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Alterations of brain structure and functions in anorexia nervosa

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SUMMARY

The eating disorder anorexia nervosa develops mostly in adolescent girls and young women and has the highest mortality rate among psychiatric diseases. Symptoms are caloric food restriction, body weight loss or maintained very low body weight, body image disturbance and hyperactivity. Clinically, the disease is well characterized, but the underlying pathophysiology still remains to be better described. Already several decades ago, physicians and researchers began to investigate potential causes of the disease in the brain with advancing neuroimaging techniques yielding important insights. The purpose of this short review is to summarize the current knowledge on brain alterations in anorexia nervosa and to stimulate future research. By using MRI and fMRI scans, structural and functional changes can be detected. In MRI scans the most common finding is gray and white matter reduction correlating with the extent of malnourishment and mostly reversible with recovery. Most fMRI studies performed in patients with anorexia nervosa focused on food, taste, physical appearance and social cognition. Although very different in terms of the study protocol, the most common findings are increased activation of the amygdala and altered activation of the cingulate cortex. Further research is required in order to connect the different findings to further investigate the

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neurobiological differences between the subtypes of anorexia nervosa.

Contents

1. Introduction

The eating disorder anorexia nervosa develops mostly in adolescence or young adulthood with a ratio of women: men of 8: 1 [1]. Anorexia nervosa was found to be the third most common chronic disease in adolescents with the highest mortality rate of all psychiatric disorders [2].

Symptoms presented encompass: self-imposed restriction of caloric intake, loss of body weight and/or low body weight, fear of gaining weight and body image disturbance [3]. Clinically, patients can be divided into two subtypes, namely restricted and binge-purge anorexia nervosa. The restricted type is characterized by continuous very low caloric intake and the binge-purge type by the intake of a big amount of food in a short time (bingeing) followed by counteracting behavior, for example starving for a longer time, use of laxatives or vomiting (purging).

Although the disease is clinically well characterized, the underlying pathophysiology is still not well understood. In the past, several concepts have been established in order to attempt to explain the cause of anorexia nervosa. From personality traits, family or genetic concepts, the research community has now come to a multifactorial concept that is mainly focusing on neurobiology [4].

In order to better characterize the disease, for several decades researchers and doctors first investigated the brain structure [5] with advances in neuroimaging representing a great leap forward in terms of insight into the disease [6]. It is to note that especially the possibility of analyzing T1- and diffusion weighted magnetic resonance images (MRI) increased our knowledge on alterations under conditions of anorexia nervosa [6].

The aim of this short review is to present the current knowledge on neurobiological brain alterations in anorexia nervosa with regards to structure and function as well as to discuss gaps in knowledge in order to stimulate future research.

2. Morphological changes in anorexia nervosa

It is well established that acute malnutrition is associated with gray and white matter reduction, with the reduction being mostly reversible with weight restoration, at least in non-chronic patients [7]. The brain mass reduction manifests with widespread sulcal enlargement and marked ventricle dilatation and is positively correlated with reductions in BMI [8]. However, not all brain areas seem to be equally affected by volume reduction. Specifically, the frontoparietal – cingulate network involved in perception and integration of body stimuli seems to be reduced in volume [9]. Additionally, differences

have been observed between adolescents and adults most likely due to ongoing brain development [8]. These alterations in brain structure may be caused by multiple processes. However, the exact underlying mechanisms still remain to be unraveled [10]. Several contributing factors have been discussed [11] such as fluid shifting from the intra- to extracellular space because of altered oncotic/colloid osmotic pressures or dehydration [12], loss/apoptosis of glial or neuronal cells, macro- and micronutrient deficiency [13,14], peptide hormone alterations such as a decrease of leptin [15] and a reduction of thyroid and gonadal hormones as well as an increase in neurotrophines and cortisol [16]. Regionally-decreased cortical thickness [17] and increased cerebrospinal fluid were also frequently reported in patients with anorexia nervosa [18]. These alterations will be briefly discussed below.

The alteration of oncotic pressure is likely to result in fluid shifts in patients with malnutrition/underweight such as anorexia nervosa as also reflected in abdominal fluid and pericardial effusion [19]. These changes in the brain may also lead to apoptosis of glial or neuronal cells. Postmortem brain studies of patients with anorexia showed histological alterations suggestive of cellular degeneration including reduced spine density and abnormal neuron types [20]. Significant astrocyte loss, in both white and gray matter, has been recently reported in the rat animal model activity-based anorexia [21]. Further evidence points towards neuronal cellular degeneration and restructuring, however, (large) apoptosis does not seem to be the main reason for gray and white matter reduction as the reduction was reversible with ~5% increase of gray matter within three months [22,23].

Patients with anorexia nervosa differ from other malnourished patients as they often particularly try to avoid food high in fat [24]. Consequently, plasma concentrations of several lipids were found to be lower or altered in patients with anorexia nervosa [25]. Although several fatty acids can be produced endogenously, patients with anorexia nervosa also lack polyunsaturated essential fatty acids that need to be provided by diet and are important for fluidity of neuronal membranes and the function of membrane bound enzymes, receptors and ion channels [25,26], dysfunctions that may well play a role in the fluid shifts and cell death discussed above. However, it is to note that although the lack of polyunsaturated essential fatty acids has been associated with alterations in brain structure [26], it has yet to be investigated in anorexia nervosa. In addition, also a lack of micronutrients such as zinc and vitamin B12 may be involved in structural brain alterations under conditions of anorexia nervosa [27], an assumption corroborated by the finding that 45% of anorexia nervosa patients suffer from at least one micronutrient deficiency with vitamin A and B9 deficiency being most frequent [28].

Hormonal alterations affect mediators involved in the regulation of food intake as well as other homeostatic functions. It has been shown that levels of the orexigenic hormone ghrelin are elevated, whereas circulating levels of anorexigenic hormones such as leptin and nesfatin-1 are decreased [29,30] likely representing – albeit insufficient – compensatory alterations. Moreover, the hypothalamic-pituitary-adrenal axis was reported to be activated in anorexia nervosa as reflected in increased cortisol concentrations [31]. Since cortisol has been shown to impact brain structure [32], the negative correlation of increased global gray matter volume during recovery and blood cortisol levels [33] may give rise to a causal relationship. Lastly, the hypothalamic-pituitary-thyroidal and–gonadal axis have been reported to be largely suppressed [31]. Further research is warranted especially in light of alterations in the different subtypes of anorexia nervosa.

3. Functional alterations in anorexia nervosa

Modern neuroimaging technologies allow – in addition to structural analyses – the investigation of functional alterations under conditions of anorexia nervosa (Table 1). Overall, functional magnetic resonance imaging (fMRI) studies indicate altered neural activity across the brain, including the frontal, parietal, temporal and occipital lobes, as well as subcortical structures such as the amygdala, striatum, thalamus and the cerebellum [34]. Despite the growing body of knowledge due to the increase in number of fMRI studies, a clear pathophysiological picture is still to be drawn.

The differentiation between alterations subsequent to the disease/malnourishment and those causally involved is still a big challenge. There are different possibilities to address this question [34], namely first, comparing patients within the first months of their disease with chronically ill patients, second, to investigate acutely ill patients compared to recovered patients, third, comparing recovered patients with healthy controls and fourth, studying patients with anorexia nervosa compared to

Table 1
Functional alterations in anorexia nervosa as assessed using functional magnetic resonance imaging (fMRI).

Reference	Tasks	Population (all female)	Brain area altered	Possible implications/additional information
Appearance/body shape				
Miyake et al., 2010 [43]	hearing negative words related to body image	AN (n = 15) Controls (n = 15)	increased activity in amygdala, medial prefrontal cortex and inferior parietal lobe	might be correlate of deficit in the cognitive evaluation of negative emotions concerning body image in patients with AN
Fladung et al., 2010 [40]	viewing images of thin bodies	AN (n = 14) Controls (n = 14)	increased activity in the ventral striatum	reward system activated → patients might show "starvation dependence", might be a disease maintaining factor
Friederich et al., 2010 [42]	comparison of oneself with images of idealized bodies	AN (n = 17) Controls (n = 17)	increased activity in insula, premotor cortex; reduced activity in rostral anterior cingulate cortex	altered interoceptive awareness to body self-comparison and altered motivational system
Miyake et al., 2010 [38]	viewing images of themselves but distorted and oversized	AN-R (n = 11) (AN-BP (n = 11) Controls (n = 11)	amygdala significantly activated in AN-R, AN-BP and controls; prefrontal cortex significantly activated in AN-BP and controls;	might reflect a general failure to represent and evaluate one's own body in a realistic fashion
Mohr et al., 2010 [39]	viewing images of themselves but distorted and thinner and a) asked to rate satisfaction with these images and b) asked to estimate their own size	AN (n = 16) Controls (n = 16)	a) stronger activation of the insula and lateral prefrontal cortex b) modulations in activation of the precuneus	a) indicates a stronger emotional involvement when patients are confronted with distorted images close to their own ideal body size b) patients overestimated their own body size → might be deficit in the retrieval of a multimodal coded body schema in precuneus/posterior parietal cortex related to over-estimation of body size
Vocks et al., 2010 [36]	a) viewing images of their own body and b) viewing images of other women in bikini	AN (n = 13) Controls (n = 27)	a) inferior parietal lobule activation reduced b) increased activity in the amygdala	a) decreased attentional processes toward one's own body, possibly reflecting body-related avoidance behavior b) stronger emotional activation and enhanced vigilance, possibly resulting from social comparison processes

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Table 1 (*continued*)

Reference	Tasks	Population (all female)	Brain area altered	Possible implications/additional information
Castellini et al., 2013 [37]	viewing images of themselves but distorted and oversized	AN-R (n = 18) Controls (n = 19)	increased activity in dorsolateral prefrontal cortex (DLPFC)	significant correlation between DLPFC activation and eating disorder psychopathology; reinforcing the key role of attentive, executive and self-evaluation networks in AN
Fladung et al., 2013 [41]	viewing images of thin and normal weight bodies	AN patients (n = 13) Controls (n = 14) (all adolescent)	increased activity of the ventral striatum (thin bodies); reduced activity of the ventral striatum (normal weight bodies)	patients on average only 13 months ill at moment of fMRI → changes of reward system occur early in illness
Food and hunger				
Gizewski et al., 2010 [45]	viewing high-calorie food images	AN-R (n = 12) Controls (n = 12)	increased activity in dorsal posterior cingulate cortex and insula	representing a dysfunction of top-down processes of the dorsal stream of emotional processing
Joos et al., 2011 [44]	viewing images of food	AN-R (n = 11) Controls (n = 11)	increased activity of the right amygdala and decreased activity of the cingulate cortex	likely represents parts of a negative feedback loop of emotional processing and disgust ratings correlating negatively with activation of amygdala
Vocks et al., 2011 [49]	drinking chocolate milk in hunger and satiety condition	AN-R (n = 12) Controls (n = 12)	hunger condition: right amygdala and left medial temporal gyrus more activated satiety condition: inferior temporal gyrus more activated	activations located in the amygdala and in the extrastriate body area (inferior temporal gyrus) might reflect fear of weight gain
Brooks et al., 2012 [46]	exposed to food and imagining eating it	AN-R (n = 11) AN-BP (n = 7) Controls (n = 24)	increased activation in the visual and prefrontal cortex; reduced activation in the cerebellum	suggestive of altered neuronal processing of visual food stimuli → possibly more rumination about controlling food intake
Oberndorfer et al., 2013 [47]	viewing images of food	Women recovered from AN (n = 14) Controls (n = 12)	increased activity in right ventral anterior insula	suggests exaggerated sensitivity and anxiety related to food and eating; cognitive processing of food-related images is still affected although women were recovered
Sanders et al., 2015 [48]	viewing images of food after fasting overnight	AN (n = 15) Women recovered from AN (n = 14) Controls (n = 15)	increased activity in caudate nucleus, medial and lateral prefrontal cortex and anterior cingulate in AN and recovered women	cognitive processing of food-related images is still affected although women were recovered

Reward system				
Frank et al., 2012 [51]	reward-conditioning task: paradigm involves learning the association between conditioned visual stimuli and unconditioned taste stimuli, as well as the unexpected violation of those learned associations	AN-R (n = 21) Controls (n = 23)	increased activity in the orbitofrontal cortex, anteroventral striatum, insula, and prefrontal cortex	suggests that brain reward circuits are more responsive to food stimuli in AN
Bär et al., 2013 [57]	thermal painful stimuli to the right arm during fMRI	AN (n = 19) Controls (n = 19)	decreased activity in left posterior insula, increased activity in ipsilateral (right) pons	significantly increased heat pain thresholds observed in patients; insular dysfunction might be correlate for reduced pain sensitivity
Fonville et al., 2014 [55]	implicit emotion processing (detecting different facial expressions)	AN-R (n = 25) AN-BP (n = 6) Controls (n = 35)	increased activity in right fusiform gyrus as response to all facial expressions; the higher the happier the face	suggests that alterations in implicit emotion processing in AN occur during early perceptual processing of social signals and illustrate greater engagement
Decker et al., 2015 [52]	task consisted of a range of monetary choices with variable delay times, yielding individual discount rates (the rate by which money loses value over time)	AN (n = 30) Controls (n = 22)	underweight AN: decreased activity in striatum and dorsal anterior cingulate; AN after treatment and controls: increased activation in reward regions (striatum and dorsal anterior cingulate) and decision-making regions (dorsolateral prefrontal cortex and parietal cortex)	before treatment the AN group showed a preference for delayed over earlier rewards (i.e., less steep discount rates) compared with controls; after weight restoration AN did not differ; AN behavior looks phenotypically like excessive self-control (choose late reward) but without enhanced prefrontal activation; the cingulostriatal circuitry's activity is increased → abnormalities in decision-making neural system might play a bigger role in AN

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Table 1 (*continued*)

Reference	Tasks	Population (all female)	Brain area altered	Possible implications/additional information
Phillipou et al., 2015 [54]	implicit emotion processing task during fMRI and eye tracking	AN (n = 24) Controls (n = 25)	increased activity to own face stimuli in AN in the right inferior and middle temporal gyri, and right lingual gyrus	suggests increased anxiety to disorder-relevant stimuli in AN
Via et al., 2015 [53]	social situation of acceptance and rejection	AN-R (n = 20) Controls (n = 20)	social acceptance: hypoactivation of the dorsomedial prefrontal cortex social rejection: hyperactivation of visual areas	suggests abnormal motivational drive for social stimuli; overlapping of alterations in social cognition and reward systems may lead to a disruption of adaptive responses in the processing of social reward. Ventral striatum activation during rejection was positively correlated in patients with clinical severity scores (Eating Disorder Inventory -EDI-2).
Social cognition				
McAdams & Krawczyk 2011 [58]	theory of mind task which involves the ability to understand the mental state of other people in a specific situation	Women recovered from AN (n = 17) Controls (n = 17)	reduced activation in social cognition network, biggest differences in right temporoparietal junction	differences in the processing of social knowledge in recovered subjects suggesting that biological impairments still play a role in social cognition of recovered AN women
Schulte-Rüther et al., 2012 [59]	theory of mind task which involves the ability to understand the mental state of other people in a specific situation	AN (n = 19) Controls (n = 21) (fMRI at admission, all adolescent)	fMRI on admission: reduced activation in middle and anterior temporal cortex and in the medial prefrontal cortex	at follow-up (1 year after admission/ fMRI) → poor social cognition reflected in fMRI correlated with poor clinical outcome

Abbreviations: AN, anorexia nervosa; AN-BP, binge-purge AN; AN-R, restricted AN.

patients with malnutrition due to any other reason. However, only few studies are available so far applying these suggested study designs. Studies on recovered patients indicated increased activation in the secondary visual processing regions and the dorsal visual stream following presentation of facial pictures compared to healthy controls as assessed by fMRI [35]. Additional studies are urgently needed, especially those applying the comparisons suggested above.

It is also to note that results from fMRI studies are difficult to compare because of different questions, pictures shown to patients or cognitive tasks the patients are asked to perform which are mostly food-, body weight- or emotion-related in anorexia nervosa studies [34].

In appearance/body shape-related fMRI studies, patients with anorexia nervosa showed reduced activation in the inferior parietal lobule, an area related to the attention network, after viewing images of their own bodies [36], a finding that might be interpreted as avoidance of perceiving the own body. Upon looking at pictures of other women in bikinis, patients with anorexia nervosa displayed increased activity in the amygdala [36]. Other studies showed that when showing patients pictures of themselves – but distorted and oversized – activation in the inferior frontal gyrus, middle temporal gyrus and amygdala was increased, while activation was reduced in the prefrontal cortex [37,38]. In response to seeing pictures of thin bodies, increased activity in the ventral striatum and in the insula have been observed [39–41]. The latter one – increased insula activation – was also detected in response to comparison of oneself with idealized bodies, together with increased premotor cortex activity and reduced rostral anterior cingulate cortex activity [42]. Increased amygdala, medial prefrontal cortex and inferior parietal lobe activation was reported when patients heard negative words related to body image [43].

Presentation of food-related pictures led to increased activity in the dorsal posterior cingulate cortex, the insula and the amygdala and reduced activity of the posterior midcingulate cortex in patients with anorexia nervosa [44,45], a finding possibly representing a dysfunction of top-down processes of the dorsal stream of emotional processing. In another study patients were exposed to food and instructed to imagine eating it. Patients with anorexia nervosa displayed reduced activation in the cerebellum along with increased activation in the visual cortex [46], suggestive of an altered neuronal processing of visual food stimuli [46]. Interestingly, studies demonstrated that the cognitive processing of food-related images is still affected in patients recovered from anorexia nervosa [47,48]. Lastly, when feeling hungry the amygdala was found to be more activated in patients with anorexia nervosa compared to healthy controls [49], pointing towards a more fearful emotional response.

Altered reward system functions in anorexia nervosa is a quite well elaborated concept [50]. Several studies have investigated differences in the reward system describing dysfunction in reward related areas of the brain, differences in processing of emotions, e.g. emotional facial expressions and higher activation in the anteroventral striatum, insula and prefrontal cortex when asked to perform reward-related tasks in the fMRI [34,43,51–55]. Moreover, patients with anorexia nervosa were shown to have reduced pain sensitivity [56], which may be associated with insular dysfunction [9,57].

In order to study social cognition, patients have been asked to perform a theory of mind task which involves the ability to understand the mental state of other people in a specific situation. Performing these tasks, acutely ill anorexic patients and those recovered from anorexia showed similarly reduced activation in areas of the temporal and medial prefrontal cortex [58,59] giving rise to lasting changes in brain function possibly involved in the risk for a relapse of the disease.

4. Conclusion

Investigating the brain of patients with anorexia nervosa, structural and functional changes can be detected [6]. In MRI scans the most common finding is gray and white matter reduction correlating with the extent of malnourishment and mostly reversible with recovery and weight normalization [7]. However, the detailed mechanisms of gray and white matter reduction are not fully understood [10]. The use of fMRI can provide important information about the functional changes underlying the symptomatology of anorexia nervosa. Different studies have been performed related to food, taste, physical appearance and social cognition [34]. When comprehensively viewed, the most common findings are increased activation of the amygdala and changes in the activation of the cingulate cortex. Despite the fact that the (suspected) factors underlying these alterations greatly differ between

research groups, it becomes more apparent that several changes still remain detectable in recovered patients pointing towards non-reversible consequences of the disease or underlying causes increasing the risk for a relapse even after recovery. Further studies are needed in order to dissect cause and consequence and better characterize the different subgroups of anorexia nervosa.

Author contributions

Sophie Scharner and Andreas Stengel wrote and finalized the paper.

Conflicts of interest

The authors declare no conflict of interest.

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References

[1] Zipfel S, Giel KE, Bulik CM, Hay P, Schmidt U. Anorexia nervosa: aetiology, assessment, and treatment. Lancet Psychiatry 2015;2:1099–111.
[2] Papadopoulos FC, Ekbom A, Brandt L, Ekselius L. Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry J Ment Sci 2009;194:10–7.
[3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). 5th ed. 2013. United States.
[4] Herpertz-Dahlmann B, Seitz J, Konrad K. Aetiology of anorexia nervosa: from a “psychosomatic family model” to a neuropsychiatric disorder? Eur Arch Psychiatry Clin Neurosci 2011;261(Suppl 2):S177–81.
[5] Heidrich R, Schmidt-Matthias H. Encephalographic findings in anorexia nervosa. Arch Psychiatry Nervenkrankh Ver Mit Z Gesamte Neurol Psychiatry 1961;202:183–201.
[6] Phillipou A, Rossell SL, Castle DJ. The neurobiology of anorexia nervosa: a systematic review. Aust N Z J Psychiatry 2014;48:128–52.
[7] Wagner A, Greer P, Bailer UF, Frank GK, Henry SE, Putnam K, et al. Normal brain tissue volumes after long-term recovery in anorexia and bulimia nervosa. Biol Psychiatry 2006;59:291–3.
[8] Seitz J, Walter M, Mainz V, Herpertz-Dahlmann B, Konrad K, von Polier G. Brain volume reduction predicts weight development in adolescent patients with anorexia nervosa. J Psychiatry Res 2015;68:228–37.
[9] Bär K-J, de la Cruz F, Berger S, Schultz CC, Wagner G. Structural and functional differences in the cingulate cortex relate to disease severity in anorexia nervosa. J Psychiatry Neurosci JPN 2015;40:269–79.
[10] Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci 2012;15:528–36.
[11] King JA, Frank GKW, Thompson PM, Ehrlich S. Structural neuroimaging of anorexia nervosa: future directions in the quest for mechanisms underlying dynamic alterations. Biol Psychiatry 2018;83:224–34.
[12] Artmann H, Grau H, Adelmann M, Schleiffer R. Reversible and non-reversible enlargement of cerebrospinal fluid spaces in anorexia nervosa. Neuroradiology 1985;27:304–12.
[13] Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. J Nutr Health Aging 2006;10:386–99.
[14] Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging 2006;10:377–85.
[15] Matochik JA, London ED, Yildiz BO, Ozata M, Caglayan S, DePaoli AM, et al. Effect of leptin replacement on brain structure in genetically leptin-deficient adults. J Clin Endocrinol Metab 2005;90:2851–4.
[16] Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol 2017;13:174–86.
[17] Lavagnino L, Mwangi B, Cao B, Shott ME, Soares JC, Frank GKW. Cortical thickness patterns as state biomarker of anorexia nervosa. Int J Eat Disord 2018;51:241–9.
[18] Seitz J, Bühren K, von Polier GG, Heussen N, Herpertz-Dahlmann B, Konrad K. Morphological changes in the brain of acutely ill and weight-recovered patients with anorexia nervosa. A meta-analysis and qualitative review. Z Kinder JugenPsychiatr Psychother 2014;42:7–17.
[19] Docx MKF, Gewillig M, Simons A, Vandenberghe P, Weyler J, Ramet J, et al. Pericardial effusions in adolescent girls with anorexia nervosa: clinical course and risk factors. Eat Disord 2010;18:218–25.
[20] Neumärker KJ, Dudeck U, Meyer U, Neumärker U, Schulz E, Schönheit B. Anorexia nervosa and sudden death in childhood: clinical data and results obtained from quantitative neurohistological investigations of cortical neurons. Eur Arch Psychiatry Clin Neurosci 1997;247:16–22.
[21] Frintrop L, Liesbrock J, Paulukat L, Johann S, Kas MJ, Tolba R, et al. Reduced astrocyte density underlying brain volume reduction in activity-based anorexia rats. World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry 2018;19:225–35.

[22] Bernardoni F, King JA, Geisler D, Stein E, Jaite C, Nätsch D, et al. Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: a longitudinal study. NeuroImage 2016;130:214–22.
[23] Nickel K, Joos A, Tebartz van Elst L, Matthis J, Holovics L, Endres D, et al. Recovery of cortical volume and thickness after remission from acute anorexia nervosa. Int J Eat Disord 2018;51:1056–69.
[24] Misra M, Tsai P, Anderson EJ, Hubbard JL, Gallagher K, Soyka LA, et al. Nutrient intake in community-dwelling adolescent girls with anorexia nervosa and in healthy adolescents. Am J Clin Nutr 2006;84:698–706.
[25] Holman RT, Adams CE, Nelson RA, Grater SJ, Jaskiewicz JA, Johnson SB, et al. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids. J Nutr 1995;125:901–7.
[26] McNamara RK, Asch RH, Lindquist DM, Krikorian R. Role of polyunsaturated fatty acids in human brain structure and function across the lifespan: an update on neuroimaging findings. Prostaglandins Leukot Essent Fatty Acids 2018;136:23–34.
[27] Marzola E, Nasser JA, Hashim SA, Shih P-AB, Kaye WH. Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. BMC Psychiatry 2013;13:290.
[28] Achamrah N, Coëffier M, Rimbert A, Charles J, Folope V, Petit A, et al. Micronutrient status in 153 patients with anorexia nervosa. Nutrients 2017;9.
[29] Bailer UF, Kaye WH. A review of neuropeptide and neuroendocrine dysregulation in anorexia and bulimia nervosa. Curr Drug Targets CNS Neurol Disord 2003;2:53–9.
[30] Ogiso K, Asakawa A, Amitani H, Nakahara T, Ushikai M, Haruta I, et al. Plasma nesfatin-1 concentrations in restricting-type anorexia nervosa. Peptides 2011;32:150–3.
[31] Warren MP. Endocrine manifestations of eating disorders. J Clin Endocrinol Metab 2011;96:333–43.
[32] van der Werff SJA, Andela CD, Nienke Pannekoek J, Meijer OC, van Buchem MA, Rombouts SARB, et al. Widespread reductions of white matter integrity in patients with long-term remission of Cushing's disease. NeuroImage Clin 2014;4:659–67.
[33] Castro-Fornieles J, Bargalló N, Lázaro L, Andrés S, Falcon C, Plana MT, et al. A cross-sectional and follow-up voxel-based morphometric MRI study in adolescent anorexia nervosa. J Psychiatry Res 2009;43:331–40.
[34] Fuglset TS, Landrø NI, Reas DL, Ø Rø. Functional brain alterations in anorexia nervosa: a scoping review. J Eat Disord 2016;4:32.
[35] Li W, Lai TM, Bohon C, Loo SK, McCurdy D, Strober M, et al. Anorexia nervosa and body dysmorphic disorder are associated with abnormalities in processing visual information. Psychol Med 2015;45:2111–22.
[36] Vocks S, Busch M, Grönemeyer D, Schulte D, Herpertz S, Suchan B. Neural correlates of viewing photographs of one's own body and another woman's body in anorexia and bulimia nervosa: an fMRI study. J Psychiatry Neurosci JPN 2010;35:163–76.
[37] Castellini G, Polito C, Bolognesi E, D'Argenio A, Ginestroni A, Mascalchi M, et al. Looking at my body. Similarities and differences between anorexia nervosa patients and controls in body image visual processing. Eur Psychiatry J Assoc Eur Psychiatry 2013;28:427–35.
[38] Miyake Y, Okamoto Y, Onoda K, Kurosaki M, Shirao N, Okamoto Y, et al. Brain activation during the perception of distorted body images in eating disorders. Psychiatry Res 2010;181:183–92.
[39] Mohr HM, Zimmermann J, Röder C, Lenz C, Overbeck G, Grabhorn R. Separating two components of body image in anorexia nervosa using fMRI. Psychol Med 2010;40:1519–29.
[40] Fladung A-K, Grön G, Grammer K, Herrnberger B, Schilly E, Grasteit S, et al. A neural signature of anorexia nervosa in the ventral striatal reward system. Am J Psychiatry 2010;167:206–12.
[41] Fladung A-K, Schulze UME, Schöll F, Bauer K, Grön G. Role of the ventral striatum in developing anorexia nervosa. Transl Psychiatry 2013;3:e315.
[42] Friederich H-C, Brooks S, Uher R, Campbell IC, Giampietro V, Brammer M, et al. Neural correlates of body dissatisfaction in anorexia nervosa. Neuropsychologia 2010;48:2878–85.
[43] Miyake Y, Okamoto Y, Onoda K, Shirao N, Okamoto Y, Otagaki Y, et al. Neural processing of negative word stimuli concerning body image in patients with eating disorders: an fMRI study. NeuroImage 2010;50:1333–9.
[44] Joos AAB, Saum B, van Elst LT, Perlov E, Glauche V, Hartmann A, et al. Amygdala hyperreactivity in restrictive anorexia nervosa. Psychiatry Res 2011;191:189–95.
[45] Gizewski ER, Rosenberger C, de Greiff A, Moll A, Senf W, Wanke I, et al. Influence of satiety and subjective valence rating on cerebral activation patterns in response to visual stimulation with high-calorie stimuli among restrictive anorectic and control women. Neuropsychobiology 2010;62:182–92.
[46] Brooks SJ, O'Daly O, Uher R, Friederich H-C, Giampietro V, Brammer M, et al. Thinking about eating food activates visual cortex with reduced bilateral cerebellar activation in females with anorexia nervosa: an fMRI study. PLoS One 2012;7:e34000.
[47] Oberndorfer T, Simmons A, McCurdy D, Strigo I, Matthews S, Yang T, et al. Greater anterior insula activation during anticipation of food images in women recovered from anorexia nervosa versus controls. Psychiatry Res 2013;214:132–41.
[48] Sanders N, Smeets PAM, van Elburg AA, Danner UN, van Meer F, Hoek HW, et al. Altered food-cue processing in chronically ill and recovered women with anorexia nervosa. Front Behav Neurosci 2015;9:46.
[49] Vocks S, Herpertz S, Rosenberger C, Senf W, Gizewski ER. Effects of gustatory stimulation on brain activity during hunger and satiety in females with restricting-type anorexia nervosa: an fMRI study. J Psychiatry Res 2011;45:395–403.
[50] Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci 2009;10:573–84.
[51] Frank GKW, Reynolds JR, Shott ME, Jappe L, Yang TT, Tregellas JR, et al. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol 2012;37:2031–46.
[52] Decker JH, Figner B, Steinglass JE. On weight and waiting: delay discounting in anorexia nervosa pretreatment and posttreatment. Biol Psychiatry 2015;78:606–14.
[53] Via E, Soriano-Mas C, Sánchez I, Forcano L, Harrison BJ, Davey CG, et al. Abnormal social reward responses in anorexia nervosa: an fMRI Study. PLoS One 2015;10:e0133539.

[54] Phillipou A, Abel LA, Castle DJ, Hughes ME, Gurvich C, Nibbs RG, et al. Self perception and facial emotion perception of others in anorexia nervosa. Front Psychol 2015;6:1181.
[55] Fonville L, Giampietro V, Surguladze S, Williams S, Tchanturia K. Increased BOLD signal in the fusiform gyrus during implicit emotion processing in anorexia nervosa. NeuroImage Clin 2014;4:266–73.
[56] de Zwaan M, Biener D, Bach M, Wiesnagrotzki S, Stacher G. Pain sensitivity, alexithymia, and depression in patients with eating disorders: are they related? J Psychosom Res 1996;41:65–70.
[57] Bär K-J, Berger S, Schwier C, Wutzler U, Beissner F. Insular dysfunction and descending pain inhibition in anorexia nervosa. Acta Psychiatry Scand 2013;127:269–78.
[58] McAdams CJ, Krawczyk DC. Impaired neural processing of social attribution in anorexia nervosa. Psychiatry Res 2011;194:54–63.
[59] Schulte-Rüther M, Mainz V, Fink GR, Herpertz-Dahlmann B, Konrad K. Theory of mind and the brain in anorexia nervosa: relation to treatment outcome. J Am Acad Child Adolesc Psychiatry 2012;51:832–841.e11.