Editorial
Future Neurology

Dysfunctional frontostriatal control systems in bulimia nervosa

"...self-regulatory processes are impaired in women with bulimia nervosa, likely owing to their failure to engage frontostriatal circuits appropriately."

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Bulimia nervosa (BN) typically begins during adolescence, and primarily affects young women with a lifetime prevalence of 1–2.5% among women in the general population [1–3]. The salient behavioral disturbances of BN are binge-eating episodes associated with a sense of loss of control, followed by inappropriate behaviors to avoid weight gain [4]. The nature of these core disturbances implies the presence of difficulties with self-regulatory control, which is consistent with the tendency of individuals with BN to engage in other impulsive behaviors, such as substance abuse and self-injurious behaviors [5–10]. In addition, studies of temperament have documented elevated measures of impulsivity in this population [11], and empirical findings indicate that impulsivity is correlated with the severity of bulimic symptoms [5,12,13]. Thus, persons with BN seem to have an impaired capacity to engage self-regulatory control.

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The term 'self-regulatory control' refers to the ability to organize feelings, memories and thoughts during the planning, execution and monitoring of any goal-directed behavior in the context of competing urges, desires or situational demands [14–16]. Self-regulatory control is present in almost every action humans perform, since choosing to execute one action always necessitates not choosing or inhibiting another. It reflects a higher level of CNS organization that is also referred to in the literature as 'cognitive control' [17] and, more broadly, 'inhibitory control' [18]. These functions rely on frontostriatal components of cortico–striato–thalamo–cortical (CSTC) circuits, including projections from ventral prefrontal cortex (PFC) and anterior cingulate cortex (ACC) to the basal ganglia [19].

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Experimental paradigms that are used to study self-regulatory functions while imaging the CNS, typically require subjects to inhibit a more automatic behavior in favor of a less automatic one. Therefore, they are regarded as experimental models for studying inhibitory control or the resolution of behavioral conflict. For example, the Simon Spatial Incompatibility (SSI) task requires individuals to ignore one salient feature of stimulus in favor of responding to a more task-relevant feature. Individuals must indicate the direction that an arrow is pointing (left or right), regardless of the side of a screen on which it appears. When the direction matches the side of the screen on which the arrow appears, participants perform the task easily, as indexed by their rapid responses and infrequent errors. When the direction does not match the side of the screen (e.g., a rightward pointing arrow on the left side), the task is more difficult, as indicated by slower responses and increased errors. Ignoring the task-irrelevant feature of these incongruent or conflict trials requires the mobilization of attentional resources, resolution of cognitive conflict, inhibition of automatic response tendencies and thus, the engagement of self-regulatory control processes. Healthy individuals activate large expanses of ACC, PFC, and striatum during performance of the SSI task [20–22], consistent with findings from studies of healthy individuals performing other tasks requiring conflict resolution and response inhibition (e.g., Stroop, Go/No-Go, flanker and Stop tasks) [22–27].

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We recently used the SSI task and functional MRI (fMRI) to investigate frontostriatal functioning in 20 adult women with BN compared with 20 healthy controls [28]. The patients with BN responded more impulsively and made more errors on the SSI task than did healthy controls, and patients with the most severe symptoms made the most errors. During correct responding on incongruent trials, patients failed to activate frontostriatal circuits to the same degree as controls, including the left inferolateral prefrontal cortex (Brodmann area [BA]: 45), bilateral inferior frontal gyrus (BA: 44), lenticular and caudate nuclei, and the anterior cingulate cortex (ACC; BA: 24/32). The number of objective bulimic episodes in the patients correlated inversely with activation in these regions, indicating reduced frontostriatal activation in those with the most severe symptoms. In addition, patients activated the dorsal ACC (BA: 32) more when making errors than when responding correctly. In contrast, controls activated the ACC more during correct rather than incorrect responses, and they activated the striatum more when responding incorrectly, likely reflecting an automatic response tendency, which, in the absence of concomitant ACC activity, produced incorrect responses. We concluded from this study that self-regulatory processes are impaired in women with BN, likely owing to their failure to engage frontostriatal circuits appropriately. Thus, our findings point to functional abnormalities within a specific neural system underlying an impaired capacity for self-regulatory control, which may contribute to binge eating and other impulsive behaviors in women with BN.

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The average duration of illness among the patients in our study was approximately 9 years. Although most began binge eating and purging at approximately 13 years of age, we do not know what aspect began first; their bulimic symptoms or their impaired capacity for self-regulatory control. In other words, our findings from adult women cannot tell us whether frontostriatal abnormalities are a cause of BN or a consequence of having had the illness for so long. Therefore, we are currently using the SSI task to investigate the functioning of frontostriatal control systems in adolescents with BN, early in the course of the illness. Although BN typically develops during adolescence [29,30], surprisingly little research has focused on persons with BN in this age range. Since many of the impulsive behaviors associated with BN tend to occur in childhood before the onset of the disorder [31,32], we suspect that impairments in the development of self-regulatory control processes may serve as susceptibility factors for developing BN.

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The capacity for self-regulatory control develops rapidly during adolescence [33,34], paralleling (and relying on) the development of frontostriatal systems in healthy individuals [22,27,35]. For example, findings from our developmental fMRI study of the Stroop Interference Task in healthy participants [27], suggested that frontostriatal circuits mature as the capacity for self-regulation improves with advancing age. Activation of the inferolateral prefrontal cortex and lenticular nucleus increased with age, as did response speed and accuracy on the task. These findings suggest that increasing activity of frontostriatal circuits improves behavioral control with maturation in healthy children, consistent with findings from other developmental imaging studies of response inhibition using the Go/No-Go, Stop Signal Reaction Time or anti-saccade tasks [34,36,37].

Thus, disturbances in the maturation of frontostriatal systems may contribute to the development of BN, as well as a variety of other psychiatric disorders that arise during adolescence and are characterized by poor self-regulatory control [38]. This hypothesis, however, can only be tested by studying the functioning of these systems longitudinally in the same adolescents with and without BN. Future research should compare the trajectories of frontostriatal development in adolescents with BN, partial-syndrome BN, and healthy adolescents, while tracking the progression of symptoms over time. Although up to 50% of adolescents in community samples engage in binge eating and purging behaviors, only 1–5% meet the criteria for a diagnosis of BN [39]. However, adolescents with partial-syndrome BN are clinically similar to their full-syndrome counterparts and may have a heightened risk for developing BN [40]. If the trajectories of frontostriatal functioning differ across adolescents who develop the full disorder and those who do not, these findings would indicate that frontostriatal abnormalities may in fact contribute to BN.

We propose a pathophysiological model of BN in which binge-eating behaviors arise from the presence of dysfunctional frontostriatal systems that release from self-regulatory control a preexisting vulnerability to developing the illness. This vulnerability likely stems from serotonergic disturbances that have been well documented in individuals with BN [7,32,41], consistent with the efficacy of selective serotonin-reuptake inhibitors (SSRIs) in reducing the frequency of binge-eating episodes [42]. Altered serotonergic functioning likely produces both impulsivity and decreased satiety in persons with BN [43]. Feelings of hunger in turn produce urges to binge, which may be released inappropriately by dysfunctional frontostriatal control systems to produce binge-eating episodes. Interactions with the aesthetic cultural ideals of thinness and physical fitness then likely produce purging behaviors to counteract the weight gain that binge eating would otherwise produce.

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Evidence suggests that frontostriatal regions depend heavily on dopaminergic transmission for proper functioning [44]. In addition, the consumption of food is associated with increased dopamine release in the frontostriatal circuits that mediate motivation and reward [45], including the orbitofrontal cortex and ventral striatum which are involved in processing the hedonic value of food [46]. Furthermore, dopaminergic increases in these regions are associated with food-seeking behavior in rats [47] and humans [48].

Thus, disturbances in this particular frontostriatal 'reward' circuit may also contribute to binge eating in individuals with BN. Consistent with our pathophysiological model involving self-regulatory disturbances in BN, binge eating may reflect an inability to control the temptation for an immediate reward (food) in favor of a more delayed reward (a slim body) [49].

In conclusion, early detection of frontostriatal disturbances in adolescents may be crucial for the prevention of BN and will likely enhance our understanding of the mechanisms that may contribute to the perpetuation of the disorder.

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Characterizing the trajectory of these disturbances in BN, beginning early in the course of the illness, is necessary for disentangling what may cause the binge eating and purging behaviors from disturbances that may arise from the presence of the chronic illness. I further suggest that studies of frontostriatal functioning in BN should include adolescents with partial-syndrome BN, an understudied group that falls into the diagnostic and statistical manual of mental disorders (DSM)-IV category of 'Eating Disorder Not Otherwise Specified'. This is especially relevant given the current nosological debate regarding the revision of this heterogenous category for DSM-V [50,51]. Finally, future studies should also assess the functioning of the specific frontostriatal circuits that subserve reward processing and their dopaminergic modulation in individuals with BN.

Financial & competing interests disclosure

This work was supported in part by NIMH grant K01-MH077652, by a grant from the National Alliance for Research on Schizophrenia and Depression (NARSAD), and by funding from the Sackler Institute for Developmental Psychobiology, Columbia University. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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