Integration: Serotonergic and Dopaminergic Pathways Implicated In the Development And Maintenance Of Behaviors In Restricting-Type Anorexia Nervosa

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Anorexia nervosa has one of the highest mortality rates of all mental illnesses (National Eating Disorders Association, 2006a). Elucidating the neurobiological basis of the disorder would be a major step toward understanding it. By integrating findings from research into depression, anxiety, and eating disorders, the present paper introduces a possible neurological mechanism that contributes to the development of anorexia nervosa. In this model, the neurological dysfunctions that underlie anorexia can be described as disturbances in excitatory and inhibitory projections to the amygdala instigated by increased dopamine and unbalanced serotonin activity. By further exploring these unique disturbances, clinicians and researchers will be able to improve prognosis and treatment.

Anorexia nervosa (AN) is a devastating illness with debilitating and sometimes irreversible physical and psychological consequences. Core features of the disorder include fear of food and weight gain, anhedonia (the decreased experience of pleasure), dysphoria, body image distortion, repetitive behavior, and perfectionism (Kaye et al., 2005; Kaye, 2008). Denial of illness is common; relapse and mortality rates are high (Kaye et al., 2005; National Eating Disorders Association, 2006a; Kaye, 2008). Despite this troubling situation, there is only limited experimental research on therapies for AN, very little of which has found adequate empirical support (Wilson, Grilo, and Vitousek, 2007). In fact, chronic anorexia nervosa cases are often extremely resistant to treatment (Wilson, Grilo, and Vitousek, 2007). Surely a more nuanced understanding of the disorder would facilitate the development of more effective and long-lasting therapeutic results. As such, this paper seeks to establish a neurological model of restricting-type anorexia nervosa (RAN) that may shed light on its etiology and possible targets for treatment.

Though little is known about the neurobiological bases of AN, other diseases that are commonly comorbid with AN have been researched in considerable depth; thus, examining AN from the perspective of these disorders could enable researchers to elucidate common neurobiological factors that may account for their comorbidity, and in course, central aspects of AN that may impact treatment. AN is often comorbid with obsessive compulsive disorder (OCD) and depression (Deep, Nagy, Weltzin, & Rao 1995; Kaye, 2008), and genetic overlaps have been found as well (Bellodi et al., 2001). The disorder also shows strong comorbidity with dependent, avoidant, and obsessive-compulsive personality disorders, which are classified as "anxious-fearful" (Cassin & von Ranson, 2005). Most importantly, anxiety, depression, and maladaptive personality traits often predate the onset of anorexia, and may even be predisposing factors (Deep et al., 1995). Finally, probands (genetic forbearers) of anorectic subjects have been found to have higher rates of anxiety disorders than control probands, suggesting common genetic and/or neurological bases (Strober, Freeman, Lampert, & Diamond, 2007).

Researchers have suggested that similarities between AN and anxiety and depression-related disorders may be due to early, possibly genetically-linked disturbances in serotonin (5-HT) and dopamine (DA) functioning. In AN, environmental factors related to food and body image could precipitate the use of disturbed eating as a coping mechanism for neurological disturbances and related negative affective symptoms (Kaye et al., 2003, 2005; Kaye, 2008). Starvation may improve mood through decreased tryptophan intake, a precursor to serotonin (Kaye et al., 2003, 2005; Kaye, 2008). Food consumption is also directly related to the release of DA in the brain (Bosanac, Norman, Burrows, & Beumont, 2005; Frank et al., 2005; Kaye, Frank, & McConaha, 1999). Thus, individuals may turn to starvation as an effective method of altering whatever neurological dysfunction has contributed to aversive emotional states.

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The association between anxiety and anorexia is particularly noteworthy. The term anorexia nervosa literally means "lack of appetite induced by nervousness." Disturbances that are highly associated with anorexia, including obsessionality, perfectionism, anhedonia, behavioral inhibition, and high harm avoidance, are behavioral expressions of anxiousness (Kaye et al., 2005; Garakani, 2006). Furthermore, anorexia is highly associated with disproportionate negative affect. In fact, von Ranson and Woodside (2005) found that as negative affect increases so too does food restriction, while chances of recovery weaken. Thus, symptoms of anxiety and depression may contribute to the development of AN.

Given this background, the current paper attempts to integrate evidence from research on depression, anxiety, and eating disorders (EDs) to describe a possible framework for understanding the neurological mechanisms underlying restricting-type anorexia nervosa (RAN)[1]. The components of the proposed model follow:

1. A genetic predisposition to disrupted serotonin (5HT) activity will lead to deficits in executive functioning and elevated baseline anxiety levels, leading to high levels of harm avoidance, behavioral inhibition, and rigidity.

2. Abnormal 5ht activity also causes a deregulation of the mesolimbic (composed of emotional brain regions) and mesocortical (composed of cortical brain regions) da systems. In response to reduced inhibition from the mesocortical da system, mesolimbic da activity will increase. This will decrease reward sensitivity in the nucleus accumbens, a region of the ventral striatum, leading to decreased motivation and reward responsiveness. Furthermore, increased da and decreased 5ht activity in the anterior cingulate cortex (acc) will inhibit this region, leading to a deregulation of the amygdala and a compromised ability to extinguish learned fear associations.

While research has looked at the nature of the relationships between AN, depression, and anxiety, too few studies have applied knowledge of the neural bases of depression and anxiety to AN. This paper will therefore use current knowledge of limbic and cortical dysfunction in abnormal emotional processing to conceptualize possible mechanisms for the development of RAN.

Cortical and Subcortical Dysfunction in Depression and Anxiety

Mood and anxiety disorders have been associated with dysfunction in the amygdala (AMG), a subcortical brain region located in the medial temporal cortex that plays a crucial role in the detection of threatening stimuli (Davidson, 2002). It has been found to be hyperactive in patients suffering from depression, and a number of anxiety disorders including OCD, specific phobias, post-traumatic stress disorder, and panic disorder (Davidson, 2002; LaBar & Cabeza, 2006). The amygdala plays a large role in anxiety because it is recruited in both the acquisition and expression of fear conditioning (Garakani et al., 2006; LaBar & Cabeza, 2006). Studies have found that in anxiety disorders, exaggerated amygdala activity mediates the formation of associations between neutral stimuli and conditioned fear responses (Garakani et al., 2006; LaBar & Cabeza, 2006; van den Heuvel et al., 2004).

While the amygdala records and expresses fear associations, the left prefrontal cortex (PFC) extinguishes them, most likely by inhibiting AMG activity. The medial PFC has been found to inhibit the firing of amygdala neurons, and in rats with medial PFC damage, fear extinction was significantly slower than in healthy controls (Garakani et al., 2006; Davidson, 2002). Furthermore, higher reported

1 This paper will focus primarily on findings about restricting-type anorexia nervosa. Restricting-type anorexia nervosa (RAN) is a subtype of anorexia nervosa, which is characterized by the maintenance of extremely low weight and persistent restriction of caloric intake. It is distinct from binge/purge anorexia nervosa, which is characterized by maintenance of low weight, as well as episodes of bingeing and purging. Elucidating this distinction is not the objective of this paper, but the particular behavioral and neurological differences found between bingeing disorders and ran provide insight into the unique neuro-behavioral manifestations of the disorder.

levels of negative affect in subjects were correlated with lower relative resting left PFC activity and/or right amygdala hyperactivity (Davidson, 2002). In the case of RAN, a disruption in the relationship between the AMG and the PFC may be taking place, leading to the appraisal of food as threatening.

The relationship between the AMG and the anterior cingulate cortex (ACC) provides another key to understanding the phenomenology of anxiety. Correlated activity has been demonstrated between the AMG and two regions of the perigenual ACC (pACC): a positive correlation between the AMG and the rostral subgenual ACC (rACC), and a negative correlation between the AMG and the caudal supragenual ACC (cACC) (Pezawas et al., 2005). A positive correlation between the rACC and cACC suggests a possible feedback loop between the three regions. Together, the distinct regions of pACC modulate AMG activity, while also promoting each other's required levels of activation. In subjects with the s allele (a serotonin transporter polymorphism related to depression and anxiety), disruption of this feedback loop was found, which was characterized by reduced AMG-rACC functional connectivity (Pezawas et al., 2005). Furthermore, the nature of this relationship accounted for 30% of the variance in harm avoidance scores, a trait strongly related to both anxiety and AN (Pezawas et al., 2005).

In sum, neurobiological factors that contribute to anxiety may also contribute to the anxious characteristics of AN (Pezawas et al., 2005). Anxious feelings and behaviors can potentially be caused or facilitated by a disruption in the relationship between the mPFC and/or the pACC and the amygdala. And as the following section will show, neuroimaging studies enable further insight into the roles of serotonin (5HT) and dopamine (DA) in AMG modulation and consequently in the behavioral manifestations of RAN.

Neurobiological Models of Anorexia Nervosa

Dopamine

Dysfunctional dopamine activity has been found in RAN subjects (Kaye et al., 1998, 2005; Frank et al., 2005; Casper, 2006; Davis and Woodside, 2002; Bosanac et al., 2005), which provides strong explanatory power for crucial behavioral manifestations of the illness, such as motivational disruptions, hyperactivity, anhedonia, excessive exercise, low novelty seeking, and withdrawal from food. Specific brain regions affected by dysfunctional dopamine activity include the striatum, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and amygdala (AMG).

There are two major dopamine pathways in the brain, the mesolimbic and mesocortical pathways. The mesocortical dopamine pathway is formed by projections from the ventral tegmental area (VTA) to the neocortex (including the PFC), while the mesolimbic dopamine pathway is formed by projections from the VTA to regions of the limbic system (including the striatum, ACC, and AMG) (Masciotra, Landreau, Conesa, & Erausquin, 2005). Findings in schizophrenic subjects indicate that DA activity levels in these two pathways are functionally inversely related: inhibiting the mesocortical pathway leads to enhanced synaptic responsiveness in the mesolimbic pathway (Masciotra et al., 2005). Such dysfunction could potentially play a role in anhedonia and depression, symptoms common to both schizophrenia and RAN, and thus could potentially be extended to theories of RAN.

Evidence exists for increased DA activity in the mesolimbic pathway. Research examining recovered anorectic subjects has shown decreased cerebrospinal fluid (CSF) concentrations of homovanillic acid, a major metabolite of DA (Kaye et al., 1998, 2005; Frank et al., 2005; Casper, 2006; Davis and Woodside, 2002; Bosanac et al., 2005). This supports increased DA receptor activity, as decreased concentrations of DA metabolites in CSF provide positive feedback to receptors, up-regulating their activity to ensure efficient use of limited DA (Frank et al., 2005). Furthermore, increased binding potential of DA receptors has been found in recovered RAN subjects in the striatum, a subcortical brain region central to reward, motivation, movement, and learning processes, and a portion of which is a

Table 1
Consequences of elevated DA activity in RAN

Mesolimbic DA pathway	Behavioral Consequences	Mesocortical	Behavioral Consequences
Striatum – nucleus accumbens	Reward responsiveness Anhedonia Excessive exercise Motivation (long over short term rewards) Stereotyped movement Low novelty seeking Withdrawal from food/reduced hunger	Prefrontal cortex	Inhibited – reduced extinction of learned fear associations
ACC	Inhibited		
Amygdala	Excited		

component of the mesolimbic DA pathway (Frank et al., 2005; Pierce and Kumaresan, 2006).

Although there is no evidence of a disruption in the mesocortical pathway in RAN, the model of mesolimbic-mesocortical interaction (i.e., the functional inverse activation relationship) indicates that mesocortical activity would be reduced. Increased mesolimbic and decreased mesocortical DA activity could lead to anorectic behaviors through maladaptive reward responsiveness and fear conditioning: receptor insensitivity has been found to promote extreme motivation for future over immediate reward (e.g., denying immediate gratification of hunger for future achievement of the "perfect" body) (Frank et al., 2005; Kaye et al., 1999, 2005, 2008; Casper, 2007).

As mentioned earlier, the AMG is recruited in the acquisition and expression of fear associations, and is regulated by the ACC and the PFC. Research has shown that DA can inhibit ACC activity, thus leading to AMG hyperactivity (Holroyd & Coles, 2002). In addition, since the mesocortical pathway is made up of DA tracts in cortical regions of the brain, decreased activity in mesocortical tracts may lead to decreased activity of the PFC, which may also contribute to AMG hyperactivity. These findings suggest that elevated DA may lead to reduced extinction of aversive conditioned associations, leading RAN patients to appraise food as threatening.

While binge-eating disorder and bulimia nervosa (BN) subjects show decreased DA receptor binding as compared with control groups (Frank et al., 2005), RAN, on the other hand, is characterized by a strong withdrawal relationship with food, suggesting a converse effect of DA receptor activity. High levels of DA in areas like the antero-ventral striatum, which includes the nucleus accumbens, a critical component of reward anticipation, may lead to reduced sensitivity to external rewards such as food, making it easier for anorectics to withdraw from food (Davis and Woodside, 2002; Kaye et al., 2003). In addition, increased DA activation may lead to a decreased sensitivity to and need for novel experiences (Kaye et al., 1999, 2008; Kandel et al., 2000). This behavior also differs between anorectics and bulimics, the latter exhibiting high impulsivity and novelty seeking behavior (Thompson-Brenner et al., 2008).

Furthermore, if DA levels were elevated in anorexia, the risk of substance abuse would be lower, as many drugs are DA agonists. In fact, research has shown a lower frequency of substance abuse in RAN, in contrast to bulimia and AN binge-

purge subtype (Deep et al., 1995; Kaye et al., 2005; Kaye, 2008; Thompson-Brenner et al., 2008). Additionally, DA agonists suppress appetite, further suggesting that high levels of dopamine inhibit feeding behavior (Frank et al., 2005). Thus it can be postulated that high DA levels in RAN are associated with decreased reward sensitivity, appetite, and approach behavior. These deficits most likely result from increased mesolimbic DA activity, as regions central to reward responsiveness reside in the limbic brain.

While hyperactivity is not a diagnostic criterion for anorexia nervosa, it is a characteristic that has been highly associated with the disorder, and has even been suggested as an addition to the next version of the Diagnostic and Statistical Manual for Mental Disorders (Davis and Woodside, 2002; Casper, 2006). In addition to excessive exercise, RAN is typified by general hyperactivity, including repetitive movement. Research has suggested that the hyperactivity seen in RAN may be in part due to increased DA activity in the striatum (Frank et al., 2005; Kaye et al., 1999, 2005, 2008; Casper, 2007). DA has also been implicated in motor control, and has been shown to play a role in displays of stereotyped (i.e., repetitive) behaviors in animals, which is analogous to hyperactivity in anorexia (Kaye et al., 1999).

Increased DA activity may also contribute to anhedonia in RAN patients. Davis and Woodside (2002) found that non-exercising anorectics had the highest anhedonia (the decreased ability to experience pleasure) scores among excessive and nonexcessive exercising anorectics, bulimics, and recovered anorectics. Exercise down-regulates DA activity, suggesting that in RAN physical hyperactivity may regulate DA hyperactivity (Davis & Woodside, 2002). Thus, physical hyperactivity may serve to reduce anhedonia by decreasing excessive DA. Excessive activity may also reduce other DA-related symptoms such as anxiety. Decreased reward responsiveness has also been associated with decreased mesocortical DA activity in depression (i.e., anhedonia), furthering the evidence for increased mesolimbic DA and, by extension, decreased reward responsiveness in RAN (Holroyd & Coles, 2002). Thus, anhedonia and hyperactivity may be associated with a disruption in both the mesocortical and mesolimbic dopamine pathways (See Table 1).

In sum, research points to dysfunctional DA activity in RAN patients. Increased mesolimbic DA activity may contribute to decreased reward sensitivity, leading to withdrawal from food and increased hyperactivity, while decreased mesocortical DA activity may contribute to an appraisal of food as threatening.

Serotonin

A number of behavioral manifestations of RAN can be explained by abnormal serotonin (5HT) activity, namely harm avoidance, behavioral inhibition, rigidity, and withdrawal from food (Bailer et al., 2005; Kaye et al., 2005). Crucially, 5HT receptor balance plays a role in the modulation of DA activity (Kaye et al., 2002). Thus, the DA dysfunction seen in RAN could be explained by upstream effects of 5HT. Specific brain regions that may be affected by disrupted serotonin activity in RAN are the ACC, AMG, and frontal and temporal cortices.

The exact nature of 5HT dysfunction in RAN is somewhat more contentious than that of DA disruption. Some research has shown differences in serotonin levels between ill and recovered RAN subjects, with recovered women showing reduced 5HT2A binding potential in the entire neocortex and cingulate cortex, but normal activity in 5HTIA receptors (Audendart et al., 2003; Bailer et al., 2005), and ill women showing elevated 5HTIA and normal 5HT2A receptor binding activity (Bailer et al., 2007). However, a number of studies have found no differences between ill and recovered subjects in dysfunctional 5-HT receptor imbalance (Bailer et al., 2004, 2005, 2007).

Further contributing to the controversy, it is not clear what imbalances may exist before and/or following chronic starvation (Kaye et al., 2005a, b; Bailer et al., 2005, 2007; Audendart et al., DATE?!; Bosanac et al., 2005; Casper, 2006). It is thus difficult to conclude

from current evidence whether restriction actually alters brain chemistry to the extent that serotonin abnormalities are actually ameliorated. However, strong biological evidence supports the notion that diet affects serotonin availability (Kaye et al., 2003, 2005; Kaye, 2008). It is possible that the brains of restricting anorectics are able to return to "normal" activity after a time even in the face of starvation, creating a vicious cycle of using transiently effective restriction to ameliorate consistently returning aversive emotional states.

In multiple studies of RAN subjects, 5HT activity has been positively correlated with harm avoidance (HA), a trait found to be significantly elevated in anorexia (Bailer et al., 2005; Kaye et al., 2005). Furthermore, 5HT receptor activity in the periaqueductal gray, a region with connections to the ACC, has been associated with the modulation of escape behavior, a measure of anxiety, in rats (Bailer et al., 2005). It is possible that the ACC is affected by 5-HT imbalances in humans as well, which could have implications for AMG activity, for which the ACC is an important modulator (Pezawas et al., 2005). High levels of anxiety (characterized in part by HA) in humans may thus be potentiated by an imbalance in 5HT receptor activity that inhibits ACC function and subsequently enhances amygdala activity. Elevated 5HT activity seems likely in this case, considering the positive association found between serotonin and HA (Bailer et al., 2005; Kaye et al., 2005). Reduced tryptophan (a precursor to 5HT) intake through restriction would presumably reduce 5HT availability and activity, leading to reduced HA and anxiety.

Cognitive and behavioral rigidity (resistance to changing beliefs, activities, and actions; commonly conceptualized as a deficit in problem-solving relating to an over-reliance on previous experience) are evidenced in RAN patients by their seemingly compulsive adherence to dieting patterns, and their dysfunctional and rigid core beliefs about themselves, others, and their illness (Bailer et al., 2005). It is highly probable that behavioral persistence and denial of illness would be caused or reinforced by such deficits. These traits may be promoted by the hyperpolarization of pyramidal cells in the frontal lobes precipitated by abnormal 5HT activity, leading to severe disruptions in learning new information, activating memories, and regulating behavior in accordance with salient stimuli (Kaye et al., 2005). In healthy women, 5HT receptor balance has also been found to contribute to modulating behavioral inhibition, further supporting a role of serotonin in decision-making (Bailer et al., 2005).

Serotonin is also implicated in satiety. Food related stimuli have been shown to activate the ACC and the anteromedial temporal cortex in healthy individuals, regions with disrupted 5HT activity in anorectic patients (Bailer et al., 2005). These regions and others may be desensitized to hedonic stimuli such as food, which along with DA-induced motivational disruptions, would facilitate withdrawal behavior. In addition, Drive for Thinness, a measure of dysfunctional motivation in eating disorders, has been significantly inversely related to 5HT2A receptor activity (Kaye et al., 2005). This supports the finding from neuroimaging studies that 5HT2A receptor activity is reduced in RAN patients (Audendart et al., 2003; Bailer et al., 2005).

Thus, 5HT has been found to be associated with elevated harm avoidance, behavioral and cognitive rigidity, behavioral inhibition, withdrawal behavior from food, and a drive for thinness, symptoms highly characteristic of restricting anorectics. Like DA, abnormalities in both cortical (e.g., frontal and temporal cortices) and limbic regions (e.g., ACC, AMG) of the brain may contribute to these maladaptive behaviors (Bailer et al., 2005; Kaye et al., 2005), though evidence suggests that 5HT receptor activity may be reduced, elevated or imbalanced depending on the brain region that is affected (See Table 2).

The Anxious-Anorectic Model

According to this proposed model, genetic variations may contribute to a disruption in serotonin activity. In response to 5-HT dysregulation, the mesocortical DA system would be inhibited, leading to reduced activation in the PFC. In addition

Table 2
Consequences of abnormal 5HT activity in RAN

Limbic Regions	Behavioral Consequences	Cortical Regions	Cortical Regions	Abnormal Activity In Unknown Regions
ACC: Inhibited	Harm avoidance (elevated 5HT) Withdrawal behavior from food (abnormal 5HT, possibly elevated)	Frontal cortex	Rigidity: behavioral persistence, denial of illness	Behavioral inhibition (receptor imbalance)
Amygdala: Excited by ACC inhibition and directly by 5HT	Harm avoidance	Temporal cortex	Withdrawal behavior from food	Drive for thinness (reduced 5HT2A receptor activity)

to causing deficits in executive functioning, this diminished activation would lead to decreased extinction of conditioned fear responses (Davidson, 2002). An amplification of conditioned fear would intensify anxiety, harm avoidance, and hypervigilance toward neutral stimuli such as food[2].

As a consequence of reduced mesocortical activity, the mesolimbic DA pathway would become hyperactive, leading to increased DA activity in the striatum and the amygdala. This would in turn contribute to the reduced reward responsiveness and deficient motivation seen in anorectic patients. ACC activity would also be inhibited by elevated DA activity, leading to learning deficits (e.g., rigidity), and weakened amygdala inhibition. Decreased 5-HT levels in the ACC may furthermore directly contribute to weak modulation of the amygdala. This would contribute to an exaggerated amygdala response to emotional stimuli, and may lead to increased feelings of threat [3].

Future Directions

The model proposed in this paper brings together previously disparate empirical research on brain systems whose functions and patterns of correlation with behavioral symptoms suggest that they may be important in understanding the neural bases of restricting-type anorexia nervosa. Since little research has focused on this topic, this model is a first step—future research must test its claims empirically before it can be considered validated.

Specific claims amenable to experimental testing include, (1) that ill, recovered and at-risk RAN populations will show elevated DA activity in mesolimbic brain regions (e.g., ACC, amygdala and ventral striatum), and reduced DA activity in mesocortical regions (e.g., frontal and parietal cortical regions), (2) that these populations will show imbalanced 5HT activity most likely characterized by reduced 5HT activity in some regions (i.e., ACC), and elevated activity in others (i.e., frontal lobes), (3) That these brain abnormalities will be altered by starvation (though possibly only in the short term); and (4) That the level of abnormal 5HT and DA activation will be statistically related

2 Many RAN subjects display increased anxiety in the face of other neutral stimuli, but food may take center stage primarily because of the very strong interactions between food, 5HT, and DA (e.g., tryptophan as a precursor for 5HT, food's role in DA potentiation). When combined with sociocultural and environmental factors (e.g., teasing about weight, media preoccupation with thinness), these relationships may lead some women to rely on extreme dieting as a coping mechanism for aversive emotional states.

3 According to this model, along with food and weight related sociocultural factors as well as the direct associations between food and these neurotransmitters, higher levels of baseline anxiety would precipitate the use of dietary restriction as a method for coping with negative emotional states.

to certain behavioral traits characteristic of RAN (e.g., 5HT with harm avoidance, behavioral inhibition, rigidity, withdrawal behavior; and DA with hyperactivity/excessive exercise, reduced reward responsiveness, disrupted motivation).

In light of all this, future research should focus on elucidating the exact nature of serotonin disruption, as well as the relationship between serotonin and dopamine pathways. Research with depressed patients, in which dopamine levels are examined before and after selective serotonin reuptake inhibitor therapy could prove quite helpful. Furthermore, research within anorectic subjects should specifically examine distinct dopamine pathways, brain regions, and stages of illness to determine if neurotransmitter disruption is affected by drug therapy.

Despite the connections made between depression, anxiety, and anorexia, it is important not to assume that they are the same illness. One arena in which this is crucial is treatment. A common treatment for both anorexia nervosa and depression today is the administration of selective serotonin reuptake inhibitors, which increase serotonin activity. However, as the evidence shows, the exact nature of 5HT disruption in AN is not yet clear. In addition, the particular disruptions in brain activity may differ from region to region. Thus, globally increasing serotonin activity may in fact exacerbate neurological and behavioral disturbances, for example by increasing serotonin activity in regions in which reduced activity is preferable (e.g., the ACC). It is clear then that medical therapies for anorexia must be targeted to the particular neurological manifestations of the illness. Researching and developing these types of therapies, based on a clearer understanding of the underlying neural blueprint of the disease, would have the potential to vastly improve treatment outcomes.

CONCLUSION

This paper has attempted to show that distinct models of anxiety and depression can be combined with personality and behavioral understandings of anorexia nervosa to elucidate the mechanisms of each illness, and to create a very strong neurological model of anorexia. To reiterate, this model proposes a genetic predisposition to disrupted serotonin activity that causes a deregulation of the mesolimbic and mesocortical DA systems. Decreased mesocortical DA activity reduces PFC functioning, leading to deficits in executive functioning, as well as reduced fear extinction by way of decreased amygdala inhibition. In response to reduced inhibition from the mesocortical DA system, mesolimbic DA activity will increase. This decreases reward sensitivity in the nucleus accumbens, leading to decreased motivation and reward responsiveness, and may overstimulate the amygdala, potentially causing an exaggerated response to emotional stimuli. Furthermore, increased DA and decreased 5HT activity in the ACC will inhibit this region, leading to a deregulation of the amygdala, and subsequently increased activation in response to threatening stimuli. ■

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