An Overlooked Brain Region in the Aetiology of Anorexia Nervosa: The Importance of Behaviourally Driven Neuroimaging Analysis

Journal of Experimental Neuroscience
Volume 12: 1–2

DOI: 10.1177/1179069518820068
SAGE

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ABSTRACT: The neurobiological contributions to anorexia nervosa (AN) remain poorly understood, hindering the development of effective neurobiological treatments such as medications and brain stimulation. A large number of studies have been undertaken utilising neuroimaging techniques, such as magnetic resonance imaging (MRI), to gain a better understanding of the brain mechanisms involved in the illness. However, the analyses undertaken by many studies have utilised a whole-brain analytical approach as much of this research has been exploratory in nature. This is, however, problematic as small brain regions that differ between groups may not have the statistical power to produce statistically significant results. This is highlighted in a recent study undertaken by our group utilising diffusion-weighted imaging. In this research, we identified widespread white matter microstructural differences in individuals with AN, but only showed differences in a small brain region (the superior colliculus) when a region-of-interest approach that was driven by behavioural findings was utilised. The importance of hypothesis-driven neuroimaging analyses is discussed in this article.

KEYWORDS: Anorexia nervosa, magnetic resonance imaging, diffusion-weighted imaging, superior colliculus, midbrain

RECEIVED: November 16, 2018. **ACCEPTED:** November 28, 2018.

TYPE: Commentary

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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COMMENT ON: Phillipou A, Carruthers SP, Di Biase MA, et al. White matter microstructure in anorexia nervosa. *Hum Brain Mapp*. 2018;39:4385-4392. doi:10.1002/hbm.24279. PubMed PMID: 29964345. https://www.ncbi.nlm.nih.gov/pubmed/29964345

Anorexia nervosa (AN) is a very serious psychiatric illness associated with significant morbidity and mortality. One in 10 individuals with AN die as a result of the physical effects of starvation or from suicide.[1,2] AN has the highest mortality rate of any mental illness,[1] yet, the efficacy of current treatments for AN is limited, resulting in among the highest relapse rates of any mental illness and a long-term recovery rate of less than 50% among those who survive it.[3,4] The serious psychological and physical symptoms of the illness have significant detrimental effects on an individual's quality of life and result in a substantial burden on clinical services. AN is a prevalent condition with an estimated lifetime prevalence of 1.5% and accounts for the greatest proportion (>80%) of the $70 billion annual socioeconomic cost of eating disorders in Australia.[5] There is a relative dearth of effective treatments for AN, in particular, neurobiological treatments. Psychotropic medications and brain stimulation techniques, which are routinely used to treat other mental illnesses, are not available to specifically treat AN. Various medications have been trialled, but have proven largely ineffective for AN treatment.[6] Brain stimulation techniques on the other hand show potentially promising effects in AN,[7] but are yet to be rigorously evaluated. The lack of neurobiological treatment options is arguably largely because the neurobiological contributions to the illness remain poorly understood, that is, the neurotransmitter systems involved in AN are unclear thereby limiting treatment with psychotropic medications; and the brain regions involved in the illness are poorly understood, therefore limiting our ability to treat AN patients with brain stimulation.

Many studies have sought to understand the neurobiological underpinnings of AN in terms of brain function and structure, but findings have been at best inconsistent and in many cases contradictory.[8] Whole-brain comparisons are most frequently employed in neurobiological research in AN, and studies are often largely exploratory in nature. This, however, creates a problem in that small brain regions that differ between groups may not have the statistical power to produce statistically significant results. This is highlighted in a recent study undertaken by our group.[9] In this research, we utilised a whole-brain approach to determine white matter microstructural differences in individuals with AN compared with healthy controls. Widespread microstructural differences were identified in the AN group encompassing a range of different cortical and subcortical brain regions. The white matter microstructure of a small, deep brain

structure called the superior colliculus, which we have hypothesised to be involved in AN from our other works,[10–14] was not found to differ in this set of analyses. A region-of-interest (ROI) approach applied to this small brain region, however, showed that individuals with AN did indeed show deficits in the white matter microstructure of this brain region. Similarly, an ROI approach used on resting state functional connectivity data acquired in the same group of AN participants[15] showed reduced functional connectivity of the substantia nigra (a small grey matter region of the brain that sends signals to and from the superior colliculus) to cortical regions of the brain, including the inferior parietal lobule. Adopting this behaviourally driven ROI approach identified structural and functional dysfunction of the superior colliculus and surrounding regions in AN that we had not observed in our whole-brain analysis. These regions have scarcely been reported in other neurobiological studies of AN[8] and highlight the potential benefits of using behavioural findings to form hypotheses and select brain regions for ROI-based neuroimaging analyses. This also emphasises the use of behavioural tasks that employ well-established neural circuitry acquired through extensive human and animal research, such as eyetracking assessments. In sum, we suggest that future research into the neurobiology of AN is hypothesis-driven, to avoid losing the opportunity to find the proverbial needle in the whole-brain analytical haystack.

Author Contributions

AP wrote the first draft of the article, and all authors contributed to and approved the final manuscript.

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