Convergent dysregulation of frontal cortical cognitive and reward systems in eating disorders

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Source of support: Self financing

A substantive literature has drawn a compelling case for the functional involvement of mesolimbic/prefrontal cortical neural reward systems in normative control of eating and in the etiology and persistence of severe eating disorders that affect diverse human populations. Presently, we provide a short review that develops an equally compelling case for the importance of dysregulated frontal cortical cognitive neural networks acting in concert with regional reward systems in the regulation of complex eating behaviors and in the presentation of complex pathophysiological symptoms associated with major eating disorders. Our goal is to highlight working models of major eating disorders that incorporate complementary approaches to elucidate functionally interactive neural circuits defined by their regulatory neurochemical phenotypes. Importantly, we also review evidence-based linkages between widely studied psychiatric and neurodegenerative syndromes (e.g., autism spectrum disorders and Parkinson's disease) and co-morbid eating disorders to elucidate basic mechanisms involving dopaminergic transmission and its regulation by endogenously expressed morphine in these same cortical regions.

Key words: cognition • reward systems• eating disorders • frontal cortex • binge eating • bulimia • anorexia • dopamine • morphine

Full-text PDF: http://www.medscimonit.com/download/index/idArt/889133

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Background

DSM IV-TR [1] coding and diagnostic criteria list 3 categories of adult eating disorders (EDs): 307.1 Anorexia nervosa; 307.51 Bulimia nervosa; and 307.50 Eating disorder not otherwise specified (EDNOS). Binge eating disorder (BED) is listed in the DSM IV-TR appendix and is often, but not exclusively, linked to obesity. Feeding and eating disorders of infancy or early childhood are listed as 307.52 Pica and 307.53 Rumination Disorder [1]. Recently, Wildes and Marcus have questioned the limitations of operational or symptom-based psychiatric classifications of EDs and have proposed alternative classification into 2 major groups: 1) those based on disordered eating symptoms; and, 2) those based on comorbid psychopathology and associated features [2]. Interestingly, the authors review models of comorbidity-based ED classification incorporating impulsivity, compulsivity, distress, and inhibition *vs.* risk-taking, with an emphasis on empirical elucidation of basic behavioral and neuropsychological mechanisms underlying these pathophysiological processes.

In light of the above, a substantive literature has drawn a compelling case for the functional involvement of mesolimbic/prefrontal cortical neural reward systems in normative control of feeding and in the etiology and persistence of severe EDs that afflict diverse human populations [3–7]. Herein, we provide a short review that develops an equally compelling case for the importance of dysregulated frontal cortical cognitive neural networks acting in concert with regional reward systems in the regulation of complex feeding behaviors and in the presentation of complex pathophysiological symptoms associated with EDs [8–11]. Our goal is to highlight working models of major EDs that incorporate complementary approaches to elucidate functionally interactive neural circuits define by their regulatory neurochemical phenotypes. Importantly, we also review evidence-based linkages between widely studied psychiatric and neurodegenerative syndromes (e.g., autism spectrum disorders [12] and Parkinson's disease [13,14]) and co-morbid EDs to elucidate basic mechanisms involving dopaminergic transmission and its regulation by endogenously expressed morphine in these same cortical regions [15–17].

Anorexia Nervosa and Bulimia Nervosa: Identification of Functionally Linked Frontal Cortical and Limbic Anatomical Loci

A perusal of the neuropsychiatric literature clearly indicates that the establishment of a functional CNS anatomy linked to EDs has been critically dependent upon the application of high-resolution biological imaging techniques to clinical studies of patient cohorts with anorexia nervosa (AN) and bulimia nervosa (BN) over the last decade. A key 2003 study used functional magnetic resonance imaging (fMRI) to monitor alterations in CNS activity subsequent to the presentation of food and emotional visual stimuli in 9 women who experienced long-term recovery from restricting AN [18]. Subject data sets were compared to those derived from matched control groups consisting of healthy women and women chronically ill with restricting AN. Subsequent to presentation of food stimuli, enhanced medial prefrontal and anterior cingulate activation was observed in the brains of recovered AN subjects in comparison to healthy controls, whereas a lack of activity was observed in the inferior parietal lobule of all subjects. Differential activation of the right lateral prefrontal, apical prefrontal, and dorsal anterior cingulate cortices was observed in the brains of recovered AN subjects in comparison to chronically ill AN subjects. Interestingly, group differences in fMRI responses were specific to food stimuli and were not observed following presentation of emotional stimuli. The authors concluded that medial prefrontal responses to AN-specific stimuli may be related to trait vulnerability and that lateral and apical prefrontal responses were associated with positive outcomes.

A complementary 2004 study monitored altered CNS activity via fMRI responses in 2 separate groups of female subjects with AN and BN in comparison to healthy controls subsequent to presentation of food and aversive emotional images [19]. Subjects with EDs identified food stimuli as threatening and disgusting and demonstrated enhanced CNS activity in the left medial orbitofrontal and anterior cingulate cortices and diminished activity in the lateral prefrontal cortex, inferior parietal lobule, and cerebellum in comparison to matched controls. Between-group differences in fMRI responses to nonspecific emotional stimuli were observed in the occipital cortex, parietal cortex, and cerebellum. Consonant with the prior 2003 study [18], the authors concluded that an enhanced medial prefrontal fMRI in response to symptom-provoking stimuli is a common feature of AN and BN, and that aberrant activation of medial prefrontal circuitry in response to inappropriate stimuli is common to eating, obsessive-compulsive, and addictive disorders.

From a complementary clinical perspective, body image distortion is a defining behavioral symptom in AN patients. Accordingly, a 2003 fMRI study evaluated the effects of digitally distorted body images using a computer-based video-technique on CNS activation patterns in female AN patients in comparison to healthy controls [20]. AN patients demonstrated enhanced activation in the prefrontal cortex and the inferior parietal lobule, including the anterior intraparietal sulcus, in comparison to matched controls. A prior study from this group using the same digitally distorted body image paradigm also monitored enhanced activation in the right amygdala, the right gyrus fusiformis, and brainstem of AN patients [21]. Subsequent validation of these observations indicated

that considerable variability in subjective emotional reactions to body shape perception in AN and BN patients is associated with differential fMRI activation responses in the prefrontal cortex [22,23] and the amygdala [24]. In reference to the amygdala, significant 'fat-image' activation was observed in restricting-type AN patients, in binging-purging type AN patients, and in healthy matched controls, but not in BN patients [24]. In contrast, the prefrontal cortex was significantly activated in binging-purging type AN patients, and in healthy matched controls, but not in restricting-type AN patients and BN patients [24]. The authors conclude that differential CNS activation patterns observed for each ED group may underlie differences in cognitive processing with respect to distorted body image. As summarized in a 2012 review [10], classification of fMRI studies on body image distortion in AN is sorted according to perceptive, affective, and cognitive categories. The perceptive component is mainly related to altered activity of the precuneus and the inferior parietal lobe, whereas the affective component is mainly related to altered activities of the prefrontal cortex, the insula, and the amygdala. The authors contend that elucidation of cognitive components of body image distortion in AN is ongoing and requires further investigation.

Impaired or compromised cognition-derived behavioral flexibility is associated as a trait marker in AN patients and highlights a working model of AN that includes hypoactivation in ventral anterior cingulate-striatothalamic circuitry that is involved in motivation-related behaviors [25,26]. Furthermore, AN patients demonstrate enhanced activation of frontoparietal circuitry that is functionally associated with supervisory cognitive control during task performance [25,26]. Importantly, when placed within this conceptual context, working models of EDs share compelling behavioral comorbidities with major neuropsychiatric disorders, including attention-deficit hyperactivity disorder (ADHD) [27,28], major depressive disorder (MDD) [29], schizophrenia [30], and bipolar disorder [31].

Recently, imaging studies have attempted to further characterize ED patient subtypes by differences in behavioral impulsivity linked to neural circuitry associated with inhibitory control mechanisms [32,33]. Additionally, hypoactivation in frontal cortical cognitive "theory of mind" brain circuitry has been functionally associated with the presentation of a social-cognitive endophenotype that reflects impaired social functioning in AN patients [34]. Kaye et al recently proposed that complex AN symptomatology is derived from dysregulated neural systems underlying reward and/or awareness of homeostatic needs, in concert with cognitive systems related to enhanced executive ability to inhibit incentive motivational drives [35]. A series of studies from a Swedish research group demonstrated differential neural activation to viewing food images via fMRI analyses in women with AN *vs*. women with BN [36,37]. The authors conclude that women with AN and BN activate top-down

cognitive control in response to food images, yet women with BN have increased activation in reward and somatosensory regions, which might impinge on cognitive control over eating [36,37]. Finally, investigators have recognized overlapping dysregulated cognitive profiles in AN patients in comparison to people with autism spectrum disorders (ASDs) [38]. These observations are complemented by a recent study that demonstrated aberrantly enhanced neural activation in response to food cues in bilateral insula and in the anterior cingulate cortex in people with ASD in comparison to matched healthy controls [12]. Overall, these observations suggest that neural responses in cortical cognitive and primary reward circuitry are convergently dysregulated in AN patients and in subsets of children with ASD.

Anorexia Nervosa and Bulimia Nervosa: Identification of Functionally Linked Neurochemical Phenotypes, with Special Reference to Comorbid Psychiatric and Neurodegenerative Disorders

Recent complementary studies using positron emission tomography (PET) and single-photon emission computed tomography with 5-HT-specific radioligands have consistently demonstrated alterations in 5-HT(1A) and 5-HT(2A) receptor and in 5-HT transporter densities in cortical and limbic circuitry of AN and BN patients [39–41]. Alterations of cortical and limbic 5-HT circuits in patients with EDs are proposed to negatively affect mood and impulse control, motivating and hedonic aspects of eating behavior, as well as behavioral inhibition and body image distortions [39–41]. Complementary PET studies have monitored alterations in dopaminergic (DA-ergic) parameters via D2/D3 receptor ligand binding in striatal areas of recovering AN patients [42], and found coordinate alterations of 5-HT transporter dopamine D2/D3 receptor densities in striatal areas of AN and BN patients that are functionally associated with harm avoidance symptomatology [43]. From a different perspective, comorbid EDs classified as impulse control disorders (ICDs) have been observed in cohorts of Parkinson's disease (PD) patients administered L-DOPA as a CNS DA restorative therapy [14]. Putative validating evidence in support of dysregulated frontal cortical DA as a neurochemical trait phenotype in EDs is provided by a recent PET study demonstrating significantly enhanced [18F]fluorodopa uptake in the medial orbitofrontal cortex of PD patients in comparison to matched controls [13]. The authors conclude that enhanced DA-ergic activity in the medial orbitofrontal cortex may be associated with increased sensitivity or vulnerability to ICDs following DA replacement therapy in PD patients.

We recently reviewed preclinical and clinical studies that support a working mechanistic scheme whereby atypical

antipsychotic drugs ameliorate negative DSM-IV diagnostic criteria in schizophrenic patients by effecting relatively potent blockade of 5-HT(2A) receptors, coupled with weaker antagonism of D(2) receptors in frontal cortical areas [44]. Notably, cognitive disorders represent a hallmark core dysfunction in schizophrenics, with the severity of cognitive symptoms serving as a better indicator of social and functional outcome (ie, quality of life) than standard measures of antipsychotic drug efficacy via DSM-IV criteria [45]. Cognitive processes that are specifically impaired in schizophrenia are verbal memory, working memory, motor function, attention, executive functions, and verbal fluency. Functional imaging studies indicate that schizophrenic patients fail to activate their frontal cortex following selective cognitive tasks [46,47]. Thus, deficiencies in cognitive measures should be recognized as a major element in social and vocational integration of schizophrenia patients, and should become a standardized assessment approach in clinical trials [48]. As discussed above, overlapping disordered cognitive behavioral profiles of EDs patients with patients who have major psychiatric disorders [27–31] are compelling and support equivalent dysregulation of convergent frontal cortical cognitive and reward neural circuits.

Recently derived neural models of EDs have drawn functional linkages of starvation in AN or binge eating in BN with DA-driven mesolimbic/mesocortical addictive processes [6,49]. Furthermore, it is proposed that executive corticostriatal processes related to extraordinary inhibition and self-control in AN and diminished inhibitory self-control in BN may modulate rewarding aspects of palatable foods as well as other consummatory behaviors. Accordingly, convergent dysregulation of interactive limbic and executive corticostriatal circuitry supports the working hypothesis that reward and inhibitory processes may contribute to comorbid symptomatology observed in major EDs and addictive disorders [49–55].

Potential Involvement of Monoaminergic Transmission and Its Regulation by Endogenous Morphine in the Frontal Cortical Regions in the Etiology of Major Eating Disorders

For over 30 years empirical studies have repeatedly demonstrated that endogenous morphine is expressed by diverse animal and human tissues. Because the prototype catecholamine DA and its major precursor L-DOPA were also found to be utilized as morphine precursors, a novel reciprocally interactive mechanism is compellingly apparent, which links DA and "morphinergic" pathways in the activation and inhibition of behavioral/cognitive responses within discrete cortical regions [56,57]. In support of these contentions, immunohistochemical studies have revealed the presence of morphine-like

immunoreactive material in the perikarya, fibers, and terminals of neurons in cortical areas of rat and human brain [58]. Furthermore, a 2011 anatomical study found colocalization of endogenous morphine-like to GABAergic cells in rodent cerebral cortex [59]. We therefore hypothesize that endogenous morphine systems are reciprocally dysregulated in schizophrenia and are intimately linked to major alterations in DA-ergic transmission and DA receptor expression.

We previously presented a case for low-dose morphine as a cognitive enhancer in schizophrenia patients based on functional and behavioral studies of cortical distributions of its type-selective mu opioid receptor in discrete prefrontal and orbitofrontal regions [44]. These contentions are strengthened by complementary human studies of interactive 5-HT(2A) receptor systems in these same cortical areas. A 2011 controlled cross-over human PET study observed significantly enhanced 5-HT(2A) receptor PET ligand binding in the orbitofrontal cortex with the performance of executive functions of working memory, and concluded that 5-HT(2A) receptor systems mediate and optimize basic cognitive functions [60]. A recent imaging study found that schizophrenic patients had significantly lower 5-HT(2A) binding in the frontal cortex than did control subjects [61]. Additionally, cortical 5-HT/5-HT2A receptor activation appears to serve as a functional indicator of CNS dopaminergic transmission via effects on circulating plasma cortisol and prolactin concentrations. Interestingly, complementary biochemical studies have demonstrated reciprocal functional interactions of the 5-HT2A receptor and the mu opioid peptide receptor following activation by morphine [62] These data suggest that selective activation of the 5-HT2A receptor, in concert with low dose morphine treatment, may mediate positive effects on cognitive processes within the orbitofrontal cortex. Based on multiple studies cited in our short review, it appears that similar functional criteria may be applied to complex cognitive and reward-oriented "morphinergic"/monoaminergic regulatory processes underlying normative eating and satiation and their dysregulation in major EDs.

Conclusions

We have highlighted formative working models of major EDs that incorporate complementary approaches to elucidate functionally interactive frontal cortical neural circuits in association with their regulatory neurochemical phenotypes. We have also presented evidence-based linkages, (ie, established comorbidities) between widely studied psychiatric and neurodegenerative syndromes and EDs. Finally, we have introduced a prospective case for the involvement of basic mechanisms involving DA-ergic/monoaminergic transmission and its regulation by endogenously expressed morphine in these same cortical regions associated with major EDs.

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