64 The neurobiology of personality and personality disorders

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Inferences about personality have traditionally been made on the basis of self-reports and actions. The use of biological measures in the study of personality has been less common, although many theorists have assumed that core personality traits were somehow rooted in underlying biology. For example, Gordon Allport (1966), one of the founders of modern personality psychology, explicitly suggested that traits were subserved by underlying biological processes. He asserted that "traits are cortical, subcortical or postural dispositions having the capacity to gate or guide specific phasic reactions. It is only the phasic aspect which is visible; the tonic is carried somehow in the still mysterious realm of a neurodynamic structure" (Allport, 1966). The assumption that core personality traits are products of underlying biological dispositions was once shared by a number of influential early workers, including Freud and Pavlov. In his *Project for a Scientific Psychology* Freud (1895/1996) suggested that individuals may differ in certain neuronal properties which would in turn account for certain psychological differences. Pavlov (1928) introduced the concept of strength of the nervous system and argued that pronounced individual variability exists in this property. His work laid the foundation for an important tradition of research on the underlying biological substrates of introversion/extroversion (e.g., Eysenck, 1972).

These early theorists argued for the general importance of examining the underlying biological substrates of personality. They believed that personality traits were entities in the mind based on specific patterns of biological activity. By examining the biological processes, these early theorists believed that a more direct measure of traits could be obtained. This enterprise, however, contains a number of thorny conceptual and methodological issues that merit some attention before we illustrate some of the more substantive areas.

CONCEPTUAL AND METHODOLOGICAL ISSUES IN THE STUDY OF THE BIOLOGICAL BASES OF PERSONALITY

Three Approaches to the Use of Biological Measures in the Study of Personality

There are three ways in which biological measures have most often been used in the study of personality. The first way has been to complement measures obtained from other domains. For example, an investigator might be interested in studying introverts and extroverts. In addition to examining how such groups differ in their behavior and self-reports, scientists have also asked how such groups might differ in their physiology. Eysenck (1967) explored this issue in considerable detail and reported a number of interesting physiological differences between such groups; for example, extroverts show less global cortical arousal than introverts. He argued that decreased arousal was actually a key factor that motivated extroverts to engage in extroverted behavior. Such behavior, Eysenck reasoned, served to increase their arousal to more optimal levels. On the other hand, introverts showed heightened global cortical arousal. Introverted behavior was thought to decrease their cortical arousal to more optimal levels. Thus, Eysenck regarded these differences in arousal as causal in producing the types of behavior that are characteristically associated with extroverts and introverts. This model, however, has been criticized as overly simplistic by some researchers (e.g., Gray, 1972).

A second way in which physiological information has been used in the study of personality is to examine relations among self-report and behavioral and physiological measures of a hypothetical construct. For example, imagine an experiment where we give a self-report measure of anxiety to a large group of subjects and select those who score low in anxiety for intensive study. If we present a moderately stressful stimulus to these subjects, some will probably show

relatively little arousal in physiological measures that are thought to reflect anxiety, while other subjects will show heightened arousal on such measures. Remember that both of these groups reported little anxiety on the self-report measure that was administered. Thus, in one group, the physiological measures seem concordant with the self-report measures, and in the other group the physiological measures are discordant with the self-report measures. Which measure are we to believe? It may be argued that *both* measures provide essential information and that what is most important in this example is the degree to which such measures are concordant or discordant.

The example described above is not entirely hypothetical. My colleagues and I (e.g., Weinberger et al., 1979; Tomarken and Davidson, 1994) and others have studied the type of person who reports himself to be low in anxiety but responds physiologically and behaviorally in ways that suggest heightened anxiety. In an early experiment (Weinberger et al., 1979) subjects who scored very low on an anxiety scale were differentiated into two groups on the basis of a second self-report measure of repressive defensiveness. Those who scored low on both were considered truly low-anxious subjects. Those who scored low on the anxiety measure but high on repressive defensiveness were considered *repressors*. We presented neutral and emotional phrases in response to which subjects were asked to say the first word or phrase that came to mind. In response to the emotional phrases, repressors showed more arousal in several autonomic measures compared to the truly low-anxious subjects. In fact, arousal in the repressors was comparable to (and in some cases, even higher than) that in a group of high-anxious subjects. This experiment illustrates the utility of measuring physiological activity in addition to self-report and action to provide a more complete account of personality. In this experiment the relation of the physiological measures to other measures of personality was most important.

The two types of approaches to the use of biological indices in personality research illustrated above both involve the use of physiological activities as *dependent variables*. A third way uses such indices as *independent variables*. In this strategy, subjects are not classified into groups on the basis of a traditional personality instrument such as paper-and-pencil measure or a projective measure. Rather, subjects are classified on the basis of a physiological measure. Relations are then examined between subjects' biological profile and relevant behavioral and/or self-report measures. Some who have used this strategy argue that one thus is not necessarily constrained by existing categories in descriptive psychiatry and personality psychology. It is possible that individual differences in certain biological processes will be discovered which do not have close analogues in categorical personality disorders or in traditional personality classification and measurement schemes. The categories of individual differences that may emerge from using biological measures in this fashion may more closely reflect "natural" individual variation.

Correlate or Substrate?

When biological measures are examined in relation to behavior or personality traits, it is useful to know whether the measure is conceptualized as a substrate of the trait in question or as a correlate. In general, substrates can be considered an actual component of the trait while correlates are merely associated events that co-occur with the trait. If the physiological measure is taken to be a correlate of the trait, experimental modification of the measure will not alter the trait. For example, a number of researchers have examined individual differences in various measures of skin concordance (e.g., see Boucsein, 1992, for review). Skin conductance primarily reflects the degree of sweating on the skin and is usually measured from surface of the palms or fingers. In all likelihood, it is safe to conceptualize skin conductance differences between groups as *correlates* of an individual difference in behavior. If we were to peripherally block the skin conductance response with a locally applied pharmacological agent, we would not alter the trait. Other physiological measures are assumed to reflect more "basic" differences between groups and are conceptualized as substrates of traits, rather than correlates. For example, some cardiac and respiratory changes associated with anxiety may, in certain circumstances, reflect substrates of this trait. In other words, if these autonomic processes were altered by a peripheral pharmacological agent, the construct of interest (i.e., anxiety) would also likely change. A specific example of this may be seen in social phobics who have been found to show heightened arousal in certain autonomic systems. One treatment is administration of a β-blocker, which blocks expression of these autonomic changes and has been found to significantly attenuate anxiety in some studies (see Price et al., 1995, for review). Some commonly used β-blockers in the treatment of social phobia have the important property of not crossing the blood–brain barrier. This allows us to conclude that the changes in behavior associated with the administration of this agent are due primarily to changes in peripheral autonomic activity and not by-products of central changes. Thus, the autonomic changes that accompany this condition are

properly conceptualized as substrates of the disorder, since altering the physiology changes the trait of interest.

It is useful to be explicit about whether a particular biological measure is to be regarded as substrate or correlate. If the measure reflects a substrate, it may be informative with respect to the underlying psychobiology of the personality trait in question. In other words, we can potentially learn about the biological mechanisms that give rise to the trait. This type of information would be useful in advancing our understanding of basic brain–behavior relations. When we measure a correlate, such information may have enormous practical utility in the prediction of behavior. However, since correlates are not directly related to underlying biological substrates, the contribution of such information to understanding of the biological bases of personality is necessarily less direct.

Does Substrate Imply Cause?

When biological substrates of personality and personality disorders are identified, researchers often assume that their presence implies a heritable cause. It is critical to underscore that such an assumption is not necessarily warranted. Identifying biological substrates of particular personality traits implies nothing about their distal cause. Causality is an entirely separate issue. The trait or disorder in question may well have heritable contributions, but it is not necessary. Biological differences among people occur for many reasons, only one of which is genetic. We know from extensive data in animals that the environment can significantly alter brain function and structure.

Experience can shape brain function and structure in two fundamental ways (Greenough and Black, 1992). Experience-expectant mechanisms appear to have evolved in cases where the information to be acquired is common to all young members of a species. For example, everyday visual and auditory input constitutes the types of experiential events that drive experience-expectant mechanisms. Experience-expectant plasticity involves the literal molding of brain synapses in response to species-typical early environmental input. It is the other form of plasticity, experience-dependent, that is more relevant to our understanding of personality since this form is driven by events that are idiosyncratic for each individual. According to Greenough and Black (1992), the critical requirement for experience-dependent plasticity is learning and memory function that will clearly vary greatly across individuals. The fact of experience-dependent plasticity and of its documented effects on brain development and synapse formation underscores the need to exercise great caution in making inferences about distal causes (in this case, whether the biological differences are a consequence of genetic or environmental factors) of biological differences. It is likely that many of the biological characteristics that will be featured below as salient in our understanding of affect-related individual differences are complex products of genetic predispositions and experience. When the proper methods for quantifying the extent of genetic contribution to complex behavioral traits are used, rarely do the findings suggest that more than 50% of the variance is attributable to genetic factors (Plomin et al., 1994).

Psychometric Considerations

Most of the psychometric considerations which apply to the measurement of personality with paper-and-pencil tests also apply to the study of individual differences in biological measures. An important concern is the reliability of the measure. If individual differences in biological measure are examined, it is important that the measure be stable, e.g., show adequate test–retest reliability. Often, physiological measures are used as correlates of personality traits, with little attention paid to psychometric considerations. If a particular measure is not stable, it will be less likely to relate to other individual difference measures that show adequate test–retest reliability.

It is also essential to demonstrate the validity of the physiological measure. In many ways, most of the research on biological correlates of personality and personality disorders is an attempt to demonstrate the validity (both concurrent and predictive) of the measures in question. For example, in Kagan's research (Kagan et al., 1988) on the biological causes of childhood shyness, he and his colleagues are exploring the degree to which early measures of autonomic activity predict later behavioral manifestations of shy and wary behavior. The physiological measures are used to enhance the construct validity of the temperamental dimension under study. In addition, the research establishes the predictive validity of the biological measures that are obtained.

AFFECTIVE NEUROSCIENCE AS A FRAMEWORK IN WHICH TO EXAMINE THE NEUROBIOLOGY OF PERSONALITY AND PERSONALITY DISORDERS

One of the most important lessons we have learned from the explosion of interest in cognitive neuroscience is the utility of decomposing complex mental processes into more elementary mental operations whose specific

neural substrates can then be determined. In the same way, affective neuroscience seeks to uncover the specific elementary constituents of emotion and to delineate the circuitry responsible for these different components. In this way, complex emotional processes are understood as instantiated in a distributed pattern of brain activity underlying the specific elementary operations that together constitute the phenomena of emotion.

Among the most striking features of human emotion is the variability that is apparent across individuals in the quality and intensity of dispositional mood and emotional reactions to similar incentives and challenges. The broad range of differences in these varied affective phenomena has been referred to as "affective style" (Davidson, 1992). Differences among people in affective style appear to be associated with temperament (Kagan et al., 1988), personality (Gross et al., 1998), personality disorders (Shapiro, 1965), and vulnerability to psychopathology (Meehl, 1975). Moreover, such differences are not a unique human attribute but appear to be present in a number of different species (e.g., Davidson et al., 1993; Kalin, 1993).

Many phenomena are subsumed under the rubric of affective style. A concept featured in many discussions of affective development, affective disorders, and personality is *emotion regulation* (Thompson, 1994). Emotion regulation refers to a broad constellation of processes that serve to either amplify or attenuate or maintain the strength of emotional reactions. Included among these processes are certain features of attention which regulate the extent to which an organism can be distracted from a potentially aversive stimulus (Derryberry and Reed, 1996) and the capacity for self-generated imagery to replace emotions that are unwanted with more desirable imagery scripts. Emotion regulation can be both automatic and controlled. Automatic emotion regulation may result from the progressive automitization of processes that initially were voluntary and controlled and have evolved to become more automatic with practice. We hold the view that regulatory processes are an intrinsic part of emotional behavior, and rarely does an emotion get generated in the absence of recruiting associated regulatory processes. For this reason, it is often conceptually difficult to sharply distinguish between where an emotion ends and regulation begins. Even more problematic is the methodological challenge of operationalizing these different components in the stream of affective behavior.

When considering the question of individual differences in affective behavior, one must specify the particular response systems in which the individual differences are being explored. It is not necessarily the case that the same pattern of individual differences would be found across response systems. Thus, for example, an individual may have a low threshold for the elicitation of the subjective experience (as reflected in self-reports) of a particular emotion but a relatively high threshold for the elicitation of a particular physiological change. It is important not to assume that individual differences in any parameter of affective responding will necessarily generalize across response systems within the same emotion. Equally important is the question of whether individual differences associated with the generation of a particular specific emotion will necessarily generalize to other emotions. For example, are those individuals who are behaviorally expressive in response to a fear challenge also likely to show comparably high levels of expressivity in response to positive incentives? While systematic research on this question is still required, initial evidence suggests that at least certain aspects of affective style may be emotion specific, or at least valence specific (e.g., Wheeler et al., 1993). These findings are predicated on the view that there is at least partially independent circuitry subserving reactivity to positive and negative incentives. Evidence in support of this claim will be reviewed below.

APPETITIVE AND AVERSIVE MOTIVATIONAL SYSTEMS: NEURAL SUBSTRATES

Although the focus of our empirical research has been on measures of prefrontal brain activity, it must be emphasized at the outset that the circuit instantiating emotion in the human brain is complex and involves a number of interrelated structures. Preciously few empirical studies using modern neuroimaging procedures that afford a high degree of spatial resolution have yet been performed (see George et al., 1995; Paradiso et al., 1997, for examples). Therefore, hypotheses about the set of structures that participate in the production of emotion must necessarily be speculative and based to a large extent on the information available from the animal literature (e.g., LeDoux, 1987) and from theoretical accounts of the processes involved in human emotion.

Based upon the available strands of theory and evidence, numerous scientists have proposed two basic circuits each mediating different forms of motivation and emotion (see, e.g., Gray, 1994; Lang et al., 1990; Davidson, 1995). The approach system facilitates appetitive behavior and generates certain types of positive affect that are approach-related, e.g., enthusiasm, pride (see Depue and Collins, in press). This form of

positive affect is usually generated in the context of moving toward a desired goal (see Lazarus, 1991; Stein and Trabasso, 1992, for theoretical accounts of emotion that place a premium on goal states). The representation of a goal state in working memory is hypothesized to be implemented in dorsolateral prefrontal cortex. The medial prefrontal cortex seems to play an important role in maintaining representations of behavioral-reinforcement contingencies in working memory (Thorpe et al., 1983). In addition, output from the medial prefrontal cortex to nucleus accumbens (NA) neurons modulates the transfer of motivationally relevant information through the NA (Kalivas et al., 1993). The basal ganglia are hypothesized to be involved in the expression of the abstract goal in action plans and in the anticipation of reward (Schultz et al., 1995a; Schultz et al., 1995b). The NA, particularly the caudomedial shell region of the NA, is a major convergence zone for motivationally relevant information from a myriad of limbic structures. Cells in this region of the NA increase their firing rate during reward expectation (see Schultz et al., 1995a). There are likely to be other structures involved in this circuit which depend upon a number of factors, including the nature of the stimuli signaling appetitive information, the extent to which the behavioral-reinforcement contingency is novel or overlearned, and the nature of the anticipated behavioral response.

It should be noted that the activation of this approach system is hypothesized to be associated with one particular form of positive affect and not all forms of such emotion. It is specifically predicted to be associated with *pregoal attainment positive affect*, that form of positive affect that is elicited as an organism moves closer toward an appetitive goal. *Postgoal attainment positive affect* represents another form of positive emotion that is not expected to be associated with activation of this circuit (see Davidson, 1994, for a more extended discussion of this distinction). This latter type of positive affect may be phenomenologically experienced as contentment and is expected to occur when the prefrontal cortex goes offline after a desired goal has been achieved. Cells in the NA have also been shown to decrease their firing rate during postgoal consummatory behavior (e.g., Henriksen and Giacchino, 1993).

Lawful individual differences can enter into many different stages of the approach system. Such individual differences and their role in modulating vulnerability to psychopathology will be considered in detail below. For the moment, it is important to underscore two issues. One is that there are individual differences in the tonic level of activation of the approach system which alter an individual's propensity to experience approach-related positive affect. Second, there are likely to be individual differences in the capacity to shift between pre- and postgoal attainment positive affect and in the ratio between these two forms of positive affect. Upon reaching a desired goal, some individuals will immediately replace the just-achieved goal with a new desired goal, and so will have little opportunity to experience postgoal attainment positive affect, or contentment. There may be an optimal balance between these two forms of positive affect, though this issue has never been studied.

There appears to be a second system concerned with the neural implementation of withdrawal. This system facilitates the withdrawal of an individual from sources of aversive stimulation and generates certain forms of negative affect that are withdrawal related. Both fear and disgust are associated with increasing the distance between the organism and a source of aversive stimulation. From invasive animal studies and human neuroimaging studies, it appears that the amygdala is critically involved in this system (e.g., LeDoux, 1987). Using functional magnetic resonance imaging (fMRI) we have recently demonstrated for the first time activation in the human amygdala in response to aversive pictures compared with neutral control pictures (Irwin et al., 1996). Amygdala activation detected by fMRI has also been observed in response to both consciously perceived (e.g., Breiter et al., 1996) and unconsciously presented (i.e., backwardly masked; Whalen et al., 1998) facial expressions of fear compared with neutral expressions. Studies using positron emission tomography have observed activation in the amygdala in response to both behavioral (e.g., Schneider et al., 1995) and pharmacological (e.g., Ketter et al., 1996) elicitors of negative affect. In addition, the temporal polar region also appears to be activated during withdrawal-related emotion (e.g., Reiman et al., 1989; but see Drevets et al., 1992). These effects, at least in humans, appear to be more pronounced on the right side of the brain (see Davidson, 1992, 1993, for reviews). In the human electrophysiological studies, the right frontal region is also activated during withdrawal-related negative affective states (e.g., Davidson et al., 1990b). At present it is not entirely clear whether this EEG change reflects activation at a frontal site or whether the activity recorded from the frontal scalp region is volume-conducted from other cortical loci. The resolution of the uncertainty must await additional studies using positron emission tomography (PET) or fMRI, which have sufficient spatial resolution to differentiate among different anterior cortical regions. In addition to the temporal polar region, the amygdala, and possibly the prefrontal cortex, it is also likely that the basal ganglia

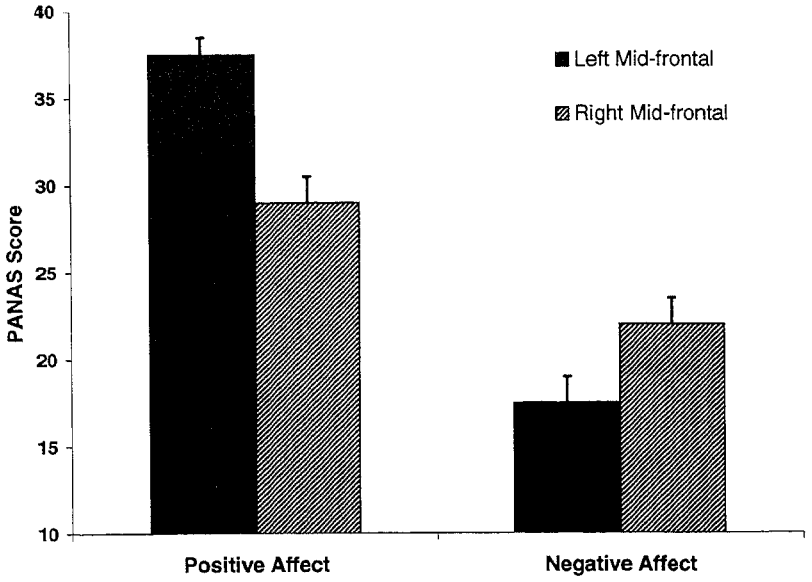

FIG. 64.1 Dispositional positive affect (from scores on the Positive and Negative Affect Schedule [PANAS]–General Positive Affect Scale) in subjects who were classified as extreme and stable left-frontally active ($N = 14$) and extreme and stable right-frontally active ($N = 13$) on the basis of electrophysiological measures of baseline activation asymmetries on two occasions separated by 3 weeks. From Tomarken et al. (1992).

and hypothalamus are involved in the motor and autonomic components, respectively, of withdrawal-related negative affect (see Smith et al., 1990).

Just as was noted in the case of the appetitive system, lawful individual differences may be present at several different stages in the aversive motivation system. Below we will consider evidence of individual differences in both subcortical and cortical components of this system and show that they each contribute to individual differences in the propensity to display aversive affects.

The nature of the relation between these two hypothesized affect systems also remains to be delineated. The emotion literature is replete with different proposals regarding the interrelations among different forms of positive and negative affect. Some theorists have proposed a single bivalent dimension that ranges from unpleasant to pleasant affect, with a second dimension that reflects arousal (e.g., Russell, 1980). Other theorists have suggested that affect space is best described by two orthogonal positive and negative dimensions (e.g., Watson and Tellegen, 1985). Still other workers have suggested that the degree of orthogonality between positive and negative affect depends upon the temporal frame of analysis (Diener and Emmons, 1984). This formulation holds that when assessed in the moment, positive and negative affect are reciprocally related, but when examined over a longer time frame (e.g., dispositional affect), they are orthogonal. It must be emphasized that these analyses of the relation between positive and negative affect are all based exclusively upon measures of self-report, and therefore the generalizability to other measures of affect is uncertain. However, we believe that a growing corpus of data does indeed indicate that one function of positive affect is to inhibit concurrent negative affect.

AFFECTIVE STYLE: THE FUNCTIONAL NEUROANATOMY OF FUNDAMENTAL DIMENSIONS OF PERSONALITY

This section presents a brief overview of recent work designed to examine individual differences in measures of prefrontal and subcortical activation and their relation to different aspects of emotion, affective style, and related biological constructs. These findings will be used to address the question of what underlying constituents of affective style such individual differences in prefrontal and limbic activation actually reflect.

In both infants (Davidson and Fox, 1989) and adults (Davidson and Tomarken, 1989) we noticed that there were large individual differences in baseline electrophysiologial measures of prefrontal activation and that such individual variation was associated with differences in aspects of affective reactivity. In infants, Davidson and 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 and 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 separated by approximately 3 weeks. At each testing session, brain activity was recorded during eight 1-minute trials, four with eyes open and four with eyes closed, presented in counterbalanced order. The data were visually scored to remove artifact 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., 1990a, for a discussion of power in different frequency bands and their relation to activation.) We computed coefficient alpha as a measure of internal consistency reliability from the data for 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 finding of import 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 sufficient test–retest reliability to be considered a trait-like index.

The large sample size in the reliability study discussed above enabled us to select a small group of extreme left- and extreme right-frontally activated subjects for MR scans to determine if there existed any gross morphometric differences in anatomical structure between these subgroups. None of our measures of regional volumetric asymmetry revealed any difference between the groups (unpublished observations). These findings suggest that whatever differences exist between subjects with extreme left vs. right prefrontal activation, those differences are likely functional and not structural.

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 the Positive and Negative Affect Schedule (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; see Fig. 64.1). More recently with Sutton (Sutton and Davidson, 1997) we showed that scores on a self-report measure designed to operationalize Gray's concepts of Behavioral Inhibition and Behavioral Activation (the BIS/BAS; Carver and White, 1994) were even more strongly predicted by electrophysiological measures of prefrontal asymmetry than were scores on the PANAS (Fig. 64.2). Subjects with greater left-sided prefrontal activation reported more relative BAS to BIS activity compared with subjects exhibiting more right-sided prefrontal activation.

We also hypothesized that our measures of prefrontal asymmetry would predict reactivity to experimental elicitors of emotion. The model that we have developed over the past several years (see Davidson, 1992, 1994, 1995, for background) features individual differences in prefrontal activation asymmetry as a reflection of a diathesis which 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) performed an experiment to examine this question. We presented short film clips designed to elicit positive or negative emotion. Brain electrical activity was recorded prior to the presentation of the film clips. Just 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 subjects in baseline mood cannot account for the prediction of film-elicited effects that were observed.

In a very recent study, we (Larson et al., 1998) examined relations between individual differences in prefrontal activation asymmetry and the emotion-modulated startle. In this study, 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

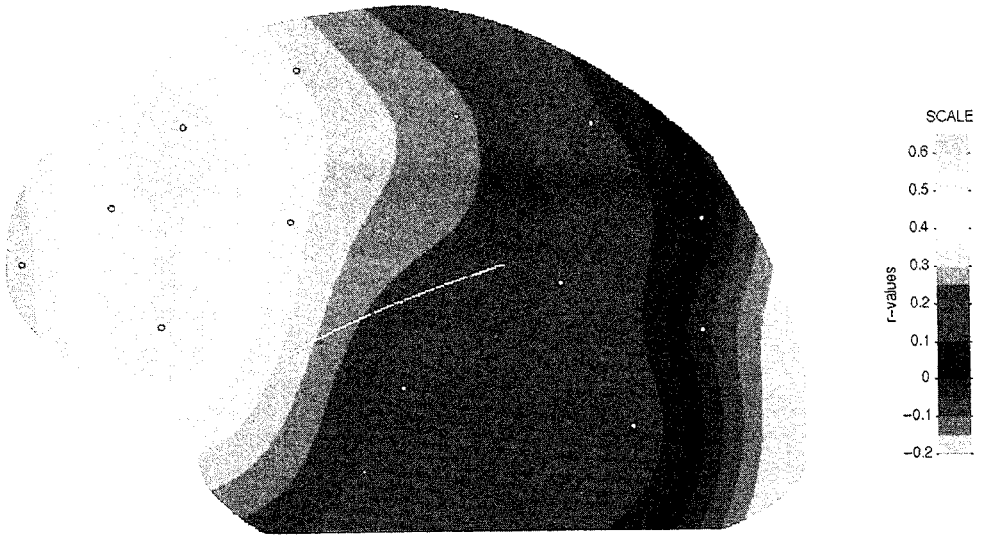

FIG. 64.2 Relations between electrophysiological measures of asymmetry and the difference between the standardized score on the Behavioral Activation and Behavioral Inhibition Scales (BIS/BAS scales; Carver and White, 1994), $N = 46$. Electrophysiological data were recorded from each subject on two separate occasions separated by 6 weeks. The BIS/BAS scales were also administered on these two occasions. Data were averaged across the two time periods prior to 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 scales. After correlations were performed for each homologous region, a spline-interpolated map was created. The yellow–orange end 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 Behavioral Activation compared with Behavioral Inhibition tendencies. The relation between asymmetric activation and the BAS–BIS difference is highly specific to the anterior scalp regions, as the correlation drops off rapidly more posteriorly. The correlation in the prefrontal region is significantly larger than the correlation in the parieto-occipital region. From Sutton and Davidson (1997).

oculi muscle region was recorded (see Sutton et al., 1997, for basic methods). Startle probes were presented both during the 6-second slide exposure as well as 500 ms 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 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, yet individuals are likely to differ dramatically in the time to recover. Similarly, we predicted that individual differences in prefrontal asymmetry would account for more variance in predicting magnitude of recovery (i.e., startle magnitude poststimulus) than in predicting startle magnitude during the stimulus. Our findings 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 this study 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 addition to the studies described above using self-report and psychophysiological measures of emotion, we have also examined relations between individual differences in electrophysiological measures of prefrontal asymmetry and other biological indices which in turn have been related to differential reactivity to stressful events. Two recent examples from our laboratory include measures of immune function and cortisol. In the case of the former, we examined differences between left and right prefrontally activated subjects in natural killer (NK) cell activity since declines in NK activity have been reported in response to stressful, negative events (Kiecolt-Glaser and Glaser, 1991). We predicted that subjects with right prefrontal activation would ex-

hibit lower NK activity compared with their left-activated counterparts because the former type of subject has been found to report more dispositional negative affect, to show higher relative BIS activity, and to respond more intensely to negative emotional stimuli. We found that right-frontally activated subjects indeed had lower levels of NK activity compared to their left-frontally activated counterparts (Kang et al., 1991).

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 were tested on two occasions 4 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 man. In the group of 50 animals, we also obtained measures of plasma cortisol during the early morning. We hypothesized that if individual differences in prefrontal asymmetry were associated with dispositional affective type, such differences should be correlated with cortisol, since individual differences in baseline cortisol have been related to various aspects of trait-related stressful behavior and psychopathology (see, e.g., Gold et al., 1988). We found that animals with right-sided prefrontal activation had higher levels of baseline cortisol than their left-frontally activated counterparts (Fig. 64.3). Moreover, when blood samples were collected 2 years following our initial testing, animals classified as showing extreme right-sided prefrontal activation at age 1 year had significantly higher baseline cortisol levels when they were 3 years of age compared with animals who were classified at age 1 year as displaying extreme left-sided prefrontal activation. These findings indicate that individual differences in prefrontal asymmetry are present in nonhuman primates and that such differences predict biological measures that are related to affective style.

The activation of the aversive motivation system is often accompanied by increased sympathetic activity and, as we have shown above, increased cortisol. A common mediator of the cascade of biological changes that accompanies aversive motivation is the amygdala. While modern neuroimaging studies are beginning to reveal reliable changes in amygdala activation in response to specific provocation, as has been reviewed above, little research has been performed on possible individual differences in amygdala activation and their relation to measures of dispositional negative affect.

Both fMRI and O^{15} PET are ill-suited, for different reasons, for examining individual differences in resting or baseline levels of activation in the amygdala. fMRI as it is currently used requires that at least two conditions be compared. What is measured is a relative difference in MR signal intensity between two or more conditions. Currently, fMRI is not calibrated in real physiological units. While O^{15} PET can be calibrated in real units, it reflects activity over a very short period of time (approximately 1 minute) and thus, for psychometric reasons, is poorly suited to capture trait-like differences. It would be the equivalent of developing a single-item self-report instrument for assessing individual differences. PET used with fluorodeoxyglucose (FDG) as a tracer, however, is well suited to capture trait-like effects since the period of active uptake of tracer in the brain is approximately 30 minutes. Thus,

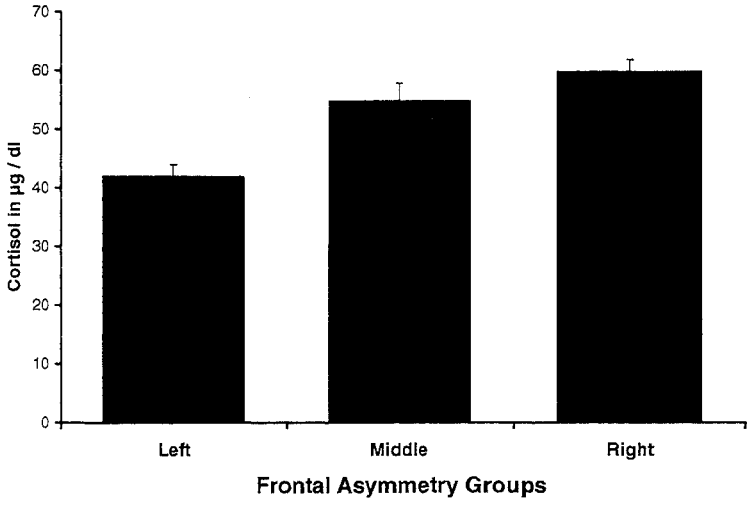

FIG. 64.3 Basal morning plasma cortisol from one-year-old rhesus monkeys classified as left ($N = 12$), middle ($N = 16$), or right ($N = 11$) frontally activated based upon electrophysiological measurements. From Kalin et al. (1998).

it is inherently more reliable since the data reflect activity aggregated over this 30-minute 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 coregistering the two image sets. Thus, for each subject, we used an automated algorithm to fit the MR scan to the PET image. Regions of interest (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 coregistered PET images. Glucose metabolism in the left and right amygdala ROIs were then extracted. The interrater reliability for the extracted glucose metabolic rate is highly significant with intraclass correlations between two independent raters ≥ 0.97. Figure 64.4 illustrates ROIs drawn around the amygdala on MR scans of three subjects and the associated coregistered PET images from the same subjects. We found that subjects with greater glucose metabolism in the right amygdala report greater dispositional negative affect on the PANAS scale (Fig. 64.5). 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. Most nondepressed controls score so low on the PANAS trait negative scale that it is not possible to examine the same relation in this group because of the severe truncation of range for the PANAS scores.

IMPLICATIONS FOR PERSONALITY DISORDERS

Most of the extant biological research on personality disorders has searched for possible dysfunction in specific neurotransmitter systems using peripheral metabolites in plasma or CSF or pharmacological challenge studies. The association between abnormalities in specific neurotransmitter systems and particular personality disorders is reviewed by Coccaro and Siever (1995). Of the personality disorders they consider, those with impulsivity and aggression as a defining feature have been among the most well studied using these paradigms. Such disorders appear to be associated with reductions in indices of central 5-HT. Neuroendocrine challenge studies have been performed that further document abnormalities in 5-HT in particular personality disorders. For example, prolactin responses to fenfluramine are blunted in borderline (Cocaro et al., 1989) and antisocial personality disordered patients (O'Keane et al., 1992). Personality disorders in which mood disturbance is a prominent feature have been evaluated using the same peripheral neurochemical paradigms

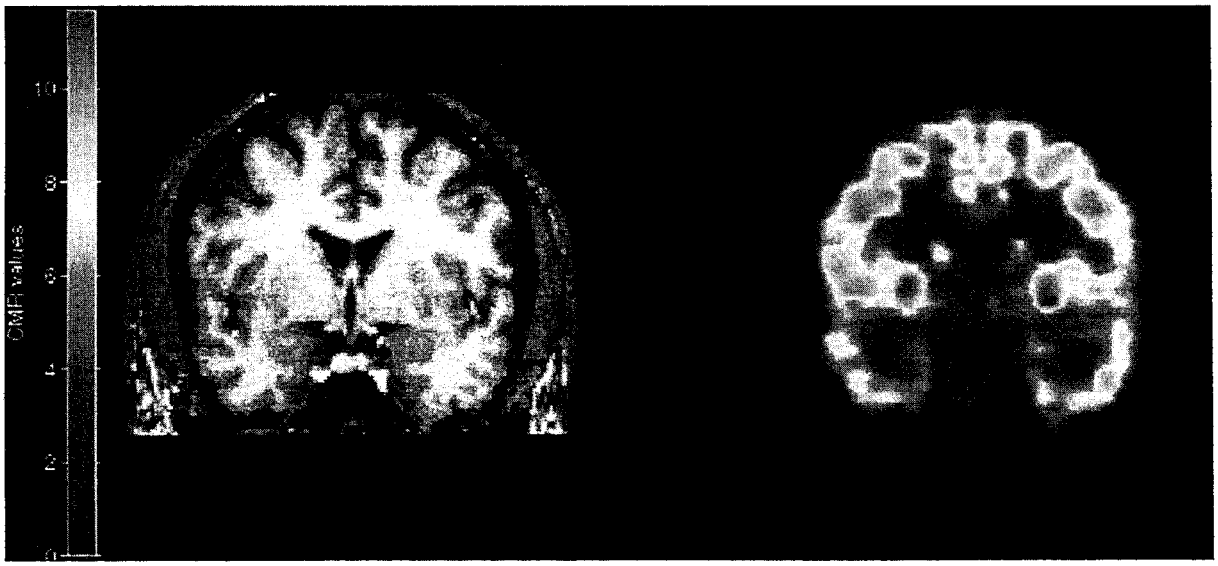

FIG. 64.4 Illustration of positron-emission tomography–magnetic resonance imaging (PET–MRI) coregistration and amygdalar RO1 delineation. This figure presents a representative image plane in the coronal orientation for one participant. The PET image plane is presented beside its corresponding coregistered MRI plane. Each actual amygdalar RO1 included data from 5–8 planes. The PET image of absolute $rCMR_{glu}$ is from a GE Advance PET camera (in-plane resolution approximately 5 mm FWHM). Units of the PET color scale are in mg/100g/min.

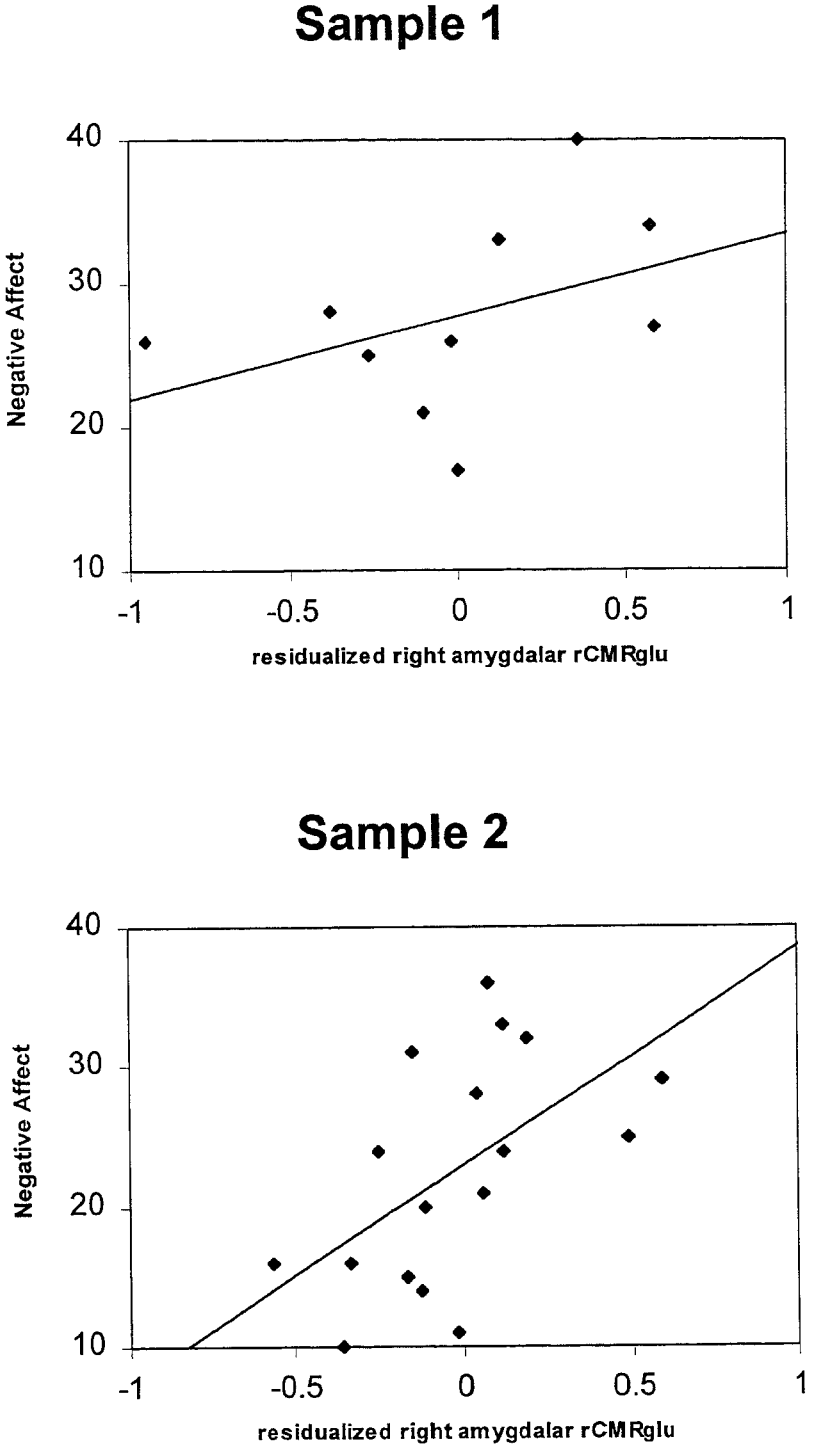

FIG. 64.5 Scatter plots of the correlations within the depressed groups between dispositional negative affect (assessed with the PANAS Negative Affect Scale—trait version) and residualized $rCMR_{glu}$ in the right amygdala, Sample 1, $r(8) = 0.41$, $P = 0.24$; Sample 2, $r(15) = 0.56$, $P < 0.02$.

that have been extensively utilized in the literature on depression, e.g., dexamethasone suppression. These studies have yielded variable and inconsistent findings with rates of cortisol nonsuppression varying between 9% and 73% (Korzekwa et al., 1991). Similar inconsistencies have been found using thyrotropin-releasing hormone stimulation testing (Kavoussi et al., 1993). Studies of patients with avoidant personality disorder where anxiety is a prominent feature have also yielded disappointing and inconsistent results on measures that reflect hypothalamic-pituitary and hypothalamic-thyroid function (see Coccaro and Siever, 1995, for review).

Other approaches to the classification of personality disorders have been advocated that putatively are more neurobiologically tractable (e.g., Cloninger, 1994). Cloninger argues that temperament and character should be distinguished and that different personality disorders may be products of specific combination of temperament and character traits. Cloninger proposes four temperament systems: behavioral activation, behavioral inhibition, behavioral dependence, and behavioral persistence. While the underlying neurobiology and functional neuroanatomy of these systems has not been characterized, Cloninger (1994) does review some promising initial trends. He underscores the importance of dopaminergic function for the behavioral activation system, though he does not specify which dopamine system is most importantly implicated. Variations in the behavioral inhibition system are linked to differences in serotonin turnover. The behavioral dependence system, reflected in warm social affiliation, is associated with oxytocin. While these associations are intriguing, they are very gross linkages between self-report measures and peripheral biochemical assays that provide little information on the functional neuroanatomy of these systems.

One of the most important lessons we have learned from cognitive and affective neuroscience is the importance of decomposing complex behavior and disorders into more specific and elementary symptoms and processes. The search for the neural substrates of these more specific components is then a more tractable problem. The DSM-IV lists 10 specific personality disorders: paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, and obsessive-compulsive. These disorders are further grouped into three clusters on the basis of common symptoms. Cluster A includes the paranoid, schizoid, and schizotypal personality disorders. Cluster B includes the antisocial, borderline, histrionic, and narcissistic personality disorders. Cluster C includes the avoidant, dependent, and obsessive-compulsive personality disorders. To advance research in this area, relations between reliably measured specific symptom clusters and particular biological characteristics must be studied. For example, the lack of remorse and failure to plan ahead that are characteristic of antisocial personality disorder may be a function of decreased activation in right prefrontal regions that have been implicated in aversive motivation and behavioral inhibition. The inhibition and fear of criticism that are hallmark signs of avoidant personality disorder may be associated with hyperactivation in the circuitry subserving the aversive motivation system. Studies are needed that examine relations between tonic activation in the amygdala and in the right prefrontal cortex in patients with this diagnosis. The affective instability that is a prominent feature of borderline personality disorder may be associated with excessive variability in activation levels in circuits mediating appetitive and aversive motivation. New research that examines within-subject variability in measures of activation in different components of this circuit is needed. Such measures of within-subject variability may underlie the instability in phenotypic manifestations of affective behavior.

A particularly promising direction for future research is the use of PET receptor ligand methods to integrate our understanding of the neurochemical and neuroanatomical substrates of personality and its disorders. For example, Farde et al., (1997) have recently reported an association between decreased D_2 receptor density in the putamen and high scores on a measure of "detachment" that reflects social isolation, indifference to other people, and a lack of intimate relationships. Future studies might profitably examine relations between PET receptor measures and objective indices of emotional reactivity and affective style.

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