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What Can Cognitive Neuroscience Teach Us About Anorexia Nervosa?

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Abstract

Anorexia nervosa (AN) is a complex illness and highly challenging to treat. One promising approach to significantly advance our understanding of the underlying pathophysiology of AN involves developing a cognitive neuroscience model of illness. Cognitive neuroscience uses probes such as neuropsychological tasks and neuroimaging techniques to identify the neural underpinnings of behavior. With this approach, advances have been made in identifying higher order cognitive processes that likely mediate symptom expression in AN. Identification of related neuropathology is beginning. Such findings have led to the development of complex neurobehavioral models that aim to explain the etiology and persistence of AN. Future research will use these advanced tools to test and refine hypotheses about the underlying mechanisms of AN.

Keywords

Anorexia nervosa; AN; Neuropsychology; Neuroimaging; Cognitive neuroscience; Cognitive flexibility; Set-shifting; Central coherence; Reward; Corticostriatal systems; Insula

Introduction

Anorexia Nervosa (AN) is a serious psychiatric illness defined by maintenance of an inappropriately low body weight and over-importance of shape and weight in identity. AN has a mortality rate among the highest of any psychiatric illness [1] and is associated with the highest mortality rate among eating disorders, with a mortality rate almost 6 times expected among young women [2]. Current treatment approaches are often ineffective, and many individuals suffer with symptoms for years. In part, the difficulty in identifying more effective treatments stems from the lack of clarity about the etiology and pathophysiology of AN. One pathway towards understanding this multifaceted illness has been through characterization of cognitive features. Among the many psychological and behavioral features of AN, obsessionality, rigidity, and perfectionism are often described. Most challenging are patients' firmly held beliefs about foods, and their concern with a "thin ideal." Even when they have expressed a desire for change in treatment, patients struggle to alter their thinking.

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The cognitive style of AN has long been noted, and many have proposed that this illness includes a neuropsychological component. There is a moderately large body of research describing cognitive abnormalities in the AN population. Some of these studies rely on neuropsychological tasks that have been well validated in other clinical populations. Others employ measures that have been used to characterize underlying neural activity in healthy populations. These methods allow for development and testing of hypotheses about the neural underpinnings of AN. These hypotheses, in turn, can be tested more directly in neuroimaging studies that examine neural activity or neural systems. Efforts to draw connections between patterns of cognition and potential underlying neuropathology have led to development of models of illness – and opportunities to test these models. This article will discuss some of the advances in neuropsychology and neuroimaging that hold promise for improving the understanding of the mechanisms of AN.

Neuropsychology: Advances in Understanding the Clinical Characteristics of AN

Classic Neuropsychology

Neuropsychology is the study of brain pathology and its relationship to behavior. Neuropsychological tasks are standardized measures of cognitive functioning across a range of domains. These cognitive domains are not discrete entities, as each depends significantly on the other, but they are reliably differentiated and have become standard in the field. In AN, clinical observations regarding distorted thinking, and difficulty incorporating treatment recommendations have often raised questions about whether cognitive processing deficits are prevalent in this population. However, neuropsychological studies using classic assessment batteries have not always supported these hypotheses. For example, initial hypotheses that AN was an illness of high intellectual quotient (IQ) were not born out in community studies which demonstrated a mean IQ within the normal range [3]. Similarly, the body image distortions that are a diagnostic criterion for AN led many researchers to wonder whether visual perception was altered in this population. The program of research designed to answer this question found that there is no visual perceptual deficit in AN, and that the shape and weight abnormality is best demonstrated in the affective evaluation of the body [4-5]. Individuals with AN can accurately perceive their size, but the degree of dissatisfaction with their body is extreme, and differs from healthy peers.

Neuropsychological findings are inconsistent across studies, likely stemming from small sample sizes and varying experimental methodologies. Studies commonly administer a large battery of tasks that evaluate across multiple cognitive domains. While studies may evaluate comparable domains, specific tasks within the battery vary between studies. For example, while the majority of studies suggest that attention is impaired in underweight AN, this is not a universal finding. Similarly, short-term memory is commonly – but not universally – impaired in the underweight state. One fairly consistent finding has been that while aspects of attention and memory may be abnormal in the acute state, there is improvement with weight restoration [6-9]. This suggests that these are manifestations of starvation and are not intrinsic to the illness.

Visuospatial processing has emerged empirically as an area of interest in AN. Visuospatial deficits have been found with some consistency in studies of underweight individuals [6], have been shown to persist after weight restoration [10] and have emerged in factor analyses even when individual task performance has varied [11]. These studies suggest that individuals with AN have difficulty replicating complex visual designs, a task that utilizes a combination of spatial memory and processing, as well as processing complex designs where individual shapes are embedded in a background. Interestingly, patients with AN can

be skilled at identifying the details within a visual task, at the cost of processing the whole image [9, 12-13]. This cognitive process has been termed “central coherence” and has recently been the subject of investigation. In short, individuals with AN show deficits on tasks that require global processing, showing a preference for local processing [13-15]. These studies link a neuropsychological finding with a common clinical observation that individuals with AN tend to focus on details and neglect the larger picture.

Some investigators have wondered whether cognitive deficits in AN may be amplified in syndrome–specific domains. That is, do individuals with AN have cognitive deficits primarily when food or shape and weight are concerned? Classic neuropsychological tasks such as the Color-Word Stroop [16] have been adapted to incorporate illness-relevant stimuli. In these tasks, the color words were replaced with words related to food or body image. These studies, too, have yielded mixed results, but tend to suggest that attention is impaired in AN when the task stimulus is illness related [17-19]. This idea is compelling, as selective attention to body image information may contribute to the persistence of an eating disorder in a culture saturated with messages emphasizing dieting and thinness. These women may pay particular attention to such cues. If true, training patients to mitigate their selective attention to messages about food and body size, and attend to other, non-eating disorder related stimuli in their environments may be a new strategy for treatment, akin to new treatments for social phobia [20]. Adaptations of tasks with relevant stimuli show promise in better characterizing some of the most salient neuropsychological deficits in AN.

Executive Functioning

Evaluation of executive functioning, defined as higher order processing primarily mediated by the frontal lobe, has further highlighted neuropsychological abnormalities that relate to clinical phenomena in AN. Two interesting trends have emerged from this body of research. First, individuals with AN show deficits in cognitive flexibility, or difficulty adapting to changing environmental cues. Second, patients with AN process and respond to reward abnormally.

Cognitive flexibility is operationalized in set-shifting tasks where participants are required to quickly and accurately modify their behavior in response to a change in the task demand. Excessive errors on these tasks, and perseverative errors in particular, have been shown among individuals acutely ill with AN [21-23] and weight restored or recovered AN [24]. Attenuated deficits have been found among unaffected siblings [24]. These findings seem to relate the entrenched nature of the symptoms of AN. That is, patients persist in dieting behavior even when environmental cues should indicate a need to change strategies. Patients have difficulty developing healthy strategies even when they ostensibly seek change.

Neuropsychological findings have to some degree supported the speculation that patients with AN may approach reward differently than healthy controls. One of the hallmark features of AN, dietary restriction, could be considered as altered reward processing: patients with AN delay or avoid the inherent reward of food. There are many potential ways to understand this phenomenon. One possibility is a difference in feedback-based learning, or how to respond to positive and negative feedback. In a decision-making task in which participants must learn to avoid the “risky” choices in order to collect the maximal monetary reward, a number of studies have demonstrated that acutely ill AN do not learn the optimal response, suggesting inability to incorporate the reward-based feedback during the task [22, 25-26]. Another possibility is that these patients differ in their response to a reward, even if the valuation of reward is not different. That is, patients with AN are able to override the reward of food. Preliminary investigation of delay of gratification, using measures developed by the field of behavioral economics, has supported the hypothesis that AN are

prone to overriding immediate rewards in favor of delayed rewards, even when the reward is monetary [27].

Together these data suggest that the rigid and restrictive eating patterns that promote the persistence of AN may be mediated by cognitive processes that are known to be involved in behavior and decision making. These findings help refine models of illness, and can contribute to a clinician's understanding of patients with AN.

Neuroimaging: Determining the Neural Mechanisms of AN

Despite decades of research, the neurobiology of AN is not well understood. Many neuroimaging techniques have been used to characterize potential structural and functional abnormalities in AN (For comprehensive review, see Kaye [28] or Fuglset [29]). To date, these studies have not elucidated a clear and coherent pathophysiology of AN. Findings are often inconsistent and large definitive studies are lacking. Despite the variability across studies, intriguing trends have emerged and several of these ideas are highlighted below.

Structural studies, primarily using CT scans, have consistently identified decreased brain volumes in underweight patients, including gray and white matter. Brain volume improves considerably with weight restoration, and in some but not all studies normalizes completely [30-31]. Neurotransmitter abnormalities in AN have been identified using PET scanning, with demonstrated abnormalities in both serotonin and dopamine systems. Receptor density abnormalities have been found for both neurotransmitters in the striatum, for example [32-34]. Patterns of cerebral blood flow identified by SPECT studies have suggested altered cerebral metabolism in cortical and subcortical regions [35] that may persist after weight restoration [36]. As methodologies have varied considerably, and many of these have been pilot investigations, no clear regions of interest have emerged. These studies have been successful at hypothesis generation, if not for definitive testing.

Functional MRI (fMRI) paradigms aim to further evaluate these hypotheses by examining regional activity with the expectation of identifying neural systems that underlie AN. Both symptom provocation and cognitive activation designs have been incorporated in fMRI paradigms used to examine AN. Symptom provocation studies aim to identify neural regions that may underlie specific acute symptoms by identifying neural activity as the patient expresses a relevant symptom. In cognitive activation designs, cognitive tasks are administered that are known to activate particular systems in healthy individuals, and activation patterns are then compared.

In AN, symptom provocation studies have primarily relied on measuring neural responses to stimuli that would be expected to be more salient for patients with AN than for their healthy peers. As expected, individuals with AN have been shown to have a differential pattern of activation in response to pictures of food [37-40] and images of bodies [41-43]. Given the variations in procedures, it is perhaps not surprising that the findings in these studies do not consistently identify activation pattern abnormalities the same regions, but common areas of hyperactivation have included subcortical regions like the amygdala, as well as a range of cortical areas. No single neural system has emerged.

Cognitive activation paradigms aim to test the integrity of targeted neural systems, and can evaluate an a priori hypothesis about neurocognitive abnormalities in AN. At this time, there is a relatively small amount of literature using this approach. One group has probed reward systems in AN and identified abnormalities in neural regions such as ventral striatum [44] and insula [45]. Another study suggested that abnormalities in set shifting may be mediated by cortico-striatal and frontoparietal systems [46]. In one study, the Stroop task modified for AN relevant stimuli also showed abnormal activation patterns in frontal cortex regions [47].

Taken together, these disparate studies have suggested frontostriatal system abnormalities that may underlie AN.

Cognitive Neuroscience Provides the Tools for Testing Models of AN

AN is a devastating illness that all too often becomes chronic. Current treatments are inadequate and no pharmacologic agents have proven effective [48]. Development of new treatments requires a better understanding of the neuropathology of AN. The neuropsychological and neuroimaging findings summarized above have supported the development of neurobehavioral models that link salient clinical characteristics of AN with likely underlying neural systems. One such model proposed that excessive fear of weight gain in AN may be mediated by a predisposition to fear learning, with neurobiological and genetic underpinnings [49]. A related model, proposed by our group, emphasized heightened anxiety *and* obsessionality in AN and proposed that the neurobiology may be similar to obsessive compulsive disorder, with abnormal functioning in corticostriatal systems [50]. In this model, limbic system abnormalities are thought to mediate heightened anxiety and corticostriatal system abnormalities underlie heightened obsessionality, which interact with each other to produce the rigid, avoidant dieting behaviors that promote the underweight state and in turn impact the underlying neuropathology [51]. Similarly, Marsh et al proposed that corticostriatal systems, which are thought to mediate self-regulatory control, may be dysfunctional in adolescence in some individuals in such a way that create particular vulnerability to the development of AN [52]. In a different approach, Nunn et al proposed that neural activity dysregulation in the insula may account for a range of symptoms present in AN, as the insula may integrate many of the perceptual and somatosensory disturbances observed in AN [53]. While these models differ in their specific neural hypotheses, they share a common approach: neural mediation of behavioral phenomena that can be tested empirically.

Conclusions

Neuropsychology has progressed from characterization of the cognitive profile of individuals with AN to the development of specific neurocognitive hypotheses suggesting that cognitive dysfunction may in fact mediate the disorder. With this progression has come several advances for AN. First, neuropsychological evaluation can continue to help clinicians in individual treatments – for example, an individual's neuropsychological deficits may yield information about prognosis. One study reported that patients with AN who manifest two or more neuropsychological deficits after weight restoration had more difficult time maintaining health at 1 year follow-up [54]. Second, the clarification of executive functioning deficits that seem to be characteristic of the illness has led to a new idea for an adjunctive treatment for AN: cognitive remediation therapy (CRT) [55]. This treatment aims to improve cognitive flexibility in particular through repeated practice with skills such as set shifting. Currently, this treatment is being investigated for its potential to enhance success with other longer term psychotherapy, such as cognitive behavioral therapy. Third, refinement of neuropsychological tasks has led to development of cognitive probes of underlying neural systems. These tasks can then be used to begin to test each of the proposed models of AN. For example, if corticostriatal dysfunction mediates AN, then this population would be expected to perform poorly on tasks of self-regulatory control, even after acute weight restoration. Advances in neuroimaging allow for further testing and refining of hypotheses. Each imaging modality contributes a piece of the puzzle, as we progress from identifying structural changes to neurotransmitter and neurohormonal changes to functional activity abnormalities. As cognitive neuroscience has evolved, paradigms have become increasingly sophisticated in testing the neural underpinnings of cognition and the relationship between cognition and behavior. These methods can be applied to the study of

AN, with the promise of identifying neural mechanisms that can explain this enigmatic and dangerous illness.

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