The Neurobiology of Anorexia Nervosa

Timothy D Brewerton, MD,' Ian Frampton, DClinPsych and Bryan Lask, MD

1. Clinical Professor, Psychiatry and Behavioral Sciences, Medical University of South Carolina; 2. Clinical Co-Director, Centre for Clinical Neuropsychology Research, University of Exeter; 3. Emeritus Professor, Child and Adolescent Psychiatry, University of London

Abstract
This article provides an overview of research findings on the neurobiology of anorexia nervosa (AN), including studies of monoamine neurotransmitter function, genetics, brain imaging, and neuropsychology. Such studies are designed to reveal the underlying neuroanatomical and pathophysiological bases of this potentially lethal condition. Notwithstanding commonly held misconceptions, there is no compelling evidence that sociocultural factors alone cause AN. Over the previous two decades, research into the role of the brain in eating disorders has been very productive and informative. Sorting out what is trait- and what is state-related has been a challenging focus of neurobiological research in AN. Many of the earlier identified abnormalities have been shown to be directly due to the effects of semi-starvation, weight loss, and/or maladaptive behaviors of AN. Results in AN patients who have been weight-recovered for at least one year indicate persistent alterations in serotonin function, set shifting, and visuo-spatial processing.

Keywords
Anorexia nervosa, neurobiology, serotonin, brain imaging, neuropsychology

Disclosure: The authors have no conflicts of interest to declare.

Received: April 17, 2008 Accepted: November 6, 2008
Correspondence: Timothy D Brewerton, MD, 216 Scott Street; Mt. Pleasant, SC 29464. E: tbrewerton1@comcast.net

This article will provide an overview of research findings on the neurobiology of anorexia nervosa (AN), including studies of neurotransmitter function, genetics, brain imaging, and neuropsychology. Such studies are aimed at elucidating the underlying neuroanatomical and pathophysiological bases of AN. Despite widely held beliefs, there is no convincing evidence that cultural factors alone cause AN. Indeed, over the past few years research into the role of the brain in eating disorders has been very fruitful. This is despite the clear realization that many earlier identified abnormalities have been found to be directly due to the effects of semi-starvation and/or the extreme eating practices of AN. Sorting out what is trait- and what is state-related has been a challenging focus of neurobiological research in AN.

Monoamine Neurotransmitters
The monoamine neurotransmitters (norepinephrine [NE], dopamine [DA], and serotonin [5-HT]) have been extensively studied during all phases of AN (actively ill, short-term weight-recovered, and long-term weight-recovered) using existing technologies. Dieting and/or semi-starvation deplete all central monoamines and lead to altered neurotransmitter levels and receptor sensitivity in animals and humans, the results of which have been reviewed in detail elsewhere. In order to minimize these starvation-state-related effects and to reveal potential trait-related disturbances or vulnerabilities, investigators have more recently studied ‘recovered’ patients, i.e. those AN patients who have attained (for at least one year) normalization of eating and weight, resumption of menses and/or normalization of gonadal hormone levels, and abatement of typical cognitive features to subclinical levels. However, the long-term effects of chronic malnutrition and disordered eating behaviors on the brain (similar to substance use disorders) cannot be dismissed. For the purposes of this article, studies of recovered AN patients will be the major focus.

Norepinephrine
The role of NE in the modulation of feeding, mood, anxiety, neuroendocrine control, metabolic rate, sympathetic tone, and temperature has made it a likely candidate for study in AN. Low-weight AN patients have been shown to have reduced measures of plasma, urinary, and cerebrospinal fluid (CSF) 3-methoxy-4-hydroxyphenylethleneglycol (MHPG), the major metabolite of NE. However, these levels completely normalize upon full weight restoration. This has been attributed primarily to the effects of stress and/or depression. In contrast, AN patients tend to have higher plasma NE levels at admission, which then decrease as treatment and weight gain progress. Like the plasma NE studies, CSF NE levels have been reported to be no different in AN patients compared with controls at low weight and after short-term weight gain, but then significantly lower after weight recovery of at least six months. This has been attributed primarily to the effects of stress and/or depression. Given that CSF NE concentrations have not yet been reported in long-term (more than one year of follow-up) recovered AN patients, the extent to which the adrenergic alterations seen in eating disorders are trait-related remains unclear, and a trait-related disturbance of the adrenergic system cannot be ruled out at this time.
Anorexia Nervosa

Dopamine
The involvement of DA in the hedonic reward responses to eating as well as to other pleasurable activities makes it a focus of interest in AN. In addition, DA is also involved in the regulation of feeding, mood, activity, perception, social behavior, and hormone and peptide release. Low-weight AN patients have been reported to have reduced measures of peripheral and central DA activity, including decreased plasma and CSF homovanillic acid (HVA). In one study of long-term recovered AN patients, there was a trend for decreased CSF HVA levels in the six restricting AN patients compared with controls and bingeing and/or purging AN patients. This suggested a possible trait-related disturbance specific to restricting AN, although this finding needs replication given the small sample size. These results could also still be due to nutritional factors given that the patients in this study may still have been at the low end of the normal weight range.

Anecdotal reports of the successful use of dopaminergic antagonists (typical antipsychotic agents) in the treatment of AN patients have generally been followed by equivocal results in controlled studies. Atypical antipsychotic agents may show more promise in the adjunctive treatment of AN given their combined antidopaminergic and antiserotonergic effects. However, the results of placebo-controlled studies remain to be seen.

Serotonin
Several lines of reasoning point to disturbances of 5-HT function in the pathophysiology and neuropsychopharmacology of the EDs, including its role in feeding, satiety, dieting/fasting, mood regulation, anxiety, obsessive-compulsiveness, perfectionism, behavioral inhibition, harm avoidance, impulsivity, aggression, motor activity, gender, seasonality, body image/perception, and social behavior. Significant findings in AN patients have included decreased CSF L-tryptophan (L-TRP) levels and CSF 5-hydroxyindoleacetic acid (5-HIAA) levels during low-weight status, with normalization of these levels with short-term weight recovery (STWR; goal weight maintenance for more than three weeks). In contrast, AN patients have significantly elevated CSF 5-HIAA levels after long-term weight recovery. The investigators suggested that AN may correspond to a primary state of excessive 5-HT tone that is subsequently masked by starvation-induced reductions in 5-HT activity during active illness, and that this hyperserotonergic trait may correspond to the personality traits of perfectionism, obsessivity, and behavioral inhibition. Corroborating the notion of hyperserotonergic status in AN, Kaye and colleagues have noted that long-term weight-restored anorexics display elevated 5-HT1A receptor binding measured by positron emission tomography (PET). In other studies using PET imaging with 5-HT-receptor-specific radioligands, Baillero and colleagues reported increased activity of 5-HT1A receptor activity in 15 low-weight AN patients compared with 29 controls. 5-HT7A receptor binding potential was positively correlated with measures of harm avoidance. After long-term weight recovery, restricting AN patients showed significantly greater 5-HT transporter-binding potential than seven binge-purge AN patients.

Although decreased prolactin (PRL) responses following serotonergic agents such as meta-chlorophenylpiperazine (PCP), L-TRP, and fenfluramine (FEN) have been reported in low-weight AN patients, there is a trend toward normalization of responses upon re-feeding and STWR. With at least a year of recovery, neurohormonal responses to m-CPP normalize in restricting AN patients. Apparently, full normalization of PRL responsivity to serotonergic agents does take place after full weight restoration, normalization of hypothalamic-pituitary-gonadal function, and abatement of overt eating disorder symptoms. However, the appetite-suppressing effect of FEN is significantly diminished in recovered AN patients despite normalization of hormonal release.

Taken together, research studies demonstrate reduced 5-HT synthesis, uptake, and turnover, along with altered post-synaptic 5-HT receptor sensitivity during the active phase of AN. Consequently, many reported alterations in 5-HT function are state-dependent. However, they probably play critical biological roles in the perpetuation of symptoms, such as the mood dysregulation, increased anxiety, obsessivity, impulsivity, self-aggression, and difficulty in learning healthier coping strategies that are so characteristic of AN patients.

Genetic Studies
Convincing results from a host of studies indicate strong genetic factors in AN that may be linked to the commonly associated personality traits of obsessivity, perfectionism, anxiety, and/or behavioral inhibition. Interest in 5-HT activity in AN has led to a number of studies on 5-HT system genes, i.e. those that control activity of 5-HT receptors, tryptophan hydroxylase (TPH; the rate-limiting enzyme for 5-HT synthesis) and 5-HT transporter (re-uptake) mechanisms. Collier et al. reported a statistically significant 5-HT2A-1438G/A receptor gene polymorphism in a group of restricting AN patients compared with healthy controls. This finding has been replicated in at least two other studies in AN and in obsessive-compulsive disorder (OCD). Nacmias et al. reported that other serotonergic polymorphisms of 5-HT2A as well as those of 5-HT2C receptors showed no differences in AN patients compared with controls. Similarly, no differences between AN patients and controls have been reported for the serotonin-transporter-gene-linked polymorphisms (5-HTTLPR), tryptophan hydroxylase polymorphisms, and 5-HT1D beta and 5-HT7 gene polymorphisms.

Genetic investigations into the role of DA have been limited to the DRD3 receptor polymorphisms, in which no differences were found between AN patients and controls. However, the polymorphisms of other genes coding for DA receptors could be tested.

There is reason to believe that the functional abnormalities found in the majority of subjects with anorexia nervosa (AN) reflect traits suggesting an underlying neurodevelopmental abnormality that may prove to be a risk factor for AN.
Neuroimaging Studies
These may be divided into studies of brain structure, brain function, and neurotransmitters. In this section we discuss the neuroimaging of structure and function, as the imaging of neurotransmitters has been discussed above.

Brain Structure
The technologies used to scan the structure of the brain are computed tomography (CT) and magnetic resonance imaging (MRI). Such studies have been conducted on children, adolescents, and adults with AN, and consistently show cortical atrophy and consequent ventricular enlargement, both of which reverse with re-feeding. The findings suggest that the changes may be due to neuronal damage secondary to malnutrition, with possible regeneration of myelin accounting for the general reversibility.

Brain Function
Functional brain imaging studies have been conducted using single-photon emission CT (SPECT) and PET, both of which explore regional cerebral blood flow, a reflection of brain activity or metabolism, and functional MRI (fMRI), which records neuronal activity.

SPECT and PET studies have fairly consistently shown that about 70% of patients there is a reduction in blood flow (hypoperfusion) in the temporal region, predominantly antero-medial, in both early-onset AN patients and in adults. Kojima et al. have reported reduced blood flow in the temporal and associated regions. The hypoperfusion seems to be positively correlated with severity of eating disorder pathology and impaired visuo-spatial memory and executive functioning, it bears no correlation with weight/body mass index (BMI), mood, age at onset, or length of illness. Furthermore, it appears not to reverse with nutritional rehabilitation. It is possible that the abnormalities described, which affect at least two-thirds of subjects, are primary phenomena pre-dating the illness, are probably risk factors, and may represent a (neurodevelopmental) subtype of AN.

In studies of adults with AN using fMRI, Uher et al. have shown differences in neural activity between normal controls, subjects with chronic AN, and those who have recovered from AN. These group differences were specific to food stimuli, whereas processing of general emotional stimuli did not differ between groups. The authors concluded that separate neural correlates underlie trait and state characteristics of AN and that different patterns of activation are associated with good or poor outcome, possibly reflecting heterogeneous subtypes. Similarly, using fMRI in combination with a computer-based life image distortion technique, Seeger et al. showed that females with AN had a different pattern of neural activity from healthy controls. In summary, there is sound evidence of abnormal brain structure and function in AN. The structural abnormalities appear to be secondary to nutritional deprivation. However, there is reason to believe that the functional abnormalities found in the majority of subjects with AN reflect traits suggesting an underlying neurodevelopmental abnormality that may prove to be a risk factor for AN.

Neuropsychological Studies
Many studies have shown neuropsychological functioning to be impaired at low weight, and this is not surprising given the brain structural and functional changes accompanying starvation. Impairments associated with low weight include executive functioning, visuo-spatial processing, attention, verbal functioning, learning, and memory. However, to demonstrate that neuropsychological deficits potentially make a causal contribution to the onset of AN, it would be necessary to assess young people before the onset of their eating disorder. Prospective studies of this type are difficult to conduct, given the rarity of the disorder. An alternative approach has been to identify those neuropsychological functioning domains that continue to be impaired after successful treatment, since these could either be irreversible changes associated with starvation or potentially predisposing factors. Such longitudinal studies have converged in identifying two domains of neuropsychological functioning that are consistently impaired in group studies: set shifting and visuo-spatial processing.

Set shifting impairments may underlie the characteristic cognitive and behavioural inflexibility displayed by people with eating disorders in terms of rigid rules around eating and exercise and 'over-valued' ideas concerning weight and shape. In an elegant series of studies, Tchanturia and her colleagues have shown persisting impairment in set shifting in patients previously diagnosed with AN several years after successful treatment. They argue that an underlying impairment in the ability to think flexibly and change perspective could increase vulnerability to developing an eating disorder. They have also developed a novel treatment approach, cognitive remediation therapy (CRT), which is designed to help patients improve their cognitive flexibility using set shifting exercises and games. This therapy is derived from previous work developing CRT for patients with schizophrenia, and is showing early promise in terms of patient satisfaction and engagement. Trials are under way to evaluate the efficacy of the treatment as a precursor to more traditional psychotherapy. The second domain of neuropsychological functioning implicated in AN, visuo-spatial functioning, has been extensively studied. Visual and spatial processes are typically categorised into object recognition (what is it?), spatial location (where is it?), and visual memory. A large number of studies have identified persistently impaired visual memory in AN, with a smaller number finding impairment in spatial processes.

These findings may help us to understand the mechanisms behind the pathognomonic yet poorly understood construct of body image disturbance in AN, which can be broken down into perceptual (what do I look like and feel like, interoceptively?), semantic (what do I think about my body?), and affective (how do I feel about my body?) elements. Recent research clarifies that young women recovered from
AN continue to have spatial and visual memory impairments that are proportional to their difficulty in accurately estimating their body size.\textsuperscript{19} Future studies in AN will need to combine neuropsychological, structural, and functioning neuroimaging methodologies to help us understand more about how these deficits potentially contribute to the development and maintenance of the disorder and, ultimately, to help guide the development of new treatment approaches. Emerging results from preliminary studies using these approaches are promising.\textsuperscript{20,21}

Conclusions

In this article we have briefly reviewed the available research studies on the neurobiology of AN, including studies of neurotransmitters, genetics, brain imaging, and neuropsychology. Results in AN patients who have been weight-recovered for at least one year indicate persistent alterations in S-HIT function (increased CSF S-HIAA) as well as in set shifting and visuo-spatial processing.\textsuperscript{22,24,25}