SERIES IN AFFECTIVE SCIENCE

Extreme Fear, Shyness, *AND* Social Phobia

Origins, Biological Mechanisms, and Clinical Outcomes

Edited by

Louis A. Schmidt

Jay Schulkin

EXTREME FEAR, SHYNESS, and SOCIAL PHOBIA

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Behavioral Inhibition and the Emotional Circuitry of the Brain

Stability and Plasticity During the Early Childhood Years

Richard J. Davidson & Maureen Rickman

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. For example, some people appear very reticent and wary, whereas others are outgoing and bold across a broad range of contexts. The myriad range of differences in these varied affective phenomena has been referred to as "affective style" (Davidson, 1992, 1998). Differences among people in affective style appear to be associated with temperament (Kagan, Reznick & Snidman, 1988), personality (Gross, Sutton & Ketelaar, 1998) 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, Kalin & Shelton, 1993; Kalin, 1993; Kalin, Larson, Shelton, & Davidson, 1998) and are apparent early in life (e.g., Kagan, Reznick, & Gibbons, 1989).

The next section presents a selective overview of the some of the key circuitry that underlies two major emotional and motivational systems—the approach and withdrawal systems. The third section considers individual differences in these basic systems, indicates how such differences might be studied, and discusses the behavioral consequences of such individual differences. In the fourth section, we specifically consider the problem of behavioral inhibition and present new findings on relations between prefrontal asymmetry and measures of behavioral inhibition in a longitudinal sample. The last section considers some of the implications of these data for understanding the mechanisms that underlie behavioral inhibition.

The Functional Neuroanatomy of Approach and Withdrawal

Although the focus of our empirical research has been on measures of prefrontal brain activity, it must be emphasized at the outset that the circuitry that instantiates 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, and 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 on 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., Davidson, 1995; Gray, 1994; Lang, Bradley, & Cuthbert, 1990). The approach system facilitates appetitive behavior and generates certain types of positive affect that are approach-related, for example, enthusiasm, pride, and so forth. (see Depue & Collins, in press, for review). This form of positive affect is usually generated in the context of moving toward a desired goal (see Lazarus, 1991, and Stein & 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, Rolls & Maddison, 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, Churchill, & Klitenick, 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, Apicella, Romo, & Scarnati, 1995; Schultz, Romo et al., 1995). 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, Apicella, et al., 1995). There are likely other structures involved in this circuit which depend on a number of factors, including the nature of the stimuli that signal appetitive information, the extent to which the behavioral-reinforcement contingency is novel or overlearned, and the nature of the anticipated behavioral response.

In a very recent study using positron emission tomography (PET) with ^{18}F-labeled deoxyglucose (FDG), we (Davidson et al., 1998) presented aversive or appetitive pictures during the FDG uptake procedure in separate sessions. We found significant left-sided metabolic increases during the appetitive condition in inferior prefrontal cortex, nucleus accumbens, and superior prefrontal, premotor, and motor regions. The significant left-sided focus of these metabolic increases was confirmed by formally testing the Condition $\times$ Hemisphere interactions for these regions. Similar findings have recently been reported by Thut et al. (1997) in response to monetary reward. These data imply that at least in humans, the circuitry for appetitive (and aversive) emotion is lateralized. Such a functional neuroanatomical arrangement may be advantageous in helping the brain to compute affective value (see Davidson et al., 1998, for additional discussion of this issue).

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 or joy (though conventional emotional terms appear inadequate in capturing these hypothesized differences) and is expected to occur when the prefrontal cortex goes off-line after a desired goal has been achieved. Cells in the NA have also been shown to decrease their firing rate during the postgoal consummatory phase (e.g., Henriksen & Giacchino, 1993).

Lawful individual differences can enter into many different stages of the approach system. 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 that 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. On 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; see figure 5.1). In addition, the temporal polar region also appears to be activated during withdrawal-related emotion (e.g., Reiman, Fusselman, Fox, & Raichle, 1989; but see Drevets, Videen, MacLeod, Haller, & Raichle, 1992). These effects, at least in humans, appear to be more pronounced on the right side of the brain (Davidson, 1992; see Davidson, 1993, for reviews). In the human PET and electrophysiological studies, the right frontal region is also activated during withdrawal-related negative affective states (e.g., Davidson, Ekman, Saron, Senulis & Friesen, 1990). In the recent FDG-PET study from our laboratory mentioned previously (Davidson et al., 1998), we observed increased glucose metabolism in response to aversive pictures (compared with appetitive pictures) in right prefrontal cortex (Brodmann's area 9) and amygdala. In addition to the prefrontal and temporal polar cortical regions and the amygdala, it is also likely that the basal ganglia and hypothalamus are involved in the motor and autonomic components, respectively, of withdrawal-related negative affect (see Smith, DeVita, & Astley, 1990).

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 inter-relations 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., Cacioppo & Berntson, 1994; Watson & Tellegen, 1985). Still others have suggested that the degree of orthogonality between positive and negative affect depends on the temporal frame of analysis (Diener & 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 on measures of self-report, and therefore their generalizability to other measures of affect are uncertain. However, based on new data from our lab that shows reciprocal relations between metabolic activity in the left prefrontal cortex and the amygdala (See Davidson, 1998, for a review of these findings), we believe that one function of positive affect is to inhibit concurrent negative affect. It seems likely that the presence of negative affect would interfere with the generation of pregoal attainment positive affect and with the production of approach behavior. It would therefore be adaptive for negative affect to be inhibited during the generation of positive affect. Of course, the time course of this hypothesized inhibition and the boundary conditions for its presence remain to be elucidated in future research.

Individual Differences in Asymmetric Prefrontal Activation: What Do They Reflect?

This section presents a brief overview of recent work from our laboratory that was designed to examine individual differences in measures of prefrontal 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 activation actually reflect.

In both infants (Davidson & Fox, 1989) and adults (Davidson & Tomarken, 1989), we noticed that there were large individual differences in baseline electrophysiological 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-sided and greater right-sided prefrontal activation during a preceding resting baseline than 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 on 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 could thus be used as a trait-like measure. Tomarken, Davidson, Wheeler, and Doss (1992) recorded baseline brain electrical activity from 90 normal participants 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, Chapman, Chapman, & Henriques, 1990, for a discussion of power in different frequency bands and their relation to activation). Using the asymmetry measures derived from each of the eight 1-minute trials as the data, we computed coefficient alpha, separately for each session, as a measure of internal consistency reliability. The coefficient alphas were quite high, with all values exceeding .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 .65 to .75 depending on the specific sites and methods of analysis. The major finding of import from this study was the demonstration that measures of activation asymmetry based on 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.

The large sample size in the reliability study discussed here enabled us to select a small group of extreme left and extreme right frontally activated participants 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 (Davidson, 1997, unpublished data). These findings suggest that whatever differences exist between participants with extreme left versus right prefrontal activation, such 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 participants would show systematic differences in dispositional positive and negative affect. We administered the trait version of the Positive and Negative Affect Scales (PANAS; Watson, Clark & Tellegen, 1988) to examine this question and found that the left frontally activated participants reported more positive and less negative dispositional affect than their right frontally activated counterparts (Tomarken et al., 1992; see figure 5.2). More recently, with Sutton (Sutton & 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 scales; Carver & White, 1994) were even more strongly predicted by electrophysiological measures of prefrontal asymmetry than were scores on the PANAS scales (see figure 5.3). Participants with greater left-sided prefrontal activation reported more relative BAS to BIS activity than participants who exhibited more right-sided prefrontal activation. Importantly, in each of these studies, measures of asymmetry from posterior scalp regions derived from the identical points in time showed no relation with the affect variables. In the Sutton and Davidson (1997) study, in which we had a sufficiently large sample size, we tested the significance of the difference in the magnitude of correlation between measures of activation asymmetry in anterior and posterior regions and the BAS-BIS scores.

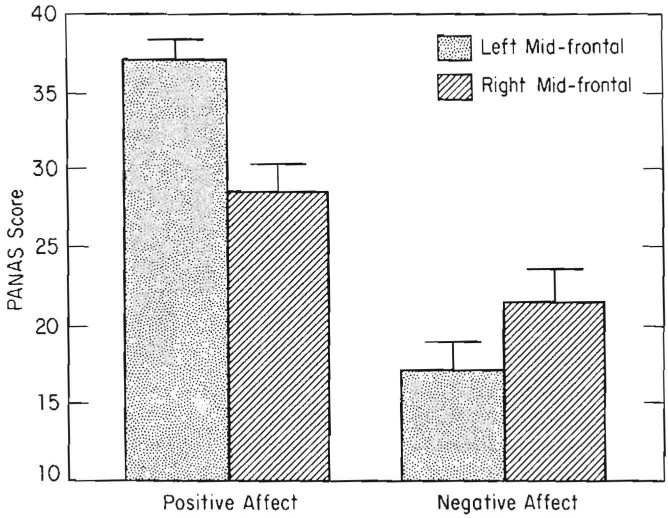

Figure 5.2. Dispositional positive affect (from scores on the PANAS-General Positive Affect Scale) in participants who were classified as extreme and stable left frontally active ($N = 14$) and extreme and stable right frontally active ($N = 13$) on the basis of electrophysiological measures of baseline activation asymmetries on two occasions separated by 3 weeks. From Tomarken, Davidson, Wheeler and Doss (1992). Copyright 1992 by American Psychological Association. Reprinted by permission.

We found that the prefrontal asymmetry measures were significantly more highly correlated with the affect measures than were the measures of posterior asymmetry from the identical periods, underscoring the specificity of this relation to the anterior scalp region.

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, Davidson, & Tomarken, 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, participants were asked to rate their emotional experience during the preceding film clip. In addition, participants 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 individuals in baseline mood cannot account for the prediction of film-elicited emotion effects that was observed.

In a very recent study, we (Davidson, Dolski, Larson, & Sutton, 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, Bradley, & Cuthbert, 1995) while acoustic startle probes were presented and the EMG-measured blink response from the orbicularis oculi muscle region was recorded (see Sutton, Davidson, Donzella, Irwin, & Dottl, 1997, for basic methods). Startle probes were presented on separate trials both during the 6-second slide exposure as well as 500 ms following the offset of the pictures. We interpreted startle magnitude during picture exposure as providing an index related to the peak of emotional response, whereas 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, because an acute emotional stimulus is likely to produce a normative response across participants, yet individuals are likely to differ dramatically in the time they take to recover. Similarly, we expected that individual differences in prefrontal asymmetry would account for more variance in predicting magnitude of recovery (i.e., post-stimulus startle magnitude) than in predicting startle magnitude during the stimulus. Our findings were consistent with our predictions and indicated that participants with greater left-sided prefrontal activation show a smaller 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 previously 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 that 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 participants in natural killer (NK) cell activity, since declines in NK activity have been reported in response to stressful, negative events (Kiecolt-Glaser & Glaser, 1991). We predicted that participants with increased right prefrontal activation would exhibit lower NK activity than their left-activated counterparts because the former type of individual 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 participants indeed had lower levels of NK activity than their left frontally activated counterparts (Davidson, et al., in press; Kang et al., 1991).

In collaboration with Ned Kalin, our laboratory has been studying similar individual differences in scalp-recorded measures of prefrontal activation asymmetry in rhesus monkeys (Davidson, Kalin & Shelton, 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 4 months apart. We found that the test-retest correlation for measures of prefrontal asymmetry was .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 style, 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., Brown et al., 1996; Gold, Goodwin, & Chrousos, 1988). We found that animals with right-sided prefrontal activation had higher levels of baseline cortisol than their left frontally activated counterparts. 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 than 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.

Childhood Behavioral Inhibition and Prefrontal Activation Asymmetry

Research efforts to address the proximal causes of childhood behavioral inhibition have implicated a pattern of biological factors that appear to be associated with the development of this temperamental style (e.g., Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984; Kagan, Reznick, & Snidman, 1987, 1988). A previously reported electrophysiological study found increased relative right cortical activation in behaviorally inhibited 3-year-olds compared with uninhibited 3-year-olds (Finman, Davidson, Colton, Straus, & Kagan, 1989), a pattern of cortical asymmetry that has been interpreted as reflecting increased vulnerability to negative emotions (Davidson, 1992, 1998).

In the Finman et al. (1989) study, behavioral inhibition was measured at age 31 months in a laboratory play session, and electrophysiology was measured at age 37 months. For sake of simplicity, these will be referred to as age 3 data. In the play session, same-gender pairs of children who were unknown to each other were exposed to the mild stressors, including a talking robot and an adult stranger who tried to engage them in play. Measures of environmental engagement (latency to touch the first toy; latency to enter a toy tunnel; time within arms' reach of mother and not playing) and of social engagement (latency to approach talking robot; latency to speak first word; latency to approach the stranger) were used to determine level of behavioral inhibition. We tested 368 children. Twenty-four of the most inhibited children and 29 of the most uninhibited returned for an electrophysiological evaluation 6 months later. A control sample of 24 children who were intermediate in their level of behavioral inhibition was also tested (Finman et al., 1989).

The inhibited children had relatively more right than left frontal brain activity, whereas uninhibited children had relatively more left than right frontal brain activity. Middle children had brain activity patterns intermediate between the extreme groups.

Behavioral Inhibition and Brain Asymmetry in Middle Childhood

This cohort of inhibited, middle, and uninhibited children returned to the laboratory at age 9 years for a follow-up evaluation (Rickman, 1997). An age-appropriate laboratory paradigm was designed to allow assessment of measures of environmental engagement and social engagement that were similar to the earlier assessment. On arrival, the child was escorted to a waiting room while the parent met with the experimenter in a separate room. The waiting room had numerous highly attractive toys on one side and chairs, end tables, and adult books and magazines on the other. A few minutes after being left alone, a female stranger entered the waiting room and over several minutes made increasingly more direct attempts to engage the child. A set of variables that had a face-valid relation to those included in the assessment at age 3 were coded from videotape: latency to touch first toy, latency to first spontaneous utterance to stranger, latency to approach within 3 feet of stranger, and total time inactive. A composite index of behavioral inhibition was calculated from these variables.

Approximately 1 year later, these children returned for an electrophysiological evaluation. EEG (electroencephalography) was recorded from 29 scalp locations with a Lycra cap fit with electrodes using the standard 10–20 system, referenced to the left ear, and placed using known anatomical landmarks. Mean power density from 7–11 Hz was used as the child equivalent of adult alpha (8–13 Hz). Asymmetry scores were calculated individually for each child as the difference in brain activity between homologous sites after correction for muscle artifact. A tercile split was done on behavioral inhibition (BI) scores extracted from the age 9 behavioral evaluation so that participants could be assigned to inhibited, middle, and uninhibited groups at age 9.

The relation between BI at age 9 and brain activity at age 10 was similar to the relation observed at age 3. Children who were inhibited at age 9 had relative right activation in frontal and lateral frontal regions measured approximately 1 year later, whereas children who were uninhibited at age 9 had relative left activation in the frontal and lateral frontal regions (vertex reference). Figure 5.4 shows that the inhibited group exhibited relative right frontal activation asymmetry, whereas the uninhibited group had a pattern of relative left frontal activation asymmetry. The middle group exhibited a pattern of activation asymmetry that was intermediate between the inhibited and uninhibited groups. The main effect of group at age 9 was statistically significant, $F(2,44) = 3.21$, $p < .05$.

A correlation was calculated between frontal asymmetry and the behavioral inhibition index (BI) to determine the extent to which extreme scores within groups contributed to the overall effect. As can be seen in figure 5.5, there is a monotonic relation between age 10 frontal asymmetry and BI score at age 9. Inhibited behav-

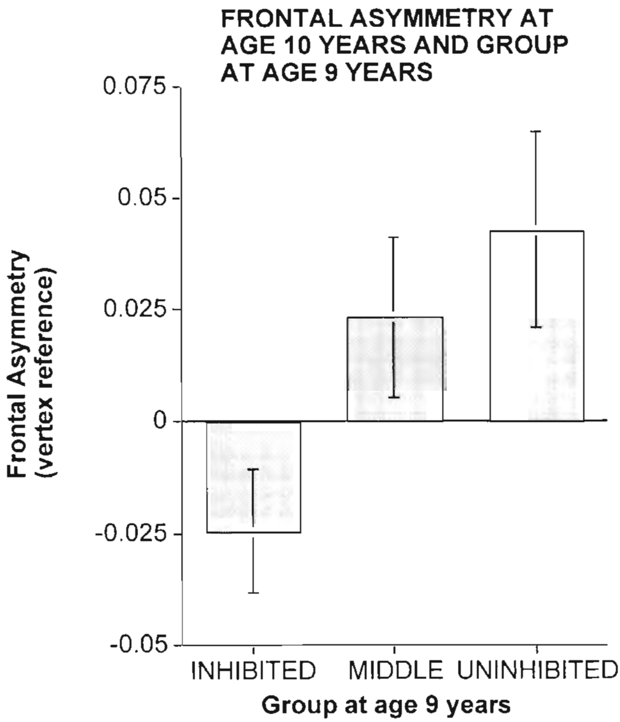

Figure 5.4. Children identified as inhibited at age 9 years had relative right frontal asymmetry at age 10 years. Uninhibited children had relative left frontal asymmetry, and middle children had intermediate asymmetry scores. (Adapted from Rickman, 1997).

ior is associated with increased relative right frontal activation. The magnitude of the correlation between frontal asymmetry and behavior at this age is comparable to that observed in early childhood.

This finding is consistent with predictions. Left frontal brain activity is associated with approach-oriented behavior, whereas right frontal brain activity appears to be associated with withdrawal. In both early childhood (age 3 years) and early school years (ages 9 and 10 years), we found the predicted relation between frontal asymmetry and behavioral inhibition.

Stability of Behavioral Inhibition and Brain Asymmetry

In figure 5.5 we represent the group status at age 3 years of each of the participants who contributed to the analysis at ages 9 and 10 years. The impression of a lack of correlation between age 3 BI and age 9 BI is born out statistically. Chi-square analysis found that BI group at age 3 was unrelated to BI group at age 10. Using the continuous distribution of BI scores at each age, BI at age 3 was uncorrelated with BI at age 9, Spearman $r = .03$, $p > .8$.

At both ages, children were given time to engage themselves in play prior to be-

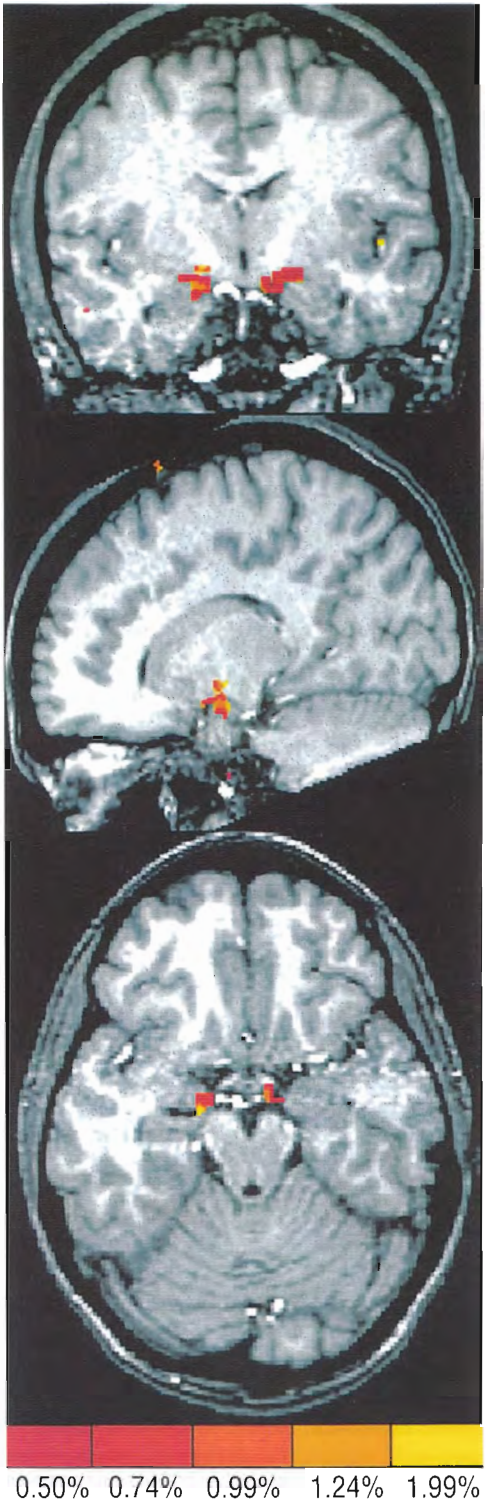

Figure 5.1 Group data showing bilateral activation in the amygdala detected with fMRI in response to aversive compared with neutral pictures. From Irwin et al. (1996).

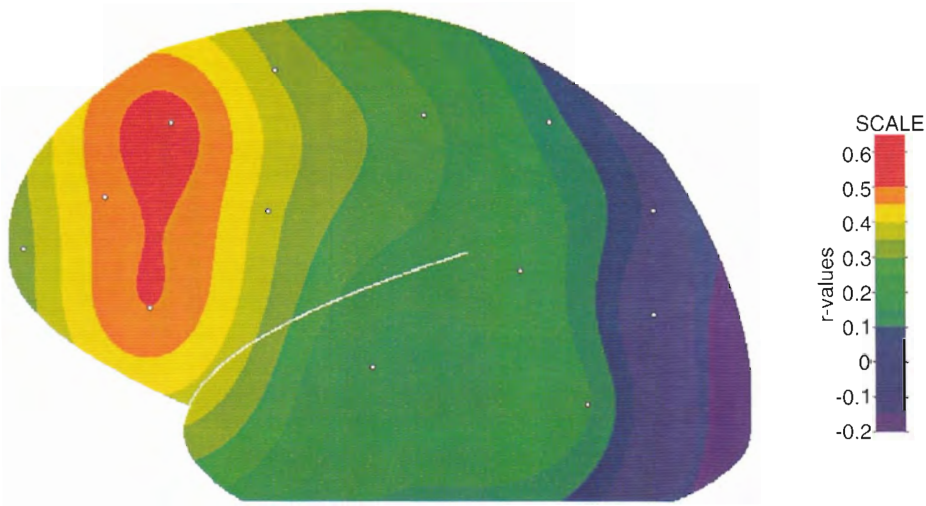

Figure 5.3 Relations between electrophysiological measures of asymmetry and the difference between the standardized score on the Behavioral Activation and Behavioral Inhibition Scales (BAS/BIS scales; Carver & White, 1994), $n = 46$. Electrophysiological data were recorded from each subject on two separate occasions at a 6-week interval. The BAS/BIS 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 denotes 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 & Davidson (1997).

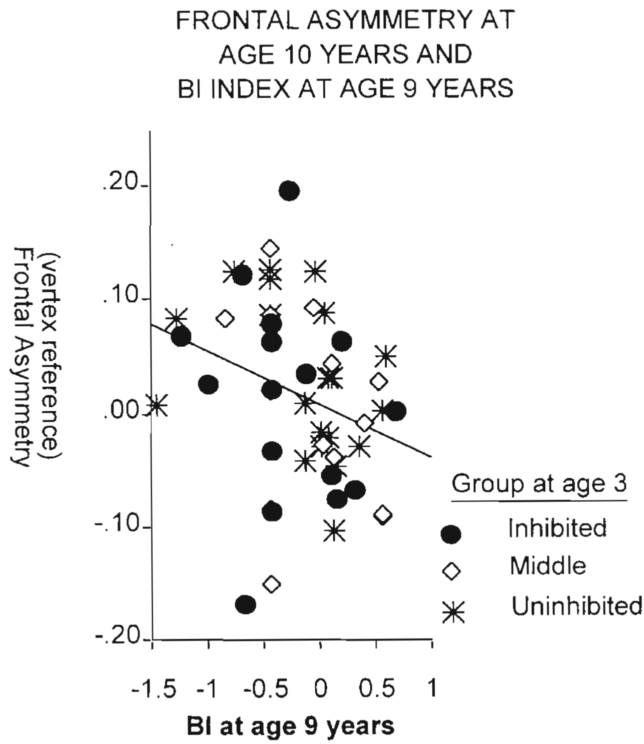

Figure 5.5. Frontal asymmetry (referenced to vertex) at age 10 years was significantly correlated with BI assessed at age 9 years, Spearman $r = -.37$, $p < .008$, $n = 50$. (Adapted from Rickman, 1997)

ing challenged. During the age 3 play session, the child was presented with two social challenges: first, a talking robot, and then an adult female stranger who brought in a tray of attractive toys. At age 9, the children were similarly given a free play "warm-up" period, followed by the introduction of a stranger. For both sessions, the stranger made increasingly more pointed attempts to engage the child. Despite the seeming similarities of the behavioral challenges at each session and of our efforts to replicate in an age-appropriate manner the manipulations at each assessment, BI at age 3 years was uncorrelated with BI at age 9 years. Table 5.1 illustrates the lack of correlation among these measures that compose the BI index at each age.

One possible explanation for the lack of stability of behavioral inhibition over time is that the scenarios in which behavior was observed were not genuinely analogous. An additional problem is that longitudinal assessment makes it difficult to be certain that the behaviors we observed were more powerfully related to individual differences in behavioral inhibition than to confounds associated with having been observed in similar situations. However, the lack of apparent stability in BI over time might be better explained as a consequence of the changing nature of the manifestations of BI.

Table 5.1 Correlations between age 3 = and age 9 = year variables used to calculate behavioral inhibition.

	Age 9 Variables			
Age 3 Variables	Latency to touch toy (n = 60)	Latency to speak word to stranger (n = 59)	Latency to approach within 3 feet of stranger (n = 56)	Time inactive (n = 59)
Proximity to mother	.07	−.05	.03	.03
Latency to approach robot	−.02	.00	−.04	−.02
Latency to speak	−.11	−.09	.12	.02
Latency to approach stranger	.06	−.02	.19	.14
Latency to touch first toy	.03	−.14	−.08	−.05
Latency to enter tunnel	−.03	.01	−.04	−.01

Note: Values are Spearman correlations.

Early measures of behavioral inhibition, like other temperamental traits, may not be strongly predictive of later behavior. When predicting temperament from early infancy (age 8 months) to age 4 years, there are few participants who retain their classification, even when participants are selected from extremes (e.g., Maziade, Cote, Bernier, Boutin, & Thivierge, 1989). Even though there is a large body of literature that documents the sequelae of behavioral inhibition, a careful reading of the literature shows that only a limited sample of children show stability in their degree of behavioral inhibition over time. In one longitudinal study (Asendorpf, 1991), behavioral inhibition was assessed at 4 years, 6 years, and 8 years of age in an unselected sample of children. Only 13 of 87 children had behavioral inhibition scores in the upper quartile for all three assessment ages. In a different study, children from an unselected sample who were observed multiple times from 14 to 48 months of age did not show significant stability in laboratory observations of BI over time (Kagan et al., 1989). Similarly, social withdrawal in an unselected sample of kindergarten children was only modestly correlated with social withdrawal in Grade 2 and was not predictive of social withdrawal in Grade 4 (Rubin, 1993).

Apparent instability in BI may also be due, in part, to phasic changes in development. Numerous developmental psychologists from diverse areas of research have observed that the development process includes periods of stability, as well as periods of instability (Block, 1982; Haan, Millsap, & Hartka, 1986; Thelen, 1989). Some authors have suggested that the best time to measure long-standing traits is when the individual is under stress (Wright & Mischel, 1987). They suggest that in day-to-day functioning, influences such as coping mechanisms, social support, and the like sometimes overwhelm the behavioral expression of a trait. These authors found that children who were judged to be prototypically aggressive or withdrawn did not show predictable behaviors in low-demand situations but were characteristically aggressive or withdrawn in high-demand situations.

Our early childhood measures of BI were obtained at a key developmental period of differentiation and separation for children. Middle childhood can be characterized as a "settled" period, where developmental challenges are at a minimum. We may have found evidence of stability of behavioral inhibition had we assessed the children at a developmentally challenging time, such as during the transition to school or during puberty.

Implicit in this explanation is the presumption of an underlying temperamental "trait" or diathesis that is activated in response to stress. We tested the extent to which brain asymmetry indexed this hypothesized diathesis by comparing asymmetry scores at age 3 with those obtained at age 10 and by comparing age 3 asymmetry with age 9 BI. There was no correlation between brain asymmetry at age 3 and brain asymmetry at age 10. Further, age 3 asymmetry failed to predict age 9 BI. Given the finding of a correlation between BI and brain asymmetry within each age period, the lack of the longitudinal predictive relation between these variables is unlikely to be a function of a lack of validity of electrophysiological measures of prefrontal activation asymmetry in indexing affective style characteristics but rather may be a function of the fact that the period across which we sampled is one during which considerable plasticity is occurring.

It also may be that individual differences in brain asymmetry and BI are jointly influenced by plastic changes in the brain. There is a large body of data that shows that brain structures undergo significant development and reorganization from early to middle childhood. There are marked increases in synaptic density, dendritic branching, myelination, and overall brain mass during this period of development, with notable growth spurts around ages 2–4 years and age 7 (Fischer & Rose, 1994). Synaptic density in the frontal cortex peaks at ages 1 year and 7 years while neurons and synapses are continuously "pruned" and modified in a dynamic growth process. Neurons in the frontal lobes are among the last to myelinate, and they continue myelination into adulthood (Spreen, Tupper, Risser, Tuokko & Edgell, 1984).

Patterns of EEG also show notable changes during this period of development. EEG coherence is a measure which has been interpreted to reflect aspects of intracortical connectivity (Thatcher, 1994). The developmental trajectory of EEG coherence in the left hemisphere differs from that of the right hemisphere, and there appear to be growth spurts in the degree of EEG coherence at ages 5 to 7 years and 9 to 11 years, especially in the lateral frontal and frontal regions (Thatcher, 1992, 1994).

It may be that even if behavioral inhibition is not stable over time, brain asymmetry measures may predict a coherent pattern of affective style, and the relation between brain asymmetry and affective style may remain stable over time. This is a view that would hold that plastic changes in affective style occur over this developmental period, produced via a combination of heritable and experiential influences. These changes in affective style are associated with changes in prefrontal brain function, along with changes in behavioral signs of inhibition.

Stability at the Extremes

Much of the published work on behavioral inhibition derives from the assumption that BI is an important temperamental trait that has long-term consequences for the individual. Shy children become shy adults and choose careers and lifestyles that are less adventuresome than those of their nonshy peers (Caspi, Bem, & Elder, 1989; Caspi, Elder, & Bem, 1988). Behaviorally inhibited children appear to be at increased risk of childhood psychiatric disorders (Rosenbaum et al., 1991). Behaviorally inhibited infants show persistence of phobic reactions to novel social situations from early childhood through adulthood (Kagan & Moss, 1962). These data and more suggest that at least for some individuals, behavioral inhibition remains stable and has long-lasting influences on personal development.

Given the large body of evidence that shows that individual differences in behavioral inhibition do have long-term consequences, we attempted to identify those children who were most likely to exhibit trait-like behavioral inhibition (Rickman, 1997). We predicted that although there was only limited evidence of stability in brain asymmetry and behavior from age 3 to age 10 overall, participants who showed stability in brain activity would also likely show stability in behavior. First, we selected individuals who showed stability in brain asymmetry from age 3 to age 10 years. A median split was done on frontal asymmetry scores at each age. Six children were categorized as stable left and nine children were categorized as stable right. Table 5.2 shows stable brain asymmetry classification by group at age 3. The distribution of stable frontal asymmetry category (stable left, stable right, unstable) to age 3 group status (inhibited, middle, uninhibited) differed marginally from chance ($p < .08$) and differed significantly from chance when the unstable group was excluded ($p < .03$). Fifty-five percent of children who showed stable right frontal asymmetry from age 3 to age 10 were inhibited at age 3 years; 83 percent of children who showed stable left frontal asymmetry from age 3 to age 10 were uninhibited at age 3 years. Three middle-group children showed stable right frontal asymmetry from age 3 to age 10 years.

We then tested the correlation between age 3 frontal asymmetry and age 9 BI in the subset of children who had stable frontal asymmetry scores. As seen in figure 5.6, frontal asymmetry referenced to vertex at age 3 was marginally significantly correlated in the predicted direction with BI at age 9, Spearman $r = -.50$, $p < .07$, $n = 14$. Among participants with stable frontal asymmetry, relative left frontal activation at age 3 was associated with uninhibited behavior at age 9, whereas relative right frontal activation at age 3 was associated with inhibited behavior at age 9.

These data suggest that when prefrontal brain asymmetry is stable, early childhood measures of these patterns predict later behavioral inhibition. This observation is similar to the findings from a recent study in which 7 of 30 infants who had

Table 5.2 Group distribution of stability of brain asymmetry from age 3 to age 10.

	Frontal asymmetry		
Group at age 3	Stable Right	Stable Left	Unstable
Inhibited	5	1	15
Middle	3	0	15
Uninhibited	1	5	19

This distribution differed marginally from chance, chi-square (4) = 8.66, Fisher's exact $p < .08$, and differed significantly from chance when the unstable group was excluded, chi-square (2) = 8.06, Fisher's exact $p < .03$.

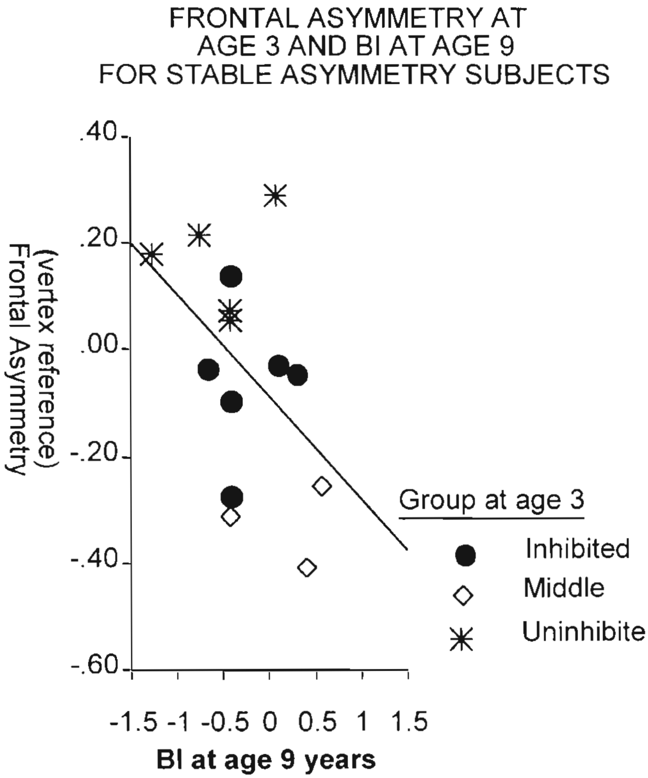

Figure 5.6. Frontal asymmetry at age 3 (referenced to vertex) was marginally correlated with BI at age 9 among children with stable frontal asymmetry scores, Spearman $r = -.50$, $p < .07$, $n = 14$. (Adapted from Rickman, 1997).

an inhibited profile at age 4 months had stable right asymmetry at ages 14 months and 24 months, but none of the infants with stable left asymmetry had an inhibited profile at 4 months (Fox, Calkins, & Bell, 1994).

We also did a separate analysis on children whose level of BI remained stable from age 3 to age 9 years (Rickman, 1997). Within this subset, there was no association between BI and frontal asymmetry at age 3. Stability in behavior does not appear to be related to early childhood brain asymmetry. However, among the behaviorally stable participants, we obtained the expected finding of a significant relation between BI at age 9 and brain asymmetry at age 10. Brain asymmetry at age 10 also significantly predicted BI at age 3.

Summary and Conclusions

We began with a selective overview of some of the key circuitry that comprises two major emotional/motivational systems of the brain—the approach and withdrawal systems. The prefrontal cortex and amygdala were identified as two important structures within these circuits. We then considered a body of research on individual differences in prefrontal activation asymmetry and their relation to behavioral and biological indices of emotional reactivity. Individuals with greater relative left-sided prefrontal activation report more dispositional positive affect and greater relative behavioral activation than behavioral inhibition. Participants with greater right-sided prefrontal activation react more intensely to negative stimuli, show slower recovery of negative-emotion potentiated startle, and have lower levels of NK activity and higher levels of basal cortisol. We then considered the relation between individual differences in prefrontal activation asymmetry and childhood behavioral inhibition. Our new findings reveal that although concurrent measures of prefrontal activation asymmetry predict behavioral measures of inhibition, neither the measures of brain function nor the behavioral measures show stability from age 3 to 10 years. This is likely a period during which considerable plasticity is present and the impact of experiential events on brain function is greatest. In a very small subset of children who show stable asymmetry from age 3 to 10 years, measures of behavioral inhibition across this developmental period are also stable.

It is important to note that although in the second section we described a number of different structures that make up the circuitry of approach and withdrawal, our discussion of individual differences has focused on prefrontal activation asymmetry. In very recent work, we have developed procedures to examine individual differences in measures of basal activation level (Abercrombie et al., 1998), as well as reactivity (Irwin et al., 1997) of amygdala function, using PET and fMRI procedures. To date, these neuroimaging procedures have not been applied to the study of childhood behavioral inhibition, though fMRI is well suited for this purpose because it is completely noninvasive. In addition, individual differences in hippocampal function are likely to play an important role in the circuitry of withdrawal, since cortisol can have deleterious effects on hippocampal function and the hippocampus appears to play an important role in modulating emotional responses in a context-sensitive fashion (e.g., Maren & Fanselow, 1997). Thus future research on the proximal neural substrates of behavioral inhibition in childhood should take advantage of the corpus of knowledge in animals and use neuroimaging procedures to examine the subcortical contributions to this temperamental characteristic.

The data we presented in the fourth section indicate that although measures of prefrontal activation asymmetry predict concurrent measures of behavioral inhibition, neither the measures of brain function nor the behavioral measures of inhibition are stable from age 3 to 10 years. These findings have important implications for understanding the role of early plasticity in the shaping of brain circuitry critical to emotional responding. It is likely that early social and interpersonal events have profound influences on the brain's emotional circuitry. In the motor (e.g., Nudo, Wise, SiFuentes, & Milliken, 1996) and cognitive domains (e.g., Merzenich et al., 1996), substantial evidence has now accumulated that demonstrates the impact of training on neural plasticity, particularly if the training is accomplished early in life. When we consider the possible impact of the emotional environment on brain function, it is clear that many individuals are saturated with a particular "emotional climate" or interpersonal context from very early in life.

Given the prolonged period of parental care in early human infancy, the capacity for experiential shaping of the emotional circuitry in the brain is profound. We believe that the lack of stability in behavioral and biological measures that reflect temperamental inhibition from ages 3 to 10 years is likely a function of plastic changes that occur during early childhood, a period during which the developing child is typically exposed to prolonged interaction with his or her mother and other caregivers. The identification of the relevant environmental factors that shape these characteristics and the documentation that such experiential exposure is associated with consistent changes in brain function should be on the agenda in the next phase of research on this topic.

Having emphasized early plasticity, it is important not to lose sight of the fact that there were a small number of children who remained stable in their patterns of prefrontal activation asymmetry from age 3 to 10 years. Note that our sample was selected at age 3 years from a group of 368 children who fell into one of three groups—extremely inhibited, extremely uninhibited, and middle. Thus our sample was extreme to begin with. Of the 64 children who were available for electrophysiology follow-up at age 10 years, 23 percent remained stable in their patterns of prefrontal asymmetry. Stability in this case was defined based on a median split at each of the two ages. Thus, to be classified as stable, a child simply had to retain his or her position in the top or bottom half of the distribution on each occasion. Of course, a more stringent criterion would result in even fewer individuals earning a classification as stable. However, those children identified as stable even with the rather coarse definition we used did show evidence of behavioral stability. These findings indicate that when these measures of prefrontal activation asymmetry exhibit stability over several years of early childhood, they do have predictive validity, and they therefore may be useful in identifying individuals early in life who may be potentially at risk for psychopathology. Longitudinal follow-up of these stable individuals will be critical in determining the utility of these measures of prefrontal brain function in the prediction of subsequent affective and anxiety disorders.

References

Abercrombie, H. C., Schaefer, S. M., Larson, C. L., Oakes, T. R., Lindgren, K. A., Holden, J. E., Perlman, S. E., Turski, P. A., Krahn, D. D., Benca, R. M., & Davidson, R. J. (1998). Metabolic rate in the right amygdala predicts negative affect in depressed patients. *NeuroReport, 9,* 3301–3307.

Asendorpf, J. B. (1991). Development of inhibited children's coping with unfamiliarity. *Child Development, 62,* 1460–1474.

Block, J. (1982). Assimilation, accommodation, and the dynamics of personality development. *Child Development, 53,* 281–295.

Brown, L. L., Tomarken, A. J., Orth, D. N., Loosen, P. T., Kalin, N. H., & Davidson, R. J. (1996). Individual differences in repressive-defensiveness predict basal salivary cortisol levels. *Journal of Personality and Social Psychology, 70,* 362–371.

Cacioppo, J. T., & Berntson, G. G. (1994). Relationship between attitudes and evaluative space: A critical review, with emphasis on the separability of positive and negative substrates. *Psychological Bulletin, 115,* 401–423.

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology, 67,* 319–333.

Caspi, A., Bem, D. J., & Elder, G. H. (1989). Continuities and consequences of interactional styles across the life course. *Journal of Personality, 57,* 375–406.

Caspi, A., Elder, G. H., & Bem, D. J. (1988). Moving away from the world: Life-course patterns of shy children. *Developmental Psychology, 24,* 824–831.

Davidson, R. J. (1992). Emotion and affective style: Hemispheric substrates. *Psychological Science, 3,* 39–43.

Davidson, R. J. (1993). Cerebral asymmetry and emotion: Conceptual and methodological conundrums. *Cognition and Emotion, 7,* 115–138.

Davidson, R. J. (1994). Asymmetric brain function, affective style and psychopathology: The role of early experience and plasticity. *Development and Psychopathology, 6,* 741–758.

Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R.J. Davidson and K. Hugdahl (Eds.), *Brain asymmetry* (pp. 361–387). Cambridge, MA: MIT Press.

Davidson, R. J. (1997). Unpublished data.

Davidson, R. J. (1998). Affective style and affective disorders: Perspectives from affective neuroscience. *Cognition and Emotion, 12,* 307–330.

Davidson, R. J., Chapman, J. P., Chapman, L. P., & Henriques, J. B. (1990). Asymmetrical brain electrical activity discriminates between psychometrically-matched verbal and spatial cognitive tasks. *Psychophysiology, 27,* 528–543.

Davidson, R. J., Coe, C. C., Dolski, I., & Donzella, B. (in press.) Individual differences in prefrontal activation asymmetry predict natural killer cell activity at rest and in response to challenge. *Brain, Behavior, and Immunity.*

Davidson, R. J., Dolski, I., Larson, C., & Sutton, S. K. (1998). *Electrophysiological measures of prefrontal asymmetry predict recovery of emotion-modulated startle.* Manuscript in preparation.

Davidson, R. J., Ekman, P., Saron, C., Senulis, J., & Friesen, W. V. (1990). Approach/withdrawal and cerebral asymmetry: Emotional expression and brain physiology. I. *Journal of Personality and Social Psychology, 58,* 330–341.

Davidson, R. J., & Fox, N. A. (1989). Frontal brain asymmetry predicts infants' response to maternal separation. *Journal of Abnormal Psychology, 98,* 127–131.

Davidson, R. J., Kalin, N. H., & Shelton, S. E. (1992). Lateralized effects of diazepam on frontal brain electrical asymmetries in rhesus monkeys. *Biological Psychiatry, 32,* 438–451.

Davidson, R. J., Kalin, N. H., & Shelton, S. E. (1993). Lateralized response to diazepam predicts temperamental style in rhesus monkeys. *Behavioral Neuroscience, 107,* 1106–1110

Davidson, R. J., Sutton, S. K., Schaefer, S. M., Ward, R. T., Larson, C. L., Abercrombie, H. C., Holden, J. E., Perlman, S. B., & Turski, P. A. (1998). *Lateralized circuitry for appetitive and aversive emotion in the human brain.* Manuscript in preparation.

Davidson, R. J., & Tomarken, A. J. (1989). Laterality and emotion: An electrophysiological approach. In F. Boller and J. Grafman (Eds.), *Handbook of Neuropsychology,* pp. 419–441. Amsterdam: Elsevier.

Depue, R. A., & Collins, P. F. (In press). Neurobiology of the structure of personality: Dopamine, incentive motivation and extroversion. *Behavioral and Brain Sciences.*

Diener, V. E., & Emmons, R. A. (1984). The independence of positive and negative affect. *Journal of Personality and Social Psychology, 47,* 1105–1117.

Drevets, W. C., Videen, T. O., MacLeod, A. K., Haller, J. W., & Raichle, M. E. (1992). PET images of blood changes during anxiety: Correction. *Science, 256,* 1696.

Finman, R., Davidson, R. J., Colton, M. B., Straus, A. M., & Kagan, J. (1989). Psychophysiological correlates of inhibition to the unfamiliar in children. *Psychophysiology, 26,* S24.

Fischer, K. W., & Rose, S. P. (1994). Dynamic development of coordination of components in brain and behavior. In G. Dawson & K.W. Fischer (Eds.), *Human Behavior and the Developing Brain* (pp. 3–66). New York: Guilford Press.

Fox, N., Calkins, S., & Bell, M. A. (1994). Neural plasticity and development in the first two years of life: Evidence from cognitive and socioemotional domains of research. *Development and Psychopathology, 6,* 677–696.

George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., & Post, R. M. (1995). Brain activity during transient sadness and happiness in healthy women. *American Journal of Psychiatry, 152,* 341–351.

Gold, P. W., Goodwin, F. K., & Chrousos, G. P. (1988). Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress. *New England Journal of Medicine, 314,* 348–353.

Gray, J. A. (1994). Three fundamental emotion systems. In P. Ekman & R. J. Davidson (Eds.), *The Nature of Emotion: Fundamental Questions* (pp. 243–247). New York: Oxford University Press.

Gross, J. J., Sutton, S. K., & Ketelaar, T. V. (1998). Relations between affect and personality: Support for the affect-level and affective-reactivity views. *Personality and Social Psychology Bulletin, 24,* 279–288.

Haan, N., Millsap, R., & Hartka, E. (1986). As time goes by: Change and stability in personality over 50 years. *Psychology and Aging, 1,* 220–232.

Henriksen, S. J., & Giacchino, J. (1993). Functional characteristics of nucleus accumbens neurons: Evidence obtained from *in vivo* electrophysiological recordings. In P. W. Kalivas & C. D. Barnes, (Eds.), *Limbic motor circuits and neuropsychiatry* (pp. 101–124). Boca Raton, FL: CRC Press.

Irwin, W., Davidson, R. J., Lowe, M. J., Mock, B. J., Sorenson, J. A., & Turski, P. A. (1996). Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *NeuroReport, 7,* 1765–1769.

Irwin, W., Mock, B. J., Sutton, S. K., Orendi, J. L., Sorenson, J. A., Turski, P. A., Kalin, N. H., & Davidson, R. J. (1997). Positive and negative affective responses: Neural circuitry revealed using functional magnetic resonance imaging. *Society for Neuroscience, 23,* 1318.

Kagan, J., & Moss, H. A. (1962). *Birth to maturity: A study in psychological development.* New York and London: Wiley.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & Garcia-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55,* 2212–2225.

Kagan, J., Reznick, J. S., & Gibbons, J. (1989). Inhibited and uninhibited types of children. *Child Development, 60,* 838–845.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58,* 1459–1473.

Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240,* 167–171.

Kalin, N. H. (1993). The neurobiology of fear. *Scientific American, 268,* 94–107.

Kalin, N. H., Larson, C., Shelton, S. E., & Davidson, R. J. (1998). Asymmetric frontal brain activity, cortisol, and behavior associated with fearful temperament in Rhesus monkeys. *Behavioral Neuroscience, 112,* 286–292.

Kalivas, P. W., Churchill, L., & Klitenick, M. A. (1993). The circuitry mediating the translation of motivational stimuli into adaptive motor responses. In P. W. Kalivas & C. D. Barnes, (Eds.), *Limbic motor circuits and neuropsychiatry* (pp. 237–287). Boca Raton, FL: CRC Press.

Kang, D. H., Davidson, R. J., Coe, C. L., Wheeler, R. W., Tomarken, A. J., & Ershler, W. B. (1991). Frontal brain asymmetry and immune function. *Behavioral Neuroscience, 105,* 860–869.

Kiecolt-Glaser, J. K., & Glaser, R. (1991). Stress and immune function in humans. In R. Ader, D. L. Felten, and N. Cohen (Eds.), *Psychoneuroimmunology* (2nd ed., pp. 849–867). San Diego, CA: Academic Press.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention and the startle reflex. *Psychological Review, 97,* 377–398.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1995). *International affective picture system (IAPS): Technical manual and affective ratings.* Gainsville, FL: Center for Research in Psychophysiology, University of Florida.

Lazarus, R. S. (1991). *Emotion and adaptation.* Oxford University Press.

LeDoux, J. E. (1987). Emotion. In F. Plum (Ed.), *Handbook of Physiology. Section I: The Nervous System: Higher Functions of the Brain* (Vol. 5, pp. 419–460). Bethesda, MD: American Physiological Society.

Maren, S., & Fanselow, M. S. (1997). Electrolytic lesions of the fibria/fornix, dorsal hippocampus, or entorhinal cortex produce anterograde deficits in contextual fear conditioning in rats. *Neurobiology of Learning and Memory, 67,* 142–149.

Maziade, M., Cote, R., Bernier, H., Boutin, P., & Thivierge, J. (1989). Significance of extreme temperament in infancy for clinical status in pre-school years. I: Value of extreme temperament at 4–8 months for predicting diagnosis at 4.7 years. *British Journal of Psychiatry, 154,* 535–543.

Meehl, P. E. (1975). Hedonic capacity: Some conjectures. *Bulletin of the Menninger Clinic, 39,* 295–307.

Merzenich, M. M., Jenkins, W. M., Johnston, P., Schreiner, C., Miller, S. L., & Tallal, P. (1996). Temporal processing deficits of language-learning impaired children ameliorated by training. *Science, 271,* 77–81.

Nudo, R. J., Wise, B. M., SiFuentes, F., & Milliken, G. W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science, 272,* 1791–1794.

Paradiso, S., Robinson, R. G., Andreasen, N. C., Downhill, J. E., Davidson, R. J., Kirchner, P. T., Watkins, G. L., Boles, L. L., & Hichwa, R. D. (1997). Emotional activation of limbic circuitry in elderly and normal subjects in a PET study. *American Journal of Psychiatry, 154,* 382–389.

Reiman, E. M., Fusselman M. J. L., Fox B. J., & Raichle, M. E. (1989). Neuroanatomical correlates of anticipatory anxiety. *Science, 243,* 1071–1074.

Rickman, M. D. (1997). *Behavioral inhibition, emotional vulnerability and brain asymmetry: A biobehavioral study of inhibited, middle and uninhibited children from age 30 months to age 10 years.* Unpublished doctoral dissertation, University of Wisconsin, Madison.

Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., Bolduc, E. A., Faraone, S. V., Kagan, J., Snidman, N., & Reznick, J. S. (1991). Further evidence of an association between behavioral inhibition and anxiety disorders: Results from a family study of children from a non-clinical sample. *Journal of Psychiatry Research, 25,* 49–65.

Rubin, K. H. (1993). The Waterloo longitudinal project: Correlates and consequences of social withdrawal from childhood to adolescence. In K. H. Rubin & J. B. Asendorpf (Eds.), *Social withdrawal, inhibition, and shyness in childhood* (pp. 291–314). Hillsdale, NJ: Erlbaum.

Russell, J. A. (1980). A circumplex model of emotion. *Journal of Personality and Social Psychology, 39,* 1161–1178.

Schultz, W., Apicella, P., Romo, R., & Scarnati, E. (1995). Context-dependent activity in primate striatum reflecting past and future behavioral events. In J. C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 11–28). Cambridge, MA: MIT Press.

Schultz, W., Romo, R., Ljungberg, T., Mirenowicz, J., Hollerman, J. R., & Dickinson, A. (1995). Reward-related signals carried by dopamine neurons. In J.C. Houk, J. L. Davis, & D. G. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 233–248). Cambridge, MA: MIT Press.

Smith, O. A., DeVita, J. L., & Astley, C. A. (1990). Neurons controlling cardiovascular responses to emotion are located in lateral hypothalamus-perifornical region. *American Journal of Physiology, 259,* R943–R954.

Spreen, O., Tupper, D., Risser, A., Tuokko, H., & Edgell, D. (1984). *Human Developmental Neuropsychology.* New York: Oxford University Press.

Stein, N. L., & Trabasso, T. (1992). The organization of emotional experience: Creating links among emotion, thinking, language and intentional action. *Cognition and Emotion, 6,* 225–244.

Sutton, S. K., & Davidson, R. J. (1997). Prefrontal brain asymmetry: A biological substrate of the behavioral approach and inhibition systems. *Psychological Science, 8,* 204–210.

Sutton, S. K., Davidson, R. J., Donzella, B., Irwin, W., & Dottl, D. A. (1997). Manipulating affective state using extended picture presentation. *Psychophysiology, 34,* 217–226.

Thatcher, R. W. (1992). Cyclic cortical reorganization during early childhood. *Brain and Cognition, 20,* 24–50.

Thatcher, R. W. (1994). Cyclic cortical reorganization: Origins of human cognitive development. In G. Dawson & K. F. Fischer (Eds.), *Human behavior and the developing brain* (pp. 232–268). New York: Guilford Press.

Thelen, E. (1989). Self-organization in developmental processes: Can systems approaches work? In M. R. Gunnar & E. Thelen (Eds.), *Systems and Development* (pp. 77–117). Hillsdale, NJ: Erlbaum.

Thorpe, S., Rolls, E., & Maddison, S. (1983). The orbitofrontal cortex: Neuronal activity in the behaving monkey. *Experimental Brain Research, 49,* 93–113.

Thut, G., Schultz, W., Roelcke, U., Nienhusmeier, M., Missimer. J., Maguire, R. P., & Leenders, K. L. (1997). Activation of the human brain by monetary reward. *Neuroreport, 8,* 1225–1228.

Tomarken, A. J., Davidson, R. J., Wheeler, R. E., & Doss, R. C. (1992). Individual differences in anterior brain asymmetry and fundamental dimensions of emotion. *Journal of Personality and Social Psychology, 62,* 676–687.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Developmental and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology, 54,* 1063–1070.

Watson, D., & Tellegen, A. (1985). Toward a consensual structure of mood. *Psychological Bulletin, 98,* 219–235.

Wheeler, R. E., Davidson, R. J., & Tomarken, A. J. (1993). Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology, 30,* 82–89.

Wright, J. C., & Mischel, W. (1987). A conditional approach to dispositional constructs: The local predictability of social behavior. *Journal of Personality and Social Psychology, 53,* 1159–1177.