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Originalarbeit

Morphological Changes in the Brain of Acutely Ill and Weight-Recovered Patients with Anorexia Nervosa

A Meta-Analysis and Qualitative Review

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Abstract. *Objective:* Acute anorexia nervosa (AN) leads to reduced gray (GM) and white matter (WM) volume in the brain, which however improves again upon restoration of weight. Yet little is known about the extent and clinical correlates of these brain changes, nor do we know much about the time-course and completeness of their recovery. *Methods:* We conducted a meta-analysis and a qualitative review of all magnetic resonance imaging studies involving volume analyses of the brain in both acute and recovered AN. *Results:* We identified structural neuroimaging studies with a total of 214 acute AN patients and 177 weight-recovered AN patients. In acute AN, GM was reduced by 5.6% and WM by 3.8% compared to healthy controls (HC). Short-term weight recovery 2–5 months after admission resulted in restitution of about half of the GM aberrations and almost full WM recovery. After 2–8 years of remission GM and WM were nearly normalized, and differences to HC (GM: –1.0%, WM: –0.7%) were no longer significant, although small residual changes could not be ruled out. In the qualitative review some studies found GM volume loss to be associated with cognitive deficits and clinical prognosis. *Conclusions:* GM and WM were strongly reduced in acute AN. The completeness of brain volume rehabilitation remained equivocal.

Keywords: anorexia nervosa, brain volume, morphometric changes, meta-analysis, recovered

Zusammenfassung. *Hirnmorphologische Veränderungen in akut kranken und gewichtsrehabilitierten Patientinnen mit Anorexia nervosa – Meta-Analyse und qualitativer Review*

Fragestellung: Patientinnen mit Anorexia Nervosa (AN) zeigen eine Reduktion cerebraler grauer (GS) und weißer Substanz (WS), die sich bei Gewichtsrehabilitation wieder bessert. Sowohl das Ausmaß der Reduktion und ihre klinische Bedeutung, als auch der zeitliche Verlauf und die Vollständigkeit der Erholung wurden bisher noch nicht systematisch erforscht. *Methodik:* Wir führten eine Meta-Analyse und einen qualitativen Review von allen Bildgebungsstudien mit Magnetresonanztomographie zu Volumenänderungen bei akuten und gewichtsrehabilitierten Patienten mit AN durch. *Ergebnisse:* Es konnten Studien mit insgesamt 214 akuten und 177 gewichts-rehabilitierten Patientinnen in die Analyse eingeschlossen werden. Die GS der Patientinnen mit akuter AN war gegenüber gesunden Kontrollen um 5.6% reduziert, die WS um 3.8%. Eine kurzzeitige Gewichts-Normalisierung von 2–5 Monaten war mit einem Rückgang von etwa der Hälfte der GS-Reduktion verbunden, während die WS schon fast vollständig normalisiert erschien. 2–8 Jahre nach Remission waren GS und WS weitgehend rehabilitiert und nicht mehr signifikant gegenüber gesunden Kontrollen reduziert (GS: –1.0% bzw. WS: –0.7%). Kleine Residualveränderungen konnten damit aber nicht ausgeschlossen werden. Im qualitativen Review zeigten einige Studien, dass GS-Reduktion mit kognitiven Defiziten und schlechterer klinischer Prognose assoziiert war. *Schlussfolgerungen:* GS und WS waren bei Patientinnen mit akuter AN stark reduziert. Die Vollständigkeit der Erholung des Gehirns blieb weiter ungeklärt.

Schlüsselwörter: Anorexia Nervosa, Gehirnvolumen, morphologische Veränderungen, Meta-Analyse, gewichts-rehabilitiert

Introduction

Marked reduction of gray matter (GM) and white matter (WM) volumes is frequently observed during the acute phase of anorexia nervosa (AN). During weight recovery the cerebral volume again increases (J. Castro-Fornieles et al., 2009; Katzman, Zipursky, Lambe, & Mikulis, 1997; Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Swayze et al., 2003). These marked acute brain changes in AN are often evident by simple visual inspection of an AN patient's MRI or CT scan (see Figure 1) and are among the strongest structural brain changes that can be observed in any adolescent mental disorder. In sharp contrast to these marked acute brain changes, adolescent patients usually present themselves even in the extreme phase of starvation with remarkably normal academic performance levels and only small impairments (Buehren et al., 2011).

So far, the exact time course of these brain changes and their underlying mechanisms and implications for cognitive deficits remain unclear. It is especially still doubtful whether structural brain abnormalities completely recover after weight rehabilitation. The influence of residual brain changes on long-term outcome as well as on the development of comorbid psychiatric disorders such as depression is poorly understood. One qualitative review and one meta-analysis recently helped to find answers to some of these questions. Van den Eynde and coworkers (2011) systematically reviewed all magnetic resonance imaging (MRI) studies using the analysis technique "voxel-based morphometry" (VBM), which uses the intensity differences in T1-weighted MRI-images to extract GM, WM, and cerebro-spinal fluid (CSF) in a voxel-based, probabilistic fashion. They concluded that "the findings do not unequivocally indicate gray or white matter volume abnormalities in people with an eating disorder." However, they summarized preliminary data showing regionally decreased GM volumes in AN. Thereafter, in a recent meta-analysis including all MRI-studies using VBM Titova Hjorth, Schiöth, and Brooks (2013) reported significant GM and WM reduction in patients with acute AN and significantly increased CSF. However, neither of the two reviews systematically analyzed whether these deficits normalized after weight gain, nor did they study the time courses of GM and WM loss and rehabilitation. Thus, a comprehensive review on this matter is still lacking.

We set out to quantify GM, WM, and CSF alterations in acute and weight-recovered patients with AN with special regard to the time course of disease and weight recovery. We included all volume-based brain-analysis techniques, thereby increasing the number of studies and the power of the meta-analysis. We further, in a qualitative fashion, extracted available results on specific regions involved, on correlations with clinical parameters, and on their prognostic value for the course of the illness.

Materials and Methods

All morphometric MRI studies with AN patients were included in the current meta-analysis, whereas PET or SPECT studies or functional MRI (fMRI) were not included in the analysis. To this end, Medline, Embase, and ISI Web of Science databases were searched for studies using the terms "eating disorder" or "anorexia nervosa" and "morphological," "gray matter," "white matter," "volume," "cortical thickness," "voxel-based morphometry," or "VBM." Origi-

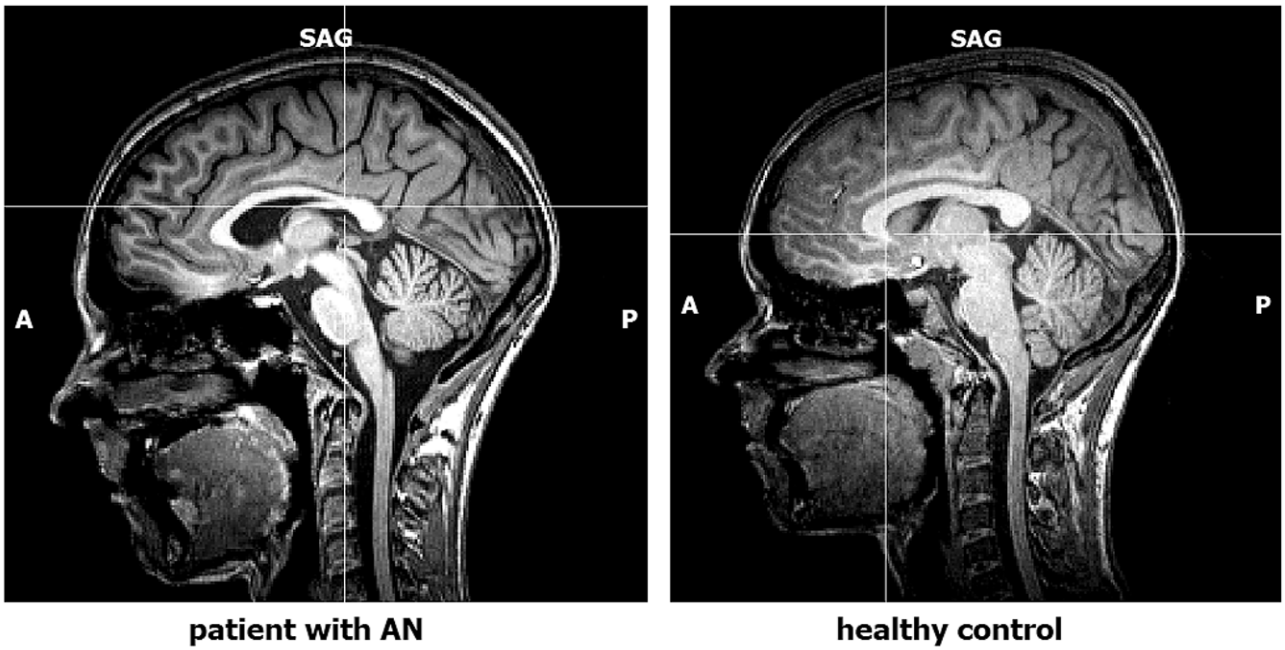

Figure 1. Volume changes in acute anorexia nervosa (AN).

nal papers focusing on volumetric changes were selected. Inclusion criteria were: (1) publication in a peer-reviewed journal, (2) cross-sectional or longitudinal case-control studies, (3) articles written in English or German, (4) publication between 1997 and June 2013. Studies on acute or recovered AN containing data on volumetric measurements of GM, WM, CSF, and intracranial volume (ICV) were further included in the quantitative meta-analysis.

For this meta-analysis, we calculated standardized global changes in GM, WM, and CSF corrected for ICV in order to compare results across studies separately for acutely ill, weight-recovered (directly after weight-restoration), and longer term weight-recovered AN. To this end, the overall mean ICV-corrected volume difference between patients and controls were calculated. Average mean volume changes were extracted from the studies, corrected for ICV, and expressed as percent volume changes of GM, WM, and CSF, respectively, of healthy controls (HC) of the same study using the same analysis method.

The statistical analysis was carried out with RevMan 5.2 (Cochrane Library, http://ims.cochrane.org/revman). ICV-corrected averages of GM, WM, and CSF, their standard deviations and the number of AN and HC of each study were entered. Standardized mean differences with 95% confidence limits (Cls) were calculated for ICV-corrected GM, WM, and CSF using a random-effects model. Due to different definitions of CSF compartments applied by different methods of analysis, only studies using the most frequently used analysis method (VBM) were included in the meta-analysis of CSF measurements. Subgroup analysis was performed for adults and adolescents for acute AN. All long-term studies on recovered subjects included adult patients, so no differentiation was possible here. Finally, longitudinal studies were used to analyze the time course of short-term weight recovery brain changes (< 6 months after weight recovery) relative to the state of admission using the same methodology as described above. Statistical heterogeneity between trials was assessed using the chi-squared (χ^2) statistic, and the extent of heterogeneity was assessed using the I^2 statistic. All tests were 2-sided and assessed at a 5%-significance level.

For descriptive reasons we calculated an average volume change over all studies. To this end averages from each study were multiplied by the number of patients included in that study, results added up and divided by the total number of patients of all studies combined.

Furthermore, we qualitatively reviewed regional volume changes as well as correlations of global and regional volume changes with clinical variables including prognosis for short- and long-term outcome of the eating disorder.

Results

Quantitative Meta-Analyses

Whole Brain Effects in Acute AN

Sixteen original studies were identified that reported changes in whole-brain volumes in acute adolescent or adult AN (see Table 1),

Table 1
GM and WM changes in MRI studies of patients with acute AN compared to healthy controls, corrected for total intracranial volume

Study	*N*/Age of AN-patients	Method	GM reduction	WM reduction
Katzman et al., 1996	13 adol., 15.4 ± 1.2 years	BIS	6.2%	3.6%
Giordano et al., 2001	20 adults, 30 ± 5.1 years	Manual tracing Amygdala/hippocampus only	27% amygdala-hippocampus	
Swayze et al., 2003	17 adults, 25.1 ± 7.3 years	BRAINS	4.2% (*ns*)	11.0%
Connan et al., 2006	16 adults, 25.4 ± 7.5 years	Manual tracing Hippocampus only	8.2% and 7.5% hippocampus	
McCormick et al., 2008	18 adults, 26.6 ± 7.2 years	BRAINS2	ACC only	12.5% ACC
Castro-Fornieles et al., 2009	12 adol., 14.5 ± 1.5 years	VBM	7.7%	6.1%
Joos et al., 2010	12 adults, 25.0 ± 4.8 years	VBM	4.0%	2.8% (*ns*)
Suchan et al., 2010	15 adults, 29.5 ± 8.2 years	VBM	0.1% (*ns*)	3.3% (*ns*)
Gaudio et al., 2011	16 adol., 15.2 ± 1.5 years	VBM	8.2%	
Boghi et al., 2011	21 adults, 29.0 ± 10.0 years	VBM	1.0% (*ns*)	7.7%
Roberto et al., 2011	32 adults, 26.9 ± 6.4 years	VBM	8.1%	5.3% (*ns*)
Brooks et al., 2011	14 adults, 26.0 ± 2.9 years	VBM	2.7% (*ns*)	–4.8% (*ns*)
Friedrich et al., 2012	12 adults, 24.3 ± 6.2 years	VBM	4.6%	0.0% (*ns*)
Mainz et al., 2012	19 adol., 15.7 ± 1.5 years	VBM	16.0%	1.9% (*ns*)
Bomba et al., 2013	11 adol., 13.6 ± 2.8 years	FSL	10.9%	6.5%
Frank et al., 2013	19 adults 23.1 ± 5.8 years	VBM	0.3% (*ns*)	1.8% (*ns*)

Note. Regional results given when global results did not reach significance; adol. = Adolescents, *ns* = not significant, BIS: Brain Imaging Software, BRAINS: Brain Research: Analysis of Images, Networks, and Systems, VBM: Voxel-Based Morphometry, FSL: FMRIB Software Library.

Table 2
MRI studies of short and long-term recovered AN-patients sorted by length of recovery

Name/Date	*N*/Age of AN patients	Method	Recovery length	Residual GM reduction	Residual WM reduction
Roberto et al., 2011	32 adults, 27.1 ± 6.4 years	VBM	Weight rec.	4.2%	1.2% (*ns*)
Swayze et al., 2003	13 adults, 25.4 ± 7.3 years	BRAINS	Weight rec.	1.9% (*ns*)	3.5% (*ns*)
Mainz et al., 2012	19 adol., 15.9 ± 1.5 years	VBM	Weight rec.	12.1%	–0.7% (*ns*)
Castro-Fornieles et al., 2009	12 adol., 14.5 ± 1.5 years	VBM	7 months post adm.	1.6% (*ns*)	–8.3%
McCormick et al., 2008	48 adults, 26.1 ± 7.2 years	BRAINS2, ACC only	1 year	4.5% rdACC (*ns*)	
Mühlau et al., 2007	22 adults, 23.7 ± 6.0 years	VBM	1.6 years	4.0%	0.7% (*ns*)
Katzman et al., 1997	6 adol., 17.0 ± 1.4 years	BIS	2.7 years	4.2%	0.5% (*ns*)
Wagner et al., 2006	30 adults, 25.0 ± 6.4 years	VBM	3 years	–0.2% (*ns*)	2.0% (*ns*)
Lambe et al., 1997	12 mixed, 18.9 ± 6.9 years	BIS	3 years	2.6%	0.5% (*ns*)
Joos et al., 2011	5 adults,19.6 ± 5.1 years	VBM	5 years	1.6% (*ns*)	0.3% (*ns*)
Friedrich et al., 2012	13 adults, 25.0 ± 4.8 years	VBM	5.7 years	0.9% (*ns*)	2.9% (*ns*)
Chui et al., 2008	66 mixed, 21.3 ± 2.3 years	INSE	6.5 years	–0.1% (*ns*)	0,00% (*ns*)
Frank, 2013	23 adults, 30.3 ± 8.8 years	VBM	7.9 years	–0.9% (*ns*)	0.8% (*ns*)

Note. Regional results given when global results did not reach significance; *ns*: not significant, adol.: adolescents, mixed: adolescents and adults; rdACC: right dorsal ACC, BIS: Brain Imaging Software, BRAINS: Brain Research: Analysis of Images, Networks, and Systems, VBM: Voxel Based Morphometry, INSE: Intensity Normalized Stereotaxic Environment for the Classification of Tissue.

Table 3
Average brain volume changes in acute and recovered AN compared to healthy controls

	Acute AN		Recovered AN (> 1.5 years)	
	%Vol.	SMD	%Vol.	SMD
Gray matter	**–5.6%**	–0.61 (–0.91, –0.31) $p < .0001$	**–1.0%**	–0.16 (–0.48, 0.16) $p = .34$
White matter	**–3.8%**	–0.39 (–0.63, –0.15) $p < .001$	**–0.7%**	–0.10 (–0.31, 0.11) $p = .36$
CSF	**12.8%**	+ 0.72(0.33, 1.12) $p < .001$	**1.3%**	0.14 (–0.09, 0.37) $p = .22$

Note. SMD: Standard mean difference, CSF: cerebro-spinal fluid.

Because three of the original studies only covered subregions of the brain, 13 studies with a total of 214 patients and 213 controls were included in the meta-analysis. In these patients, global GM was on average reduced by 5.6% compared with HC. WM was reduced by 3.7%, CSF was increased by 12.9% compared to HC (see Figure 1a). All results proved to be significant. Standardized mean differences and CIs were GM: –0.61 (–0.91, –0.31), $p < .0001$, WM: –0.39 (–0.63, –0.15), $p < .001$, CSF: 0.72 (0.33, 1.12), $p < .001$. GM and CSF outcome contained a certain degree of heterogeneity (GM: $I^2 = 55\%$, $p < .001$, CSF: $I^2 = 67\%$, $p = .004$) while WM outcome were mostly homogeneous (WM: $I^2 = 25\%$, $p = .20$). The one source of heterogeneity that could be identified was age: In studies with adolescent AN containing 71 patients, no heterogeneity could be proven ($I^2 = 0\%$, $p > .05$ for all three measures), whereas in studies with adults (142 patients) a moderate extend of heterogeneity was detected ($I^2 = 47$–54%, $p = .05$–$.07$). The studies on adolescent AN patients also showed larger effects for changes in GM and CSF than those concerning adults. WM changes did not differ significantly according to age (GM: adolescents 10.8%, adults 3.1%; WM: adolescents 3.2%, adults 4.0%; CSF: adolescents 33.1%, adults 9.0%). All subgroups were significantly different from HC (see supplementary data).

Whole Brain: Long-Term Recovered AN

Eight studies were identified that reported whole-brain data on long-term recovered AN patients with a total of 177 patients and 195 controls (all containing adults, see Table 2). One study analyzed a subregion only and was omitted from the meta-analysis.

The average duration of weight recovery was 4.4 years (range 1.6–7.9 years). GM tended to remain reduced by 1.0% (17.5% of original reduction), WM 0.7% (18.9%), while CSF tended to remain increased by 1.3% at follow-up (10.0% of original increase, see Table 3). These remaining changes did not reach significance. Standardized mean dif-

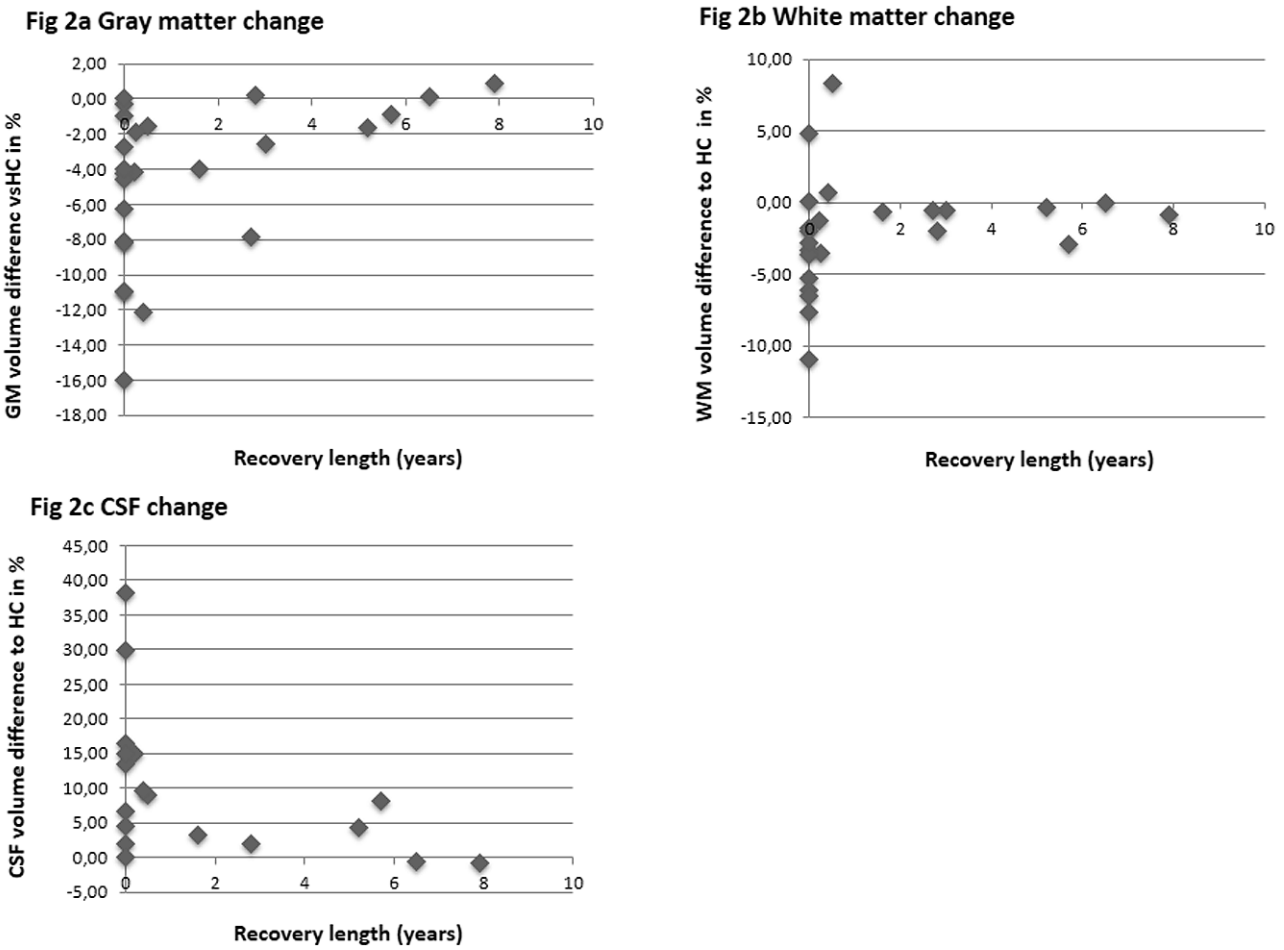

Figure 2. Average brain volume changes in acute and recovered AN compared to healthy controls.

ferences (CIs) were GM: –0.16 (–0.48, 0.16), $p = .34$, WM: –0.10 (–0.31, 0.11), $p = .36$, CSF: 0.14 (–0.09, 0.37), $p = .22$. A moderate extend of heterogeneity could be detected between studies on GM ($I^2 = 51\%$, $p = .05$), while no heterogeneity could be proven between studies on WM and CSF ($I^2 = 0\%$, $p > .05$).

Whole Brain: Time Course of Brain Recovery in Longitudinal Studies

Four longitudinal studies were identified with a total of 81 patients at admission and 76 weight-recovered patients on average 4 months after admission (range 3–6 months, see Table 1 and Table 2). Again, during the acute phase GM and WM were also reduced and CSF was increased compared to HC (see Figure 2). After short-term weight recovery, initial GM deficits were restored by 43%, WM deficits were restored completely, and CSF increases were restored by 50% compared to initial changes in acute AN. WM deficit reduction and CSF restoration were significant, GM deficit reduction did not reach significance. Standardized mean differences (CIs) were GM changes: –0.25 (–0.57, 0.06), $p = .12$, WM changes: –0.46(–0.87, –0.05), $p = .03$, CSF changes 0.92 (0.33, 1.51), $p = .002$). All studies reported significant GM changes within each study using more sensitive repeated measures statistics. Between CSF studies a moderate degree of heterogeneity could be demonstrated ($I^2 = 65\%$, $p = .04$), while between GM and WM studies a low extend could be proven ($I^2 = 0\%/I^2 = 34\%$, $p > .05$, respectively), however the small number of studies requires special care when interpreting heterogeneity findings.

Qualitative Review

Regional Volume Changes

Apart from global volume changes, some brain regions seem to show more pronounced volume changes. GM changes in hippocampal (Brooks et al., 2011; Chui et al., 2008; Connan et al., 2006; Giordano et al., 2001; Mainz et al., 2012) and cingulate regions (Brooks et al., 2011; Friederich et al., 2012; Gaudio et al., 2011; Joos et al., 2010; McCormick et al., 2008; Muhlau et al., 2007) are especially

well documented. Midbrain GM changes (Boghi et al., 2011; Friederich et al., 2012), cerebellar GM changes (Boghi et al., 2011; Mainz et al., 2012), and reductions in the left extrastriate body area in the lateral occipital cortex (Suchan et al., 2010) have also been detected. Only two studies reported increased GM in acute AN: Brooks et al. (2011) found a greater volume of the dorsolateral prefrontal cortex (DLPFC). Frank (2013) found increased medial orbitofrontal cortex in acute and recovered AN employing VBM and manual tracing analysis.

Associations Between Brain Volume Changes and Clinical Parameters

Inconsistent findings exist with respect to the association between brain volume changes and the severity of starvation as measured by the body mass index (BMI). BMI correlated inversely with GM and WM changes (Muhlau et al., 2007), while delta BMI (i.e., difference between premorbid BMI and BMI at the acute stage) correlated with GM loss (Bomba et al., 2013). A more rapid weight loss (delta-BMI/disease duration) correlated with a higher CSF increase (Boghi et al., 2011). The ACC volume correlated with the lowest lifetime BMI (Muhlau et al., 2007). GM cerebellar changes were more pronounced in patients with longer duration of illness (Boghi et al., 2011). Because other studies could not find clear associations, these results have to be regarded as preliminary.

Further studies were able to show correlations of global or regional GM changes with neuropsychological and psychopathological parameters. Global GM reduction correlated with visuospatial functioning (Rey-Figure copying, Castro-Fornieles et al., 2009). Reduced right dorsal ACC volume was related to perceptual organization and reasoning skills (McCormick et al., 2008), and reduced right inferior parietal cortex GM correlated with drive for thinness (Joos et al., 2010). Dietary restraint and BMI combined predicted 57% of the variance of increased DLPFC volume (Brooks et al., 2011), and sucrose pleasantness ratings were correlated with increased medial orbitofrontal cortex volume (Frank, 2013). Suchan et al. (2010) showed that the extrastriatal body area GM that was reduced in acute AN also had less functional connectivity with related brain areas in an fMRI examination of body-image distortion (Vocks, Busch, Grönemeyer, et al., 2010). After a body-image directed therapy the latter finding remained no longer significant (Vocks, Busch, Schulte et al., 2010).

Hormonal Effects

Referring to potential mechanisms of this widespread reduction of GM and WM, some studies implicated hormones as potential mediators. Increased cortisol serum levels present in acute AN have been linked to brain volume loss (Castro-Fornieles et al., 2009; Chui et al., 2008) and increased sulcal width, an indirect measure for GM/WM volume loss (Nogal, Pniewska-Siark, & Lewinski, 2008). The latter study also found correlations between sulcal width and thyroxine deficits. Recently, gonadal hormones were found to play a potential role, not only for sulcal width (Nogal et al., 2008), but also for amygdala and hippocampal volumes (Mainz et al., 2012). Finally, one study of recovered patients with AN linked persisting amenorrhea with decreased cognitive functioning, underlining the importance of a restoration of sex-hormones for brain recovery (Chui et al., 2008).

Clinical Prognosis

The first study to find an influence of brain volume normalization on long-term outcome of AN was conducted by McCormick et al. (2008), who documented volume reduction in right dorsal ACC in acute AN. While ACC normalization occurred with weight restoration in most patients, smaller changes predicted relapse after treatment at 1-year follow-up in a longitudinal study.

Discussion

GM and WM Global Changes

We quantified marked GM (5.6%) and WM (3.7%) decreases as well as CSF increases (12.9%) in studies of patients with acute AN. These meta-analytic results fit well with findings of the smaller meta-analysis of AN by Titova et al. (2013), who also found GM and WM to be significantly reduced and CSF significantly increased compared to HC. We could show that the volume changes in GM and CSF were more pronounced in adolescent patients than in adults. Adolescent studies also presented more homogeneous results. For recovered patients with AN, this is the first time, that potential residuals of volumetric brain deviations have been examined systematically across different studies. Short-term weight recovery in longitudinal studies resulted in about half of GM and CSF changes being normalized relatively quickly upon initial weight recovery (on average after 4 months). WM seemed to increase more rapidly during the first months after weight gain to almost total recovery, showing a markedly different temporal pattern than GM and CSF. The meta-analysis of the long-term recovered patients did not find a significant residual volume change. However, there could be small ($z < -1$) persisting deficits even after 2–8 years of weight recovery, as all parameters found in acutely ill patients remained altered in the same direction in long-term weight-recovered patients (GM –1.0%, WM –0.7%, CSF +1.3%). As these effects were small, the sample-size potentially did not suffice to show their significance.

The differential time courses for GM and WM recovery point to the involvement of potentially different mecha-

nisms. Moreover, while GM changes seem to be more pronounced in adolescent patients, WM changes seem not to show an age-related effect. One hypothesis for the age-related effect could be that a greater GM plasticity in the still developing adolescent brain leads to a greater susceptibility to starvation effects.

The relatively quick regain of almost half of the GM volume loss is mirrored by the first two case studies analyzing the inverse effect of weight loss on brain volume in patients with AN. They found a rapidly reoccurring GM loss in patients exhibiting a relapse of the eating disorder and significant weight loss in a similar timeframe of 3–4 months (Seitz et al., under review; Suda et al., 2011).

GM Regional Changes

Apart from global GM changes, our qualitative summary indicated that some regions like the hippocampus, cingulate gyrus, and the midbrain seemed to be especially susceptible to regional GM change. This is in line with the review of Van den Eynde et al. (2011) and also fits well with recent findings from the previous ALE meta-analysis (Titova et al., 2013), which is particularly suited to summarize regional GM changes across different studies on a voxel-by-voxel level: They reported regional overlap for hippocampus (three studies) and for parietal cortex and for lentiform and caudate nuclei (two studies each) as well as nonoverlapping cingulate areas. GM volume deficits in the hippocampal region might be involved in memory and learning impairments (Schacter, Norman, & Koutstaal, 1998). Various studies have investigated memory and learning in AN with mixed results. However, there seem to be small but significant deficits especially with regard to verbal and visuospatial learning and memory (see Nikendei et al., 2010, for a recent overview). Indeed, research from our group (Buehren et al., 2011) found correlations between impaired memory and levels of estrogen as well as between the estrogen-stimulating hormone FSH and amygdala and hippocampus volumes (Mainz et al., 2012). A direct link between hippocampal volume and memory impairment, however, is missing so far (Connan et al., 2006; Giordano et al., 2001). Volume changes in the cingulate gyrus have been associated with clinical outcomes of patients (McCormick et al., 2008). The ACC is involved in reward networks (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005) and affective processing (Bush, Luu, & Posner, 2000). This brain region could furthermore be linked to deficits in set-shifting among AN patients (Holliday et al., 2005). In a functional MRI study of AN patients (Zastrow et al., 2009), patients showed significantly less activity in the ACC correlating with their set-shifting ability. Regarding the extrastriate body area, Suchan and coworkers (2010) conducted a series of elegant studies. They showed that the same extrastriate region showing reduced GM volume in acute AN also had less functional connectivity in a functional MRI task concerning body image distortion (Vocks, Busch, Grönemeyer et al., 2010). This hypoconnectivity partially normalized after body-image distortion specific psychotherapeutic interventions (Vocks, Busch, Schulte et al., 2010). Two studies found increased regional GM volume changes in DLPFC and orbitofrontal cortex against the trend of general volume loss (Brooks et al., 2011; Frank, 2013). These changes were linked to dietary restraint and sucrose liking respectively. These might represent preexisting changes in the brain that predispose for the development of AN or the changes that might also occur secondary to disease related plasticity.

WM Regional Changes: Diffusion Tensor Imaging (DTI)

Regional structural integrity of WM in AN was recently studied using DTI in two preliminary studies, which found reduced WM fiber tract integrity in the fimbria fornix bilaterally, fronto-occipital fasciculus and posterior cingulum (Kazlouski et al., 2011), and posterior thalamic radiation (Frieling et al., 2012). However, the findings between the two studies did not correspond. The fimbria fornix is an important fiber tract originating from the hippocampus and projecting to the midbrain and the cingulate structures. All three regions have been found to show reduced GM volumes. Their fractional anisotropy (FA), the measure for WM tract integrity, inversely correlated with harm avoidance and trait anxiety ratings of patients. This could form a possible link between GM and WM structural changes and clinical symptoms; however these findings have to be replicated before further interpretation.

Potential Pathomechanisms of Brain Volume Change in AN

GM and WM volume reduction found during starvation of AN could mainly represent trophic changes that are reversible upon weight gain. A smaller part of these changes might result from either preexisting deviations or disease process related alterations (“scars”) that are less likely to recover. The acute trophic changes seem to consist in smaller neurons, shorter dendrites, and less synapses (Neumärker et al., 1997), and are accompanied and potentially mediated by increased cortisol and reduced estrogen levels. They could lead to less connectivity between the neurons and less new connections being formed during learning processes. This reduced neuroplasticity might be responsible for neuropsychological deficits, such as impaired memory and learning and reduced cognitive flexibility. It is tempting to relate these deficits with the behavioral rigidity, preoccupation with

the illness, social withdrawal and the low motivation to change in therapy of patients. This time period of "missed learning" and paused normal brain development, especially in chronically ill patients, could possibly explain any long-lasting effect of reduced GM and WM volume even after weight recovery. It might also partly explain the increased rate of affective disorders found in weight-recovered patients with AN later in their lives (Wentz, Gillberg, Anckarsäter, Gillberg, & Råstam, 2009). This cannot, however, be distinguished from potentially preexisting brain changes that predisposed for AN and prevail after recovery. They could equally explain remaining volume differences and increased comorbidities. Very large population-based or sibling studies would be needed to learn more about preexisting deviations.

To date, not much is known about the mechanism of the striking phenomenon of relatively quick volume alterations during weight changes in AN patients. The fact that substantial regeneration is possible upon weight restoration makes significant neuronal cell death unlikely, because these cells only minimally regenerate. Also colloidal osmotic effects seem unlikely, as they would rather favor an increase in GM/WM volumes, not a decrease. Thus, the observed effect could be better explained by a reduction in the number of supporting glia cells, in the size of neurons and glia cell bodies, or in altered protein synthesis that results in fewer and smaller dendrites and synaptic junctions. This latter part of the hypothesis receives support from one of the few neurohistological postmortem examinations where reduced dendritic ramification patterns and reduced dendritic spine density were found in a 13.5-year-old girl with AN (Neumärker et al., 1997). In addition, studies with starved rats (Garcia-Ruiz, Diaz-Cintra, Cintra, & Corkidi, 1993) and malnourished infants (Benitez-Bribiesca, De, & Mansilla-Olivares, 1999) revealed smaller neurons and fewer and smaller dendrites in these individuals. There are indications that these changes might be mediated by increased cortisol levels and/or decreased thyroid and gonadal hormones. However evidence is scarce and information on an association with further potentially trophic hormones that are altered in AN-like leptin or brain-derived neurotrophic growth factor (BDNF) are lacking (Ehrlich et al., 2009; Hebebrand et al., 1997; Holtkamp et al., 2006).

Attempts have been made to gain further insight into the pathophysiological mechanisms of GM and WM changes using magnetic resonance spectroscopy (MRS), but results are conflicting (for a recent summary of the literature, see Blasel et al., 2012). While some authors reported increased cholin as a marker of altered membrane turnover (Blasel et al., 2012; Castro-Fornieles et al., 2010; Hentschel et al., 1999; Möckel et al., 1999; Schlemmer et al., 1998), others do not support these findings (Castro-Fornieles et al., 2007; Grzelak et al., 2005; Roser et al., 1999). These results could be interpreted as catabolic changes of neural and glial cell membranes during starvation. Results concerning the neuronal cell marker N-acecylic aspartate (NAA) are also mixed. It has been found to be reduced (Castro-Fornieles et al., 2007), unchanged (Grzelak et al., 2005; Hentschel et al., 1999; Roser et al., 1999), and increased (Blasel et al., 2012). Furthermore, some studies showed reduced concentrations of the neurotransmitter glutamate (Castro-Fornieles et al., 2010; Ohrmann et al., 2004), while others found increased levels (Blasel et al., 2012). Apart from methodological differences, these findings seem to represent different phases of brain metabolism during starvation and refeeding. Results during starvation or early stages in therapy tend to show low levels of cholin, NAA, and glutamate thought to reflect hypometabolism or reduced cell mass. During refeeding, hypermetabolism in the brain tissue seems to reflect rebuilding processes in the brain (Blasel et al., 2012). However, these interpretations have be considered with care as not all studies contained information about the timepoint in therapy and the stage of weight recovery at which the patients were scanned. Two longitudinal studies appear to support the latter hypothesis: The state of hyper-metabolism seems to persist even after short-term weight rehabilitation (Castro-Fornieles et al., 2010; Möckel et al., 1999). These results generally tend to be more pronounced for GM (Blasel et al., 2012). Some studies, however, found reduced lipid signals in WM (Grzelak et al., 2005; Roser et al., 1999) in acute patients with AN, interpreted as a potential correlate of WM volume reduction.

Limitations

There is always a risk when combining different methods. However, to include as many studies as possible, we did not limit our meta-analysis to VBM studies only. To minimize potential errors, we standardized all results by dividing them by the total intracranial volume, by comparing them to results of healthy controls, acquired with the same method, and by using standardized mean differences in the statistical analysis.

Conclusion

GM and WM are diminished in acute AN, while recovered individuals with AN show nearly normalized brain volumes after weight rehabilitation. To date, only a few longitudinal studies with small sample sizes and short follow-up periods exist. Thus, the implications for researchers are threefold: First, to conduct longer and larger studies to confirm potential long-lasting deficits; second, to determine whether a residual volume loss applies to all or just selective patients with AN; third, to test the pathophysiological hypotheses. Basic research and longitudinal multidimensional clinical studies are needed to learn more about the requirements for a complete recov-

ery of the brain of patients with AN. Studies with siblings could be used to detect preexisting changes in the brain predisposing for AN and help differentiating them from changes resulting from the illness ("scars"). Clinicians should focus on early weight recovery to end the catabolic state that the brain is affected by after acute weight loss as quickly as possible. They should also keep in mind that the learning abilities and cognitive flexibility necessary for a successful psychotherapeutic treatment may only be present after successful partial weight rehabilitation. Furthermore, extensive (re-)training of these cognitive functions like in cognitive remediation therapy might positively influence short- and long-term outcome of these patients.

References

Benitez-Bribiesca, L., De, la R.-A., & Mansilla-Olivares, A. (1999). Dendritic spine pathology in infants with severe protein-calorie malnutrition. *Pediatrics*, *104*(2), e21.

Blasel, S., Pilatus, U., Magerkurth, J., von Stauffenberg, M., Vronski, D., Mueller, M., . . . Hattingen, E. (2012). Metabolic gray matter changes of adolescents with anorexia nervosa in combined MR proton and phosphorus spectroscopy. *Neuroradiology*, *54*, 753–764. doi 10.1007/s00234-011-1001-9

Boghi, A., Sterpone, S., Sales, S., D'Agata, F., Bradac, G. B., Zullo, G., & Munno, D. (2011). In vivo evidence of global and focal brain alterations in anorexia nervosa. *Psychiatry Research*, *192*, 154–159.

Bomba, M., Riva, A., Veggo, F., Grimaldi, M., Morzenti, S., Neri, F., & Nacinovich, R. (2013). Impact of speed and magnitude of weight loss on the development of brain trophic changes in adolescents with anorexia nervosa: A case control study. *Italian Journal of Pediatrics*, *39*, 14. doi 10.1186/1824-7288-39-14

Brooks, S. J., Barker, G. J., O'Daly, O. G., Brammer, M., Williams, S. C., Benedict, C., . . . Campbell, I. C. (2011). Restraint of appetite and reduced regional brain volumes in anorexia nervosa: A voxel-based morphometric study. *BMC Psychiatry*, *11*, 179. doi 10.1186/1471-244X-11-179

Buehren, K., Konrad, K., Schaefer, K., Kratzsch, J., Kahraman-Lanzerath, B., Lente, C., & Herpertz-Dahlmann, B. (2011). Association between neuroendocrinological parameters and learning and memory functions in adolescent anorexia nervosa before and after weight recovery. *Journal of Neural Transmission (Vienna, Austria: 1996)*, *118*, 963–968. doi 10.1007/s00702-010-0567-4

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*, 215–222.

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. *Journal of Psychiatric Research*, *43*, 331–340.

Castro-Fornieles, J., Bargalló, N., Lázaro, L., Andrés, S., Falcon, C., Plana, M. T., & Junqué, C. (2007). Adolescent anorexia nervosa: Cross-sectional and follow-up frontal gray matter disturbances detected with proton magnetic resonance spectroscopy. *Journal of Psychiatric Research*, *41*, 952–958. doi 10.1016/j.jpsychires.2006.09.013

Castro-Fornieles, J., Garcia, A. I., Lazaro, L., Andrés-Perpiñá, S., Falcón, C., Plana, M. T., & Bargallo, N. (2010). Prefrontal brain metabolites in short-term weight-recovered adolescent anorexia nervosa patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*, 1049–1053. doi 10.1016/j.pnpbp.2010.05.020

Chui, H. T., Christensen, B. K., Zipursky, R. B., Richards, B. A., Hanratty, M. K., Kabani, N. J., . . . Katzman, D. K. (2008). Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa. *Pediatrics.*, *122*, e426–e437.

Connan, F., Murphy, F., Connor, S. E., Rich, P., Murphy, T., Bara-Carill, N., . . . Treasure, J. (2006). Hippocampal volume and cognitive function in anorexia nervosa. *Psychiatry Research*, *146*, 117–125.

Ehrlich, S., Salbach-Andrae, H., Eckart, S., Merle, J. V., Burghardt, R., Pfeiffer, E., . . . Hellweg, R. (2009). Serum brain-derived neurotrophic factor and peripheral indicators of the serotonin system in underweight and weight-recovered adolescent girls and women with anorexia nervosa. *Journal of Psychiatry and Neuroscience: JPN*, *34*, 323–329.

Frank, G. K., Shott, M. E., Hagman, J. O., & Mittal, V. A. (2013). Alterations in brain structures related to taste reward circuitry in ill and recovered anorexia nervosa and in bulimia nervosa. *American Journal of Psychiatry, 170*, 1152–1160. doi 10.1176/appi.ajp.2013.12101294

Friederich, H. C., Walther, S., Bendszus, M., Biller, A., Thomann, P., Zeigermann, S., . . . Herzog, W. (2012). Gray matter abnormalities within cortico-limbic-striatal circuits in acute and weight-restored anorexia nervosa patients. *Neuroimage, 59*, 1106–1113.

Frieling, H., Fischer, J., Wilhelm, J., Engelhorn, T., Bleich, S., Hillemacher, T., . . . Peschel, T. (2012). Microstructural abnormalities of the posterior thalamic radiation and the mediodorsal thalamic nuclei in females with anorexia nervosa: A voxel-based diffusion tensor imaging (DTI) study. *Journal of Psychiatric Research, 46*, 1237–1242. doi 10.1016/j.jpsychires.2012.06.005

Garcia-Ruiz, M., Diaz-Cintra, S., Cintra, L., & Corkidi, G. (1993). Effect of protein malnutrition on CA3 hippocampal pyramidal cells in rats of three ages. *Brain Research*, *625*, 203–212.

Gaudio, S., Nocchi, F., Franchin, T., Genovese, E., Cannata, V., Longo, D., & Fariello, G. (2011). Gray matter decrease distribution in the early stages of anorexia nervosa restrictive type in adolescents. *Psychiatry Research*, *191*, 24–30.

Giordano, G. D., Renzetti, P., Parodi, R. C., Foppiani, L., Zandrino, F., Giordano, G., & Sardanelli, F. (2001). Volume measurement with magnetic resonance imaging of hippocampus-amygdala formation in patients with anorexia nervosa. *Journal of Endocrinological Investigation*, *24*, 510–514.

Grzelak, P., Gajewicz, W., Wyszogrodzka-Kucharska, A., Rotkiewicz, A., Stefańczyk, L., Góraj, B., & Rabe-Jabłońska, J. (2005). Brain metabolism alterations in patients with anorexia nervosa observed in 1H-MRS. *Psychiatria Polska*, *39*, 761–771.

Hebebrand, J., Blum, W. F., Barth, N., Coners, H., Englaro, P., Juul, A., . . . Remschmidt, H. (1997). Leptin levels in patients with anorexia nervosa are reduced in the acute stage and elevated upon short-term weight restoration. *Molecular Psychiatry*, *2*, 330–334.

Hentschel, J., Möckel, R., Schlemmer, H. P., Markus, A., Göpel, C., Gückel, F., ... Schmidt, M. H. (1999). 1H-MR-Spektroskopie bei Anorexia nervosa: Charakteristische Unterschiede zwischen Patienten und gesunden Probanden [1H-MR spectroscopy in anorexia nervosa: The characteristic differences between patients and healthy subjects]. *RöFo: Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin*, *170*, 284–289. doi 10.1055/s-2007-1011041

Holliday, J., Tchanturia, K., Landau, S., Collier, D., & Treasure, J. (2005). Is impaired set-shifting an endophenotype of anorexia nervosa? *American Journal of Psychiatry.*, *162*, 2269–2275.

Holtkamp, K., Herpertz-Dahlmann, B., Hebebrand, K., Mika, C., Kratzsch, J., & Hebebrand, J. (2006). Physical activity and restlessness correlate with leptin levels in patients with adolescent anorexia nervosa. *Biological Psychiatry*, *60*, 311–313.

Joos, A., Kloppel, S., Hartmann, A., Glauche, V., Tuscher, O., Perlov, E., ... Tebartz van, E. L. (2010). Voxel-based morphometry in eating disorders: Correlation of psychopathology with gray matter volume. *Psychiatry Research*, *182*, 146–151.

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. *Archives of Pediatrics and Adolescent Medicine*, *151*, 793–797.

Kazlouski, D., Rollin, M. D. H., Tregellas, J., Shott, M. E., Jappe, L. M., Hagman, J. O., ... Frank, G. K. W. (2011). Altered fimbria-fornix white matter integrity in anorexia nervosa predicts harm avoidance. *Psychiatry Research*, *192*, 109–116. doi 10.1016/j.pscychresns.2010.12.006

Mainz, V., Schulte-Rüther, M., Fink, G. R., Herpertz-Dahlmann, B., & Konrad, K. (2012). Structural brain alterations in anorexia nervosa patients before and after weight recovery. *Psychosomatic Medicine, 51*, 832–841.

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. *International Journal of Eating Disorders*, *41*, 602–610.

Möckel, R., Schlemmer, H. P., Gückel, F., Göpel, C., Becker, G., Köpke, J., ... Georgi, M. (1999). [1H-MR spectroscopy in anorexia nervosa: Reversible cerebral metabolic changes]. *RöFo: Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin*, *170*, 371–377. doi 10.1055/s-2007-1011056

Muhlau, M., Gaser, C., Ilg, R., Conrad, B., Leibl, C., Cebulla, M. H., ... Nunnemann, S. (2007). Gray matter decrease of the anterior cingulate cortex in anorexia nervosa. *American Journal of Psychiatry.*, *164*, 1850–1857.

Neumärker, K. J., Dudeck, U., Meyer, U., Neumärker, U., Schulz, E., & Schönheit, B. (1997). Anorexia nervosa and sudden death in childhood: Clinical data and results obtained from quantitative neurohistological investigations of cortical neurons. *European Archives of Psychiatry and Clinical Neuroscience*, *247*, 16–22.

Nikendei, C., Funiok, C., Pfüller, U., Zastrow, A., Aschenbrenner, S., Weisbrod, M., ... Friederich, H.-C. (2010). Memory performance in acute and weight-restored anorexia nervosa patients. *Psychological Medicine*, *41*, 829–838. doi 10.1017/S0033291710001121

Nogal, P., Pniewska-Siark, B., & Lewinski, A. (2008). Relation of trophic changes in the central nervous system, measured by the width of cordical sulci, to the clinical course of anorexia nervosa (II). *Neuroendocrinology Letters, 29*, 879–883.

Ohrmann, P., Kersting, A., Suslow, T., Lalee-Mentzel, J., Donges, U.-S., Fiebich, M., ... Pfleiderer, B. (2004). Proton magnetic resonance spectroscopy in anorexia nervosa: Correlations with cognition. *Neuroreport*, *15*, 549–553.

Roser, W., Bubl, R., Buergin, D., Seelig, J., Radue, E. W., & Rost, B. (1999). Metabolic changes in the brain of patients with anorexia and bulimia nervosa as detected by proton magnetic resonance spectroscopy. *The International Journal of Eating Disorders*, *26*, 119–136.

Schacter, D. L., Norman, K. A., & Koutstaal, W. (1998). The cognitive neuroscience of constructive memory. *Annual Review of Psychology*, *49*, 289–318.

Schlemmer, H. P., Möckel, R., Marcus, A., Hentschel, F., Göpel, C., Becker, G., ... Georgi, M. (1998). Proton magnetic resonance spectroscopy in acute, juvenile anorexia nervosa. *Psychiatry Research*, *82*, 171–179.

Seitz, J., Bühren, K, Bitar, R, von Polier, G, Herpertz-Dahlmann, & Konrad, K. (under review). *Consistant regionally specific gray matter increase and decrease in a relapsing patient with anorexia nervosa.*

Suchan, B., Busch, M., Schulte, D., Grönemeyer, D., Herpertz, S., & Vocks, S. (2010). Reduction of gray matter density in the extrastriate body area in women with anorexia nervosa. *Behavioral Brain Research*, *206*, 63–67.

Suda, M., Narita, K., Takei, Y., Aoyama, Y., Takahashi, K., Yuki, N., ... Mikuni, M. (2011). Changes in gray matter volume with rapid body weight changes in anorexia nervosa: A voxel-based morphometric study. *Biological Psychiatry, 70*, 35–36.

Swayze, V. W., Andersen, A. E., Andreasen, N. C., Arndt, S., Sato, Y., & Ziebell, S. (2003). Brain tissue volume segmentation in patients with anorexia nervosa before and after weight normalization. *International Journal of Eating Disorders*, *33*, 33–44.

Titova, O. E., Hjorth, O. C., Schiöth, H. B., & Brooks, S. J. (2013). Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: A meta-analysis of VBM studies. *BMC Psychiatry*, *13*, 110. doi 10.1186/1471-244X-13-110

Van den Eynde, F., Suda, M., Broadbent, H., Guillaume, S., Van den Eynde, M., Steiger, H., ... Schmidt, U. (2011). Structural magnetic resonance imaging in eating disorders: A systematic review of voxel-based morphometry studies. *European Eating Disorders Review, 20*, 94–105.

Vocks, S., Busch, M., Grönemeyer, D., Schulte, D., Herpertz, S., & Suchan, B. (2010). Neural correlates of viewing photographs of one's own body and another woman's body in anorexia and bulimia nervosa: An fMRI study. *Journal of Psychiatry and Neuroscience*, *35*, 163–176.

Vocks, S., Busch, M., Schulte, D., Grönemeyer, D., Herpertz, S., & Suchan, B. (2010). Effects of body image therapy on the activation of the extrastriate body area in anorexia nervosa: An fMRI study. *Psychiatry Research*, *183*, 114–118. doi 10.1016/j.pscychresns.2010.05.011

Wentz, E., Gillberg, I. C., Anckarsäter, H., Gillberg, C., & Råstam, M. (2009). Adolescent-onset anorexia nervosa: 18-year outcome. *The British Journal of Psychiatry*, *194*, 168–174. doi 10.1192/bjp.bp.107.048686

Zastrow, A., Kaiser, S., Stippich, C., Walther, S., Herzog, W., Tchanturia, K., ... Friederich, H. C. (2009). Neural correlates of impaired cognitive-behavioral flexibility in anorexia nervosa. *American Journal of Psychiatry*, *166*, 608–616.

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CME-Fragen

1. Welche der folgenden Aussagen trifft nicht auf Patienten mit akuter Anorexia Nervosa zu?
   a) Das Volumen der grauen Substanz ist erniedrigt
   b) Das Volumen der weißen Substanz ist erniedrigt
   c) Das Liquorvolumen ist erhöht
   d) Diese Veränderungen sind mit bloßem Auge fast nie zu erkennen
   e) Jugendliche haben größere Volumenverluste der grauen Substanz als Erwachsene

2. Welche Aussage zur Volumenänderung bei Gewichtsrehabilitation treffen nicht zu
   a) Die Verlust an grauer Substanz ist nach akuter Gewichtsrehabilitation wieder zu ca. 50% ausgeglichen
   b) Der weitgehende Ausgleich des Volumenverlustes der grauen Substanz scheint mehrere Jahre zu erfordern
   c) Der Verlust der weißen Substanz scheint bereits bei Gewichtsrehabilitation fast vollständig ausgeglichen zu sein
   d) Ein Rest-Volumenverlust ("Narbe") kann auch nach 2–8 Jahren nicht ausgeschlossen werden
   e) Eine mangelnder Ausgleich des Volumenverlustes im Gehirn hat keine Auswirkung auf die klinische Prognose

3. Welche Regionen im Gehirn sind besonders betroffen
   a) Die graue Substanz scheint global betroffen zu sein, besonders Hippocampus und Hirnstamm
   b) Die graue Substanz scheint global betroffen zu sein, besonders Hippocampus und Cingulum
   c) Die graue Substanz scheint global betroffen zu sein, besonders Cingulum und Hirnstamm
   d) Die graue Substanz scheint nicht global betroffen zu sein, wohl aber Hippocampus und Hirnstamm
   e) Die graue Substanz schein nicht global betroffen zu sein, wohl aber Hippocampus und Cingulum

4. Mit welchen klinischen Parametern ist der Volumenverlust in der Starvation nicht assoziiert?
   a) Niedriger Body Mass Index bei Aufnahme
   b) Hoher Gewichtsverlust vor Aufnahme
   c) Niedrigeres neuropsychologisches Funktionsniveau
   d) Erhöhte Marker für neuronalen Zelltod
   e) Erhöhtes Cortisol und erniedrigte Sexualhormone

5. Welche Aussagen zur Pathophysiologie treffen nicht zu?
   a) Postmortem Studien weisen auf eine geringere Dendriten- und Synapsen-Dichte hin
   b) Ödembildung durch erniedrigte Serumproteine könnte der Volumenabnahme im Gehirn zu Grunde liegen
   c) Diffusions-gewichtete (DTI) Studien finden strukturelle Veränderungen in der weißen Substanz
   d) Spektroskopische (MRS) Studien finden Hinweise für katabole Prozesse in der akuten Starvation
   e) Spektroskopische (MRS) Studien finden Hinweise für anabole Prozesse nach Gewichtsrehabilitation

Um Ihr CME-Zertifikat zu erhalten (mind. 3 richtige Antworten), schicken Sie bitte den ausgefüllten Fragebogen **mit einem frankierten Rückumschlag** bis zum 28.2.2014 an die nebenstehende Adresse. Später eintreffende Antworten können nicht mehr berücksichtigt werden.

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FORTBILDUNGSZERTIFIKAT

Die Ärztekammer Niedersachsen erkennt hiermit 2 Fortbildungspunkte an.

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Kinder- und Jugendpsychiatrie und Psychotherapie 1/2014

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«Morphological Changes in the Brain of Acutely Ill and Weight-Recovered Patients with Anorexia Nervosa – A Meta-Analysis and Qualitative Review»

Die Antworten bitte deutlich ankreuzen!

	1	2	3	4	5
a.	☐	☐	☐	☐	☐
b.	☐	☐	☐	☐	☐
c.	☐	☐	☐	☐	☐
d.	☐	☐	☐	☐	☐
e.	☐	☐	☐	☐	☐

Ich versichere, alle Fragen ohne fremde Hilfe beantwortet zu haben.

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