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An approach to the psychobiology of personality disorders

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Abstract

Human variability in temperament allows a unique natural experiment where reactivity, self-regulation, and experience combine in complex ways to produce an individual personality. Personality disorders may result from changes in the way past memories filter new information in situations of emotional involvement with others. According to this view, disorders are specific to their initiating circumstances rather than a general difficulty that might extend to classes of information processing remote from triggers for the disorder. A different view suggests a more general deficit in attentional control mechanisms that might extend to a wide range of situations far from those related to the core abnormality. This paper outlines methods for examining these views and presents data from the study of borderline personality disorder, arguing in favor of high negative emotionality being combined with a deficit in an executive attentional control network. Because this attentional network has already been well described in terms of anatomy, the cognitive operations involved, development, chemical modulators, and effects of lesions and candidate genes, these findings may have implications for understanding the disorder and its treatment. We consider these implications in terms of a general approach to the study of personality development and its disorders.

This paper resulted from a collaboration exploring whether an approach to borderline personality disorder (BPD) based upon the study of normal attention (Posner & Fan, in press; Posner & Petersen, 1990; Posner et al., 2002), individual differences in temperament (Derryberry & Rothbart, 1997; Rothbart & Derryberry, 1981), and brain imaging (Silbersweig & Stern, 2001; Stern & Silbersweig, 2001) could illuminate the psychobiology of the disorder. Although the direct goal of this work was the understanding of borderline personality disorder, we believe the approach has implications for the investigation of normal development as well as its disorders (Cicchetti, 1993).

Understanding biological connections to mental processes was one original goal of psychoanalysis, and the rapid development of cognitive and affective neuroscience built on brain imaging methods might help achieve this goal (Kandel, 1998, 1999). BPD is one mental health problem that has been identified and studied by psychoanalytic (Kernberg, 1996) as well as behaviorally oriented therapists (Linehan, 1993). There is no question about the devastating reality of the behavioral problems of people diagnosed with BPD. Estimates of prevalence run from .3 to 1.8 in the adult population of the United States (Lezenweger, Loranger, Korfine, & Neff, 1997). Up to 75% of individuals diagnosed with BPD

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engage in self-destructive disorders such as self-mutilation, alcohol and drug abuse, serious over- or undereating, and suicide (Clarkin, Widiger, Frances, Hurt, & Gilmore, 1983). The completed suicide rate is between 3 and 9.5% (McGlashan, 1986). Because of its behavioral complexity and lack of clear organic markers, BPD poses one of the greatest challenge to understanding the psychobiology of its development. However, success with this complex disorder might provide important clues for studying the equally complex trajectories of normal development (Cicchetti, 1993).

Variability in temperamental reactivity and self-regulation creates a unique natural experiment in which genes and experience combine in complex ways to produce an individual personality. This natural variation may also underlie both personality and the various disorders of personality represented in *DSM-IV*. Personality disorders represent an opportunity to examine the complex mental structures of people who experience extreme difficulty in interacting with their social environment (Kernberg, 1996).

As defined by *DSM-IV*, BPD includes five or more of the following symptoms, presenting by early adulthood (Kernberg, Weiner, & Bardenstein, 2000, p. 133):

> Frantic efforts to avoid real or imagined abandonment; a pattern of unstable and intense interpersonal relationships. . . . identity disturbance. . . . impulsivity in at least two areas that are potentially self-damaging. . . . recurrent suicidal behavior, gestures or threats, or self-mutilating behavior; affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability or anxiety . . .); chronic feelings of emptiness; inappropriate, intense anger or difficulty controlling anger; transient, stress-related paranoid ideation or severe dissociative symptoms.

We define temperament as individual differences in constitutionally based reactivity and self-regulation, as observed in the areas of emotionality, activity, and attention (Rothbart & Bates, 1998). Although several of these symptoms go well beyond differences in temperament, two aspects of temperamental differences could contribute to the disorder. The first is *negative affectivity*, which would support the high negative mood and the volatile anger described in BPD. The second is *effortful control*, which would support instability of relationships, impulsivity, and difficulties in controlling emotion. We therefore hypothesized that BPD patients would differ from nondisordered controls by showing higher levels of negative affectivity and lower levels of effortful control as assessed in the Adult Temperament Questionnaire (ATQ; Rothbart, Ahadi, & Evans, 2000). We also wished to investigate a control group matched in temperament with the BPD patients.

Our approach allowed us to explore these directions for understanding the disorder:

1. addressing whether a specific pathology or a temperamental variant is involved;
2. providing a set of tasks appropriate for imaging;
3. suggesting an anatomy and circuitry that might differ in these patients;
4. examining the developmental process related to the disorder; and
5. exploring genetic contributions to the disorder.

We believe this approach might provide a general model for research in personality-related disorders, as well as the study of normal individuals. In carrying out this approach it is important to know first which computations are involved in either a given task (task approach) or in patients suffering from a given disorder (symptom approach).

In the case of symptom analysis of BPD, one direction is to specify the dimensions of temperament or personality that appear to be problematic in the patient. If there is a specific disorder in the performance of specific brain areas or their connections, then patients have a unique pathophysiology and this could be true even if the disorder was acquired in socialization. Another possibility is that borderline personality is an extreme variant of normal functioning, so that normal people with the same temperamental structure as BPD patients would operate in a similar manner.

As noted above, given the definition of borderline personality, the temperamental dimension of effortful control appears to be low and negative affect high. Kochanska (1997) has argued that empathy and prosocial interpersonal behavior may result from temperaments involving strong effortful control mechanisms. A temperament high in negative emotionality (including fear and anger) and low in effortful control would appear to provide the basis for poor interpersonal relations, thus producing one of the central difficulties in BPD.

Neuropsychological investigation provides some clues as to the brain regions involved. Patients with lesions of the frontal midline appear to be impaired in their ability to maintain strong social relationships and make useful decisions in social contexts (see, e.g., the case of patient EVR; Damasio, 1994). In addition, areas of the frontal midline (e.g., anterior cingulate) have proven important in tasks requiring the control of emotion. Imaging studies have suggested that activation of dorsolateral prefrontal cortex and parts of the basal ganglia are crucial to impulsivity in go–no go tasks (Casey et al., 1997).

To test these ideas, we propose first to examine the temperamental basis of patients diagnosed with BPD by use of self-report questionnaires designed to elicit behavioral information related to temperament (Derryberry & Rothbart, 1988; Rothbart et al., 2000). We expect to find a pattern of low effortful control (as assessed by items measuring attentional control, inhibitory control, and activation control) and high negative affect (as assessed by items measuring fear, sadness, discomfort, and frustration). A sample of normal subjects matched in age and background are used to select subjects with similar temperamental patterns (temperamental match group) and quite different patterns on the temperament variables (temperamental average control).

The next step is to examine whether consistent patterns of performance on tests of attention would emerge from both the diagnosed population and the temperamental matched group, while a different pattern would emerge from the average controls.

If the patients differed from both control groups, we would expect the functions in which they differed to provide a basis for hypotheses about the pathophysiology of the disorder.

If patients and temperamentally matched normals showed very similar performance in the cognitive tasks, we would suggest that the borderline personality arises in the socialization of people with a particular form of temperament. This would fit proposals made by Kernberg (1996) that the disorder arises in socialization and would argue for an examination of the mechanisms by which persons with a particular type of reactive temperament acquire the skills of interpersonal relations. One of those mechanisms would be the genes involved in forming the networks related to attention, which could relate to individual differences in their attentional efficiency.

In the next section of this paper, we report our findings regarding the temperamental differences between patients and average controls and a specific disorder of executive attention. We then consider the implications of our findings for the anatomy that may be involved in BPD and discuss the development of executive attention in normal children. The next section deals with genes related to executive attention and presents our preliminary data on the frequency of these genes in BPD patients and controls. Finally, we consider the implications of our findings for normal development and personality disorders.

Findings

Because the symptoms of BPD include dysregulation of negative emotions, particularly in interpersonal relations, we hypothesized that borderline patients would be high in negative affect and low in effortful control as measured by common temperament and personality scales (Evans & Rothbart, 2003; Rothbart et al., 2000). The ATQ was adopted because it had scales for negative affect and effortful control and because it was based upon measures that had been widely used for young children (e.g., Rothbart, Ahadi, Hershey, & Fisher, 2001). A sample of normal subjects was then used to select subjects with

Table 1. *Group demographics*

	N	Female	Mean Age
BDP patients	39	38	30
Unmedicated BPD	18	17	32
Medicated BPD	21	21	29
Controls matched in temperament	22	20	20
Average controls	30	22	22

Note: BPD, borderline personality disorder.

similar temperamental patterns (temperamentally matched controls) and an average profile on the relevant variables (average controls). The comparison of patients with normal persons of similar temperament represents an effort to use normal variation in the population as a means of examining the nature of the deficit.

One hundred patients were diagnosed with BPD and assigned randomly to treatment conditions. The diagnosis was made by highly trained clinicians using standardized interview schedules, including the Structured Clinical Interview for Diagnosis (First, Gibbon, Spitzer, & Williams, 1996) and the International Personality Disorder Examination (IPDE: Loranger, 1999). Approximately half of the patients were not medicated by their own report, and half were taking various medications, mainly antidepressants. Table 1 describes the basic demography of the patients and the two types of controls.

We screened about 1,000 students at Hunter College in New York who were administered the ATQ developed by Rothbart and associates (Rothbart et al., 2000). The data from this study were presented in more detail elsewhere (Posner et al., 2002), so they will be summarized briefly in this report. The questionnaire required participants to respond on a 7-point scale indicating the degree to which each of 118 questions applied to them. Of primary interest were the factors of negative affect and of effortful control.

As expected, the patients showed quite high levels of negative affect (5.1 on a 7-point scale, almost 2 standard deviations above the average level). They were also about 1 standard deviation lower than normal on effortful control, averaging 3.4 in comparison with a mean value of 4.2. Their scores in these temperamental dimensions did not differ according to their medication status.

We selected two groups of controls. The temperamentally matched control group was selected to show a similar temperamental profile to the patients, that is, high negative affect and low effortful control. We also selected average controls whose scores on negative affect and effortful control were close to the middle scale score of 4 on both of these variables. All control subjects were screened for personality disorders using the IPDE, and they did not meet criterion for any diagnosis. Although the temperamentally matched controls did not have a personality disorder, we did note difficulty in working with some members of this population due to frequent changes of address and phone number, unreliability in keeping appointments, and/or their heightened anxiety and paranoia regarding experimental procedures. Our general feeling was that these were people whose behavior seemed to show evidence of dysregulation, even though they were functioning in school and did not meet the criteria for any personality disorder.

All of these subjects were given the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) to provide an evaluation of the efficiency in three aspects of attention: alerting, orienting, and conflict resolution. The ANT scores have proven reliable and show some degree of independence between the networks. The time course of events during a typical trial is shown in Figure 1c. The participants were asked to indicate by a key press whether the central arrow in the target display pointed left or right. The target arrow could be flanked by arrows which matched (congruent) or were in the opposite direction (incongruent) of the target arrow (Figure 1b). Neutral trials used a line instead of an arrow. Prior to the target, no cue, a double cue, a single cue at the location of the upcoming target, or a single central cue was given (Figure 1a). Three subtractions illustrated in Figure 1 were used to assess the efficiency of each network. By subtracting the congruent reaction times (RTs) from the in-

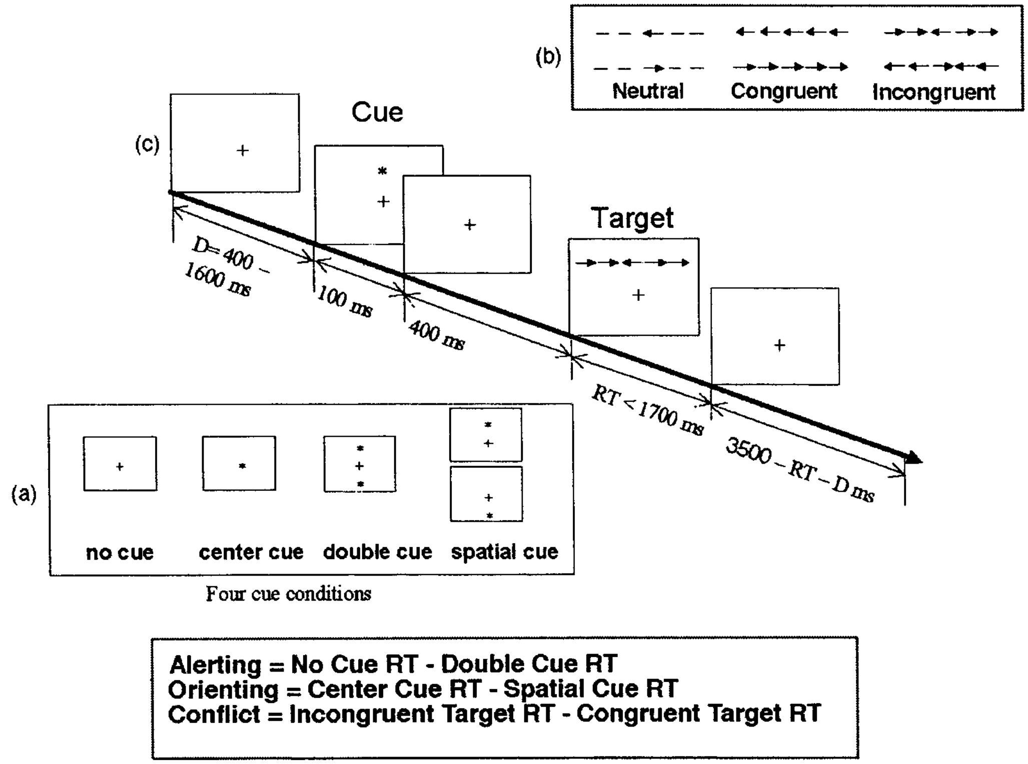

Figure 1. The Attention Network Test (ANT) (a) indicates the four cues involved, (b) shows the target types, and (c) provides an overall time line of trials. At the bottom are the three subtractions that produce the networks scores.

congruent RTs we have a measure of the ability of subjects to resolve conflict introduced by the flankers when they are in the opposite direction from the target. Subtraction of the double cue from the no cue condition RTs provides a measure of the ability of subjects to maintain alertness on trials where they are not cued and to take advantage of a warning signal. Finally, by subtracting RTs to a cue at the target location (either above or below fixation) from a central cue (where no targets are ever presented) provides information on the skill of orienting to the target location.

The overall attention results are shown in Figure 2 and have been reported in detail elsewhere (Posner et al., 2002). In an overall analysis of variance, we found that the three groups showed a statistically significant difference in the conflict network, but not in any other attentional network nor in overall RT or error rate. In subsequent analyses, patients differed from average controls but did not show a statistically significant difference from temperamentally matched controls. The direction of the difference was for temperamental control subjects to have a larger conflict score than the average controls. They did not show statistically significant differences from either the average controls or the patients.

We evaluated whether the difference between patients and controls could be explained by differences in age or medication. Although the medicated patients showed a somewhat larger conflict score than nonmedicated patients, this result was not significant. The medicated patients may show a somewhat larger effect because they tend to have more severe symptoms than unmedicated patients. Although the controls were somewhat younger than the patients, there were no significant correlations between age and conflict scores in any of the groups. Moreover, when groups were constructed with similar ages, the same overall results were apparent. We thus

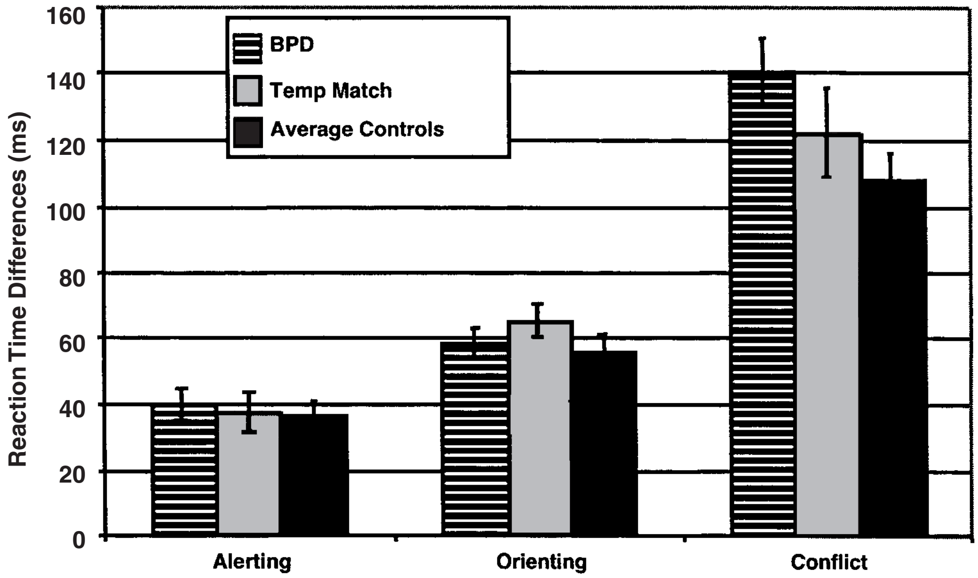

Figure 2. Network scores for the Attention Network Test (ANT) in Alerting, Orienting, and Conflict (executive) for Borderline Personality Disorder (BPD) patients, temperament-matched controls and average controls. For subtractions, see bottom of Figure 1.

concluded that the difference between patients and average controls could not be explained by age or medication.

The conflict scores of the patients were larger than either of the two control groups. In the case of the average controls this result was statistically significant. This shows an abnormality in the ability of the patients to exercise control over their conflicting cognitions and emotions (Bush, Luu, & Posner, 2000). In order to determine whether this difference was unique to BPD patients, we compared their conflict scores to the temperamentally matched controls. Although the patient group conflict scores were larger than this control group, this difference did not reach statistical significance. However, the temperamentally matched controls were actually lower in effortful control (2.82) than the patients (3.51). If the abnormality of the patients were due to temperamental differences in effortful control alone, we would have expected the matched controls to actually have a larger conflict effect than the patients. Thus, our data suggest that in addition to the influence of temperament, the patients had some other deficit in the attentional network.

Anatomy

Imaging studies have consistently implicated the amygdala in many aspects of negative affect (Whalen et al., 1998) and have shown that areas of the frontal midline (e.g., anterior cingulate gyrus) are important in tasks requiring the control of cognition and emotion (Bush et al., 2000). Pediatric imaging studies have suggested that activation of the dorsolateral prefrontal cortex and parts of the basal ganglia are crucial to impulsivity in certain cognitive tasks (Casey et al., 1997; Vaidya et al., 1998). In Damasio's study (1994), patients with lesions of the frontal midline appear to have impaired ability to maintain strong social relationships and to make useful decisions in social contexts. Moreover, early damage to this area appears to produce a lifelong inability to adapt to social conventions (Anderson, Damasio, Tranel, & Damasio, 2000).

At a recent meeting of the BPD Research Foundation, many papers presented preliminary data comparing the influence of negative events from picture stimuli (Donegan, 2002; Herpertz, 2002), words (Silbersweig et al., 2003) and emotional sounds (Sefritz, 2002) on borderline patients and normals. The universal finding was that borderline patients showed either larger amygdala activation or in some cases responded strongly to a greater range of events than did normals. These findings suggest an important role for the amygdala in the high levels of negative affect found in the patients. In addition, a reduction in the size of the amygdala in patients with BPD was also reported (Van Elst, 2002), making even more remarkable the higher level of activity found in imaging studies.

Many of the same patients and controls whose data is presented in Table 1 have been scanned with functional magnetic resonance imaging (fMRI) in a study using positive, negative, and neutral words (Silbersweig et al., 2003). This study used an emotional go–no go task. The emotional words were selected to be highly negative to borderline patients. The task required patients and controls to respond to all words in one font and to withhold their response to words in another font. This go–no go task introduced a degree of conflict by the need to control whether to respond. Preliminary data from this study were reported at the same meeting of the Borderline Personality Disorder Research Foundation discussed above and will be fully reported elsewhere (Silbersweig et al., 2003). The data suggest patients show amygdala overactivity compared to average controls when presented with neutral words. This suggests that BPD patients were inclined to interpret a broader range of stimuli as negative. The anterior cingulate also showed overactivity in patients and there was reduced activity in frontal circuits related to inhibitory control. Other results from this study are currently being analyzed and should help address whether these effects are unique to patients or are more generally related to temperament.

Our results also indicate two important findings about attention in the BPD patients. First, there is evidence for a specific abnormality in the functioning of the executive attentional network involved in control of conflict. No other attentional system seems to be impaired in these patients. Second, the abnormality is only clearly present in the patients; although the temperamental controls also show elevated conflict scores, they do not show a statistically significant difference from average controls. We conclude that whereas temperament may play a role in the disorder, possibly in predisposing individuals to develop BPD, some other genetic or environmental factor must be involved. Studies of the etiology of BPD strongly implicate the experience of trauma; in one study of 358 BPD inpatients, 91% reported having been abused and 92% reported having been neglected before age 18 (Zanarini, Williams, Lewis, & Reich, 1997). BPD patients were significantly more likely thant other personality disorder patients to report emotional and physical abuse by a caretaker and sexual abuse by a noncaretaker. Zanarini and Frankenberg (1997) suggested that three factors contribute to the developmental of BPD: a traumatic childhood, a vulnerable temperament, and a triggering event or series of events.

The idea arising from our findings is that the deficit in executive attention coupled with a temperament of high negative affect could lead to the core deficit of BPD patients in the dysregulation of emotion. According to the neuropsychological data reviewed in the introductory section of this paper, negative affect might involve the amygdala whereas effortful control and executive attention would be related to functioning of the anterior cingulate.

Development

A developmental perspective on mechanisms related to the executive attention network emphasizes its role in the self-regulation of emotional and cognitive responses to stimulation (Rueda, Posner, & Rothbart, in press). There is substantial animal work suggesting that frontal midline areas connect with and regulate brain systems related to emotion such as the amygdala (Davidson, Putnam, & Lareson, 2000). While much of the fMRI work has involved negative emotion (Whalen, Rauch, et al., 1998), there is now evidence that efforts to control positive emotional states, such as erotic responses to explicitly sexual movies, also activate a cingulate generator (Beauregard, Levesque, & Bourgouin, 2001; see Rueda

Table 2. *Development of attention networks*

	Overall		Conflict Effect	
Age (years)	RT (ms)	Errors (%)	RT (ms)	Errors (%)
4.4	1443	6.8	273	8.9
6	930	13	95	15.6
7	835	5.6	70	0.5
8	811	4.8	70	–0.2
9	740	2.4	67	1.6
10	643	2.2	72	2.1
Adults	492	1.2	63	1.6

A comparison of children 4.4–9 years with the child Attention Network Test (ANT) and a comparison of 10-year-old children and adults with the child ANT.

et al., in press, for a review of attention and self-regulation).

The idea that the cingulate region is involved in self-regulation also comes from our studies of the development of the executive attention network. We found strong evidence of development of this network in 2- to 5-year-olds using a spatial task that induces conflict between identity and location, two of the earliest developing visual system operations (Gerardi–Caulton, 2000; Rothbart, Ellis, & Posner, in press). In adults, the spatial conflict task activates the cingulate in an area similar to the color Stroop and flanker tasks (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003).

In work with the child version of the ANT (Rueda et al., 2002), we found that development in the executive attention network continues up to about age 7, but not after that age (see Table 2). We also compared 10-year-olds and adults in the adult version of the ANT and found no differences in performance of the conflict network, although overall RT and alertness measures continued to develop. Recent studies of adolescents indicate about the same level of conflict as found in children above 7 and adults (Ellis, 2002). Work summarized by Shapiro and Perry (1976) pointed to Freud's thinking and subsequent biological data showing the importance of age 7 as a transition to more adult levels of social responsibility. The work summarized in that paper points out that a striking feature of development in children between 2 and 7 years of age is the increase in their ability to regulate their emotions. We tested whether development of these skills is related to self-regulation by computing correlations between children's performance in conflict tasks and parental reports of the ability of the child to control themselves in the practical situations of real life (effortful control).

We found positive correlations between children's successful performance on the spatial conflict and parental reports of effortful control (Gerardi–Caulton, 2000; Rothbart et al., in press). In addition, we recently found some evidence of a similar correlation between a self-report measure of effortful control and performance on the conflict network of the ANT when our sample involved a broad range of adults that included both normals and BPD patients (Posner et al., 2002).

These data suggest that the attentional network we found related to BPD undergoes substantial development relatively early in childhood. One might speculate that this network would be especially vulnerable during its development. This period in childhood does seem a time when environmental events can lead toward personality disorders (Kernberg et al., 2000).

Studies have found substantial heritability for both effortful control (Goldsmith, Lemery, Buss, & Campos, 1999) and the conflict network (Fan, Wu, Fossella, & Posner, 2001). Moreover, empathy is strongly related to effortful control, with children high in effortful control showing greater empathy (Rothbart, Ahadi, & Hershey, 1994). To display empathy toward others requires that we interpret their signals of distress or pleasure. Imaging work in normals shows that sad faces activate the amygdala. As sadness increases in intensity, this activation is accompanied by activity in the anterior cingulate as part of the attention network. It seems likely that the cingulate activity represents the basis for our attention to the distress of others. Psychopaths fail to show behavioral responses to sad faces and lack empathy to the distress of others (Blair, Morris, Frith, Perrett, & Dolan, 1999). Recently, Ellis (2002) found evidence that both effortful control and conflict measured by the ANT aided in the prediction of antisocial outcomes in adolescence. Lesions of this general area in children (Anderson et al.,

2000) and adults (Damasio, 1994) also produce a tendency toward psychopathic behavior.

Consistent with its influence on empathy, effortful control appear to play a role in the development of conscience (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996). The internalization of moral principles is facilitated in fearful preschool-aged children, especially when their mothers use gentle discipline (Kochanska, 1995). Two separable control systems, one reactive (fear), and one self-regulative (effortful control) influence the development of conscience.

Genes and Environment

A goal of our overall research effort is to understand how a personality disorder emerges in childhood. The scenario that seems most likely is that certain individuals possess a genetic propensity related to temperamental characteristics present prior to the disorder. Patients with BPD often report incidents of abuse during childhood (Zanarini, 2000). These environmental events, together with the genetic propensity, may interfere with development of executive control, which in turn influences the ability to develop clear ideas and empathy for the minds of others as well as the experience of diffusion of one's own identity. We have not conducted any test of this hypothesis. However, we review below some efforts to determine which genes might contribute to executive attention and to various developmental disorders, and then report our preliminary attempt to locate genes related to BPD.

Candidate genes

To determine whether the executive network is likely to be under genetic control, we conducted a small-scale twin study to investigate its heritability (Fan et al., 2001). The study showed impressive correlations among twin pairs in overall reaction time, conflict resolution, and alerting and a substantial heritability estimate (.79) for the conflict network. These results indicate the validity of the network scores because they are correlated among pairs of subjects with similar genomes and encourage the search for candidate genes related to the executive network.

The use of genetic analysis with chronometric studies has been applied to the neuropsychology of reading disorders (Olson, Datta, Gayan, & DeFries, 1999), early Alzheimer dementia (Greenwood, Sunderland, Friz, & Parasuraman, 2000), and attention-deficit disorder (Swanson et al., 2000). For example, Parasuraman and colleagues were able to show a deficit in orienting networks in early Alzheimer disease. Patients had difficulty in using central orienting cues to improve their orienting toward subsequent targets. This chronometric analysis was supported by a finding of a reduction in blood flow specific to the superior parietal lobe, an area known to be important in orchestrating voluntary shifts of attention toward targets. Patients with early Alzheimer disease frequently have a characteristic genetic allele related to the tendency to produce deposits of amyloid. In a study of asymptomatic subjects who carried this genetic variant, they found a small deficit in orienting to central cues that closely resembled what they had reported for early Alzheimer disease (Greenwood et al., 2000). This remarkable finding suggests that the study of mental chronometry may be useful in dealing with subtle differences in normal function that would not be called pathology, but might be useful in directing treatment.

Similarly, we have been using the links between specific neural networks of attention and chemical modulators to investigate the genetic basis of normal attention (Fan, Wu, Fossella, & Posner, 2001; Fossella, Posner, Fan, Swanson, & Pfaff, 2002) and psychopathologies (Swanson et al., 2000). In general, we examined genes related to dopamine, because there is clear evidence that the anterior cingulate gyrus expresses all of the dopamine receptors and is modulated by input from the ventral tegmental dopamine system. We first tested 200 normal persons using the ANT. Because each of our subjects used a kit provided by us to collect a DNA sample from their cheek cells, we were able to collect genotypic information. We then attempted to relate differences in executive attention performance on the ANT to alleles of various common polymorphisms by testing whether significant differences in the efficiency of the conflict network were found for different alleles.

Table 3. *Frequency of alleles in borderline patients compared to normals in the dopamine genes related to good and poor efficiency of executive attention network*

Gene	Frequency: Good Efficiency Allele — Patients (N = 39)	Good Efficiency Allele — Normal (N = 200)	Poor Efficiency Allele — Patients (N = 39)	Poor Efficiency Allele — Normal (N = 200)
Dopamine D4 receptor exon III VNTR	0.29	0.24	0.71	0.76
Dopamine D4 receptor C to T-521	0.46	0.49	0.54	0.51
Dopamine transporter 3′ VNTR	0.28	0.23	0.72	0.77
Catechol-*O*-methyl transferase Met 108 Val	0.65	0.61	0.35	.039
Monoamine oxidase A promoter repeat	0.51	0.51	0.49	0.49
Monoamine oxidase A C to T 1460	0.63	0.58	0.37	0.42

We found evidence that people with different alleles of two genes related to dopamine, *DRD4* and *MAOA*, showed statistically significant differences in their ability to resolve conflict as measured by RT differences in the ANT. A later study involving 16 people in an fMRI study found that differences in these same genes (*MAOA* and *DRD4*) were related to statistically significant differences in the strength of anterior cingulate activation while performing the ANT (Fan, Fossella, et al., 2003).

After identifying alleles associated with poor executive attention, we then determined whether these alleles were overrepresented in BPD patients, that is, whether these alleles were present at frequencies significantly higher than in a population of control subjects. This simple method provides a rapid means to evaluate the role that candidate genes play in normal cognitive function and subsequently whether a genetic risk towards BPD arises from deficits in cognitive performance. Although the advantage of this method is its speed and ease, there are also several limitations and caveats when comparing allele frequencies across different populations that are summarized by Sullivan and Kendler (2001).

Table 3 shows genes for which differences in alleles were accompanied by significant differences in the conflict score on the ANT. We focused on six dopaminergic genetic polymorphisms that had shown a tendency to be related to the efficiency of the executive attention network (Fossella, Sommer, et al., 2002). We hypothesized that if candidate genes that contribute to poor executive attention serve as risk factors for BPD, then the frequency of alleles associated with poor executive performance would be significantly overrepresented in BPD populations. As shown in Table 3, in five of the six comparisons, the patients did not have a greater frequency of the allele pattern associated with poorer performance on executive attention. Only in the case of a polymorphism in the dopamine 4 receptor gene was the patient pattern in the direction of a greater frequency of the poor efficiency allele than found for the overall population, and this effect was small and not statistically significant.

Our results are preliminary but provide no evidence that the alleles associated with poor efficiency in executive attention are more common in borderline patients. Although there is evidence of heritability of personality disorders as a whole, there is currently no strong evidence that BPD is heritable (Kernberg et al., 2000). Our preliminary results certainly do not indicate that borderline disorder is not heritable, but only that we do not have as yet an account of its genetic basis.

Future directions

Regardless of whether we are able to uncover the genetic basis of the disorder, knowing the temperamental pattern of adults who have BPD could be very useful for experimental studies of children. Rothbart and colleagues have developed temperament scales from early infancy to adulthood (e.g., Gartstein & Rothbart, 2003). Negative affect is present during infancy, whereas effortful control begins to play a role during the toddler and early childhood period. Temperament scales can be used to select children who have the characteristics that could lead to borderline personality. It would then be possible to examine responses to small negative and positive experiences in such children to see if the response to the environment is different in children with more extreme patterns of temperament.

In populations of children who have been abused or neglected, it should be possible to determine the influence of that abuse on temperament and attentional networks. One could determine if consequences of abuse are more severe for children who show the temperamental pattern of high negative affect and/or low effortful control found in adults.

A recent report suggests that a gene influencing the expression of monoamine oxidase can play a moderating effect of the likelihood that abuse will produced antisocial behavior in children (Caspi et al., 2002). This is the same polymorphism we found to be related to the efficiency of the conflict network in normals, which did not seem to be overexpressed in BPD. Nonetheless, the research presented in this paper supports an approach of looking at combinations of genetics and experience in children. From age 7 onward, imaging studies in targeting mechanisms of self-regulation may help us assay the growth of control systems in children. We could then study children who undergo socially stressful experiences to determine the role of temperament in their response.

If studies of children are successful in locating those with patterns similar to adults, it might be useful to intervene with a range of children to improve the development of effortful control by training attention. As noted above, the executive attention network appears to show substantial development between ages 2 and 7. We have been able to index that development both from behavioral tests (Table 2) and from brain measurements of frontal areas involved in conflict resolution. Recently, several examples of training oriented programs have resulted in improved executive control within special populations and domains. For example, training of patients with specific brain injury using attention process training has resulted in specific improvements in executive attention in tasks quite remote from those who have undergone training (Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000). Training of children with attention-deficit/hyperactivity disorder has also been found to be effective in a few rather scattered reports (e.g., Klingberg, Forssberg, & Westerberg, 2002).

In studies of monkeys trained for space flight, a series of training programs was found to be very appealing to the primates and to result in more efficient attention and more general improvements in aggression, social relations, and hyperactivity (Washburn & Rumbaugh, 1992). We have now adapted these programs for use with toddlers and young children, and trials are underway to see the range of improvement possible and to determine which children and which brain networks are likely to reflect those improvements.

Implications

Our current data show it is possible to observe aspects of BPD that appear to involve a specific neural network. Brain imaging studies are a natural complement of this approach. Our results to date are congruent with a biological basis of BPD that has substantial implications for its diagnosis, treatment, and prevention and could provide a more general approach to personality and its disorders.

The temperamental pattern and attentional abnormality discussed in this paper are not themselves a sufficient basis for diagnosis of BPD. The temperamental controls suggest that similar temperamental patterns can be found in normals and that the patients show high variability in both negative affect and attentional regulation. That temperament may be important in the course and duration of treatment is suggested in papers examining the symptom clusters of BPD patients with different levels of effortful control (Clarkin & Kernberg, 2002; Clarkin & Posner, in press). Patients with higher degrees of effortful control have the fewest symptoms and the best chance of recovery from treatment. Thus, although temperament and attention do not supplant current diagnosis, they may provide important hints regarding the selection of treatment.

In a treatment study being run, 120 borderline patients are randomly assigned to three treatment groups in a double blind design. One group receives a manualized psychoanalytically oriented treatment. A second group receives a cognitive behavioral treatment (Linehan, 1993), and a third group receives the pharmacological and counseling treatments common in the community. Changes that might take place in self-reported temperamental dimensions of negative affect and effortful control will be examined following therapy. Because these assays involve reports of recent experiences, it is possible that these will be influenced by the therapies. The brain scans to be carried out after the therapy will show if the stronger activation of the amygdala found in patients compared to average controls prior to therapy will be reduced with therapy.

It will also be important to see if executive attention is influenced by the therapeutic interventions. If amygdala activation is reduced in patients, it will also seem likely that control systems related to emotion would be affected. However, because the ANT does not involve any emotional system, it will be interesting to see if therapy generalizes to this form of cognitive control.

A preliminary analysis after 4 months of therapy was made in all patients who had reached this point, but without breaking the code describing which therapy was involved. There was a good deal of symptom improvement (Clarkin & Kernberg, 2002). The degree of improvement was influenced by the initial severity of the disorder and by the strength of effortful control as reported by the patients prior to entering therapy.

It is possible that attentional training accomplished at the time of development of the executive system might help a broad range of children to overcome the deficits involved in development with this inadequate self-regulation. Although the chances that this will be effective in overcoming the dramatic deficits of BPD do not seem very great, it is important that our understanding of the nature of the disorder and its development lead to a consideration of that possibility.

Borderline personality is only one of several disorders of personality that have been described and studied, and research on other disorders may also benefit from the kind of analysis we have described in this paper. Paranoid personality disorder, for example, might share with BPD higher negative affect but not lower effortful control in comparison with average controls. Antisocial personality disorder may be linked to higher anger/frustration, low fear, and low effortful control. We do not know whether similar or quite different mechanisms are involved in other personality disorders. However, the approach we have been taking is quite general because it is built on neural systems that can be studied in the course of normal development. The use of temperament scales to define populations of normal persons with similar traits and attentional tests with imaging to probe the mechanisms related to the expression of the symptoms may provide a very general approach to personality disorders, as well as normal development.

In addition, the data we have collected in the course of these studies provide support for the utility and generality of the mechanisms of temperament and attention found in normative studies (Posner & Rothbart, 1998). It suggests that the dimensions of temperament and personality, together with specific tests of attentional networks, may provide a fruitful base for examination of individual differences in brain anatomy, function, and connectivity.

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