Journal of Psychiatric Research 163 (2023) 337–349

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Can neuroimaging measures differentiate the disease course of anorexia nervosa? A systematic review

Katrien F.M. Bracké [a,b], Cathelijne P.M. Steegers [a], Tess van der Harst [a], Marjolein H.G. Dremmen [b], Meike W. Vernooij [b], Tonya J.H. White [a,b,c], Gwen C. Dieleman [a,*]

[a] Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands
[b] Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands
[c] Section of Social and Cognitive Developmental Neuroscience, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Keywords:
Anorexia nervosa
Neuroimaging
Magnetic resonance imaging
Prediction
Prognosis
Disease course

ABSTRACT

Anorexia nervosa (AN) entails many uncertainties regarding the clinical outcome, due to large heterogeneity in the disease course. AN is associated with global decrease in brain volumes and altered brain functioning during acute illness. However, it is unclear whether structural and functional brain alterations can predict clinical outcome. We aimed to systematically review the predictive value of volumetric and functional brain outcome measures of structural and functional brain magnetic resonance imaging (MRI) on the disease course of AN. Four databases (Embase, Medline, Psycinfo, and Cochrane Central Register) were systematically searched. A total of 15 studies (structural MRI: n = 6, functional MRI: n = 9) were reviewed. In total 464 unique AN patients, and 328 controls were included. Follow-up time ranged between 1 and 43 months. Structural neuroimaging studies showed that lower brain volumes of the cerebellum, subcortical grey matter, and cortical white matter at admission predicted a worse clinical outcome. A smaller increase of the anterior cingulate cortex volume in the early phase of the disease predicted a worse clinical outcome. Lower overall gyrification, and a higher clustering coefficient predicted a worse clinical outcome. Functional MRI studies showed that frontal, parietal and temporal activity during task-based algorithms predicted follow-up body mass index, although results were bidirectional possibly due to the large heterogeneity in methodological approaches. Neuroimaging measures may predict the clinical outcome of AN. However, there is a lack of replication studies. Future studies are needed to validate the prognostic utility of neuroimaging measures in AN patients, and should harmonize demographic, clinical and neuroimaging features in order to enhance comparability.

1. Introduction

Anorexia nervosa (AN) is a severe psychiatric disorder characterized by an extremely low body weight, excessive fear to gain weight, and a disturbed body image (AP, 2013). AN is associated with high rates of morbidity and has the highest mortality rate of all psychiatric disorders (Arcelus et al., 2011; Papadopoulos et al., 2009). The onset of the disorder is often during adolescence and has a lifetime prevalence of 1–4% in females, and 0.2–0.3% in males (Bulik et al., 2006; Galmiche et al., 2019). The course of the disease is heterogeneous, whereas a subset of patients have a short and milder disease course, e.g. recovery within a year and others have a prolonged illness with multiple relapses (Berkman et al., 2007; Steinhausen, 2002). The mean illness duration lasts approximately four years (Ruijter and Schoemaker, 2003). Although biological underpinnings of AN are widely recognized, the underlying disease mechanisms are not yet fully elucidated, which makes it difficult to treat and predict the disease course of AN during the acute phase of the disease (i.e. in a very early treatment phase focusing on weight recovery) (Kaye et al., 2013; Moskowitz and Weiselberg, 2017; Walton et al., 2022). Since AN is a serious mental disorder with a high disease burden and health-threatening consequences due to starvation, it is important to identify predictors of the clinical outcome in order to tailor interventions and improve clinical care for individual patients. In recent years, there has been an increasing interest in neuroimaging of the brain, not only as a method to unravel the neural underpinnings of AN, but also with the goal to predict prognosis.

* Corresponding author. Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Centre – Sophia Children's Hospital, P.O. Box 2060, 3015 GD, Rotterdam, the Netherlands.
E-mail address: g.dieleman@erasmusmc.nl (G.C. Dieleman).

https://doi.org/10.1016/j.jpsychires.2023.05.059
Received 24 February 2023; Received in revised form 20 April 2023; Accepted 16 May 2023
Available online 22 May 2023

Previous studies investigating predictors of other psychiatric disorders, i.e. major depressive disorder (MacQueen, 2009; McGrath et al., 2013; Siegle et al., 2012) or post-traumatic stress disorder (Bryant et al., 2008), suggested neuroimaging outcome measures as possible biomarkers for treatment response. The translation of volumetric and functional brain outcome measures as possible predictors for the disease course for patients with AN may be promising. It is already known that AN patients show alterations in brain structure and function during the acute phase of the disease (Castro-Fornieles et al., 2009; Collantoni et al., 2021; Fladung et al., 2013; Fuglset et al., 2016; Fujisawa et al., 2015; Garcia-Garcia et al., 2013; Horndasch et al., 2018; Kappou et al., 2021; Van den Eynde et al., 2012; Zhu et al., 2012). A recent meta-analysis reported that reductions in cortical volume and thickness are related to the clinical stage of the disease. The largest brain volume reductions were observed during the acute phase of the disease; whereas brain volume reductions were less severe in partially weight-restored patients (Walton et al., 2022). Structural brain volume reductions likely reflect malnutrition, rather than pointing to the underlying etiology of AN, which makes it challenging to assess brain structure separate from the effects of malnutrition. Another meta-analysis reported a reduction of grey matter volume of 4.6% and white matter volume of 2.7% in patients with acute AN compared to healthy controls (Van den Eynde et al., 2012). In AN patients, local grey matter volume reductions were found in the prefrontal and insular cortex, temporal and parietal lobes (Castro-Fornieles et al., 2009; Fujisawa et al., 2015; Kappou et al., 2021). Furthermore, patients with AN had lower overall gyrification (i.e. the degree of cortical folding) (Dubois et al., 2008; White et al., 2010), with in particular lower gyrification in the frontal lobe, sensorimotor region, and parieto-temporal regions compared to healthy controls (Collantoni et al., 2021).

Studies investigating functional magnetic resonance imaging (fMRI) of the brain have primarily utilized specific stimuli, such as food-, body-, and reward-related tasks related to the core clinical symptoms of AN (Garcia-Garcia et al., 2013; Zhu et al., 2012). In acutely ill AN patients, increased brain activity was found in multiple brain regions, including the prefrontal and cingulate cortex, insula and striatum, compared to healthy controls (Fladung et al., 2013; Fuglset et al., 2016; Horndasch et al., 2018). Most previous studies were cross-sectional, therefore it is still unclear whether these structural and functional brain alterations during the acute phase of the disease can predict the disease course. Longitudinal studies are critical to identify predictors of the disease course. Currently, neuroimaging outcome measures have no clinical use in the treatment of AN. Potentially, volumetric and functional brain outcome measures may help health care professionals identifying patients at high risk of a poor clinical course who need tailored therapeutic interventions.

To our knowledge, there are no studies that have systematically reviewed the predictive value of structural and functional MRI brain measures on the course of AN. Therefore, the present study aimed to conduct a systematic literature review of published studies to identify predictors of disease outcome of AN using MRI.

2. Methods

2.1. Search strategy

The following databases were searched up to February 10th, 2023: Excerpta Medica dataBASE (Embase), Medline (OvidSP), Web of Science, PsychINFO ovid, Cochrane Central Register, and Google Scholar using appropriate keywords (adjusted for the specific database, see supplementary material Appendix A): (I) "anorexia nervosa", (II) "Magnetic Resonance Imaging (MRI)", (III) "Clinical course" and (IV) "Prediction". Papers were categorized in (1) "structural MRI studies" and "functional MRI studies". Subsequently, selected articles were subdivided into two categories based on the outcome: "predictors of clinical outcome" (i.e. body mass index (BMI), eating disorder symptoms) and "predictors of correlates of eating disorders" (i.e. treatment response, task performance, cognitive abilities, comorbid psychiatric symptomatology).

2.2. Eligibility criteria

To be included in this review, studies had to fulfill the following criteria: (I) the study sample consists of patients diagnosed with AN according to Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III), DSM-IV, DSM-V or the International Classification of Diseases 10th Revision (ICD-10) criteria; (II) structural MRI outcome measures, (III) functional MRI outcome measures with either task-based neural activity or brain resting state connectivity, (IV) longitudinal study-design, (V) original research published in a peer-reviewed, indexed scientific journal, and (VI) article in English. All studies identified through database searching before February 10th, 2023 were considered. Studies were excluded when they described case series and case reports.

2.3. Quality assessment and retrieval process

The current systematic review was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). The systematic literature review was preregistered in the international prospective register of systematic reviews, PROSPERO, registration number CRD42021285402. The search strategy was developed together with a biomedical information specialist, specialized in conducting search strategies for systematic reviews. Eligibility was assessed by screening titles and abstracts by two independent investigators (KFMB, physician and PhD-student and MAA, psychologist and PhD-student). Through our systematic search we screened 529 articles, of which 494 were excluded on basis of title and abstract. We retrieved 35 full-text articles of which 15 were ultimately included in our systematic review. Disagreements (n = 3) were resolved through consensus by discussing the discrepancies and reevaluating the articles based on the eligibility criteria. See Fig. 1 for a PRISMA flow-chart of the study selection.

Quality assessment was performed using the Joanna Briggs Institute critical appraisal tool for case-control studies, which is an approved method of an international evidence-based research institution to assess the methodological quality taking into account the possibility of bias in the study design and analysis (Moola S et al., 2020). This tool consisted of 10 questions with *Yes, No, Unclear* or *Not applicable.* For our literature review only 7 questions were applicable, since we did not have an exposure. We adapted the tool in order to add relevant questions for the data of interest. Since it was not required to have a control group, we calculated an adjusted score as appropriate to the items. An overview of the quality/risk of bias assessment is displayed in Appendix B. The total adjusted score was 1.00 point. We considered a score >0.80 as good, 0.60–0.80 as fair and <0.60 as poor quality. The mean quality adjusted score was 0.89 (range 0.61–1.00), which is considered good quality. 13 studies were of good quality (Bodell et al., 2014; Boehm et al., 2021; Collantoni et al., 2019; DeGuzman et al., 2017; Dunlop et al., 2015; Favaro et al., 2015; Garrett et al., 2014; McCormick et al., 2008; Milos et al., 2021; Schulte-Ruther et al., 2012; Seidel et al., 2018; Seitz et al., 2015; Young et al., 2020). Two studies were of fair quality (Steward et al., 2022; Xu et al., 2017). In order to increase comparability between studies, effect sizes of the reviewed studies were converted to Cohen's *d* if applicable. Effect sizes of 0.2 were considered as small effect sizes, 0.5 as moderate effect sizes and 0.8 as large effect sizes (Cohen, 2013).

2.4. Data extraction

The study design, sample size, age at inclusion, sex, classification system (DSM-III, DSM-IV, DSM-V, ICD-10), follow-up time, duration of illness, type of measurement (functional or structural MRI) and outcome

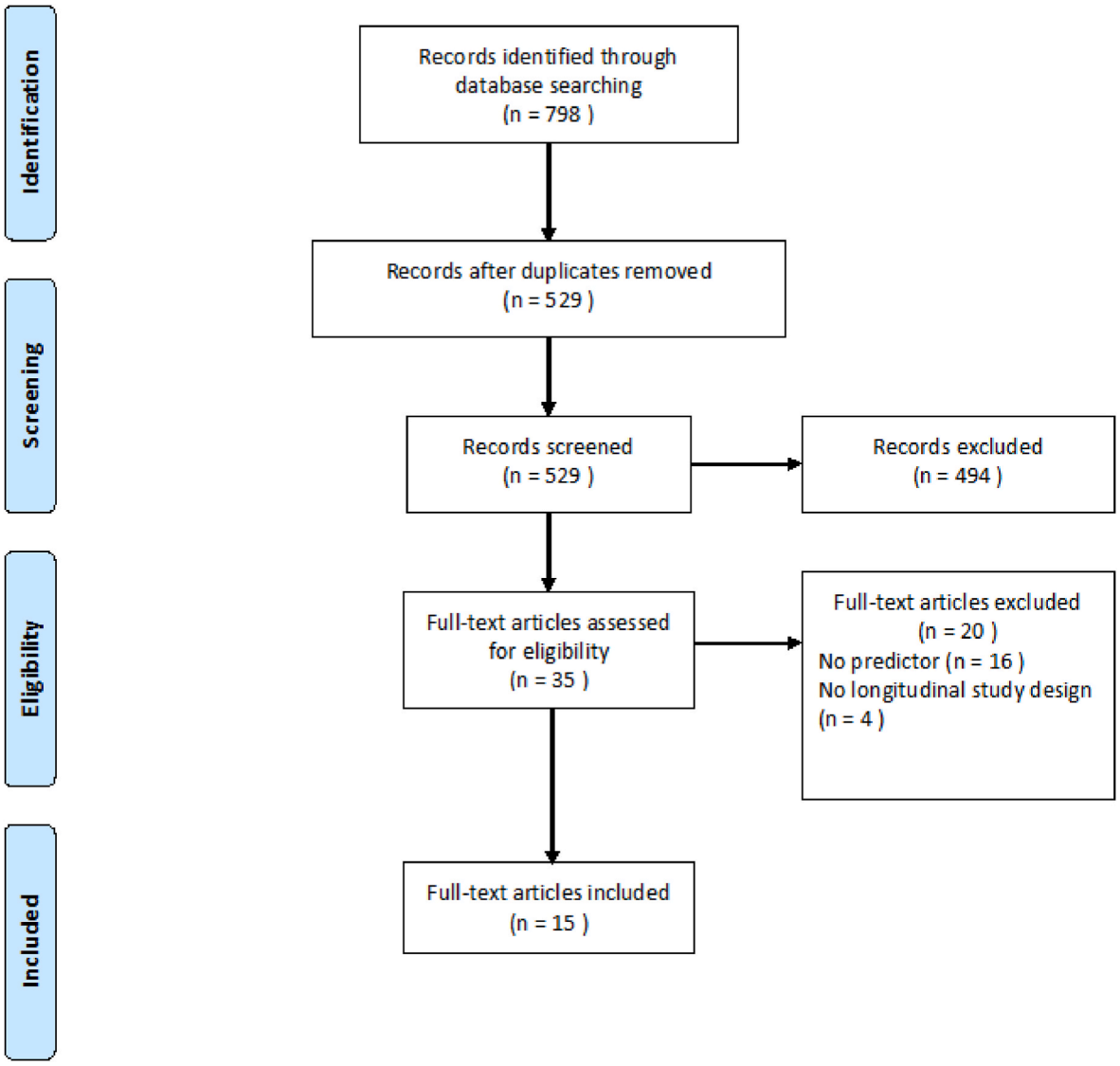

Fig. 1. PRISMA Flow-chart of study selection.

measures were extracted. Furthermore, the country and institution where the study was conducted was extracted. Searches were limited to studies published in English and were further assigned to either studies that investigate predictors of the clinical outcome or studies that investigate predictors of correlates of eating disorders.

3. Results

In this systematic review 15 articles were included. In total, 464 unique patients diagnosed with AN according to the DSM-criteria, and 328 controls were included. We retrieved six papers that focused on structural MRI and nine papers that examined functional MRI. Of these, 11 papers focused on predictors of clinical outcome. Four papers assessed the predictive value of correlates of eating disorders. Characteristics of the included articles are presented in Table 1.

3.1. Structural MRI studies

Six structural neuroimaging studies reported data on the predictive value of volumetric measures and the gyrification pattern on the course of AN (Table 2). Five papers focused on adults and one paper focused on adolescents. These studies were subdivided into studies focusing on clinical outcome (n = 5) and studies focusing on correlates of eating disorders (n = 1). Overall, the studies included 204 patients with AN and 126 controls. Mean duration of illness was 5.2 years (range 1.0–6.6) and mean follow-up time was 22.2 months (range 6–42). Results of the included articles are presented in Fig. 2.

3.1.1. Predictors of clinical outcome

McCormick et al. (McCormick et al., 2008) performed a study in adult AN patients admitted to the hospital and they investigated the association between anterior cingulate cortex (ACC) volume change between admission and weight recovery (varying from 56 to 196 days after admission), and clinical outcome after one year of follow-up. They selected the ACC, because previous studies (Naruo et al., 2001; Takano et al., 2001) found altered brain activity in the ACC in patients with AN. McCormick et al. (2008) showed that at follow-up, the volume change of the right dorsal ACC between admission and weight restoration was predictive of the clinical outcome, i.e. a greater increase in ACC volume shortly after weight recovery predicted sustained remission of weight at follow-up. In addition, a smaller increase in the volume of the right dorsal ACC between admission and weight restoration predicted a higher rate of relapse (defined as a BMI <18 kg/m^2) at follow-up. These results remained significant even after controlling for total grey matter volume change. The ACC volume change between admission and weight recovery did not predict BMI at follow-up (McCormick et al., 2008).

Table 1
Characteristics of included studies.

Author (year)	Study design	Country	Participants (N)	Age AN Group (Years)	Classification system	Female (%)	Mean BMI AN group (Kg/m^2)	Follow-up time (Months)	Duration of Illness (Years)
Structural MRI studies									
Bodell et al. (2014)	Longitudinal Case-control	USA	AN-R: 4 AN-BP: 17 HC: 20	25.6 (5.8)	DSM-IV	100	15.8 (2.3)	–	5.9
McCormick et al. (2008)	Longitudinal Case-control	USA	AN: 18 HC: 18	25.2 (7.3)	DSM-III-R	67	13.5 (2.1)	12	6.5
Seitz et al. (2015)	Longitudinal Case-control	Germany	AN: 56 HC: 50	15.5 (1.7)	DSM-IV	100	15.1 (1.4)	12	1.0
Collantoni (2019)[A]	Longitudinal Case-control	Italy	AN: 38 ANwr: 20 HC: 38	26.1 (7.2) 26.3 (7.1)	DSM-IV	100	15.8 (1.8) 19.6 (1.6)	42 38	6.6 3.8
Favaro (2015)[A]	Longitudinal Case-control	Italy	AN:38 ANwr: 20 HC:38	26.1 (7.2) 26.3 (7.1)	DSM-IV	100	15.8 (1.8) 19.6 (1.6)	42 38	6.6 3.8
Milos et al. (2021)	Longitudinal	Switzerland	AN-R: 42 AN-BP: 8	22.2 (4.1)	ICD-10	–	14.3 (1.0)	6	6.3
Functional MRI studies									
Boehm et al. (2021)	Longitudinal Case-control	Germany	AN:35 ANwr: 33 HC: 58	16.2 (3.5) 22.2 (3.5)	DSM-V	100	14.6 (1.5) 20.7 (1.7)	12	1.1 4.9
DeGuzman et al. (2017)	Longitudinal Case-control	USA	AN: 21 HC: 21	15.2 (2.4)	DSM-V	100	20.4 (2.4)	1	–
Dunlop et al. (2015)	Longitudinal	Canada	AN-BP:11 BN: 17	31.1 (9.5)	DSM-V	93	19.1 (5.3)	2	14.8
Garrett et al. (2014)	Longitudinal	USA	AN:21	23.4 (5.7)	DSM-IV	100	17.4 (1.1)	4	7.1
Schulte-Rüther (2012)	Longitudinal Case-control	Germany	AN: 19 HC: 21	15.7 (1.5)	DSM-V	100	15.3 (1.5)	12	–
Seidel et al. (2018)	Longitudinal Case-control	Germany	AN: 35 HC: 35	16.5 (3.7)	DSM-V	100	14.7 (1.3)	3	0.9
Xu et al. (2017)	Longitudinal Case-control	USA	AN: 24 HC: 18	16.4 (2.0)	DSM-IV	100	19.5 (1.9)	21	2.3
Steward et al. (2022)	Longitudinal Case-control	UK	AN: 22 (AN-R/BP: 18/4) HC: 21	22.2 (4.5)	DSM-V	100	16.3 (1.1)	3	3.9
Young et al. (2020)	Longitudinal Case-control	UK	AN:16 HC:21	31.4 (11.2)	DSM-IV	100	15.9 (1.3)	1	15.4

Characteristics of included studies are reported as means and standard deviations (SD) or frequencies. AN: anorexia nervosa; BN: Bulimia Nervosa; AN-R: anorexia nervosa restrictive subtype; AN-BP: anorexia nervosa binge-purge subtype; ANwr: weight-restored anorexia patients; ANnr: non-weight restored anorexia patients; BMI: body mass index; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD-10: International Classification of Diseases 10th Revision; HC: healthy controls; UK: United Kingdom; USA: United States of America. [A] Studies utilized the same patient sample.

The studies of Favaro and Collantoni (Collantoni et al., 2019; Favaro et al., 2015) used the same patient sample and investigated the predictive role of the gyrification pattern on clinical outcome after three years of follow-up. Both studies investigated 38 patients with AN and 38 healthy controls. Favaro et al. (2015) found that AN patients with a poor outcome after three years of follow-up had a significantly lower baseline overall gyrification compared to both healthy controls and AN patients who recovered. The results remained significant even after correction for other clinical prognostic factors and duration of illness. Recovered patients were defined as having normal weight, absence of body dissatisfaction and excessive physical activity, and regular menses for at least three months. On the other hand, in the AN group a lower degree of gyrification in the left superior parietal lobe and right postcentral gyrus were predictive for identifying patients with a worse clinical outcome (Favaro et al., 2015). The study of Collantoni et al. investigated the predictive value of both cortical thickness based networks and gyrification based networks using structural covariance analysis. They performed a structural MRI scan at baseline and assessed clinical symptoms after three years of follow-up. Analysis of the cortical based networks revealed that a higher clustering coefficient (i.e. the degree of connectivity in a node's neighborhood) (Watts and Strogatz, 1998) of the cortical thickness of the left inferior frontal gyrus predicted a poor clinical outcome after three years of follow-up. The degree of connectivity in a node's neighborhood was determined by the number of connected triangles around one individual node, which can be interpreted as a degree of redundancy of an individual node. The higher the degree of redundancy, the less distinctive information the individual node added to the network (Costantini and Perugini, 2014). In addition, both global and local gyrification measures were predictive of clinical outcome after three years of follow-up. A higher overall clustering coefficient in gyrification-based networks predicted a poorer outcome. At regional level, a higher clustering of the left superior temporal gyrus and a lower clustering of the insula predicted a poorer outcome after three years of follow-up. A higher characteristic path length (i.e. the average shortest path length between all pairs of nodes) (Watts and Strogatz, 1998) of the gyrification was associated with poor outcome, and tended towards significance. A higher characteristic path length indicated a less efficient transmission of information (Lee and Mashour, 2018). Global cortical thickness measures had no predictive value for the clinical outcome (Collantoni et al., 2019).

In adult inpatients with severe AN, Milos and colleagues (Milos et al., 2021) used a voxel-based whole-brain approach in order to investigate the predictive role of local grey matter volume at admission on treatment outcome. All patients followed an intensive treatment program focusing on weight recovery. A favorable treatment outcome was defined as a BMI $\geq$17.5 kg/m^2. They performed a T1-weighted MRI scan at admission and divided the patient group in either a group patients which achieved a BMI$\geq$17.5 kg/m^2 and a group patients which did not

Table 2a
Structural MRI studies – clinical outcome.

Author (year)	Method	Data analyses	Regions of interest	Outcome	Predictors of clinical outcome	Effect size (Cohen's *d*)
McCormick et al. (2008)	MRI 1.5T	T1-weighted; 3-D spoiled gradient recall acquisition sequence	8 regions in ACC; 4 subregions per hemisphere – rostral, subcallosal, subgenual and left and right dorsal	BMI	A greater increase in ACC volume shortly after weight recovery predicted sustained remission of weight after one-year of follow-up. On the other hand, a smaller increase in the volume of the right dorsal ACC over time predicted relapse after one-year of follow-up.	0.65
Seitz et al. (2015)	MRI 3T	T1-weighted; magnetization-prepared rapid acquisition with gradient echo (MPRAGE)	Cortical white and grey matter; subcortical white and grey matter; cerebellar grey and white matter	BMI-SDS	A lower 1. Subcortical grey matter 2. Cortical white matter (located above the brain stem), and 3. Cerebellar white matter predicted a lower BMI-SDS after one year follow-up.	 1.63 1.59 1.49
Collantoni et al. (2019)[A]	MRI 1.5T	T1-weighted gradient-echo sequence	Cortical thickness and gyrification pattern	Eating disorder symptoms	1.A higher clustering coefficient of 1.1 Cortical thickness of the left inferior frontal gyrus 1.2 Overall gyrification, especially in the left superior temporal gyrus 2. A lower level of connected edges in the gyrification of the insula predicted a poor outcome after three years of follow-up	–
Favaro (2015)[A]	MRI 1.5T	T1-weighted gradient-echo sequence	Gyrification pattern	Eating disorder symptoms	Significantly lower gyrification at baseline in the 1. Left hemisphere 2. Right hemisphere 3. Left superior parietal cluster 4. Right postcentral cluster predicted a poor clinical outcome after three years of follow-up, after correction for age (of onset), BMI and illness duration	 0.91 0.74 0.80 0.68
Milos et al. (2021)	MRI 3T	T1-weighted 3D Turbo-Field-Echo sequence	Grey matter volume	BMI-SDS	A lower volume of the right cerebellum (crus I) predicted a worse clinical outcome, i.e. less weight gain during therapy.	-

ACC: anterior cingulate cortex; BMI-SDS: body mass index-standard deviation score; MRI: magnetic resonance imaging;. [A] Studies utilized the same patient sample.

Table 2b
Structural MRI studies – correlates of eating disorder.

Author (year)	Method	Data analyses	Regions of interest	Outcome		Effect size (Cohen's *d*)
Bodell et al. (2014)	MRI 3T	T1- and T2-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE)	Total cerebral cortex grey matter volume; left and right medial and lateral OFC	Decision making skills	OFC volume at baseline did not predict decision-making skills assessed by the IGT at follow-up.	-

IGT: Iowa Gambling Task; MRI: magnetic resonance imaging; OFC: orbitofrontal cortex.

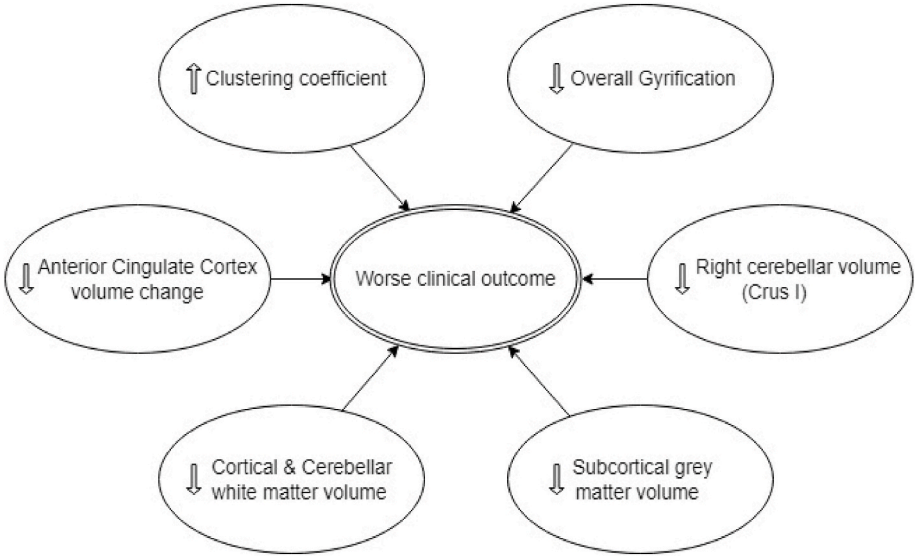

Fig. 2. Summary of main results of structural MRI papers. This figure depicts the main conclusions of the reviewed articles (n = 5) concerning the predictive role of structural MRI on the clinical outcome of patients with anorexia nervosa.

achieve weight recovery. The follow-up period was equal to treatment duration. For weight recovered patients the mean treatment duration was six months; the mean treatment duration for non-weight recovered patients was 2.5 months. They found that a smaller grey matter cluster volume in crus I (anterior part of the cerebral peduncle) located in the right cerebellum at admission predicted a less favorable clinical outcome, i.e. less weight gain during treatment. Ventricular cerebrospinal fluid, local grey, and white matter volume at admission did not predict treatment outcome (Milos et al., 2021).

In adolescent inpatients with AN, only one study using structural brain MRI was performed. Seitz and colleagues (Seitz et al., 2015) assessed the clinical relevance of brain volume reductions at admission in adolescents with AN on the clinical outcome after one-year of follow-up. They demonstrated that lower subcortical grey matter, and cortical - and cerebellar white matter volumes predicted a poorer clinical outcome, defined as low BMI-standard deviation score (BMI-SDS). These results were consistent with the study of Milos et al. (2021), who found that a lower grey matter volume in the cerebellum at admission predicted a poor treatment outcome in adult inpatients with AN. In adolescents, cortical - and cerebellar grey matter volume at baseline did not predict the clinical outcome (Seitz et al., 2015).

3.1.2. Predictors of correlates of eating disorder

The study of Bodell et al. (Bodell et al., 2014) examined decision-making skills using the Iowa Gambling Task (IGT) in 22 patients with AN during the acute phase of the disease and after weight recovery. The IGT was designed to stimulate decision-making under specific conditions, including reward, punishment and uncertainty. They discovered that the left medial orbitofrontal cortex (OFC) volume was positively correlated with IGT scores at baseline after correction for BMI. However, OFC volume at baseline did not predict decision-making skills after weight recovery (Bodell et al., 2014).

3.2. Functional MRI studies

Nine studies reported data concerning the predictive value of functional brain outcome measures on the course of AN. Overall, the studies included 260 patients with AN and 202 controls. Mean duration of illness was 6.8 years (range 0.9–15.4) and mean follow-up time was 6.6 months (range 1–21). Four papers focused on adults, four on adolescents, and one paper included both adults and adolescents. Six articles focused on predictors of clinical outcome and three studies focused on predictors of correlates of eating disorders. Results of the included articles are presented in Table 3 and Fig. 3.

3.2.1. Predictors of clinical outcome

Steward and colleagues (Steward et al., 2022) performed an emotion regulation task during brain scanning, in both young patients with AN receiving day-hospital treatment versus healthy controls. They showed that a higher activity in the dorsolateral prefrontal cortex (DLPFC) during the emotion regulation task in AN patients predicted a more favorable clinical outcome, in terms of a larger increase in BMI and body fat mass percentage after 12 weeks of treatment. DLPFC-amygdala connectivity did not predict BMI and body fat percentage after 12 weeks of follow-up (Steward et al., 2022).

Seidel and colleagues (Seidel et al., 2018) performed an emotion regulation task during fMRI after an overnight fast in AN patients during acute illness and in healthy controls. Data concerning both physical health and psychometrics were collected at baseline, and after 30, 60 and 90 days after admission. They showed that lower ventral striatum (VS) activity in AN patients during an emotion regulation paradigm at baseline predicted a worse clinical outcome at follow-up after 60 and 90 days follow-up. A worse clinical outcome was defined as a lower BMI-SDS at follow-up corrected for BMI-SDS and eating disorder severity at baseline (Seidel et al., 2018).

Four articles reported data on the predictive value of functional brain outcome measures performed in adolescents with AN. Two studies used a comparable task paradigm involving social evaluations. One study investigated AN patients which were admitted to the hospital during the acute phase of the illness. They utilized a social attribution task, which was designed to test the subjects' capability to understand the mental states of other individuals. This task was performed shortly after admission to the hospital and after weight restoration at discharge. One year after admission, the clinical outcome of patients was assessed using the Morgan-Russel Average Outcome Score (MRAOS). This assessment investigated psychometrics subdivided into five subscales, including: mental state, nutritional state, menstrual function, socioeconomic status and sexual adjustment. Lower brain activity in a part of the right medial PFC during the social attribution task at baseline predicted a poor clinical outcome at one-year of follow-up according the MRAOS (Schulte-Ruther et al., 2012). Xu and colleagues (Xu et al., 2017) performed a similar task in both acute ill and recovered AN patients. During the task, patients had to reflect on their own thoughts, their friends' thoughts, and reflect on their own thoughts from another perspective. They found that a higher neural activity in the posterior cingulate cortex and precuneus for friend evaluations, rather than for self-evaluations in adolescents, predicted recovery. AN patients were considered as recovered when they were weight-recovered, had adequate control of their eating disorder symptoms, maintained school/work since the last MRI-visit, and received no treatment, including outpatient treatment, one year after finishing the study. In addition, a trend was observed towards a higher activation in either the cluster in the medial prefrontal cortex (mPFC) and the dorsal anterior cingulate cortex (dACC) and the mPFC-Cingulate cluster among recovered patients at follow-up, compared to those that remained ill. There was no relationship between clinical outcome and differences in neural activity during the tasks for self-reflection and reflecting on their own thoughts from another perspective (Xu et al., 2017).

A third study investigated the association between neural representations/responses during a reward-related task and treatment outcome assessed with MRAOS in acutely ill AN patients, recovered AN patients, and healthy controls. They identified neural patterns measured via multivariate-pattern analyses, which is a method that discovers patterns of neural activation in the brain. Via this method, different categories of stimuli could be decoded via neural activations. During brain MRI participants passively viewed social-, food- and neutral stimuli. They found that a higher accuracy of the classification of food-stimuli vs. neutral stimuli in the fusiform gyrus in acute ill AN patients predicted a more favorable clinical outcome, in terms of a higher score on the MRAOS, one year after follow-up (Boehm et al., 2021).

DeGuzman et al. (DeGuzman et al., 2017) utilized a reward task in female adolescents with AN during fMRI at two timepoints: before and after treatment. They used a computational model to predict reward response (receipt and omission). The response was based on dopamine response in the brain during the task. A positive prediction error implicated a phasic burst of neural activity in dopamine neurons after an unexpected reward. On the other hand, a negative prediction error response implicated a dip in dopamine response after an unexpected reward. They found that a higher activation of the middle orbitofrontal cortex during the monetary reward expectation task before treatment predicted a lower BMI increase at follow-up. Higher caudate prediction error values before treatment predicted a lower BMI at discharge. Furthermore, they found that a higher prediction error response in the substantia nigra was related to a longer duration of treatment. In addition, lower levels of prediction error response in the head of the caudate predicted a higher rate of weight gain. BMI change during treatment was not predicted by the level of prediction-error at baseline (DeGuzman et al., 2017).

3.2.2. Predictors of correlates of eating disorder

Garrett et al. (Garrett et al., 2014) used both a set-shifting and a central coherence task during fMRI. It was shown that patients with AN

Table 3a
Functional MRI studies – clinical outcome.

Author	Task-paradigm	Task description	Method	Data analyses	Regions of Interest	Outcome	Predictors of clinical outcome	Effect size (Cohen's *d*)
Boehm et al. (2021)	Reward related task	During fMRI, multiple food-, social- and neutral stimuli were presented to participants either supraliminally or subliminally	MRI 3T	Predefined regions of interest	Fusiform gyrus, cuneus, parahippocampal gyrus	Eating disorder symptoms	Higher accuracy of the classification of food-stimuli vs. neutral stimuli in the fusiform gyrus predicted a favorable clinical outcome after one year of follow-up	0.04
DeGuzman et al. (2017)	Reward task	During fMRI, three monetary unconditioned stimuli were presented: win, no-win, or neutral. Participants acquired skills in differentiating single visual conditioned stimuli with the unconditioned stimuli	MRI 3T	Predefined regions of interest	OFC, ventral and dorsal anterior insula, posterior insula, caudate body and head, substantia nigra, ventral caudate/nucleus accumbens	BMI/ Treatment duration	Higher activation of the middle OFC during the reward task predicted a lower BMI increase at follow-up. Higher caudate prediction error values before treatment predicted a lower BMI at follow-up. A higher prediction error response in the substantia nigra predicted a longer treatment duration. Lower levels of prediction error response in the caudate head predicted an increased rate of weight gain	1.77 0.97 1.53 2.12
Schulte-Rüther et al. (2012)	Social attribution task	During fMRI, three white figures (circle, triangle, and diamond) were presented while moving on a black background. Participants had to decide whether the shapes were "friends" or not.	MRI 3T	Predefined regions of interest and whole-brain analyses	Superior and middle temporal gyrus and the temporal pole	Eating disorder symptoms	Lower activity in the medial PFC during a theory-of-mind task predicted a worse clinical outcome at one-year follow-up.	-
Xu et al. (2017)	Social evaluation task	During fMRI, participants were asked to read and respond to statements regarding thinking about oneself, one's friend, or what one's friend thinks of her.	MRI 3T	Predefined regions of interest	Left and Right Inferior Frontal Gyrus, medial PFC-dorsal ACC, medial PFC-Cingulate	BMI/Eating disorder symptoms	A higher neural activity in the posterior cingulate cortex and precuneus for friend evaluations, relative to self-evaluations predicted recovery.	1.58
Steward et al. (2022)	Emotion regulation task	The fMRI-task consisted of three conditions: 'LookNeutral', 'LookNegative' and 'Regulate'. Based on the condition, participants were asked to react in a specific way and apply their acquired reappraisal skills.	MRI 3T	Whole-brain analyses	Frontal -, temporal -, occipital -, and parietal lobe, amygdala, thalamus, insula, caudate, cerebellum	BMI/Body composition	A higher activity in the DLPFC during an emotion regulation task predicted 1. a higher body mass index 2. a higher body fat mass percentage after 12 weeks of treatment.	 1.07 1.54
Seidel et al. (2018)	Emotion regulation task	During fMRI, participants were instructed to either passively view positive, negative and neutral stimuli or to actively downregulate their emotions when viewing positive or negative pictures.	MRI 3T	Predefined regions of interest	Bilateral ventral striatum	BMI-SDS	A lower ventral striatum activity during an emotion regulation paradigm at baseline was predictive for a worse clinical outcome after respectively 1. 60 days follow-up and 2. 90 days follow-up	 −0.77 −1.07

ACC: anterior cingulate cortex; BMI: body mass index; dmPFC: dorsomedial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; fMRI: functional magnetic resonance imaging. OFC: orbitofrontal cortex; PFC: prefrontal cortex; rTMS: repetitive Transcranial Magnetic Stimulation; VLPFC: ventrolateral prefrontal cortex.

Table 3b
Functional MRI studies – correlates of eating disorder.

Author	Task-paradigm	Task description	Method	Data analyses	Regions of Interest	Outcome	Predictors of correlates of eating disorder	Effect size (Cohen's *d*)
Dunlop et al. (2015)	Resting state functional MRI	Patients were asked to have their eyes closed during the MRI scan.	MRI 3T	Seed-based	Dorsomedial PFC and dorsal ACC	Treatment response to rTMS	Lower functional connectivity in respectively 1. dmPFC-insula 2. dmPFC-OFC 3. dACC-insula before treatment was an indicator for good response (binge/purge improvement) on rTMS.	 −0.93 −1.04 −0.82
Garrett et al. (2014)	Set-shifting and central coherence task	The set shifting task was based on the Wisconsin Card Sort Task (Lie et al., 2006) and adjusted for fMRI. The central coherence task was based on an embedded figures task (Lee et al., 2007).	MRI 3T	Voxel-based whole-brain analyses	DLPFC, VLPFC, fysiform gyrus, insula, caudate, anterior middle frontal, occipital, - temporal and - parietal cortex, fusiform, cerebellum, precuneus	Set-shifting and central coherence abilities	A combination of 1. higher anterior middle frontal activation 2. and lower VLPFC/insula activation during the set-shifting task predicted improvement of set-shifting abilities after 16 weeks of follow-up.	 2.00 2.92
Young et al. (2020)	Food-related task	During fMRI, food-stimuli and non-food stimuli were presented in random order. After a set of images participants were asked how anxious they feel.	MRI 1.5T	Predefined regions of interest and whole-brain analyses	Amygdala, insula, DLPFC, medial OFC and ACC	Food-anxiety	A higher neural activity in the insula prior to treatment predicted lower self-reported food-anxiety in patients with anorexia nervosa after treatment.	-

ACC: anterior cingulate cortex; BMI: body mass index; dmPFC: dorsomedial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; fMRI: functional magnetic resonance imaging; OFC: orbitofrontal cortex; PFC: prefrontal cortex; rTMS: repetitive Transcranial Magnetic Stimulation; VLPFC: ventrolateral prefrontal cortex.

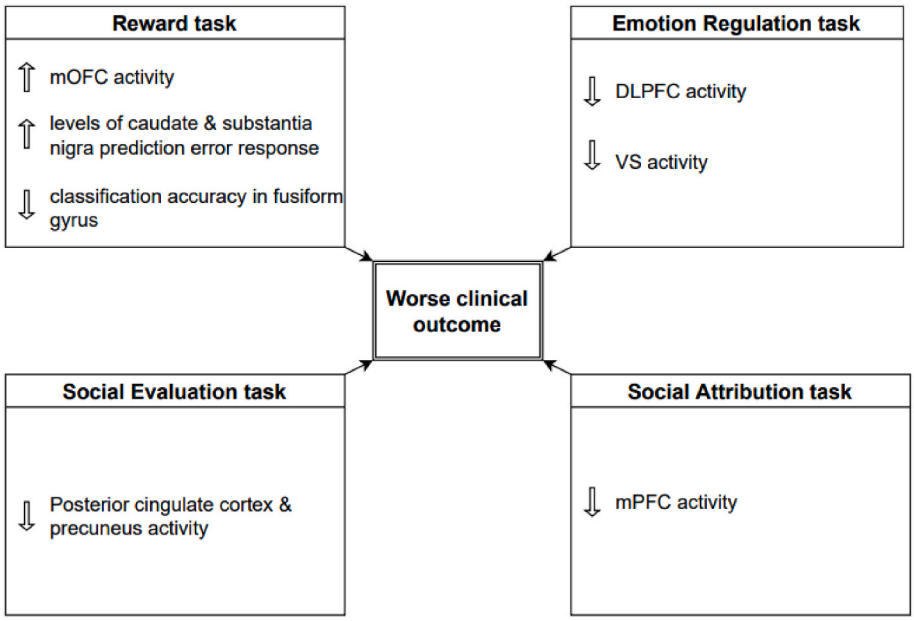

Fig. 3. Summary of main results of functional MRI papers. This figure depicts the main conclusions of the reviewed articles (n = 6) concerning the predictive role of fMRI on the clinical outcome of patients with anorexia nervosa. mOFC: medial orbitofrontal cortex; DLPFC: dorsolateral prefrontal cortex; VS: ventral striatum; mPFC: medial prefrontal cortex.

had deficits in central coherence and set-shifting abilities during the acute phase of the disease. The goal of this study was to analyze the predictive value of set-shifting and central coherence tasks after 16 weeks of treatment among patients with AN. They found that a combination of higher anterior middle frontal activation and lower ventrolateral prefrontal cortex (VLPFC) activation during the set-shifting task at baseline predicted improvement of set-shifting abilities at follow-up. During the central coherence task a significant change in brain activation was found in the left superior frontal gyrus, superior parietal lobe, and bilateral posterior occipital lobe. However, these local changes in brain activation did not correlate with changes in task performance, physical or neuropsychological outcome. Therefore the central

coherence task had no predictive value for the clinical course (Garrett et al., 2014).

Young et al. (Young et al., 2020) investigated the association between neural activity and self-reported food anxiety in a small sample of patients with AN following multiple sessions of food-exposure therapy. A food-related task was assessed during the MRI scan before and after food-exposure therapy. Before treatment, AN patients had a lower activity in the ACC compared to the control group. A higher neural activity in the insula prior to treatment predicted lower self-reported food-anxiety in subjects with AN. Neural activity in the ACC did not predict changes in eating disorder symptomatology.

Dunlop et al. (Dunlop et al., 2015) focused on the predictive value of resting state functional connectivity on treatment response to repetitive transcranial magnetic stimulation (rTMS) in AN patients. The application of rTMS is a novel and alternative approach in the treatment of eating disorders (Duriez et al., 2020). rTMS has been widely used and showed promising results in several other psychiatric disorders, including major depressive disorder (Somani and Kar, 2019), obsessive-compulsive disorder (Liang et al., 2021) and substance use disorder (Zhang et al., 2019). rTMS is a non-invasive technique that induces changes in brain activity using electromagnetic pulses through the scalp (Klomjai et al., 2015). Previous fMRI-studies showed that AN patients have altered resting state connectivity in multiple brain circuitries (e.g. default mode network, executive control network), which may be linked to the core AN symptoms (Gaudio et al., 2016). Therefore, several studies explored the application of rTMS in AN patients (Dalton et al., 2021; McClelland et al., 2016). In the study of Dunlop et al. both patients with bulimia nervosa and the binge-purge AN subtype were investigated and underwent two MRI sessions; one session prior to rTMS and one after rTMS. No separate analyses were performed for both subtypes. Nor was there any blinding or randomization either. Good responders to rTMS were defined as having a decrease of more than 50 percent in binge and purge episodes after four weeks rTMS treatment. From the dorsomedial PFC (dmPFC) seed, both a lower connectivity between the and dmPFC-OFC, and dmPFC-insula at baseline were predictors of good response on rTMS. A lower connectivity between dACC-insula at baseline was also a predictor of good response (Dunlop et al., 2015).

4. Discussion

Since to our knowledge there have been no prior systematic reviews exploring the predictive role of volumetric and functional brain outcome measures on clinical outcomes in AN (i.e. BMI, eating disorder symptomatology) and the correlates of AN (i.e. treatment response, task performance, cognitive abilities, comorbid psychiatric symptomatology), it was our goal to provide a current comprehensive review of the literature related to this topic. There was a large heterogeneity between studies, which made it difficult to pool the results. Overall, there was little overlap in the identified brain outcome measures that were predictive for the disease course between structural and functional neuroimaging studies. Structural neuroimaging studies identified primarily global brain outcome measures that were predictive for the disease course, whereas functional neuroimaging studies identified primarily local brain outcome measures, related to the specific task-paradigm. Structural neuroimaging studies showed that lower brain volumes of the cerebellum, subcortical grey matter, and cortical white matter at admission predicted a worse clinical outcome (Milos et al., 2021; Seitz et al., 2015). In addition one study demonstrated that decreased ACC volume shortly after admission predicted a less favorable clinical outcome (McCormick et al., 2008). Furthermore, lower overall gyrification and a higher clustering coefficient in structural brain MRI scans were predictive for a poorer outcome. A lower degree of connectedness in measures of gyrification in the insula specifically predicted a worse clinical outcome (Collantoni et al., 2021; Favaro et al., 2015). During the task-paradigms lower brain activity in the DLPFC, mPFC, posterior cingulate cortex, VS and precuneus predicted an unfavorable clinical outcome (Schulte-Ruther et al., 2012; Steward et al., 2022; Xu et al., 2017). Higher brain activity in the mOFC predicted a worse outcome (Schulte-Ruther et al., 2012; Seidel et al., 2018). In addition, one study used a computational model to predict reward response based on dopamine activity in the brain, and they showed that higher levels of caudate, and substantia nigra prediction error dopamine response predicted a less favorable outcome (DeGuzman et al., 2017). Another study identified neural patterns associated with clinical outcome and found that a lower classification accuracy in the fusiform gyrus predicted a less favorable clinical outcome (Boehm et al., 2021). Effect sizes of the studies were moderate to large (0.65–1.63), which are quite high for fMRI studies. This raises questions regarding the possibility of false positives. Thus, replication studies will be crucial to support the moderate to large effect estimates in these studies.

Studies evaluating the predictors of correlates of eating disorders found that lower brain activity in PFC-insula, OFC-PFC and ACC-insula predicted a favorable treatment (rTMS) response (Dunlop et al., 2015). Furthermore, a higher anterior middle frontal activation and a lower VLPFC/insula activation predicted an improvement in set-shifting abilities (Garrett et al., 2014). A higher brain activity in the insula predicted lower levels of food-anxiety at follow-up (Young et al., 2020).

4.1. Structural MRI studies

Two studies (Milos et al., 2021; Seitz et al., 2015) showed that a lower cerebellar volume (grey and white matter) at admission predicted a lower BMI-SDS at follow-up (range follow-up time: 2.5–12 months). A lower cortical white matter, and subcortical grey matter volume also predicted a lower BMI-SDS after one year of follow-up (Seitz et al., 2015). Previous studies showed that brain changes are dependent of the stage of the disease and often fully resolve with re-nutrition (Katzman et al., 1997; Roberto et al., 2011; Walton et al., 2022). These findings seems to support that an increase in ACC volume shortly after weight recovery predicted sustained weight recovery after one-year of follow-up (McCormick et al., 2008). Previous cross-sectional studies found lower ACC volumes in patients with acute AN which were linked to the key features of AN (Gaudio et al., 2015; Geisler et al., 2017; Lee et al., 2014).

The ACC has been implicated in several cognitive functions, e.g. emotion regulation, working memory, planning and organizing, and effective coping styles (Etkin et al., 2011; Gu et al., 2010; Mulert et al., 2008; Stevens et al., 2011). It is known that effective coping mechanisms play an important role in daily life, e.g. dealing with stressful events. Effective emotional self-regulation in patients with AN is beneficial in accomplishing treatments goals, and therefore enhances clinical outcome (Hernando et al., 2019). Due to alterations in the ACC AN patients may be less able to learn from their own experiences, which hinders the efficacy of the treatment. Thus, a focus on different elements of the ACC in patients with AN will be important to parse the role of this region in the clinical characteristics of AN.

Two studies performed in adult AN patients reported that a lower degree of gyrification at baseline predicted a worse clinical outcome after three-years of follow-up (Collantoni et al., 2019; Favaro et al., 2015). Abnormalities in the gyrification pattern have been found in multiple psychiatric diseases, such as major depressive disorder, schizophrenia, bipolar disorder, and autism spectrum disorder (Alemany et al., 2021; Ansorge et al., 2007; Blanken et al., 2015; Durkut et al., 2022; Fornito et al., 2007; Koolschijn and Geurts, 2016; Weinberger, 1987; White et al., 2003; White and Gottesman, 2012). Abnormal gyrification patterns are thought to reflect neurodevelopmental pathology, since the cortical folding occurs during the gestational phase. Early studies on postmortem brains suggested that the gyrification pattern remained fairly stable through development, which would make the gyrification a more static marker of neurodevelopment (Armstrong et al., 1995). However, recent studies have shown changes

in MRI-based measures of gyrification during development (White et al., 2010). In twin studies gyrification has been shown to be more influenced by environmental factors, and relied less on heritability compared to cortical thickness (Thambisetty et al., 2010; White et al., 2002). Brain imaging studies found an association between abnormal gyrification patterns and certain genotypes implying a genetic predisposition (Palaniyappan et al., 2019; Takahashi et al., 2015). Another study found that a higher clustering coefficient, and a lower degree of connected edges in the gyrification of the insula predicted a worse outcome after three-years of follow-up (Collantoni et al., 2019). Hence, these findings strengthen previous literature which stated that insula dysfunction may play an important role in the pathophysiology of AN due to the main function of the insula to process all information from the external environment concerning body perception and emotion experience, which influences self-awareness and decision making (Kerr et al., 2016; Nunn et al., 2011).

4.2. Functional MRI studies

Task-based functional neuroimaging studies used emotion regulation, social attribution, social evaluation, and reward tasks. These studies showed that brain activity in the frontal, parietal and temporal lobes at admission were predictive for the clinical outcome of AN. However, due to large methodological differences between studies, it is difficult to harmonize the results. Larger replication studies will be important to assess the role of social and reward related brain patterns of activity and connectivity in patients with AN.

Two studies investigated brain activity in patients versus controls during an emotion regulation task showed that a lower activity in the DLPFC and a higher activity in the ventral striatum predicted a worse clinical outcome (range follow-up time 2–3 months) (Seidel et al., 2018; Steward et al., 2022). Effect sizes of the studies evaluating the predictive value of the emotion regulation task were large. The striatum and DLPFC are connected and both integrally involved in executive functioning, including decision-making and reward-perception. A study using animal-models found a positive relationship between a conditioned striatal activity and self-starvation (Kim, 2012). A higher striatal activity is also observed in addictive disorders, implying a starvation dependence in AN. Altered brain activity in the DLPFC and striatum could explain the impaired executive functioning in AN patients (Jones and Graff-Radford, 2021; Monchi et al., 2006). Studies evaluating social tasks (Schulte-Ruther et al., 2012; Xu et al., 2017) found separately that lower brain activity in the medial PFC, and an higher activity in the posterior cingulate cortex and precuneus predicted a worse clinical outcome (range follow-up time: 12–21 months) (36, 43). The cingulate cortex and precuneus are implicated in visual perception. Furthermore, the precuneus plays an important role in self-reflection, social aspects and mind-wandering (Cavanna and Trimble, 2006). Alterations in these regions may explain the rumination on body-weight and -shape, and food in AN patients (Lee et al., 2014). Studies using a reward task showed that a higher activation of the middle OFC predicted a lower BMI increase at follow-up (DeGuzman et al., 2017). The OFC has been implicated in decision-making, which is impaired in AN patients, in particular during the acute phase of the disease (Wallis, 2007). The effect size of this finding was large. Higher levels of caudate and substantia nigra error response (large effect sizes 0.97–1.53), and a lower accuracy of the classification of the fusiform gyrus (small effect size 0.04) predicted a worse clinical outcome. The substantia nigra and caudate nuclei are implicated in reward, which may explain the alterations in reward processing in AN patients. The fusiform gyrus plays a role in visual perception, e.g. facial recognition (Weiner and Zilles, 2016).

Studies focusing on symptoms and associated features of eating disorders have shown that a combination of a higher anterior middle frontal activation and a VLPFC activation during the set-shifting task predicted improvement of set-shifting abilities after sixteen weeks of follow-up. Additionally, a higher activity in the insula prior to treatment predicted lower self-reported food-anxiety in patients with anorexia using a food-related task (Garrett et al., 2014). The effect sizes were large. A higher neural activity in the insula predicted a favorable treatment response on rTMS (Dunlop et al., 2015). While rTMS has been widely used and approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (McClintock et al., 2018) and obsessive-compulsive disorder (George, 2019), the application of rTMS in AN patients is still in an exploratory phase (Dalton et al., 2021; McClelland et al., 2016).

Hence, the observed alterations in brain activity could be linked to the main clinical symptoms of AN. Despite a lack of replication and validation, the results indicate the promising prognostic utility of fMRI in predicting the course of AN.

4.3. Limitations

Several limitations of consolidating the existing literature must be considered. First, the varying results may be due to methodological issues, in particular in the fMRI studies, considering the different task paradigms applied. However, if the task paradigms were able to tap similar cognitive domains associated with AN, this could also be considered a strength. The sample sizes of the studies tended to be small (range 16–56 AN patients) and the effect estimates high, suggesting the possibility of false positives for some of the findings. Second, another issue could be a difference between the samples, e.g. age, duration of illness, and comorbidities. In particular, the stage of illness and the age of onset could influence clinical outcome. Most reviewed studies were performed in adults, while the peak onset of AN is during adolescence, this may bias the measures for predicting clinical outcome. Another example is the study of Dunlop et al. (Dunlop et al. (2015) which not only included AN patients, but also patients with bulimia nervosa and they did not analyze the groups separately. The studies were mainly conducted in women, which limits the generalizability to men with AN. Third, in addition to sample heterogeneity, the length of the follow-up period could be a factor, since the follow-up range varied in the study between 1-to-43 months. Since the mean illness duration of AN is four years, the follow-up period of the reviewed studies may be too short to identify predictors of clinical outcome (Ruijter and Schoemaker, 2003). Fourth, in one study (Dunlop et al., 2015) AN patients underwent rTMS, which is not the care as usual, which may have an influence on the clinical course. Most reviewed studies did not correct for psychiatric comorbidity, which may bias the results. Fifth, despite the quality of most of the articles was considered as fair to good, there was a large heterogeneity in outcome parameters, e.g. physical health, neurocognitive functioning, behavior, which makes it difficult to generalize outcomes.

Moreover, most studies selected regions of interest based on previous literature, which may limit the identification of novel regions of interest. Strikingly, most studies were performed in Europe and the United States of America, which may be a selection bias. Finally, since most studies reported large effect sizes, this could also suggest a publication bias.

4.4. Recommendations for future research

We recommend future research to replicate existing studies in order to validate the prognostic utility of volumetric and functional brain outcome measures. Future studies should use prediction modelling considering established predictors and psychiatric comorbidity as covariates. We also recommend, and this is key, that different research groups that study patients with AN come together to harmonize at least a subset of different demographic, clinical, cognitive, and neuroimaging features that allow for better comparisons between future studies. Future studies should include larger sample sizes, and also include male patients, patients from diverse ethnic, geographic, and social economic backgrounds. Moreover, given the mean duration of illness of AN is four years, a longer follow-up period should be implemented.

4.5. Conclusions

Altogether, the results of this systematic review suggests that volumetric and functional brain outcome measures may predict the clinical outcome of AN patients. To date, there are few studies about the predictive value of neuroimaging measures on the differential course of AN. Although, the results are promising, since the reviewed articles showed large effect sizes. It may serve as a potential biomarker for predicting clinical outcome and will provide more information regarding a more reliable prognosis at admission, and it may give an indication of a patients' disease stage. However, given the lack of replication and validation there is currently insufficient basis to recommend using MRI in routine clinical practice to prognosticate the course of AN. Further research into identifying predictors of the clinical outcome of AN should be initiated, and should in particular focus on the PFC, ACC and insula.

Funding

This work was supported by the Sophia Foundation for Scientific Research (SSWO) (Grant numbers: S15-13, S22-65) and an internal Erasmus MV grant of the department of Radiology and Nuclear Medicine of the Erasmus University Medical Center. The work of TW was supported in part by the Intramural Research Program from the National Institutes of Mental Health.

Declaration of competing interest

None.

Acknowledgements

We would like to thank M. Aukes (MAA) for her help in the selection of eligible articles and the quality assessment. In addition, we would like to thank the biomedical information specialists S. Meertens-Geenput and M.F.M. Engel of the Erasmus Medical Centre for developing and updating the search strategies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.05.059.

References

Alemany, S., Blok, E., Jansen, P.R., Muetzel, R.L., White, T., 2021. Brain morphology, autistic traits, and polygenic risk for autism: a population-based neuroimaging study. Autism Res. 14 (10), 2085–2099.
Ansorge, M.S., Hen, R., Gingrich, J.A., 2007. Neurodevelopmental origins of depressive disorders. Curr. Opin. Pharmacol. 7 (1), 8–17.
Ap, A., 2013. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Arlington, VA.
Arcelus, J., Mitchell, A.J., Wales, J., Nielsen, S., 2011. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch. Gen. Psychiatr. 68 (7), 724–731.
Armstrong, E., Schleicher, A., Omran, H., Curtis, M., Zilles, K., 1995. The ontogeny of human gyrification. Cerebr. Cortex 5 (1), 56–63.
Berkman, N.D., Lohr, K.N., Bulik, C.M., 2007. Outcomes of eating disorders: a systematic review of the literature. Int. J. Eat. Disord. 40 (4), 293–309.
Blanken, L.M., Mous, S.E., Ghassabian, A., Muetzel, R.L., Schoemaker, N.K., El Marroun, H., van der Lugt, A., Jaddoe, V.W., Hofman, A., Verhulst, F.C., Tiemeier, H., White, T., 2015. Cortical morphology in 6- to 10-year old children with autistic traits: a population-based neuroimaging study. Am. J. Psychiatr. 172 (5), 479–486.
Bodell, L.P., Keel, P.K., Brumm, M.C., Akubuiro, A., Caballero, J., Tranel, D., Hodis, B., McCormick, L.M., 2014. Longitudinal examination of decision-making performance in anorexia nervosa: before and after weight restoration. J. Psychiatr. Res. 56, 150–157.
Boehm, I., Mohr, H., King, J.A., Steding, J., Geisler, D., Wronski, M.L., Weigel, K., Roessner, V., Ruge, H., Ehrlich, S., 2021. Aberrant neural representation of food stimuli in women with acute anorexia nervosa predicts treatment outcome and is improved in weight restored individuals. Transl. Psychiatry 11 (1), 532.
Bryant, R.A., Felmingham, K., Kemp, A., Das, P., Hughes, G., Peduto, A., Williams, L., 2008. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol. Med. 38 (4), 555–561.
Bulik, C.M., Sullivan, P.F., Tozzi, F., Furberg, H., Lichtenstein, P., Pedersen, N.L., 2006. Prevalence, heritability, and prospective risk factors for anorexia nervosa. Arch. Gen. Psychiatr. 63 (3), 305–312.
Castro-Fornieles, J., Bargallo, N., Lazaro, L., Andres, S., Falcon, C., Plana, M.T., Junque, C., 2009. A cross-sectional and follow-up voxel-based morphometric MRI study in adolescent anorexia nervosa. J. Psychiatr. Res. 43 (3), 331–340.
Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129 (Pt 3), 564–583.
Cohen, J., 2013. Statistical Power Analysis for the Behavioral Sciences. Academic press.
Collantoni, E., Madan, C.R., Meregalli, V., Meneguzzo, P., Marzola, E., Panero, M., D'Agata, F., Abbate-Daga, G., Tenconi, E., Manara, R., Favaro, A., 2021. Sulcal characteristics patterns and gyrification gradient at different stages of Anorexia Nervosa: a structural MRI evaluation. Psychiatry Res. Neuroimaging. 316, 111350.
Collantoni, E., Meneguzzo, P., Tenconi, E., Manara, R., Favaro, A., 2019. Small-world properties of brain morphological characteristics in Anorexia Nervosa. PLoS One 14 (5), e0216154.
Costantini, G., Perugini, M., 2014. Generalization of clustering coefficients to signed correlation networks. PLoS One 9 (2), e88669.
Dalton, B., Maloney, E., Rennalls, S.J., Bartholdy, S., Kekic, M., McClelland, J., Campbell, I.C., Schmidt, U., O'Daly, O.G., 2021. A pilot study exploring the effect of repetitive transcranial magnetic stimulation (rTMS) treatment on cerebral blood flow and its relation to clinical outcomes in severe enduring anorexia nervosa. J Eat Disord 9 (1), 84.
DeGuzman, M., Shott, M.E., Yang, T.T., Riederer, J., Frank, G.K.W., 2017. Association of elevated reward prediction error response with weight gain in adolescent anorexia nervosa. Am. J. Psychiatr. 174 (6), 557–565.
Dubois, J., Benders, M., Borradori-Tolsa, C., Cachia, A., Lazeyras, F., Ha-Vinh Leuchter, R., Sizonenko, S.V., Warfield, S.K., Mangin, J.F., Huppi, P.S., 2008. Primary cortical folding in the human newborn: an early marker of later functional development. Brain 131 (Pt 8), 2028–2041.
Dunlop, K., Woodside, B., Lam, E., Olmsted, M., Colton, P., Giacobbe, P., Downar, J., 2015. Increases in frontostriatal connectivity are associated with response to dorsomedial repetitive transcranial magnetic stimulation in refractory binge/purge behaviors. Neuroimage Clin 8, 611–618.
Duriez, P., Bou Khalil, R., Chamoun, Y., Maatoug, R., Strumila, R., Seneque, M., Gorwood, P., Courtet, P., Guillaume, S., 2020. Brain stimulation in eating disorders: state of the art and future perspectives. J. Clin. Med. 9 (8).
Durkut, M., Blok, E., Suleri, A., White, T., 2022. The longitudinal bidirectional relationship between autistic traits and brain morphology from childhood to adolescence: a population-based cohort study. Mol. Autism. 13 (1).
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cognit. Sci. 15 (2), 85–93.
Favaro, A., Tenconi, E., Degortes, D., Manara, R., Santonastaso, P., 2015. Gyrification brain abnormalities as predictors of outcome in anorexia nervosa. Hum. Brain Mapp. 36 (12), 5113–5122.
Fladung, A.K., Schulze, U.M., Scholl, F., Bauer, K., Gron, G., 2013. Role of the ventral striatum in developing anorexia nervosa. Transl. Psychiatry 3, e315.
Fornito, A., Malhi, G.S., Lagopoulos, J., Ivanovski, B., Wood, S.J., Velakoulis, D., Saling, M.M., McGorry, P.D., Pantelis, C., Yucel, M., 2007. In vivo evidence for early neurodevelopmental anomaly of the anterior cingulate cortex in bipolar disorder. Acta Psychiatr. Scand. 116 (6), 467–472.
Fuglset, T.S., Landro, N.I., Reas, D.L., Ro, O., 2016. Functional brain alterations in anorexia nervosa: a scoping review. J Eat Disord 4, 32.
Fujisawa, T.X., Yatsuga, C., Mabe, H., Yamada, E., Masuda, M., Tomoda, A., 2015. Anorexia nervosa during adolescence is associated with decreased gray matter volume in the inferior frontal gyrus. PLoS One 10 (6).
Galmiche, M., Dechelotte, P., Lambert, G., Tavolacci, M.P., 2019. Prevalence of eating disorders over the 2000-2018 period: a systematic literature review. Am. J. Clin. Nutr. 109 (5), 1402–1413.
Garcia-Garcia, I., Narberhaus, A., Marques-Iturria, I., Garolera, M., Radoi, A., Segura, B., Pueyo, R., Ariza, M., Jurado, M.A., 2013. Neural responses to visual food cues: insights from functional magnetic resonance imaging. Eur. Eat Disord. Rev. 21 (2), 89–98.
Garrett, A.S., Lock, J., Datta, N., Beenhaker, J., Kesler, S.R., Reiss, A.L., 2014. Predicting clinical outcome using brain activation associated with set-shifting and central coherence skills in Anorexia Nervosa. J. Psychiatr. Res. 57, 26–33.
Gaudio, S., Piervincenzi, C., Zobel, B.B., Montecchi, F.R., Riva, G., Carducci, F., Quattrocchi, C.C., 2015. Altered resting state functional connectivity of anterior cingulate cortex in drug naive adolescents at the earliest stages of anorexia nervosa. Sci Rep-Uk 5.
Gaudio, S., Wiemerslage, L., Brooks, S.J., Schioth, H.B., 2016. A systematic review of resting-state functional-MRI studies in anorexia nervosa: evidence for functional connectivity impairment in cognitive control and visuospatial and body-signal integration. Neurosci. Biobehav. Rev. 71, 578–589.
Geisler, D., Ritschel, F., King, J.A., Bernardoni, F., Seidel, M., Boehm, I., Runge, F., Goschke, T., Roessner, V., Smolka, M.N., Ehrlich, S., 2017. Increased anterior cingulate cortex response precedes behavioural adaptation in anorexia nervosa. Sci. Rep. 7, 42066.
George, M.S., 2019. Whither TMS: a one-trick pony or the beginning of a neuroscientific revolution? Am. J. Psychiatr. 176 (11), 904–910.

Gu, X., Liu, X., Guise, K.G., Naidich, T.P., Hof, P.R., Fan, J., 2010. Functional dissociation of the frontoinsular and anterior cingulate cortices in empathy for pain. J. Neurosci. 30 (10), 3739–3744.
Hernando, A., Pallas, R., Cebolla, A., Garcia-Campayo, J., Hoogendoorn, C.J., Roy, J.F., 2019. Mindfulness, rumination, and coping skills in young women with Eating Disorders: a comparative study with healthy controls. PLoS One 14 (3), e0213985.
Horndasch, S., Roesch, J., Forster, C., Dorfler, A., Lindsiepe, S., Heinrich, H., Graap, H., Moll, G.H., Kratz, O., 2018. Neural processing of food and emotional stimuli in adolescent and adult anorexia nervosa patients. PLoS One 13 (3), e0191059.
Jones, D.T., Graff-Radford, J., 2021. Executive dysfunction and the prefrontal cortex. Continuum 27 (6), 1586–1601.
Kappou, K., Ntougia, M., Kourtesi, A., Panagouli, E., Vlachopapadopoulou, E., Michalacos, S., Gonidakis, F., Mastorakos, G., Psaltopoulou, T., Tsolia, M., Bacopoulou, F., Sergentanis, T.N., Tsitsika, A., 2021. Neuroimaging findings in adolescents and young adults with anorexia nervosa: a systematic review. Children 8 (2).
Katzman, D.K., Zipursky, R.B., Lambe, E.K., Mikulis, D.J., 1997. A longitudinal magnetic resonance imaging study of brain changes in adolescents with anorexia nervosa. Arch. Pediatr. Adolesc. Med. 151 (8), 793–797.
Kaye, W.H., Wierenga, C.E., Bailer, U.F., Simmons, A.N., Bischoff-Grethe, A., 2013. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. Trends Neurosci. 36 (2), 110–120.
Kerr, K.L., Moseman, S.E., Avery, J.A., Bodurka, J., Zucker, N.L., Simmons, W.K., 2016. Altered insula activity during visceral interoception in weight-restored patients with anorexia nervosa. Neuropsychopharmacology 41 (2), 521–528.
Kim, S.F., 2012. Animal models of eating disorders. Neuroscience 211, 2–12.
Klomjai, W., Katz, R., Lackmy-Vallee, A., 2015. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med 58 (4), 208–213.
Koolschijn, P., Geurts, H.M., 2016. Gray matter characteristics in mid and old aged adults with ASD. J. Autism Dev. Disord. 46 (8), 2666–2678.
Lee, P.S., Foss-Feig, J., Henderson, J.G., Kenworthy, L.E., Gilotty, L., Gaillard, W.D., Vaidya, C.J., 2007. Atypical neural substrates of embedded figures task performance in children with autism spectrum disorder. Neuroimage 38 (1), 184–193.
Lee, S., Kim, K.R., Ku, J., Lee, J.H., Namkoong, K., Jung, Y.C., 2014. Resting-state synchrony between anterior cingulate cortex and precuneus relates to body shape concern in anorexia nervosa and bulimia nervosa. Psychiat Res-Neuroim 221 (1), 43–48.
Lee, U., Mashour, G.A., 2018. Role of network science in the study of anesthetic state transitions. Anesthesiology 129 (5), 1029–1044.
Liang, K., Li, H., Bu, X., Li, X., Cao, L., Liu, J., Gao, Y., Li, B., Qiu, C., Bao, W., Zhang, S., Hu, X., Xing, H., Gong, Q., Huang, X., 2021. Efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. Transl. Psychiatry 11 (1), 332.
Lie, C.H., Specht, K., Marshall, J.C., Fink, G.R., 2006. Using fMRI to decompose the neural processes underlying the Wisconsin Card Sorting Test. Neuroimage 30 (3), 1038–1049.
MacQueen, G.M., 2009. Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder. J. Psychiatry Neurosci. 34 (5), 343–349.
McClelland, J., Kekic, M., Campbell, I.C., Schmidt, U., 2016. Repetitive transcranial magnetic stimulation (rTMS) treatment in enduring anorexia nervosa: a case series. Eur. Eat Disord. Rev. 24 (2), 157–163.
McClintock, S.M., Reti, I.M., Carpenter, L.L., McDonald, W.M., Dubin, M., Taylor, S.F., Cook, I.A., O'Reardon, J., Husain, M.M., Wall, C., Krystal, A.D., Sampson, S.M., Morales, O., Nelson, B.G., Latoussakis, V., George, M.S., Lisanby, S.H., rTMS, N.N.D. C., Res, A.P.A.C., 2018. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J. Clin. Psychiatr. 79 (1), 35–+.
McCormick, L.M., Keel, P.K., Brumm, M.C., Bowers, W., Swayze, V., Andersen, A., Andreasen, N., 2008. Implications of starvation-induced change in right dorsal anterior cingulate volume in anorexia nervosa. Int. J. Eat. Disord. 41 (7), 602–610.
McGrath, C.L., Kelley, M.E., Holtzheimer, P.E., Dunlop, B.W., Craighead, W.E., Franco, A. R., Craddock, R.C., Mayberg, H.S., 2013. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatr. 70 (8), 821–829.
Milos, G., Kaufmann, L.K., Jancke, L., Piccirelli, M., Blatow, M., Martin-Soelch, C., von Kanel, R., Hanggi, J., Baur, V., 2021. Does local cerebellar volume predict treatment success in anorexia nervosa? Psychiat Res-Neuroim 317.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J. Clin. Epidemiol. 62 (10), 1006–1012.
Monchi, O., Ko, J.H., Strafella, A.P., 2006. Striatal dopamine release during performance of executive functions: a [(11)C] raclopride PET study. Neuroimage 33 (3), 907–912.
Moola S, M.Z., Tufanaru, C., Aromataris, E., Sears, K., Sfetcu, R., Currie, M., Qureshi, R., Mattis, P., Lisy, K., Mu, P.-F., 2020. Systematic reviews of etiology and risk. In: Aromataris E, M.Z. (Ed.), JBI Manual for Evidence Synthesis. JBI.
Moskowitz, L., Weiselberg, E., 2017. Anorexia nervosa/atypical anorexia nervosa. Curr. Probl. Pediatr. Adolesc. Health Care 47 (4), 70–84.
Mulert, C., Seifert, C., Leicht, G., Kirsch, V., Ertl, M., Karch, S., Moosmann, M., Lutz, J., Moller, H.J., Hegerl, U., Pogarell, O., Jager, L., 2008. Single-trial coupling of EEG and fMRI reveals the involvement of early anterior cingulate cortex activation in effortful decision making. Neuroimage 42 (1), 158–168.
Naruo, T., Nakabeppu, Y., Deguchi, D., Nagai, N., Tsutsui, J., Nakajo, M., Nozoe, S., 2001. Decreases in blood perfusion of the anterior cingulate gyri in Anorexia Nervosa Restricters assessed by SPECT image analysis. BMC Psychiatr. 1, 2.
Nunn, K., Frampton, I., Fuglset, T.S., Torzsok-Sonnevend, M., Lask, B., 2011. Anorexia nervosa and the insula. Med. Hypotheses 76 (3), 353–357.
Palaniyappan, L., Batty, M.J., Liddle, P.F., Liddle, E.B., Groom, M.J., Hollis, C., Scerif, G., 2019. Reduced prefrontal gyrification in carriers of the dopamine D4 receptor 7-repeat allele with attention deficit/hyperactivity disorder: a preliminary report. Front. Psychiatr. 10, 235.
Papadopoulos, F.C., Ekbom, A., Brandt, L., Ekselius, L., 2009. Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br. J. Psychiatry 194 (1), 10–17.
Roberto, C.A., Mayer, L.E.S., Brickman, A.M., Barnes, A., Muraskin, J., Yeung, L.K., Steffener, J., Sy, M., Hirsch, J., Stern, Y., Walsh, B.T., 2011. Brain tissue volume changes following weight gain in adults with anorexia nervosa. Int. J. Eat. Disord. 44 (5), 406–411.
Ruijter, d.C., Schoemaker, C., 2003. Nationale Monitor Geestelijke Gezondheid. Trimbos intstituut, Utrecht.
Schulte-Ruther, M., Mainz, V., Fink, G.R., Herpertz-Dahlmann, B., Konrad, K., 2012. Theory of mind and the brain in anorexia nervosa: relation to treatment outcome. J. Am. Acad. Child Adolesc. Psychiatry 51 (8), 832–841 e811.
Seidel, M., King, J.A., Ritschel, F., Boehm, I., Geisler, D., Bernardoni, F., Holzapfel, L., Diestel, S., Diers, K., Strobel, A., Goschke, T., Walter, H., Roessner, V., Ehrlich, S., 2018. The real-life costs of emotion regulation in anorexia nervosa: a combined ecological momentary assessment and fMRI study. Transl. Psychiatry 8 (1), 28.
Seitz, J., Walter, M., Mainz, V., Herpertz-Dahlmann, B., Konrad, K., von Polier, G., 2015. Brain volume reduction predicts weight development in adolescent patients with anorexia nervosa. J. Psychiatr. Res. 68, 228–237.
Siegle, G.J., Thompson, W.K., Collier, A., Berman, S.R., Feldmiller, J., Thase, M.E., Friedman, E.S., 2012. Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. Arch. Gen. Psychiatr. 69 (9), 913–924.
Somani, A., Kar, S.K., 2019. Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. Gen Psychiatr 32 (4), e100074.
Steinhausen, H.C., 2002. The outcome of anorexia nervosa in the 20th century. Am. J. Psychiatr. 159 (8), 1284–1293.
Stevens, F.L., Hurley, R.A., Taber, K.H., 2011. Anterior cingulate cortex: unique role in cognition and emotion. J. Neuropsychiatry Clin. Neurosci. 23 (2), 121–125.
Steward, T., Martinez-Zalacain, I., Mestre-Bach, G., Sanchez, I., Riesco, N., Jimenez-Murcia, S., Fernandez-Formoso, J.A., De las Heras, M.V., Custal, N., Menchon, J.M., Soriano-Mas, C., Fernandez-Aranda, F., 2022. Dorsolateral prefrontal cortex and amygdala function during cognitive reappraisal predicts weight restoration and emotion regulation impairment in anorexia nervosa. Psychol. Med. 52 (5), 844–852.
Takahashi, T., Nakamura, M., Nakamura, Y., Aleksic, B., Kido, M., Sasabayashi, D., Takayanagi, Y., Furuichi, A., Nishikawa, Y., Noguchi, K., Ozaki, N., Suzuki, M., 2015. The Disrupted-in-Schizophrenia-1 Ser704Cys polymorphism and brain neurodevelopmental markers in schizophrenia and healthy subjects. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 56, 11–17.
Takano, A., Shiga, T., Kitagawa, N., Koyama, T., Katoh, C., Tsukamoto, E., Tamaki, N., 2001. Abnormal neuronal network in anorexia nervosa studied with I-123-IMP SPECT. Psychiatr. Res. 107 (1), 45–50.
Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J.L., Resnick, S.M., 2010. Longitudinal changes in cortical thickness associated with normal aging. Neuroimage 52 (4), 1215–1223.
Van den Eynde, F., Suda, M., Broadbent, H., Guillaume, S., Van den Eynde, M., Steiger, H., Israel, M., Berlim, M., Giampietro, V., Simmons, A., Treasure, J., Campbell, I., Schmidt, U., 2012. Structural magnetic resonance imaging in eating disorders: a systematic review of voxel-based morphometry studies. Eur. Eat Disord. Rev. 20 (2), 94–105.
Wallis, J.D., 2007. Orbitofrontal cortex and its contribution to decision-making. Annu. Rev. Neurosci. 30, 31–56.
Walton, E., Bernardoni, F., Batury, V.L., Bahnsen, K., Lariviere, S., Abbate-Daga, G., Andres-Perpina, S., Bang, L., Bischoff-Grethe, A., Brooks, S.J., Campbell, I.C., Cascino, G., Castro-Fornieles, J., Collantoni, E., D'Agata, F., Dahmen, B., Danner, U. N., Favaro, A., Feusner, J.D., Frank, G.K.W., Friederich, H.C., Graner, J.L., Herpertz-Dahlmann, B., Hess, A., Horndasch, S., Kaplan, A.S., Kaufmann, L.K., Kaye, W.H., Khalsa, S.S., LaBar, K.S., Lavagnino, L., Lazaro, L., Manara, R., Miles, A.E., Milos, G. F., Monteleone, A.M., Monteleone, P., Mwangi, B., O'Daly, O., Pariente, J., Roesch, J., Schmidt, U.H., Seitz, J., Shott, M.E., Simon, J.J., Smeets, P.A.M., Tamnes, C.K., Tenconi, E., Thomopoulos, S.I., van Elburg, A.A., Voineskos, A.N., von Polier, G.G., Wierenga, C.E., Zucker, N.L., Jahanshad, N., King, J.A., Thompson, P. M., Berner, L.A., Ehrlich, S., 2022. Brain structure in acutely underweight and partially weight-restored individuals with anorexia nervosa: a coordinated analysis by the ENIGMA eating disorders working group. Biol. Psychiatr.
Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393 (6684), 440–442.
Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch. Gen. Psychiatr. 44 (7), 660–669.
Weiner, K.S., Zilles, K., 2016. The anatomical and functional specialization of the fusiform gyrus. Neuropsychologia 83, 48–62.
White, T., Andreasen, N.C., Nopoulos, P., 2002. Brain volumes and surface morphology in monozygotic twins. Cerebr. Cortex 12 (5), 486–493.
White, T., Andreasen, N.C., Nopoulos, P., Magnotta, V., 2003. Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. Biol. Psychiatr. 54 (4), 418–426.
White, T., Gottesman, I., 2012. Brain connectivity and gyrification as endophenotypes for schizophrenia: weight of the evidence. Curr. Top. Med. Chem. 12 (21), 2393–2403.
White, T., Su, S., Schmidt, M., Kao, C.Y., Sapiro, G., 2010. The development of gyrification in childhood and adolescence. Brain Cognit. 72 (1), 36–45.

Xu, J., Harper, J.A., Van Enkevort, E.A., Latimer, K., Kelley, U., McAdams, C.J., 2017. Neural activations are related to body-shape, anxiety, and outcomes in adolescent anorexia nervosa. J. Psychiatr. Res. 87, 1–7.
Young, K.S., Rennalls, S.J., Leppanen, J., Mataix-Cols, D., Simmons, A., Suda, M., Campbell, I.C., O'Daly, O., Cardi, V., 2020. Exposure to food in anorexia nervosa and brain correlates of food-related anxiety: findings from a pilot study. J. Affect. Disord. 274, 1068–1075.
Zhang, J.J.Q., Fong, K.N.K., Ouyang, R.G., Siu, A.M.H., Kranz, G.S., 2019. Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis. Addiction 114 (12), 2137–2149.
Zhu, Y., Hu, X., Wang, J., Chen, J., Guo, Q., Li, C., Enck, P., 2012. Processing of food, body and emotional stimuli in anorexia nervosa: a systematic review and meta-analysis of functional magnetic resonance imaging studies. Eur. Eat Disord. Rev. 20 (6), 439–450.