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Neuroscience of anorexia nervosa: state of the art

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Recent research in anorexia nervosa has demonstrated specific and persistent neuropsychological deficits associated with specific, localized and unilateral abnormalities on neuroimaging. These point to an underlying neurobiological substrate, with a disconnection in neural circuitry being implicated. This article summarizes the most relevant studies presented at the 9th London International Conference on Eating Disorders and discusses the treatment implications.

Anorexia nervosa (AN) is a serious illness with a poor prognosis; less than half making a full and sustained recovery within 5 years. It affects between 0.5 and 1% of young females (12–23 years of age), is very rare in males of any age and is more common in adolescence than adult life [1].

The core symptoms are: a relentless pursuit of thinness; marked food avoidance; severe weight loss; a morbid preoccupation with body shape and weight; and distortion of body image. In addition, sufferers have low self-esteem and high self-disgust, and common comorbid features include anxiety, depression and obsessive–compulsive disorder. Furthermore, they have an enhanced sense of reward, raised pain threshold and an inability to integrate thoughts and feelings.

The etiology of AN is not clearly understood. For a long time, sociocultural explanations have been dominant [2]. However, they are in themselves inadequate, for otherwise many more young females would have an eating disorder. What has been lacking is an explanation for why some are affected but not others. Recently, more attention has been paid to other etiological factors, in particular, the genetic and neurobiological basis, which can account for such a serious illness. Twin studies have demonstrated that AN has an estimated heritability of 60–75%. Recent advances in the sophistication of neuropsychology and neuroimaging have allowed for more detailed investigations into the role of the brain in the pathogenesis and maintenance of AN.

Neuropsychological assessments of patients with AN consistently show average to high average IQ scores, with strong verbal skills and a significant verbal/nonverbal discrepancy.

This discrepancy may be partly explained by the commonly noted, impaired visuospatial memory [3] and weak global processing, in other words, to overemphasize on the fine details at the expense of the bigger picture [9]. In addition, there have been many reports of impaired executive functioning, and specifically, a lack of cognitive flexibility, impairing the ability to multitask [3,4]. All these neuropsychological features persist after nutritional restoration [5,6].

Structural brain imaging studies, using CT and MRI, have demonstrated cortical atrophy and ventricular enlargement [7,8]. These changes are almost certainly secondary to starvation as they reverse with nutritional restoration. Functional brain imaging studies of AN have relied mostly upon single photon emission computed tomography (SPECT). These have consistently shown abnormalities of blood flow, usually unilateral, in the temporal region, and predominantly anteromedial [9–12]. The blood flow abnormalities are unrelated to BMI, length of illness or mood states, and do not reverse with nutritional restoration.

The brain is clearly relevant to our attempts to understand the etiology of AN and, thus, to inform more effective treatments. This was reflected in the program at the 9th International Eating Disorders Conference, recently held in London, UK, and attended by 650 delegates from 40 countries. The neuroscientific aspects of AN were covered in four different areas, plenary, short paper sessions, workshops and a special interest group. The main themes presented were neuropsychology, neuroimaging and treatment, and with overlaps between each theme.

Studies focusing exclusively on neuropsychology were presented by Kate Kucharska-Pietura *et al.* from Hull York Medical School,

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UK; Maria Øveras *et al.* from the University of Oslo, Norway; Kate Tchanturia *et al.* from the Institute of Psychiatry, London; and Mark Rose *et al.* from the Universities of Oslo and London.

The Hull York team have been studying the cognitive deficits and their correlates. A total of 25 patients with AN and 25 controls were randomly selected and compared for depression, obsessive–compulsive traits and emotional regulation. The patients scored higher than the controls on depression and obsessive–compulsive traits and showed more deficits in visuospatial perception. Contrary to findings from earlier studies, emotional regulation problems were not found; however, this may be caused by the small sample size. Future work will be based on larger samples.

The Oslo team examined the relationship between body checking and weak global processing, testing the hypothesis that body checking is linked to poor central coherence. A study of 20 patients with AN or subthreshold AN and 20 controls demonstrated that there was a significant correlation between frequency of body checking and low scores on the central coherence index of the Rey Complex Figure Test, thus, supporting the hypothesis. The implication is that the poor global processing leads to overfocusing on the finer details, such as disliking parts of the body. The results have clinical implications, whereby compulsive body checking may be alleviated using treatments that are focused on the cognitive deficits.

Tchanturia *et al.* have explored how individuals with AN identify and label emotions. Using the ‘reading the mind in the eyes’ test [13], which involves identifying the emotions of subjects based on a picture of their eyes only, they demonstrated that those with AN do less well than controls. Other tests confirmed these findings and supported the impression that those with AN have difficulty identifying and labeling emotions.

The teams from the Universities of London and Oslo presented the Ravello Profile, a collaboration between clinicians and researchers to promote a standardized global neuropsychological assessment battery for AN [101]. Previous studies have used a wide array of neuropsychological tests, making comparisons between studies very difficult. Based on factor analysis of approximately 100 cases using the Ravello Profile, preliminary analysis demonstrates discreet factors of neuropsychological tasks:

- Visuospatial component;
- Elements of executive functioning – cognitive flexibility and inhibition;
- Executive functioning linked to cognitive flexibility, concept formation and planning.

The next stage is to analyze how patients cluster around these factors. The Ravello Profile is now being used in several different countries and will ultimately provide an enormous database to examine the neuropsychological correlates of AN.

The only study to focus exclusively on neuroimaging was that of Konrad *et al.* [KONRAD *ET AL.*, GERMANY, UNPUBLISHED DATA]. They investigated brain structure in early onset AN before and after weight restoration. As with previous studies, the group found a decrease in grey matter during acute starvation, which reversed shortly after weight restoration. However, some small deficits remained in the cingulate and hippocampus. The team concluded that brain development is not completely normalized in the short term. However, most, but not all, previous long-term follow-ups have shown almost complete reversal. It remains unclear whether this is simply ‘a matter of time’ or whether there is some long-term damage.

Two series of studies were presented using a combination of neuropsychological testing and brain imaging. Joanna Steinglass of Columbia University, NY, USA, discussed her team’s attempts to shed light on the neural underpinnings of mental processes, using both neuroimaging and neuropsychological assessments. They have hypothesized that limbic abnormalities predisposed individuals to an increased fear response, and that frontostriatal abnormalities causes impaired cognitive flexibility and habit learning. Habit learning is an unconscious process mainly involving the basal ganglia. Owing to the frontostriatal abnormalities, it is suggested that patients with AN are often unable to rely on these unconscious mechanisms, and therefore, have rigid and definite routines. The hypothesis was not supported since there was no significant difference between patients and controls. Steinglass intends to use a larger, homogenous sample, employing more sophisticated neuropsychology tests in a future study.

Lask and his teams from the Universities of Oslo and London reported their series of studies using both neuropsychological testing and functional neuroimaging. They have confirmed the consistent findings of abnormalities

in visuospatial functioning, specifically visuospatial memory, and in cognitive flexibility, as well as weak central coherence. These correlate with a reduction in blood flow (using SPECT) in the medial temporal region. Taken together, these findings, along with the characteristic features of AN (outlined above) suggest abnormal function in the frontal, parietal and temporal regions, as well as in subcortical structures, such as the amygdala, the basal ganglia and the nucleus accumbens. Such widely disseminated abnormalities seem exceedingly unlikely, and should they exist, would be accompanied by a far more profound clinical picture. Instead, Lask's team hypothesize that there is a disconnection between the structures, leading to the very specific features of AN [14]. They propose that some form of dysfunction in the insula may be central to the pathogenesis of AN. The concept of disconnection has already been proposed to explain schizophrenia and dyslexia, and the insula seems a likely candidate, given that it serves as an integration cortex for convergence of various neural networks [15].

In order to test their insula hypothesis, the team has designed a study using functional MRI with simultaneous neuropsychological testing. This is currently ongoing in Oslo, with similar studies planned in London, Budapest and Basel.

Turning to treatment, Lask stated that the consistent finding of cognitive deficits pointed to the need to develop treatments for them. He proposed that the lack of attention to remedying these deficits may explain the poor prognosis of AN. Lask suggested that cognitive remediation therapy (CRT), which deals with thought processes rather than thought content, should have a central role in any treatment program for those patients with cognitive deficits.

Tchanturia, from the Institute of Psychiatry in London, has led to the development of CRT for the treatment of AN [16]. She has borrowed ideas from the treatment for schizophrenia and brain injury and carefully adapted them to the needs of AN patients. She argues that when the thinking process is a component of the illness itself, it should be addressed in treatment. For example, in the treatment of schizophrenia and brain injury, CRT has been gaining a prominent role as a frontline treatment, which taps the inherent plasticity of the brain. Whereas the more traditional psychotherapies address what patients think, CRT deals with how they

think. Similar to Lask, Tchanturia believes that the prognosis could be improved by treating the underlying deficits and she has been able to demonstrate improvements using with CRT even with chronically ill patients [16].

Tchanturia and her team have also developed a Cognitive Remediation and Emotion Skills Training (CREST) method. The treatment consists of ten sessions out of which the first two sessions involve cognitive remediation. They help clients to improve flexibility and to look at the bigger picture. The remaining eight sessions focus on emotions. The aim of this new type of therapy is to extend the focus from cognitions to emotions, given the findings that patients with AN have more problems with emotion processing. CREST aims to help patients reflect on their thinking styles, assist with recognizing their own emotions and build their capacity to recognize those of others.

Towards the end of the conference, a neuroscience special interest group met to discuss the *status quo* and future prospects for neuroscience research in the study of eating disorders. Over and above the further development of the aforementioned studies, a number of additional studies are planned. Graham Redgrave's team from Johns Hopkins University, MD, USA, intends to use neuroimaging markers to see whether any predict treatment response. Steinglass plans to look at neuropsychological tasks that use a number of memory systems in order to shed light on the functioning of these systems. For example, what is the nature of the interaction between the hippocampal and striatal systems? Her team is also interested in the idea of delayed discounting, a concept borrowed from neuroeconomics. This examines how people make decisions and, in particular, how they choose between an immediate rather than to a delayed reward. It is thought that there are different neural systems for each of these. Understanding more about how those with AN function in this area may shed further light on neural systems.

Lask's team in Oslo is commencing a study of the experience of brain scanning for those with AN, and what effect the process has upon their identity and understanding of the illness. The same team is exploring the commonly reported spring season of birth bias in AN by testing a number of neuroscience-based hypotheses to explain the bias [17]. Lastly, they are investigating the possibility of some cases of AN being a variant of pediatric autoimmune neurodevelopmental disorder associated with

streptococcus (PANDAS) on the same basis as PANDAS tics/Tourette's syndrome and PANDAS/obsessive-compulsive disorder [18].

The 9th International Eating Disorders Conference has demonstrated that neuroscience is at the forefront of research into AN. Key findings include further evidence of neuropsychological deficits and of neural circuitry disconnection. The thrust of ongoing research is to understand the link between these maladaptive cognitive processes and the abnormal brain activity. Future studies will continue to draw on a careful combination of insights from neuropsychological tests and brain imaging techniques such as functional MRI. In particular,

the insula hypothesis will be further examined. Several promising strands of research have the potential to improve our understanding and inform our treatment of this mysterious and often treatment-resistant illness.

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Website

- A global neuropsychological assessment in anorexia nervosa.
www.ravelloprofile.org

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