC cluster with left amygdala, $r = -0.81$, $p < 0.001$. (From Urry *et al.* (2003).)

and bottom quartile on measures of prefrontal activation asymmetry and found large differences between these extreme groups in antibody titres to influenza vaccine (see figure 4), with the left-prefrontally activated subjects showing significantly greater antibody titres than their right-activated counterparts.

In collaboration with Kalin, our laboratory has been studying similar individual differences in scalp-recorded measures of prefrontal activation asymmetry in rhesus monkeys (Davidson *et al.* 1992, 1993). Recently, we (Kalin *et al.* 1998) acquired measures of brain electrical activity from a large sample of rhesus monkeys ($n = 50$). EEG measures were obtained during periods of manual restraint. A subsample of 15 of these monkeys was tested on two occasions four months apart. We found that the test–retest correlation for measures of prefrontal asymmetry was 0.62, suggesting similar stability of this metric in monkey and human. In the group of 50 animals, we also obtained measures of plasma cortisol during the early morning. We proposed that if individual differences in prefrontal asymmetry were associated with dispositional affective style, such differences should be correlated with cortisol, since individual differences in baseline cortisol have been related to various aspects of trait-related stressful behaviour and psychopathology (see Gold *et al.* 1988). We found that animals with left-sided prefrontal activation had lower levels of baseline cortisol than their right-frontally activated counterparts (see figure 5). As can be seen from figure 5, it is the left-activated animals that are particularly low compared with both middle- and right-activated subjects. Moreover, when blood samples were collected 2 years after our initial testing, animals classified as showing extreme left-sided prefrontal activation at age 1 year had significantly lower baseline cortisol levels when they were 3 years of age compared with animals who were classified at age 1 year as displaying extreme right-sided prefrontal activation. Similar findings were obtained with cerebrospinal fluid levels of CRH. Those animals with greater left-sided prefrontal activation showed lower levels of CRH (Kalin *et al.* 2000; figure 6). These findings indicate that individual differences in prefrontal asymmetry are present in non-human primates and that such differences predict biological measures that are related to affective style.

With the advent of neuroimaging, it has become possible to investigate the relation between individual differences in aspects of amygdala function and measures of affective style. We have used PET with FDG as a tracer to investigate relations between individual differences in glucose metabolism in the amygdala and dispositional negative affect. FDG-PET is well suited to capture trait-like effects since the period of active uptake of tracer in the brain is *ca.* 30 min. Thus, it is inherently more reliable than ^{15}O blood flow measures since the FDG data reflect activity aggregated over a 30 min period. We have used resting FDG-PET to examine individual differences in glucose

metabolic rate in the amygdala and its relation to dispositional negative affect in depressed subjects (Abercrombie *et al.* 1998). We acquired a resting FDG-PET scan as well as a structural MR scan for each subject. The structural MR scans are used for anatomical localization by co-registering the two image sets. Thus, for each subject, we used an automated algorithm to fit the MR scan to the PET image. ROIs were then drawn on each subject's MR scan to outline the amygdala in each hemisphere. These ROIs were drawn on coronal sections of subjects' MR images and the ROIs were then automatically transferred to the co-registered PET images. Glucose metabolism in the left and right amygdala ROIs was then extracted. The inter-rater reliability for the extracted glucose metabolic rate is highly significant with intraclass correlations between two independent raters equal to or greater than 0.97. We found that subjects with lower levels of glucose metabolism in the right amygdala reported less dispositional negative affect on the PANAS scale (see figure 7). These findings indicate that individual differences in resting glucose metabolism in the amygdala are present and that they predict dispositional negative affect among depressed subjects.

In a small sample of 12 normal subjects, we (Irwin *et al.* 1998) have been able to examine the relation between the magnitude of MR signal change in the amygdala in response to aversive, compared with neutral, pictures and dispositional negative affect on the PANAS scale. We correlated the average value of the voxels with the maximum Student's *t*-value from the left and right amygdala with dispositional negative affect. There was a robust correlation, such that subjects showing the least increase in signal intensity in the right amygdala reported the lowest levels of dispositional negative affect. The findings from the fMRI and PET studies of amygdala function indicate that individual differences in both tonic activation and phasic activation in response to aversive stimuli predict the intensity of dispositional negative affect.

8. EMOTION REGULATION: A KEY COMPONENT OF AFFECTIVE STYLE

One of the key components of affective style is the capacity to regulate negative emotion and, specifically, to decrease the duration of negative affect once it arises. We have suggested in several recent articles that the connections between the PFC and amygdala play an important role in this regulatory process (Davidson 1998*a*; Davidson & Irwin 1999; Davidson *et al.* 2000*d*). In two recent studies, we (Larson *et al.* 1998; Jackson *et al.* 2003) examined relations between individual differences in prefrontal activation asymmetry and the emotion-modulated startle. In both studies, we presented pictures from the International Affective Picture System (Lang *et al.* 1995) while acoustic startle probes were presented and the EMG-measured blink response from the orbicularis oculi muscle region was recorded (see Sutton *et al.* 1997*a* for basic methods). Startle probes were presented both during the slide exposure as well as at various latencies following the offset of the pictures, on separate trials. We interpreted startle magnitude during picture exposure as providing an index related to the peak of emotional response, while startle magnitude following the *offset* of the pictures was taken to reflect the automatic recovery from emotional challenge. Used in this way, startle probe methods can potentially provide new information on the time-course of emotional responding. We expected that individual differences during actual picture presentation would be less pronounced than individual differences following picture presentation since an acute emotional stimulus is likely to pull for a normative response across subjects, while individuals are more likely to differ once the stimulus has terminated. Similarly, we predicted that individual differences in prefrontal asymmetry would account for more variance in predicting magnitude of recovery (i.e. startle magnitude post-stimulus) than in predicting startle magnitude during the stimulus. Our findings in each study were consistent with our predictions and indicated that subjects with greater right-sided prefrontal activation show a larger blink magnitude following the offset of the negative stimuli, after the variance in blink magnitude *during* the negative stimulus was partialled out. Measures of prefrontal asymmetry did not reliably predict startle magnitude during picture presentation. The findings from these studies are consistent with our hypothesis and indicate that individual differences in prefrontal asymmetry are associated with the time-course of affective responding, particularly the recovery following emotional challenge. In a related study, we have found that subjects with greater baseline levels of left prefrontal activation are better able to suppress negative affect voluntarily (see Jackson *et al.* 2000). Moreover, using functional MRI we have demonstrated that when subjects are instructed to regulate their negative emotion voluntarily, reliable bilateral changes in amygdala MR signal intensity are found (Schaefer *et al.* 2002) and that the magnitude of MR signal decreases in the amygdala during instructions to down-regulate negative affect are predicted by increased MR signal in the vmPFC (Urry *et al.* 2003; figure 8).

The findings from these studies indicate that individual differences in prefrontal activation may play an important role in emotion regulation. Individuals who report less dispositional negative affect and more dispositional positive affect may be those individuals who have increased facility at regulating negative affect and specifically in modulating the intensity of negative affect once it has been activated.

9. PLASTICITY IN THE CENTRAL CIRCUITRY OF EMOTION

The circuits that underlie emotion regulation, in particular the amygdala and PFC, have both been the targets of intensive study of plasticity (see Davidson *et al.* 2000*a* for an extensive discussion). In a series of elegant studies in rats, Meaney and colleagues (Francis & Meaney 1999) have demonstrated that an early environmental manipulation in rats—frequency of maternal licking/grooming and arched-back nursing—produces a cascade of biological changes in the offspring that shape the central circuitry of emotion and, consequently, alter the animal's behavioural and biological responsivity to stress. For example, the offspring of mothers high in licking and grooming show increased central benzodiazepine receptor densities in various subnuclei of the amygdala as well as in the LC, increased α_2 adrenoreceptor density in the LC and decreased CRH receptor density in the LC (Caldji *et al.* 1998). In other research, Meaney and co-workers have reported that rats exposed to high licking/grooming mothers exhibited a permanent

increase in concentrations of receptors for glucocorticoids in both the hippocampus and the PFC (Meaney *et al.* 1988, 1996; Liu *et al.* 1997). All of these changes induced by early maternal licking/grooming and related behaviour involve alterations in the central circuitry of emotion that result in decreased responsivity to stress later in life.

These findings in animals raise the possibility that similar effects may transpire in humans. There are clearly short-term changes in brain activation that are observed during voluntary emotion regulation, as noted in § 8. Whether repeated practice in techniques of emotion regulation lead to more enduring changes in patterns of brain activation is a question that has not yet been answered in extant research. There are limited data available that indicate that cognitive behavioural therapy for certain disorders (e.g. obsessive compulsive disorder; simple phobia) produces changes in regional brain activity, which are comparable to those produced by medication (Baxter *et al.* 1992; Paquette *et al.* 2003). What is largely absent are data on plastic changes in the brain that might be produced by the practice of methods specifically designed to increase positive affect, such as meditation. In a recent study, we examined changes in brain electrical activity and immune function following an eight-week training programme in mindfulness meditation (Davidson *et al.* 2003). In this study subjects were randomly assigned to a meditation group or a wait-list control group and each of these groups was tested before and after the eight-week training programme, as well as four months following the end of the programme. We found that subjects in the meditation group showed significantly larger increases in left-sided anterior activation compared with their counterparts in the control group. Subjects received an influenza vaccine just after the eight-week programme was completed and we found that influenza antibody titres were significantly higher in the meditators compared with the controls. Most remarkably, we observed that those subjects who showed the largest magnitude change in brain activity also showed the largest increase in antibody titres (see figure 9). These findings suggest that training procedures designed explicitly to facilitate well-being result in demonstrable and predictable changes in brain and immune function.

The Dalai Lama himself has raised this question in his recent book *The art of happiness* (Dalai Lama & Cutler 1998) where he explains that 'The systematic training of the mind—the cultivation of happiness, the genuine inner transformation by deliberately selecting and focusing on positive mental states and challenging negative mental states—is possible because of the very structure and function of the brain. ... But the wiring in our brains is not static, not irrevocably fixed. Our brains are also adaptable' (pp. 44–45). We are now at the point in the development of affective neuroscience where we can rigorously address this question by using neuroimaging methods to probe changes in patterns of activation and transmitter function that might be produced by the systematic practice of techniques such as meditation that are designed to promote the cultivation of positive affect. By also examining how changes in the central circuitry of emotion might be related to peripheral biology (endocrine, autonomic and immune function), we can begin to examine mechanistically how well-being may be consequential for our mental and physical health.

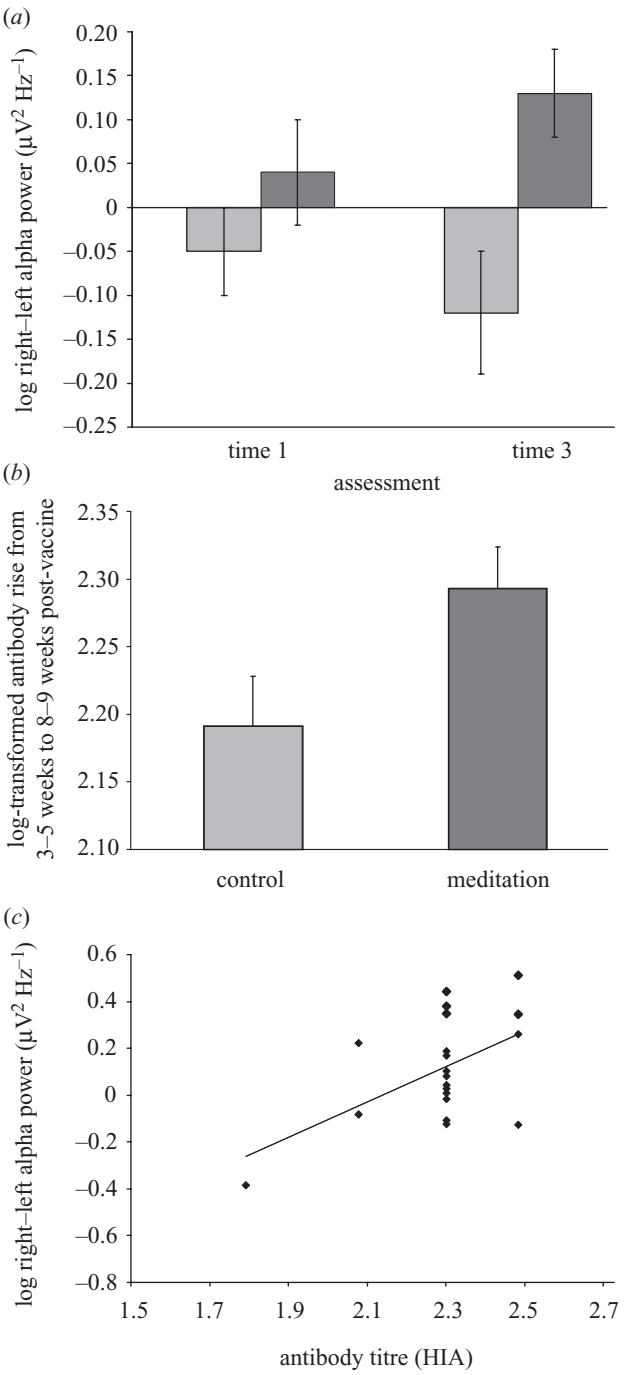

Figure 9. (*a*) Pre- and post-training brain electrical asymmetry measures from subjects in the meditation and control groups. Note that positive numbers denote greater left-sided activation and negative numbers denote greater right-sided activation. (*b*) Differences between the meditation and control groups in antibody titres in response to influenza vaccine. Errors bars in (*a*, *b*) denote s.e.m. (*c*) The relation between pre-to-post test increases in left-sided activation and rise in antibody titres to influenza vaccine among subjects in the meditation group only ($n = 25$ for meditation group; $n = 16$ for control group). (From Davidson *et al.* (2003).)

10. SUMMARY AND CONCLUSIONS

The circuitry underlying emotion and affective style was reviewed with an emphasis on the contributions of different sectors of the PFC and amygdala to positive affect and well-being. Individual differences in patterns of prefrontal

and amygdala activation are related to behavioural and biological constituents of affective style and emotion regulation. Recent data highlight the role of particular sectors of the PFC in emotion regulation, particularly the regulation of the duration of negative affect and the downregulation of negative emotion once it is elicited. These individual differences are conceptualized as diatheses that alter a person's vulnerability or resilience. Recent evidence in animals underscores the extraordinary plasticity of this circuitry and demonstrates that early social experience in particular has profound consequences for the developing nervous system. The possibilities of transforming this circuitry in adulthood with specific methods designed to cultivate positive affect were considered. New longitudinal research is needed to address these questions.

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GLOSSARY

ACC: anterior cingulate cortex
BIS: behavioural inhibition scales
BAS: behavioural activation scales
CRH: corticotropin-releasing hormone
DLPFC: dorsolateral prefrontal cortex
EEG: electroencephalogram
FDG: fluorodeoxyglucose
fMRI: functional magnetic resonance imaging
LC: locus ceruleus
NK: natural killer
OFC: orbitofrontal cortex
PANAS: positive and negative affect scales
PET: positron emission tomography
PFC: prefrontal cortex
PTSD: post-traumatic stress disorder
ROI: region of interest
vmPFC: ventromedial prefrontal cortex