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Abstract: Anorexia nervosa (AN) is difficult to treat with up to half of patients failing to gain weight during treatment. Neurobiological factors predicting treatment response in AN are poorly understood. In this longitudinal study, we aimed to identify morphological characteristics in the grey matter which predict treatment success in patients with AN. Fifty patients with severe AN participated in an eating disorder-specific inpatient treatment. On admission, T1-weighted magnetic resonance images were acquired from all patients. Half of the patients successfully gained weight, reaching a body-mass index 17.5 kg/m2. Using voxel-based morphometry, local grey matter volumes were compared between the two groups of patients who gained weight and those who did not. This approach allowed us to identify anatomical characteristics which predict treatment success in terms of post-treatment weight status. Patients who did not reach the weight threshold at discharge had a smaller volume in the right cerebellar crus I at the time of admission. In this group, smaller volume was associated with a greater alexithymia score. The findings suggest that a trophic state within the cerebellum before treatment might be prognostic for treatment success. Consistent with previous reports, this result further substantiates the possible role of the cerebellum in the psychopathology of AN.

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Does local cerebellar volume predict treatment success in anorexia nervosa?

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ABSTRACT

Anorexia nervosa (AN) is difficult to treat with up to half of patients failing to gain weight during treatment. Neurobiological factors predicting treatment response in AN are poorly understood. In this longitudinal study, we aimed to identify morphological characteristics in the grey matter which predict treatment success in patients with AN. Fifty patients with severe AN participated in an eating disorder-specific inpatient treatment. On admission, T1-weighted magnetic resonance images were acquired from all patients. Half of the patients successfully gained weight, reaching a body-mass index $\geq$ 17.5 kg/m^2. Using voxel-based morphometry, local grey matter volumes were compared between the two groups of patients who gained weight and those who did not. This approach allowed us to identify anatomical characteristics which predict treatment success in terms of post-treatment weight status. Patients who did not reach the weight threshold at discharge had a smaller volume in the right cerebellar crus I at the time of admission. In this group, smaller volume was associated with a greater alexithymia score. The findings suggest that a trophic state within the cerebellum before treatment might be prognostic for treatment success. Consistent with previous reports, this result further substantiates the possible role of the cerebellum in the psychopathology of AN.

1. Introduction

Treatment of anorexia nervosa (AN) often proves to be difficult, with less than half of the patients reaching full remission (Fichter et al., 2017; Steinhausen, 2002). Despite the broad availability of multi-modal therapies in structured clinical settings, a considerable proportion of patients fail to complete treatment programmes and face a chronic course of the illness (Fichter et al., 2017; Steinhausen, 2002). The persistence of the illness is an unsolved problem in the treatment of AN (Compan et al., 2015) and the neurobiological factors predicting treatment response are poorly understood.

Magnetic resonance imaging (MRI) studies on AN focusing on the subgroup of patients with a positive treatment outcome, which is primarily measured by normalization of body weight, report the reversibility of global and local grey matter (GM) reduction (Bernardoni et al., 2016; Bomba et al., 2015; Kaufmann et al., 2020; Mainz et al., 2012) as a *correlate of treatment success*. Studies investigating *predictors of treatment success* report that lower GM volume of the cerebellum at admission is associated with lower body mass index (BMI) at 1–year follow–up in adolescent patients with AN (Seitz et al., 2015). Moreover, a region–of–interest analysis of the anterior cingulate cortex revealed that higher GM volume is associated with more stable remission at 1–year follow-up in AN (McCormick et al., 2008).

Prospective MRI studies investigating the subgroup of patients with a poor outcome are lacking. Involving both subgroups and their direct comparison has the potential to shed light on the mechanisms underlying favourable and unfavourable illness courses in AN. In the present study, we thus aimed to identify characteristics in brain anatomy which predict the achievement of a body weight above a clinically relevant threshold (BMI $\geq$ 17.5 kg/m^2) in response to an eating disorder–specific

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inpatient treatment. To this end, we assessed the GM volume of patients with AN at the time of admission and compared patients who later successfully gained weight ("AN weight-restored", ANwr) to patients who did not ("AN non-weight–restored", ANnr). Thus, the pattern resulting from this contrast would be a *predictor of treatment success*. Poorer treatment outcome in AN has been associated with higher autistic and obsessive–compulsive traits accompanying the disorder, such as a premorbid obsessive-compulsive personality (Wentz et al., 2009), a comorbid autism spectrum disorder or obsessive–compulsive disorder (Råstam et al., 2003). To account for a possible influence of these characteristics, psychometric parameters depicting these aspects were collected in addition to clinical measures.

Given of the overall scarce empirical background and the use of different samples (adolescents, adults) in the abovementioned MRI studies, specific hypotheses regarding brain regions which may be predictive for treatment success are not obvious. We therefore chose a data–driven whole-brain approach to test the hypothesis that *smaller* local GM volume (McCormick et al., 2008; Seitz et al., 2015) is associated with a *lack* of treatment success, i.e. poorer weight gain during treatment. Additionally, we explored associations with clinical and psychometric variables capturing patients' physical and psychosocial state at the time of admission.

2. Methods

2.1. Participants and design

Fifty patients with severe AN (42 restrictive, 8 binge–purge) participated in an eating disorder-specific interdisciplinary multimodal inpatient treatment programme to achieve a BMI of at least 17.5 kg/m^2 (diagnostic cut-off level according to ICD-10 (WHO ICD-10, 2016)) and were consecutively recruited for the study (mean BMI 14.3 ± 0.97 kg/m^2, min 11.9 kg/m^2, max 16.1 kg/m^2). The main objectives of the treatment were weight normalization (with an average weekly weight gain of 700 g), normalization of eating and exercise behaviour, and overcoming dysfunctional attitudes towards eating. The duration of treatment depends on weight at admission an of weight gain during treatment but is generally limited to about 24 weeks. Patients who repeatedly did not achieve the required weekly weight gain had to discontinue hospitalization. Patients underwent regular somatic examinations. MRI scans were performed at least two weeks after admission to rule out acute dehydration as a confounding factor. Treatment success was operationalized as weight gain, more specifically as achieving a BMI of at least 17.5 kg/m^2 in response to the inpatient treatment described above. Based on treatment success, two patient groups were differentiated: Patients who achieved a BMI ≥ 17.5 kg/m^2 were assigned to the "weight–restored" (ANwr) group, while patients who did not (BMI < 17.5 kg/m^2) were assigned to the "non-weight-restored" (ANnr) group. The difference in weight gain over time between ANwr and ANnr is illustrated in Fig. 1. Specific characteristics of ANwr and ANnr are presented in Table 1.

To confirm the diagnosis of severe AN and to identify comorbidities, patients were assessed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002). Fourteen patients in the ANwr group and 11 patients in the ANnr group had a comorbid mental disorder: major depression (ANwr: 11; ANnr: 9), major depression and anxiety disorder (ANwr: 2; ANnr: 1), obsessive-compulsive disorder (ANwr: 1), and major depression and obsessive-compulsive disorder (ANnr: 1). Patients who were taking psychotropic medication when they entered the study (see Table 1) were instructed to continue the regimen as prescribed. Exclusion criteria for the study comprised current or past neurological disorders, substance abuse or addiction, and contraindications to MRI. The study was approved by the local ethics committee and the study protocol complied with the latest version of the Declaration of Helsinki. All participants gave written informed consent prior to study enrolment. Data of the present sample overlaps in part with previous reports of our group (Kaufmann et al., 2020, 2017).

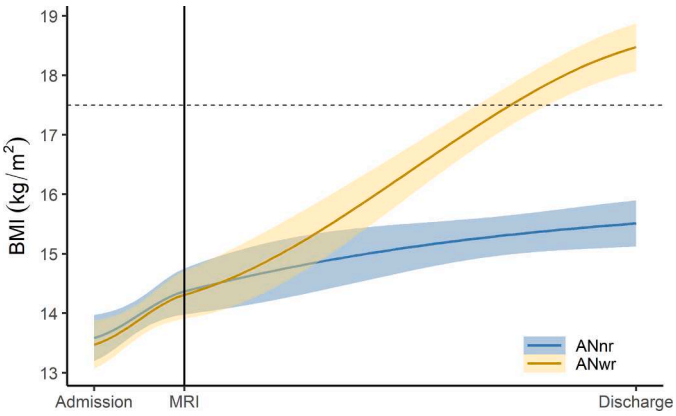

Fig. 1. BMI development in the two patient subgroups ANwr (weight-restored patients with anorexia nervosa) and ANnr (non-weight-restored patients with anorexia nervosa) during inpatient treatment. Since patients who do not gain weight over a longer period of time despite sufficient portion size and support from the treatment team have to leave the treatment programme, treatment duration of the ANnr group was shorter compared to the ANwr group (see results section). The coloured lines are local regression curves per subgroup, with the shaded area representing the 95% confidence interval for the curve. The dashed–line marks a BMI of 17.5 kg/m^2.

Table 1
Clinical and psychometric characteristics of the patients.

	ANnr		ANwr		
	mean	*SD*	*mean*	*SD*	*p*
age [yrs]	22.3	4.1	22.0	4.1	0.78
age of illness onset [yrs]	15.8	2.2	16.4	2.7	0.44
illness duration [yrs]	6.6	4.2	5.8	4.5	0.52
education [yrs] [a]	12.5	2.9	13.3	2.5	0.33
BMI at admission [kg/m^2]	13.5	1.2	13.3	1.2	0.48
BMI at MRI scan [kg/m^2]	14.4	0.9	14.3	1.1	0.67
BMI at discharge [kg/m^2]	15.9	1.4	18.4	0.9	< 0.001
EDEQ total [b]	3.3	1.1	3.2	1.3	0.76
EDEQ eating constraint [b]	3.1	1.2	3.2	1.6	0.89
EDEQ restraint [b]	3.3	1.3	3.3	1.8	0.89
EDEQ shape concern [b]	3.7	1.2	3.5	1.3	0.60
EDEQ weight concern [b]	3.2	1.6	2.9	1.2	0.41
BDI (depressiveness) [b]	24.8	12.0	23.4	9.8	0.67
STAI trait (anxiety) [b]	57.3	11.3	55.9	12.3	0.71
OCI (obsessive-compulsive traits) [b]	38.4	7.8	34.6	10.0	0.16
TAS (alexithymia) [c]	53.6	7.1	52.0	5.5	0.44
WMT (non-verbal intelligence) [d]	115.0	20.0	122.0	17.8	0.21
WST (verbal intelligence) [d]	101.7	10.1	106.0	8.8	0.13
	ANnr		**ANwr**		
	n		***n***		***p***
AN restrictive/binge-purge	21/4		21/4		1.0
unmedicated/medicated	16/9		13/12		0.57

Note: Psychometric data was collected at the time of admission. ANwr: Patient with anorexia nervosa, weight-restored; ANnr: patient with anorexia nervosa, non-weight-restored; SD: standard deviation; BMI: body-mass index; EDEQ: Eating Disorders Examination Questionnaire; BDI: Beck Depression Inventory, STAI: Spielberger State-Trait Anxiety Inventory; OCI: Obsessive-Compulsive Inventory; TAS: Toronto Alexithymia Scale; WMT: Viennese Matrices Test for non-verbal intelligence; WST: Viennese Vocabulary Test for verbal intelligence. Medication comprised antidepressants, atypical antipsychotics, or anxiolytics.
Missing data:
[a] ANwr: 1.
[b] ANnr: 6.
[c] ANnr: 6, ANwr: 1.
[d] ANnr: 2 (and for WST, ANwr: 1).

2.2. Acquisition and analysis of psychometric data

Validated German versions of the following psychometric tests were

used in this study: Viennese Matrices Test for non–verbal intelligence (Formann and Piswanger, 1979), Viennese Vocabulary Test for verbal intelligence (Schmidt and Metzler, 1992), Spielberger State–Trait Anxiety Inventory for trait anxiety (Laux et al., 1981), Beck Depression Inventory (Hautzinger et al., 1994) for depression severity, Obsessive-Compulsive Inventory (short version) for obsessive-compulsive traits (Foa et al., 2002), 20–item Toronto Alexithymia Scale (Bagby et al., 1994) for alexithymia traits and Eating Disorder Examination Questionnaire (Hilbert et al., 2004) for eating disorder cognitions. To assess group differences in the psychometric data, Welch's t-tests for two samples were applied using R version 4.0.2 (R Core Team, 2020).

2.3. Acquisition and analysis of magnetic resonance imaging data

Brain images were acquired with a 3.0 Tesla whole-body MRI system (Ingenia, Philips, Best, The Netherlands), equipped with a 32-channel head coil. Whole–brain 3D T1–weighted structural images were acquired using a 3D Turbo-Field-Echo sequence (echo time = 3.8 ms, repetition time = 8.3 ms, inversion time = 1020 ms, shot interval = 2010 ms, field of view = 240 × 240 mm^2, acquisition matrix = 240 × 240, 160 slices, isotropic voxel size = 1 mm^3, flip angle = 8°, TFE factor = 240, duration = 4.5 min). For all subjects, T1-weighted (and additional diagnostic T2-weighted) images were inspected for relevant brain pathology or anomalies by a trained neuroradiologist.

Differences in local GM volume between ANwr and ANnr were evaluated using whole-brain voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001). T1-weighted MRI scans were pre-processed and analysed with the FSL–VBM tool (Douaud et al., 2007) (fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimized VBM protocol (Good et al., 2001) implemented in FSL (Smith et al., 2004). First, structural images were brain-extracted and GM-segmented before being registered to MNI152 space using non-linear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template. Second, all native GM images were non-linearly registered to the study-specific template and modulated to correct local contraction or expansion of voxels due to the non–linear component of the spatial transformation (Jacobian modulation). This modulation preserves absolute volumes such that the inclusion of total intracranial volume in subsequent statistical models as a covariate becomes obsolete (Ashburner and Friston, 2000; Good et al., 2001; Malone et al., 2015). The modulated GM maps were then smoothed with an isotropic Gaussian kernel with a sigma of 3, corresponding to a full width at half maximum (FWHM) Gaussian kernel of about 7 mm. Finally, voxel-wise general linear models were calculated using permutation-based non-parametric testing with 5000 permutations of the group label (Smith and Nichols, 2009). The significance threshold was set at $\alpha = 0.05$, correcting for multiple comparisons with the threshold free cluster enhancement method using family-wise error correction.

After group comparison, individual cluster means were extracted to (i) visualize the data and check for anomalies or outliers and to (ii) systematically examine group-specific Pearson correlations with the clinical (age of illness onset, duration of illness, BMI at MRI scan) and psychometric variables (eating disorder symptom severity, depression, obsessive-compulsive trait, anxiety trait, alexithymia trait). As we conducted eight correlation analyses, we adjusted the significance level to $\alpha = 0.006$ using the Bonferroni correction.

Global brain tissue volumes for GM and white matter (WM) and ventricular cerebrospinal fluid (CSF), normalised for patients head size, were calculated with SIENAX version 2.6 (Smith et al., 2002), part of FSL (Smith et al., 2004). Brain extraction was run with optimised parameters for robust brain centre estimation (using the option '-R'). Group comparisons were calculated using Welch's t–tests for two samples in R version 4.0.2 (R Core Team, 2020).

3. Results

For ANwr, the mean duration of treatment was 24 ± 4 weeks (mean ± standard deviation), for ANnr, the mean time between admission and discharge was 14 ± 7 weeks. ANwr and ANnr did not differ in any of the clinical and psychometric variables at the time of admission (Table 1). Moreover, the proportion of patients who had a comorbid diagnosis of depression did not differ between groups ($X^2(1) = 0.322$, $p = 0.57$).

VBM yielded a cluster with smaller GM volume in ANnr compared to ANwr. This cluster was located in the crus I of the right pontocerebellum (cluster size: 311 voxels, $p = 0.009$, MNI coordinates: $x/y/z$: 32 / −88 / −32, see Fig. 2). There were no clusters with increased GM volume in ANnr compared to ANwr. Further, there was no evidence for differing global GM, WM or ventricular CSF volumes between ANnr and ANwr (Table 2). Exploratory correlation analyses showed that in the ANnr group, the mean GM volume of the identified cluster negatively correlated with alexithymia score ($r = -0.58$, $p = 0.009$). However, this correlational result was not significant according to an adjusted significance level of $\alpha = 0.006$. Further, there were no significant or trend correlations with clinical (age of illness onset, duration of illness, BMI at MRI scan) or with other psychometric variables (eating disorder symptom severity, depression, obsessive-compulsive trait, anxiety trait) in either group (Table 3).

4. Discussion

In the present study, we aimed to identify GM characteristics predictive of treatment success (i.e., post–treatment weight status) in patients with AN. Using VBM in a whole–brain approach, we found a smaller volume in the crus I of the right cerebellum in ANnr compared to ANwr. Crucially, the smaller volume of the identified cluster was measured after initial weight restoration to exclude dehydration effects and was independent of illness duration or patients BMI at MRI scan. This is further evidence for the hypothesis that a *lack* of treatment success is associated with *smaller* GM volume. Our results are consistent with a previous report of an association between smaller cerebellar

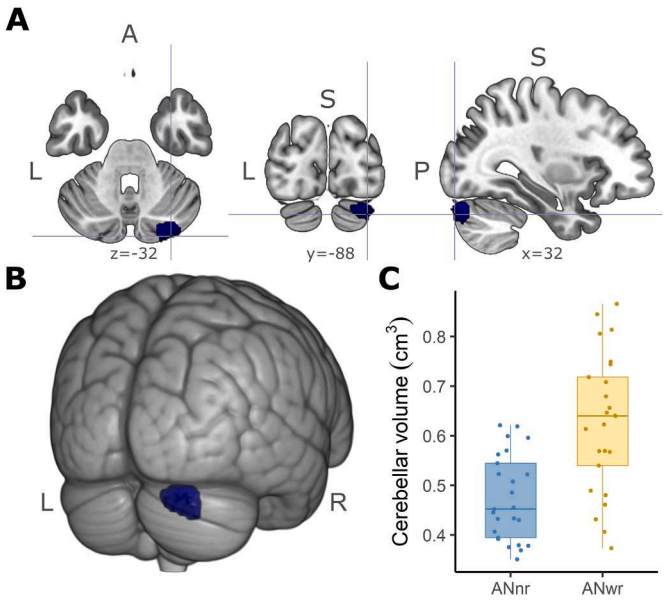

Fig. 2. Grey matter volume differences between non–weight–restored anorexia nervosa (ANnr) patients and weight–restored (ANwr) patients, detected using voxel–based morphometry. ***A*** + ***B*:** Cluster of significantly smaller grey matter volume in ANnr patients compared to ANwr patients in the right crus I (cluster size: 311 voxels, $p = 0.009$, MNI coordinates: x/y/z: 32 / −88 / −32). **C:** Boxplots comparing the cluster-specific volume (cm^3) of the two groups. A = anterior, P = posterior, S = superior, L = left, R = right.

Table 2
Comparison of global brain volumes (cm^3) of ANnr and ANwr patients.

	ANnr		ANwr		
	mean	*SD*	*mean*	*SD*	*p*
Grey matter	799.70	45.09	784.72	53.82	0.291
White matter	743.63	35.88	741.18	32.36	0.801
CSF ventricular	36.03	10.78	36.14	13.618	0.976

Notes: ANwr: Patient with anorexia nervosa, weight-restored; ANnr: patient with anorexia nervosa, non-weight-restored; CSF: cerebrospinal fluid; SD: standard deviation.

Table 3
Group-specific Pearson correlations of cluster means with clinical and psychometric variables.

	ANnr		ANwr	
Variables	***r***	***p***	***r***	***p***
age of illness onset [yrs]	0.24	0.240	−0.12	0.580
illness duration [yrs]	0.17	0.422	0.02	0.934
BMI at MRI scan [kg/m^2]	−0.15	0.476	0.22	0.287
EDEQ total [a]	−0.19	0.430	0.13	0.538
BDI (depressiveness) [a]	−0.05	0.855	0.004	0.983
STAI trait (anxiety) [a]	−0.28	0.242	0.33	0.112
OCI (obsessive-compulsive traits) [a]	−0.35	0.138	0.23	0.275
TAS (alexithymia) [b]	−0.58	0.009	−0.07	0.757

Note: ANwr: Patient with anorexia nervosa, weight-restored; ANnr: patient with anorexia nervosa, non-weight-restored; BMI: Body-Mass Index; EDEQ: Eating Disorders Examination Questionnaire; BDI: Beck Depression Inventory, STAI: Spielberger State-Trait Anxiety Inventory; OCI: Obsessive-Compulsive Inventory; TAS: Toronto Alexithymia Scale.
Missing data:
[a] ANnr: 6.
[b] ANnr: 6, ANwr: 1.

volume and weight status at 1–year follow–up in adolescent patients with AN (Seitz et al., 2015). In addition, smaller cerebellar volume has been associated with a chronic trajectory of AN (Boghi et al., 2011). Together, these results suggest that a neural mechanism within the cerebellum might play an important role in treatment adherence in AN.

The cerebellar crus I, especially the right one, is known as the cerebellar association zone: In contrast to the sensorimotor functions represented by adjacent parts of the cerebellum, it is connected to the prefrontal cerebral cortex, to the fronto–parietal control network and to the default-mode network (Buckner, 2013). As such, it is involved in a great variety of social, executive, cognitive and self-referential processes, which are targeted in the multi-modal treatment of AN, e.g., dealing with the intense fear of gaining weight or detaching from ruminations about what (not) to eat.

A core psychopathological feature of AN is that thought and behaviour have a rigid, repetitive and compulsive character (Friederich and Herzog, 2011), similar to autism spectrum (Kerr-Gaffney et al., 2021) and obsessive-compulsive disorders (Bastiani et al., 1996). Studies investigating patients with these disorders have previously reported volume reductions in crus I (D'Mello et al., 2015; Narayanaswamy et al., 2016), the same region as in the present study. Both autistic behaviour and obsessive-compulsive behaviour have a prognostic value for therapeutic outcome in AN, whether at a subclinical level as a personality trait (Wentz et al., 2009) or as a clinical comorbidity (Råstam et al., 2003). Taken together, one possible interpretation is that the failure of ANnr patients to gain weight may stem from a neurobiological predisposition linked to rigid and compulsive psychological traits. That is, a smaller volume of the right crus I of the cerebellum could reflect a deficient integration of cognitive, emotional and behavioural input ("the new") from treatment, such that patients continue to adhere rigidly and inflexibly to "the old". This interpretation would align with an animal study in which disruption of the right crus I function led to repetitive and inflexible behaviour (Stoodley et al., 2017). However, for obsessive-compulsive traits (measured with the obsessive-compulsive inventory), we did *not* observe a significant difference between ANwr and ANnr or a correlation with cluster volume in either group. Conversely, for alexithymia (measured with the Toronto Alexithymia Scale), which is considered to represent a psychological link between autistic traits and AN (Vuillier et al., 2020), there was marginal evidence for a correlation with cluster volume in ANnr. That is, the lower the volume, the higher the alexithymia of these patients. The link between autism-related traits and treatment outcome in AN is also supported by reports linking lower brain activation during a theory-of-mind task to poorer treatment outcome in patients with acute AN (Schulte-Rüther et al., 2012). However, since the correlation between cluster volume and alexithymia in ANnr was not significant considering the adjusted significance level, this exploratory result should be considered with caution. Given (i) the existing reports of high alexithymia as a predictor of a poorer treatment outcome (Speranza et al., 2007) and (ii) the great topical interest of researchers in the connection between alexithymia and therapeutic outcome in AN (Gramaglia et al., 2020), we consider the present result to be worth mentioning.

Another interpretation is that the smaller crus I volume in ANnr reflects an unspecific, biological predisposition within this patient subgroup. Indeed, the cerebellum has been argued to be susceptible to persistent deficits (Seitz et al., 2016) and less "recoverable over time" in the context of early life stress (Adamaszek et al., 2017) and prenatal stress (Koning et al., 2017). Against this background, ANnr patients' cerebellar deficit would represent an unspecific biological vulnerability that expresses as a low susceptibility to treatment and a lack of success in weight gain in AN. The lack of a group difference of illness duration and the lack of a correlation of cerebellar crus volume with illness duration supports the interpretation of an unspecific vulnerability.

This study is, to our knowledge, the first to identify potential neurobiological predictors of treatment success in adults with AN. Several limitations should be considered when interpreting our results. First, the time frame of the present study focused on the current treatment episode, independent of previous therapies or long-term patient outcomes. It is possible that patients in the ANnr group gained weight as they progressed. However, clinical experience shows that this is rarely possible without additional treatment. Second, the sample size is moderate. Inferences regarding long-term outcomes thus require replication in larger samples with a longer observation period. Furthermore, a more detailed analysis of the influence of individual pharmacological treatments is not viable with the present sample and should be investigated in future studies. Third, the nature of our analysis approach does not allow for prediction on an individual level, but rather represents a first step for future efforts in this direction.

To conclude, our results suggest that distinct structural deficits in the cerebellum before treatment are predictive of a poorer weight status after treatment in patients with AN. This finding provides new insights into the role of the cerebellum in AN.

Declaration of Competing Interest

All authors state that there are no conflicts of interest and all authors have read and approved the final version of the manuscript. The material in the current manuscript is original research and the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language. There is no overlap with prior work that is already published.

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Contributors

GM, LKK and VB designed the study. GM, LKK, MP, MB and JH collected and analysed the data. GM, LKK and VB interpreted the results. GM, LKK and VB wrote the first draft of the manuscript. All authors contributed to further drafts of the manuscript and approved the final version of the manuscript.

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