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The Promise of Neurobiological Research in Anorexia Nervosa

Joanna E. Steinglass, MD, **Maya Dalack**, **Karin Foerde, PhD**

Department of Psychiatry, Columbia University Irving Medical Center, New York State Psychiatric Institute

Abstract

Purpose of review—This article reviews new research in the context of existing literature to identify approaches that will advance understanding of the persistence of anorexia nervosa (AN).

Recent findings—Neuroscience research in AN has yielded disparate findings: no definitive neural mechanism underlying illness vulnerability or persistence has been identified and no clear neural target for intervention has emerged. Recent advances using structural and functional neuroimaging research, as well as new techniques for applying and combining these approaches, have led to a refined understanding of changes in neural architecture among individuals who are acutely ill, have undergone renourishment, or are in recovery/remission. In particular, advances have come from the incorporation of computational and translational approaches, as well as efforts to link experimental paradigms with illness-relevant behavior. Recent findings converge to suggest abnormalities in systems involved in reward learning and processing among individuals with AN.

Summary—AN is associated with neurobiological abnormalities. Aberrant learning and reward processing may contribute to the persistence of illness. To better utilize new techniques to understand the neural mechanisms of persistent AN, it may help to distinguish stages of illness and to link neurobiology with maladaptive behavior.

Keywords

Anorexia nervosa; neuroimaging; cognitive neuroscience; reward

INTRODUCTION

Anorexia nervosa (AN) commonly begins during adolescence and early treatment is associated with higher rates of remission (1, 2). As duration of illness increases, so does the mortality rate (3). The presence of both response to treatment in some forms and severe, chronic illness in other forms underscores the need to better understand how persistent illness develops. Here, we reviewed the neuroscience of AN with an emphasis on how recent translational research contributes to understanding the neuropathology of illness. Much of the recent literature relates to new methodological and analytic tools that are becoming available.

Corresponding Author: Joanna Steinglass MD, 1051 Riverside Drive, Unit 98, New York, New York 10032, 646-774-6345, Js1124@cumc.columbia.edu.

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Are there differences in the way the brain is organized in AN?

One approach to neuropathology of AN is to examine whether there are changes in brain organization with illness. Organization can be measured both through structural imaging and through measures of neural activity when the brain is at rest (i.e., in the absence of any specified stimulus).

Structural Neuroimaging—The effects of starvation are readily apparent when viewing MRI images of the brains of individuals with AN: decreased grey matter and increased ventricular size with elevated cerebrospinal fluid are common. Numerous studies have verified that there are significant differences between individuals with AN and healthy controls (HC) in both grey and white matter (4, 5). Structural MRI scanning can measure the integrity of gray matter structure via techniques such as voxel based morphometry, cortical thickness, and cortical folding. Although there are some inconsistencies in findings, a preponderance of studies have reported decreases in both cortical and subcortical gray matter among individuals with acute AN relative to HC (4). More recent analyses of specific regions have suggested that there may be both increases (6, 7) and decreases (7–12) in regional brain volume.

Studies of individuals recovered from AN have often failed to find gray matter differences (9, 13, 14). Several recent studies provide evidence that nutritional status is linked to brain volume in AN. One study followed individuals with AN over time and found strong correlations between changes in BMI and changes in brain volume, even with considerable heterogeneity in age and duration and severity of illness (11). Longitudinal studies following participants from acute starvation through partial renourishment have confirmed the central role of starvation in the gray matter abnormalities observed in AN (9, 15). Additionally, a study of individuals with atypical AN, who have the psychopathology of AN but are in a normal weight range, did not find differences in gray matter volume (16); and another study assessing adolescents at the very earliest stage of illness also found no gray (or white) matter differences compared to HC (17). On the other hand, some studies have reported structural abnormalities in recovered AN long after initial illness (8, 18), which may indicate either long-term changes or a predisposing abnormality. However, caution is warranted in interpreting such effects as the confounding effects of medication use and long-term effects of medication use are not well understood or adequately controlled in many current studies.

The anatomical loci of structural abnormalities in AN have been quite widespread, but there has been particular focus on subcortical regions, including striatal nuclei, the amygdala, hippocampus, and thalamus. Interestingly, some data identify *increased* gray matter volume in AN in regions that are also implicated in studies using other measures of brain function (e.g. caudate). Some reported increases in brain volume in specific regions may only be apparent after normalization relative to overall brain atrophy (7). One interesting possibility is that overall brain volume decreases due to malnutrition may mask regional increases that could be disease rather than nutrition related.

There are fewer studies of white matter abnormalities in AN. Myelin is dependent on fatty acids, some of which are supplied through diet; therefore, the extreme fat avoidance by individuals with AN might be expected to be particularly devastating to white matter. The

few existing studies show abnormalities in the underweight state in AN that are not present after acute renourishment, among long-term recovered AN, or among those with atypical AN (19–22).

Functional Neuroimaging: Resting State Connectivity—Resting state connectivity is a measure of the functional organization of the brain, examining temporal associations in neural activity between different regions that are not evoked by experimenter presented stimulation. Notably, structurally similar brains may show different patterns of spontaneous activity at rest. Organizational abnormalities may play a role in vulnerability to AN, result from starvation, or contribute to the persistence of illness. Resting state functional connectivity abnormalities have been reported in a variety of brain networks (23–25), including default mode network, frontoparietal (26) and frontostriatal (27, 28) systems.

A recent, small study in adolescents and adults with AN (restricting subtype) found hypoconnectivity in both ventral (nucleus accumbens with superior frontal gyrus) and dorsal (caudate with widely distributed cortical and subcortical regions) frontostriatal systems (29). Another small study of adolescents and adults (restricting and binge-purge subtype) also found ventral frontostriatal abnormalities, but in the opposite direction (hyperconnectivity) (30), partially replicating a prior finding (31). Of note, the abnormalities in this study were not readily reversed with nutrition and weight restoration (30).

Newer methods for understanding brain organization have emerged (14, 17, 30, 32–34). Some of these offer new windows into resting state neuronal activity, which may prove informative (33, 34). For example, one study found that a measure of local spontaneous neuronal fluctuation (ALFF) is affected by starvation in AN (34). Others offer new ways to examine connectivity between networks (17, 30). One of these studies included only adolescents with recent onset of illness, and found some organizational differences even at that early stage (17).

Although the effect of starvation on the brain appears dramatic, the evident resolution of structural abnormalities with weight restoration offers hope that long-term consequences of AN on the brain may be mitigated, especially if intervention is timely. Taken together, recent work using resting state fMRI methods provides novel windows into brain organization in AN. Future work informing the relationship between functional and structural organization and how that may differ between AN and HC will be important for understanding this illness.

Are there differences in the way the brain behaves in AN?

Task-based fMRI provides an opportunity to more directly link functional brain abnormalities to specific cognitive and behavioral processes that are hypothesized to be important in the development and maintenance of AN.

Reward Systems—Research to date has not identified one clear neural mechanism of AN, but data are beginning to converge around reward and decision-making and associated neural systems (35). Reward systems, which are involved in both passive responses to stimuli as well as more complex processes of reinforcement learning, are important in

shaping behavior. Several models of AN have proposed that abnormal reward processing is central in the disorder (36–38). These models find support in existing studies showing impaired learning from feedback (39–41), and abnormal temporal discounting with a preference for delayed reward (42). In addition, passive viewing of food images during fMRI scanning has tended to show hypoactivation in reward related regions (43, 44). At face value, measuring brain responses to food seems to be a form of symptom provocation, but the relevance to symptoms and eating behavior has not been established (45). Furthermore, fMRI tasks that do not require action by the participant are likely probing distinct cognitive and neural processes from those that do (46, 47), which may limit reliability in interpreting measures of brain function as related to maladaptive behaviors in AN. Examining active food choice (48) has demonstrated that patients with AN differ from HC in the neural circuits related to decision making: patients with AN engage dorsal frontostriatal neural circuits during food based decision making, which may reflect a fundamental difference in mechanisms of eating behavior (49).

Additional advances in neuroimaging come from translationally-based fMRI paradigms that can help refine understanding of the neuropathology of AN. One translational approach pairs visual stimuli with receipt of liquid to assess the prediction error when liquid is not received as expected (or is received unexpectedly) (50). Such a prediction error is thought to be reported through dopamine signaling in the midbrain and striatum in non-human animals when a reward-expectation is violated (51). In humans, a similar prediction error signal is observed in BOLD responses in the striatum (52). Using computational modeling with fMRI, prediction error has been associated with increased activation in the striatum among adolescents and young adults with AN (38). More recently, this research has been extended by exploring the computational parameters associated with expected value (differentiated from prediction error) (53). This research suggests abnormalities in the basic functioning of the dopamine reward system, which may have implications for learning – and, by extension, for changing behavior.

Further parsing basic differences in reward and learning processes, one study compared learning rate changes to positive and negative feedback during fMRI scanning between individuals (adolescents and young adults) with AN and HC. Individuals with AN showed more rapid learning from negative feedback. This behavior was associated with differential activation in AN in the posterior medial prefrontal cortex (54), a region involved with learning on the task.

One study has examined how patients with AN respond to food odors (55), which adds a sensory dimension that has the potential to augment existing literature on taste (50) and food choices (49). The individuals with AN showed decreased sensory pleasure for the odors of high energy dense foods (as compared with the rest of the odors), which is intriguing as individuals with AN are known to specifically restrict intake from dietary fat (56, 57). Consistent with prior studies of responses to food, the AN group had hyporesponsiveness in reward pathways (specifically, the ventral tegmental area) and in the precuneus (55).

Body awareness—Somatosensory and interoceptive awareness has gained increasing attention in AN as one approach to integrating body image distortions with abnormal eating

behavior (58), and studies have had mixed findings. Models that emphasize these components of AN pathology postulate abnormalities in a range of regions and often include insula abnormalities (59), but the assessment relies on quite varied modalities and methods. In response to images of bodies, individuals recovered from AN showed abnormal frontostriatal activation (60). Adults with AN have also shown difference in the social and perceptual processes related to self-assessment, with related differences in activation in the insula (61). Pleasantness ratings of light touch and activation patterns during fMRI scanning show inconsistent results in patients with AN (or a history of AN) (62, 63). Patients with AN did not show the predicted differences in insula activation (63), whereas individuals recovered from AN differed from HC in insula activation during parts of the touch experience (62).

Affect/Limbic Systems—Mood and anxiety symptoms are part of the common presentation of AN. Emotions and emotion regulation have been studied primarily through self-report measures (64), with a few efforts to understand the neural correlates. Aberrant activation in parts of the limbic system has been demonstrated in some studies (65, 66), including amygdala activation during passive viewing of food images (43). In a recent fMRI study using an emotion regulation task (67) the group of adolescents and young adults with AN differed somewhat from HC in the strategies utilized to create distance from an emotionally arousing stimulus. The degree of emotional arousal was not significantly different between groups, though the individuals with AN showed greater amygdala response to negative pictures. There were no differences in activation during emotion regulation. The centrality of affect and anxiety disturbances in AN point to a need for greater effort in connecting these symptoms to specific cognitive and neural processes in order to understand their role in maintaining persistent illness.

Identifying illness relevant paradigms is challenging, and existing approaches have certain limitations. Notably, behavioral results do not always match expectations (e.g., sweet liquid being rated equally pleasant by AN and HC, whereas AN might be expected to like sugary liquids less). Continued development of paradigms should proceed with explicit testing of illness relevance (assessing relationship with symptoms and behavior) rather than rely on apparent/surface validity.

What do we know about the neuroprogression of AN?

A central challenge in understanding existing research is that patients have been studied at various stages of illness. While some studies differentiate between adolescent and adult populations, just as often, studies include a wide range of ages. Furthermore, while duration of illness is reported, populations are not compared based on duration of illness or stages of disease, with the exception of some research that differentiates individuals who have recovered from AN. In addition, the interpretation of the presence of brain abnormalities in individuals recovered from AN can be complicated by the confounding effects of long-term use of psychotropic medication. It may be that more homogeneity of populations will be helpful. Staging framework models for AN have been proposed (68), but these have not been widely adopted, and the data to empirically delineate stages of illness do not yet exist.

The heterogeneity in clinical characteristics in existing studies raises important general issues about how to design studies that are capable of answering the most important questions. Is the neurobiology of the development of AN similar or different from the neurobiology of persistent AN? Can findings from individuals who have recovered from the illness be extrapolated to draw inferences about the pathophysiology of AN, or are those individuals a unique subgroup? Furthermore, the differences in findings between studies (hyperactivity versus hypoactivity in similar regions) underscores the need for reliable experimental paradigms. In this respect, structural neuroimaging findings may be more robust than functional neuroimaging, but may be less sensitive to any variation that is informative about illness vulnerability and prognosis. Ongoing development of paradigms with demonstrated relevance to disturbances in eating may contribute to reliability of findings (69).

The impact of data analysis choices on the directionality of results points to the need for standardization of measurement approaches, and for reporting raw and normalized outcomes to facilitate comparison across studies. Many researchers are increasingly sophisticated about the pitfalls of imaging analysis choices and are applying the rapidly developing tools (32, 70), which is likely to generate more definitive, reproducible results. An additional concern that is also increasingly being redressed is the need for much larger sample sizes, with more adequately powered studies emerging in recent years (9, 22). Together, these developments bode well for beginning to understand the brain in AN. Computational psychiatry approaches, including machine learning methods, are currently nascent but have potential to aid diagnosis and prognosis through the combination of rich datasets and techniques that identify critical factors (70).

Conclusions

Neurobiological understanding of AN is slowly advancing. Neuroscience methods evolve rapidly and analytic techniques as well as cognitive and computational methods hold promise. And yet, existing data raise numerous questions about how to understand the causes and consequences of structural and functional abnormalities in AN. The rapid remediation of brain volume with renourishment suggests that studies of brain size during acute illness are unlikely to fully explain neurobiology of illness vulnerability. And, the effect of illness duration and age of onset on “normalization” of brain volume is not well understood--the effect of starvation on brain volume may be more extreme during adolescence (4), but so may be the ability to recover. Further longitudinal studies across a broader range of ages and illness durations will be needed to understand the contribution of brain alterations to maintenance and persistence of severe illness. By understanding the neurobiology and neuropathology of illness, we can clarify the progression of illness and improve opportunities for intervention.

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KEY POINTS

- Neural mechanisms that contribute to the persistence of anorexia nervosa (AN) are not clear.
- Convergent data from different types of research suggest that there are abnormalities in reward processing systems, and in behavioral aspects of reward learning and processing in AN.
- Approaches that link brain findings with actual maladaptive behavior can contribute to understanding the mechanisms that underlie psychopathology.
- More standardized characterization of participant populations to compare early illness with persistent illness may further advance understanding of progression of illness and clarify treatment targets.