Anorexia Nervosa: Neurobiological alterations across acute and weight-restored states

Doctoral Thesis

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Abstract

The objective of this thesis was to investigate various aspects of brain structure and function in individuals diagnosed with anorexia nervosa (AN) or with a history of AN diagnosis, across various stages of the illness. This investigation employed a multimodal approach, integrating MRI-based methods and blood-based biomarkers. Widespread reductions in gray matter cortical thickness and volume have been consistently replicated in the acute state of anorexia nervosa. These alterations have been observed to partially reverse following short-term weight restoration and appear to fully normalize after long-term weight restoration. However, the mechanisms underlying these severe structural brain alterations, and their implications for functional changes remain to be elucidated.

In states of severe malnutrition, such as anorexia nervosa, limited resources may impair the maintenance and repair of cells and neural functions. Rapid recovery upon refeeding indicates that apoptosis is an improbable explanation for the gray matter reductions observed. Instead, it is more likely that a complex interplay of cellular structural changes and disrupted repair processes explains structural and functional alterations in AN. These processes vary according to cell type, function, and relative importance within the brain.

Study I investigated brain metabolite concentrations in gray and white matter using magnetic resonance spectroscopy, comparing patients diagnosed with AN to healthy controls. Results revealed reduced N-acetyl-aspartate (NAA) and increased choline concentrations in gray matter, but not white matter, suggesting altered oligodendrocyte function and increased membrane lipid turnover. Importantly, concentrations of blood-based neurofilament light (NF-L), were predicted by NAA concentrations, suggesting ongoing neural damage processes.

Study II tested whether known alterations in blood-based biomarkers, including NF-L, tau protein (associated with axonal damage), and glial fibrillary acidic protein (associated with astroglial injury), previously observed in the acute state of AN, persist following long-term weight restoration. The findings demonstrated that these markers underwent complete normalization, thereby suggesting the absence of persistent damage processes.

Study III examined previously reported alterations in functional connectivity using degree centrality (DC) and regional homogeneity (ReHo) metrics. DC indicates the relevance of a given voxel to the transfer of information across the brain, while ReHo is the degree of functional similarity between a single voxel and its direct neighbors. The findings indicated that the spatial distribution of DC alterations aligned with neurotransmitter transporter densities—specifically VAChT, DAT, and SERT—using the *neuromaps* toolbox. Notably, this alignment served as a predictor of short-term weight gain during weight restoration therapy.

Together, these results unveil a multifaceted interplay of structural and functional alterations in AN, driven by resource limitations and subsequent recovery mechanisms. The discussion section of this thesis explores an integrative perspective and contextualizes the results within an energy allocation framework. Furthermore, the results demonstrate that biomarkers such as NAA and NF-L offer a promising avenue for the monitoring of treatment response and the elucidation of recovery dynamics. The alignment of functional alterations and neurotransmitter systems shows predictive qualities for therapeutic outcomes. Future studies should encompass additional time points and employ chemoarchitectural maps, which may eventually help inform neuromodulation therapies and treatment stratification.