

## **The Neurobiology and Genetics of Borderline Personality Disorder**

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The diagnosis of borderline personality disorder undoubtedly includes a heterogeneous group of disorders. In fact the diagnosis itself was developed without field trials for validation, and it is therefore not surprising that the agreement using different diagnostic tools is actually quite low (52%) (Kavoussi et al, 1990). Because of the lack of clarity in the phenomenology of the diagnosis, neurobiologic research has been more productive when focusing on temperamental dimensions of the diagnosis (Siever & Davis, 1991). The principal dimensions that have been the focus of biological research into borderline pathology include impulsive aggression and affective instability (Koenigsberg et al, 2001). A factor analysis of DSM-III-R criteria for borderline personality disorder suggests that impulsivity and affective instability formed two of three homogeneous factors underlying the disorder; a third "relatedness" factor was also identified. (Sanislow et al, 2000). While these symptoms are seen across personality disorders, they predominate in the Cluster B personality disorders.

### **Impulsive Aggression:**

#### ***Phenomenology:***

Patients with borderline personality disorder frequently come to medical attention because of their difficulty with impulse control, leading to behaviors such as self-mutilation, domestic violence, assault, and destruction of property.

The significance of impulsive aggressive symptomatology in patients with personality disorders is demonstrated by the frequency of personality disorders in the forensic population. In one study of violent offenders and impulsive fire setters, 47% of the subjects were found to have a personality disorder diagnosis, especially borderline and antisocial personality disorders (Virkkunen et al, 1996). In a sample of wife batterers, higher scores on a measure of borderline personality organization (similar to scores seen in a sample of borderline patients diagnosed by DSM-III criteria) were found compared to controls (Dutton et al, 1996).

#### ***Neuroendocrine:***

Numerous studies have demonstrated that decreased central serotonergic activity is associated with measures of impulsive aggression in patients with personality disorders (Goodman & New, 2000). Specifically, reductions of serotonergic activity have been identified, as reflected in diminished concentrations of the principal metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), in the cerebrospinal fluid (CSF) of personality disordered patients with impulsive aggression, as well as in depressed patients, volunteers, and violent alcoholic offenders and more recently in mentally disordered violent offenders (Linnoila et al, 1989; Virkkunen et al, 1994; Lidberg et al, 2000). Suicide attempts are often viewed as a subtype of aggressive behavior, and reduced CSF 5-HIAA has also been associated with attempted or completed suicides in a variety of populations (Lidberg et al, 2000; Asberg et al, 1997; Brown et al, 1982).

The relationship between impulsive aggression and the serotonergic system have also been supported by studies utilizing hormonal responses to pharmacologic interventions that increase activity in the serotonergic system. Blunted prolactin responses to d,l-fenfluramine, a serotonin releasing agent and post-synaptic agonist, are found in male patients with borderline personality disorder (Coccaro et al, 1989) and antisocial personality disorder (O'Keane et al, 1992). In a larger series of personality disorder patients, blunted prolactin responses to d-fenfluramine were associated with impulsivity and aggression (Coccaro et al, 1995). Taken together these findings support an association between blunted serotonergic responsiveness and impulsive aggression. See Table 1.

In some studies, patients with major depressive disorder have demonstrated a blunted prolactin response to fenfluramine compared to controls (Coccaro et al, 1989; Siever et al, 1984; Mitchell & Smythe, 1990; Lopez-Ibor et al, 1988), although not all studies support this finding (Asnis et al, 1988). One study showed no correlation between Hamilton Depression Rating Scales scores and the magnitude of the prolactin response to fenfluramine in depressed patients (Coccaro et al, 1989). Similarly, in personality disorder patients, no relationship was found between depression rating scores and prolactin responses (Coccaro et al, 1989). However, depressed patients with "anger attacks" had a blunted prolactin response to fenfluramine compared to depressed patients without anger attacks (Fava et al, 2000). This suggests that it might be the subset of depressed subjects with irritability and angry outbursts which is most closely associated with decreased serotonergic activity. Suicide attempts have also been associated with blunted prolactin responses to fenfluramine in a personality disorder cohort, as well as in a depressed patient cohort (Coccaro et al, 1989). More recent studies support correlations between reduced serotonergic activity and non-suicidal self-injurious behavior (New et al, 1997). These findings are consistent with the view that some suicide attempts may be seen as a subtype of aggressive behavior and that it is the disorder of impulse control rather than the mood component that may be most closely associated with serotonergic dysregulation. The findings of decreased serotonergic responsivity in impulsive aggression led to placebo controlled trials showing efficacy for the serotonergic agent, fluoxetine, in non-depressed patients with personality disorders (Coccaro et al, 1997).

### ***Genetics:***

Family and twin studies of borderline personality disorder suggest that while the disorder itself may not be heritable, the prominent features of impulsivity appears run in families (Silverman et al, 1991, Torgersen et al, 1994, 2000). Studies of personality characteristics have shown suicidality, affective instability and impulsivity to be heritable (Bouchard, 1994). Impulsive aggression has also been shown clearly to be at least partially heritable as established by both twin (Coccaro et al, 1993) and adoption (Bohman et al, 1984) studies, with suggested heritability estimates from 20-62% (Coccaro et al, 1993).

Candidate gene studies provide a window into which specific receptors might be involved in the control of aggression. Candidate gene studies involve the use of polymorphic genes to explore the relationship between

#### **Impulsive/aggression and serotonergic abnormalities**

- Low CSF 5-HIAA in impulsive aggression
- Decreased neuroendocrine response to serotonergic agents in impulsive aggression
- The SSRI, fluoxetine, is effective in the treatment of impulsive aggression in personality disorders

genotype and a particular phenotype (in this case impulsive aggression). A polymorphic gene is one in which slight differences in DNA sequence at a particular gene locus can be found in a population, which may or may not confer a difference in the activity or function of the resulting gene product. The different copies of the gene are called “alleles”. Candidate gene studies investigate an association between a particular allele and behavior. The selection of genes involved in serotonin functioning as candidate genes comes from the observation that decreased serotonergic activity has been associated with impulsive aggression. This approach has not been undertaken in affective instability as the neurochemistry provides much less information about the appropriate candidate genes to study. Polymorphisms in genes coding for gene products involved in serotonin synthesis, reuptake, metabolism, and receptors have been identified, enabling candidate gene studies in this area. It is beyond the scope of this text to review comprehensively all candidate gene studies of aggression, but the following reviews some of the most promising findings.

Tryptophan Hydroxylase: Tryptophan hydroxylase (TPH) is the rate-limiting enzyme involved in the synthesis of serotonin. A polymorphism for TPH has been identified, with two common alleles, designated "L" and "U" (Nielsen et al, 1992) with frequencies of 0.40 and 0.60 respectively in unrelated Caucasians. The "L" TPH allele has been associated with reduced CSF 5-HIAA concentrations and a history of suicide attempts (Nielsen et al, 1994, 1998), while a subsequent report found no association between suicidality and TPH genotype (Abbar et al, 1995). In two separate cohorts of Finnish violent alcohol offenders, the "L" TPH allele was associated with reduced CSF 5-HIAA concentrations and a history of suicide attempts (Nielsen et al, 1994, 1998). Another study, however, reported that patients with the "U" allele had a higher incidence of suicide attempts (particularly violent attempts) in patients with major depression (Mann et al, 1997); while other studies have reported no association between TPH genotype and suicide (Kunugi et al, 1999; Geijer et al, 2000). Increased impulsive aggression in Caucasian men with personality disorders with the "LL" genotype as compared to the "UL" and "UU" genotypes has been reported (New et al, 1998), although a recent study has reported an association between the "U" allele and measures of aggression and anger (Manuck et al, 1999). It should be noted, however, that the functional significance of this polymorphism is unknown.

Serotonin Transporter: Another serotonin related gene that has been implicated in mediating the heritability of impulsive aggression is the serotonin transporter gene (5-HTT). A polymorphism in the promoter region of the transporter gene has been identified; this polymorphism has demonstrated *functional significance* in coding for high and low transporter production. Studies of this polymorphism have yielded conflicting results. Evidence suggests that the "s" promoter is less active than the "l" promoter and may be associated with increased measures of harm avoidance and impulsivity in a sample of university students, as measured by the NEO personality disorder inventory (Lesch et al, 1996), although other studies did not replicate this finding (Ebstein et al, 1997; Gelernter et al, 1998). This polymorphism has also been examined in its association with suicide. Several studies revealed no association between the 5-HTTLPR allele and suicide (Mann et al, 2000; Geijer et al, 2000, Russ et al, 2000). However, two other studies demonstrated a significant increase in the (s, s) homozygous group among violent suicide victims (Bondy et al, 2000; Bellivier et al, 2000). In summary,

associations between particular alleles in functionally important polymorphisms suggests the possibility that genetically altered proteins in the 5-HTT might be involved in the control of impulsive aggression, although the results are as yet inconclusive.

**Serotonin 1B:** Enhanced aggressive behavior has been demonstrated in mice entirely lacking the serotonin 1B receptor gene (Saudou et al, 1994). The mouse 5-HT<sub>1B</sub> receptor is hypothesized to be functionally similar to the human 5-HT<sub>1B</sub> receptor in that they share over 93% of the amino acid sequence. Another report on a family with antisocial behavior lends support to the heritability of impulsive aggression through monoamine activity: a family in Holland has been reported with a point mutation in the monoamine oxidase-A gene and this point mutation segregate with aggression in males in this family (Brunner et al, 1993). These studies suggest that genetic differences in the serotonin system may be associated with behavioral traits related to impulsive aggression.

The gene coding for the 5-HT<sub>1B</sub> receptor (HTR1B) is an intronless gene located on chromosome 6 (Hamblin et al, 1992; Jin et al, 1992). In a study of Finnish alcoholic and Southwest American Indians, antisocial alcoholism showed significant evidence of sib-pair linkage to HTR1B G816C in both populations (Lappalainen et al, 1998). Preliminary evidence suggests that a silent polymorphism in the gene coding for the 5-HT<sub>1B</sub> receptor may be associated with different susceptibilities to suicidal behavior in personality disorders (New et al, in press). However, in a postmortem study of human brain tissue, there was no difference in allele frequency of this 861 polymorphism in HTR1B between suicide victims and non-suicide victims, nor between those with a history of major depression, alcoholism or pathological aggression (Huang et al, 1999). Other post-mortem studies have reported a decreased number of 5-HT<sub>1B</sub> receptors in the frontal cortex of non-depressed suicide victims (Arranz et al, 1994), whereas another study reported increased 5-HT<sub>1B</sub> receptors in the globus pallidus of violent suicide victims (Lowther et al, 1997). A functional significance for this polymorphism has not been established, although one study did demonstrate fewer 5-HT<sub>1B</sub> receptors in human post mortem brain tissue to be associated with the G861 allele of this polymorphism (Huang et al, 1999).

In general, genetic studies of impulsive aggression have been difficult to replicate. There are a number of reasons why this might be so. Some of the problems include: 1) A behavior as complex as impulsive aggression may be the result of additive effects of several alleles, each contributing only a small effect. This is a major issue in impulsive aggression, which is likely to be determined by a number of genes and is only pathological in an extreme form when it results in destructive behavior. 2) Clearly for a behavior as complex as impulsive aggression, environmental factors will play a role in the development of the phenotype, these include facts such as early life trauma and exposure to violence and education level. Once a specific set of genes have been clearly identified, it will become important to examine gene-environment interactions. 3) Polymorphisms most often vary in different ethnic groups; this is called "population stratification". For genes with small effect sizes studied in case control study design, ethnic differences can overshadow the effect of genotype on the implicated behavior. Alternatively, ethnic differences in the sample population between cases and controls can create an apparent difference by genotype, which turns out only to reflect ethnic differences between the groups.

For these reasons, there are few solidly identified and replicated gene-behavior associations. The present approach is to look at intermediate phenotypes to tease out the effect of each gene, several of which may converge to create a disorder like borderline personality disorder.

### ***Functional Neuroimaging:***

Another approach to understanding impulsive aggression is to explore brain regions involved in the control of these behaviors. Preclinical and human studies involving brain lesions suggest regional control of aggression. Prefrontal cortex, particularly prefrontal orbital cortex and adjacent ventral medial cortex, appears to play a central role in the regulation of aggressive behavior. Prefrontal cortex activity is modulated by ascending serotonergic tracts from mid-brain raphe nuclei where serotonergic cell bodies are located which synapse on neocortex, acting on a number of receptors, particularly the 5-HT<sub>2a</sub> receptor.

The critical role of prefrontal orbital cortex is exemplified by the case of Phineas Gage, who, after a penetrating injury to his orbital frontal cortex, became irritable, hostile, and displayed a tendency to engage in verbal aggression with profanity. Computerized reconstruction of his skull demonstrated that the location of the lesion to Phineas Gage's brain was in the anterior and mesial aspects of the orbital cortex as well as anterior cingulate and anterior mesial aspects of frontal cortex superior to orbital cortex, with more marked damage in the left hemisphere (Damasio et al, 1994). Irritability and angry outbursts have also been associated with damaged orbital frontal cortex in neurologic patients (Weiger & Bear). Lesions of prefrontal cortex, particularly orbital frontal cortex, early in childhood can result in antisocial disinhibited, aggressive behavior later in life (Anderson et al, 1999), and reduced prefrontal gray matter has been associated with autonomic deficits in antisocial personality disordered individuals characterized by aggressive behaviors (Raine et al, 2000). These studies suggest that orbital frontal and adjacent medial frontal cortex exert an inhibitory influence on aggression presumably to regulate or control emergence of aggression.

**Functional Imaging (PET and SPECT) and Aggression:** Positron Emission Tomography (PET) studies of regional glucose metabolism reveal abnormalities in prefrontal cortex in individuals with a history of impulsive aggression (Spoont, 1992). A study of 41 murderers demonstrated decreased regional activity in the lateral and medial zones of the prefrontal cortex, and increased activation of the right amygdala compared to controls (Raine et al, 1997). A subsequent reanalysis of these data showed that it was the subset of murderers who committed impulsive murders, in contrast to those with premeditated murders who showed reductions in lateral prefrontal cortex metabolism (Raine et al, 1998). Patients meeting criteria for borderline personality disorder had decreased metabolism in frontal regions corresponding to Brodmann areas 46 and 6 and increased metabolism in superior and inferior frontal gyrus (Brodmann areas 9 and 45)(Goyer et al, 1994). Taken together, the results of these PET studies suggest reduced metabolism in prefrontal cortex, particularly orbital and adjacent ventral medial frontal cortex, is associated with increased impulsive aggressive behavior.

**Serotonergic Probes and Regional Brain Glucose Metabolism:** Ascending serotonergic neurons from the raphe nuclei project widely throughout the brain including

projections to dorsolateral prefrontal cortex and medial temporal lobe. The dorsal raphe-median forebrain bundle directly innervates the amygdala, and dorsal raphe tracts outside the medial forebrain bundle project to the parietotemporal cortex. Diffuse tracts extend from the dorsal and medial raphe in midbrain and project to the frontal lobe.

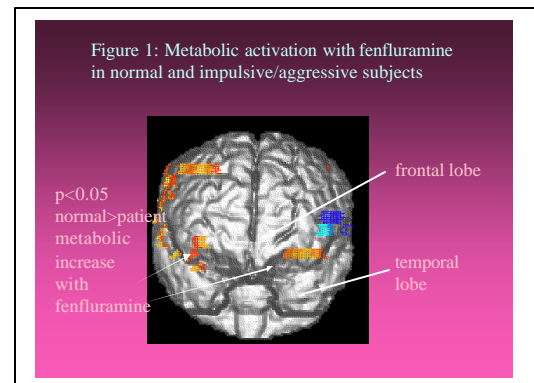
Serotonergic agents have been shown to modulate selectively specific regional brain glucose metabolism. In previous PET studies evaluating regional brain glucose metabolism, depressed subjects demonstrated no significant changes in glucose metabolism in response to d, l-fenfluramine compared to placebo (Mann et al, 1996a, 1996b), but those patients who also had a history of suicide attempts had particularly decreased metabolic responses to d-fenfluramine. In another study, administration of d-fenfluramine increased left cingulate gyrus metabolism, and prefrontal cortex metabolism in normals; however, depressed patients did not differ from normal controls (Meyer et al, 1996). This suggests that the results of the Mann et al study may depend on the large representation of suicidally depressed patients in their sample. In a study, which directly compared glucose metabolism following fenfluramine and placebo in personality disordered patients with high levels of impulsive aggression, normal subjects showed increased metabolism in orbital frontal and adjacent ventral medial frontal

cortex as well as cingulate and inferior parietal cortex following fenfluramine compared to placebo, while impulsive aggressive subjects showed significant metabolic increase only the in inferior parietal lobe (Siever et al, 1999). See Figure 1. This study's results were replicated in a study of patients with borderline personality disorder (Soloff et al, 2000). While, *in vivo* imaging studies in humans have not been performed in impulsive aggression populations, the data to date in imaging studies of depression may suggest that 5-HT<sub>2a</sub> receptor number is differentially regulated in simple depression and suicide/impulsive aggression, where 5-HT<sub>2a</sub> number may be increased. The model we have hypothesized is that ascending serotonergic neurons from the raphe nuclei through the cingulate gyrus exert a net stimulatory effect on the orbital cortex. Orbital cortex in turn, appears to have an inhibitory role on other regions such as the amygdala and other subcortical structures (Siever et al, 1999; New et al, 1997; Davidson et al, 2000). Individuals with impulsive aggressive behavior appear to show reduced serotonergic modulation of orbital frontal cortex compared to that of non-impulsive subjects, which produces disinhibition of downstream limbic/subcortical regions, such as the amygdala and thus are predisposed to aggression.

### **Affective Instability:**

#### ***Phenomenology:***

Affective instability has been defined as “a predisposition to marked, rapidly reversible shifts in affective state that are extremely sensitive to meaningful environmental events” (Siever & Davis, 1991). Affective instability is among the defining characteristics of borderline personality disorder. However, some have viewed



that affective instability as secondary to “affective temperamental dysregulation” and have seen the borderline diagnosis as representing a part of the bipolar spectrum (Akiskal et al, 2000). Recent work from our group suggests that while bipolar II patients share the attribute of affective instability with borderline patients, the bipolar II patients appeared to move between euthymia and depression while borderline patients moved between euthymia and anger (Henry, Chantal; personal communication). In addition, borderline patients had high levels of impulsivity and hostility, whereas bipolar II patients did not.

### ***Neuroendocrine:***

Although the neurochemistry of affective instability has been studied less than that of impulsive aggression, there is some evidence that the cholinergic system has a role in regulating affect. Depressive symptoms can be elicited with the administration of cholinomimetics (Janowsky et al, 1974), and patients with depression experience an increase in depression, hostility and anxiety in response to arecholine (Risch et al, 1983). Although cholinergic agents appear to induce depressed mood in normals and patients with depression, this effect appears to be even more intense in patients with borderline personality disorder. Procaine, a cholinergic agonist, has been shown to induce a high degree of dysphoria in borderline personality disorder compared to subjects with affective disorders and normal controls (Kellner et al, 1987). The cholinomimetic, phsyostigmine, has been shown to produce significantly more depressive symptoms in borderline personality disorder than placebo, and this effect is greater and more rapid than that seen in healthy controls (Steinberg et al, 1997).

There is also evidence of a disturbance in noradrenergic activity in affectively unstable patients with borderline personality disorder (Gurvits et al, 2000). In healthy subjects, a dysphoric response to dextroamphetamine, a catecholaminergic agent, correlated with measures of affective instability (Steinberg et al, 1997). Furthermore, a heightened growth hormone (GH) response to the alpha-2 agonist, clonidine, has been demonstrated in subjects who are highly reactive to their environment (Lane et al, 1997). GH response to clonidine directly correlated with measures of irritability, a related symptom to affective instability, in subjects with BPD but not in depressed subjects, heightening the importance of affective instability as compared to simple depression (Coccaro et al, 1991). In PET studies of normal subjects, the dysphoric response to procaine correlated with metabolic activation of the left amygdala (Ketter et al, 1996).

### ***Functional Neuroimaging:***

There have been no neuroimaging studies specifically of affective instability in personality disorders. There is evidence from PET studies of depression that abnormalities in the cingulate and dorsolateral prefrontal cortex may be present (Baxter et al, 1989; DeAsis et al, 1999; George et al, 1997; Mayberg et al, 1997). Studies of mania have shown a state-related decrease in orbitofrontal cortical activity in mania (Blumberg et al, 1999), and an increase in left dorsal anterior cingulate and left head of the caudate in the manic state (Blumberg et al, 2000). Studies of emotional regulation in normal subjects implicate the anterior cingulate gyrus in emotional processing (Lane et al, 1998).

**Summary:**

In summary, the neurobiological research that has been the most useful in shedding light on the physiology underlying borderline personality disorder has examined this multifaceted disorder by examining simpler dimensions of behavior separately, including impulsive aggression and affective instability. Evidence suggests that impulsive aggression involves a deficit in serotonergic activity. However, the specific mechanism underlying this remains unknown. It is clear that this component of behavior is substantially genetically encoded, and so new research has focused on elucidating the specific receptors underlying impulsive aggression through the examination of genes coding for specific receptors. Additional research has focused on the brain regions that underlie aggression and it is likely that prefrontal orbital frontal cortex exerts an inhibitory control over aggressive behavior in normal people. It appears that these regions may be under active in persons with impulsive aggression and specifically may not be recruited in these patients in response to a serotonergic activation. Less is understood about the physiology of affective instability in personality disorders, but emerging information suggests that it is quite different from the affective instability in primary affective disorder. Preliminary evidence implicates the cholinergic system in the control of affective instability, but more research will be required to confirm this.

Further elucidation of the physiology of impulsive aggression and affective instability may provide more specific targets in the future for the pharmacological management of these components of borderline personality disorder.

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