Supplementary Material for

**Dynamic changes in white matter microstructure in anorexia nervosa: findings from a longitudinal study**

# SM Methods

## SM Sample

We analyzed the data of a total of 120 female volunteers: 60 healthy controls (HC) and 60 acute patients of anorexia nervosa (acAN). The cross-sectional arm (contrast: acAN at timepoint 1 [acAN-Tp1] versus HC) included 56 subjects per group, of which 15 patients did not participate in the longitudinal arm. 44 acAN after weight restoration (acAN-Tp2) were included in the comparison between acAN-Tp2 and HC. However, not all HC which were included in the cross-sectional comparison between acAN-Tp1 and HC were also included in the comparison between acAN-Tp2 and HC. Therefore, four additional HC were recruited; resulting into 60 HC in total (to optimize the pairwise age-matching). For the longitudinal study arm, the data of 44 acAN was analyzed at Tp1 and Tp2. This sample also includes the data of 27 subjects of the acAN-Tp1 sample of Pfuhl *et al.* (2016). For the cross-sectional arm 89% acAN-Tp1 and 66% HC are overlapping with Pfuhl *et al.* (2016). Additionally, our sample was overlapping with Bernardoni *et al.* (2016) who investigated cortical thickness (CT) in a similar longitudinal and cross-sectional design. From our longitudinal sample 72% were also analysed in Bernardoni *et al.* (2016), while in the cross-sectional design there was an overlap of 80%.

## SM MRI acquisition

Data acquisition was performed at Neuroimaging Center, Technische Universität Dresden using a 3 T whole-body magnetic resonance imaging (MRI) system (Tim Trio, Siemens, Erlangen, Germany). As in our previous studies in anorexia nervosa (AN; e.g. King *et al.* 2015; Bernardoni *et al.* 2016; Pfuhl *et al.* 2016), all participants underwent MRI between 8:00 a.m. and 9:00 a.m. following an overnight fast.

Diffusion tensor imaging (DTI) data was collected using a spin-echo sequence at 2.4 mm3 isotropic voxel resolution, 307×307×144 mm³ field of view (FoV), 128×128 matrix size, 60 slices, no inter slice gap, TE=104 ms, TR=15 s, BW=2056 Hz/Px, GRAPPA acceleration factor 2, 24 reference lines, and prescan normalize. Thirty-two diffusion sensitizing gradients (b=1300 s/mm2) were applied and four images without diffusion weighting (b=0 s/mm2) were acquired.

Additionally, high-resolution 3D T1-weighted structural scans were acquired using a rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters: voxel size=1.0×1.0×1.0 mm, FoV=256×224×176 mm3, 176 sagittal slices, no inter slice gap, TE=2.26 ms, TR=1.9 s, flip angle=9°, bandwidth of 200 Hz/pixel, and prescan normalize.

## SM Inclusion/Exclusion criteria

AcAN were admitted to an eating disorder program at a major university hospital. HCs were recruited through advertisements among middle school, high school, and university students. Ascertained by SIAB-EX and our semi-structured interview HC did not have a lifetime body mass index (BMI) below the 10th age percentile (when younger than 18 years)/BMI below 18.5kg/m2 (when older than 18 years). Further, participants of all study groups had no lifetime history of any of the following clinical diagnoses: organic brain syndrome, schizophrenia, substance dependence, psychosis NOS, bipolar disorder, bulimia nervosa, or binge-eating disorder (or “regular” binge eating - defined as bingeing at least once weekly for three or more consecutive months). Further exclusion criteria for all participants were intelligence quotient (IQ) lower than 85; obesity, current substance abuse; current inflammatory, neurologic, or metabolic illness; chronic medical or neurological illness that could affect appetite, eating behavior, or body weight (e.g., diabetes); clinically relevant anemia; pregnancy; breast feeding.

One patient participating in the longitudinal study (Tp1 and Tp2) took antidepressants (Sertralin 50mg/day). All other patients did not take any psychotropic medication at the time of scanning and within two weeks prior to the study. Besides, three were diagnosed with major depression disorder.

## SM Clinical assessments

Diagnoses was established as mentioned previously with the SIAB-EX (Structured interview for anorexia and bulimia nervosa for DSM-IV; Fichter & Quadflieg 2002). The SIAB-EX is a well-validated 87-item semi-standardized interview that assesses the prevalence and severity of specific eating-related psychopathology over the past three months. The interview provides diagnoses according to the ICD-10 and DSM-IV and is suitable for adolescents as well as adults. A good inter-rater reliability (k=.81) for the diagnostic interview has been demonstrated (Fichter & Quadflieg 2002). Interviews were conducted by clinically experienced and trained research assistants under the supervision of the attending child and adolescent psychiatrist.

For AN, comorbid psychiatric diagnoses other than eating disorders were derived from medical records and confirmed by an expert clinician with over 10 years of experience after careful chart review (including consideration of medical and psychiatric history, physical examination, routine blood tests, urine analysis, and a range of psychiatric screening instruments and the SIAB-EX interview). All diagnostic information was ascertained at the time of treatment and the principal investigator of this study is also the chief consultant of the eating disorder treatment center.

We used a short version of the German adaptation of the Wechsler Intelligence Scale for Children (Petermann & Petermann 2006), which included the following subtests: vocabulary, letter number sequencing, matrix reasoning, and symbol search. The short version of the German adaptation of the Wechsler Adult Intelligence Scale (von Aster *et al.* 2006) included the subtests: picture completion, digit symbol coding, similarities and arithmetics.

Handedness was assessed using a short version of the Annett Scale of Hand Preference (Annett 1970). This questionnaire asks for handedness in typical daily life situations as writing or brushing teeth. Response categories range from 0 ‘right hand’, 1 ‘both hands’ to 2 ‘left hand’. A mean score for handedness was calculated.

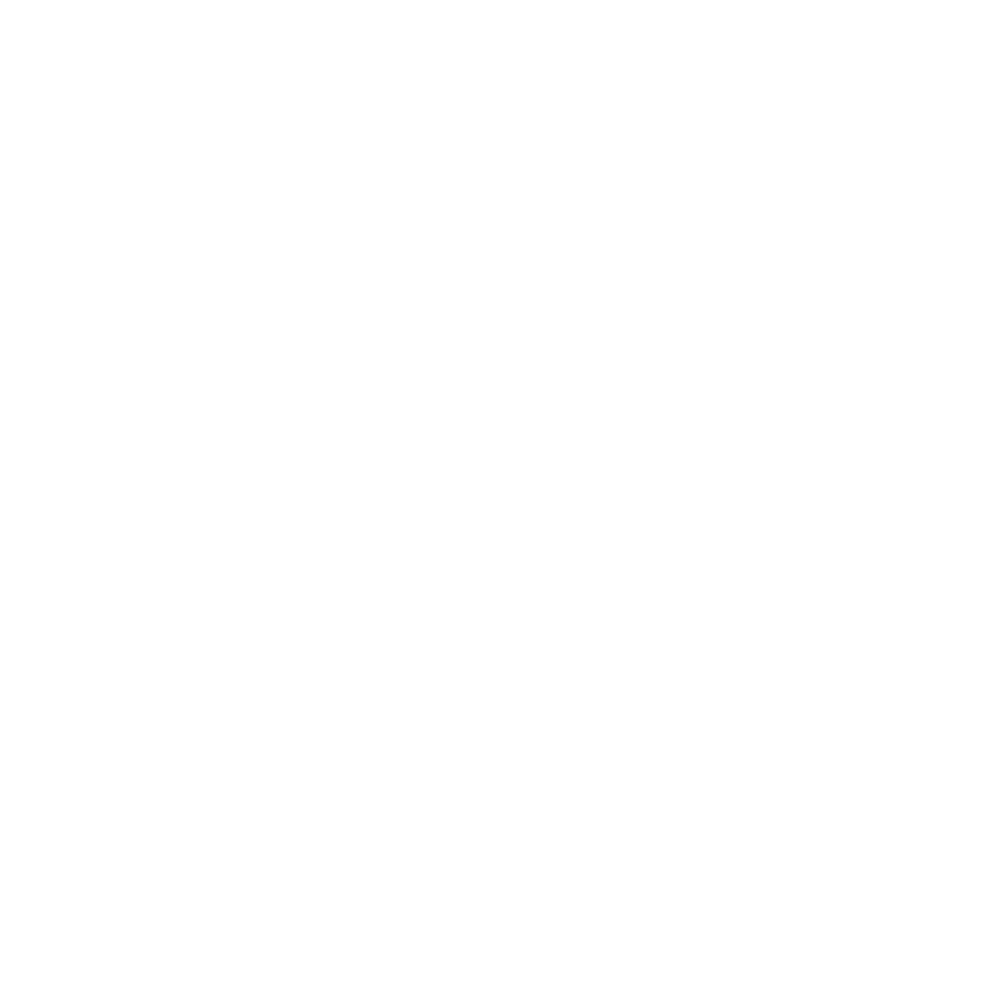
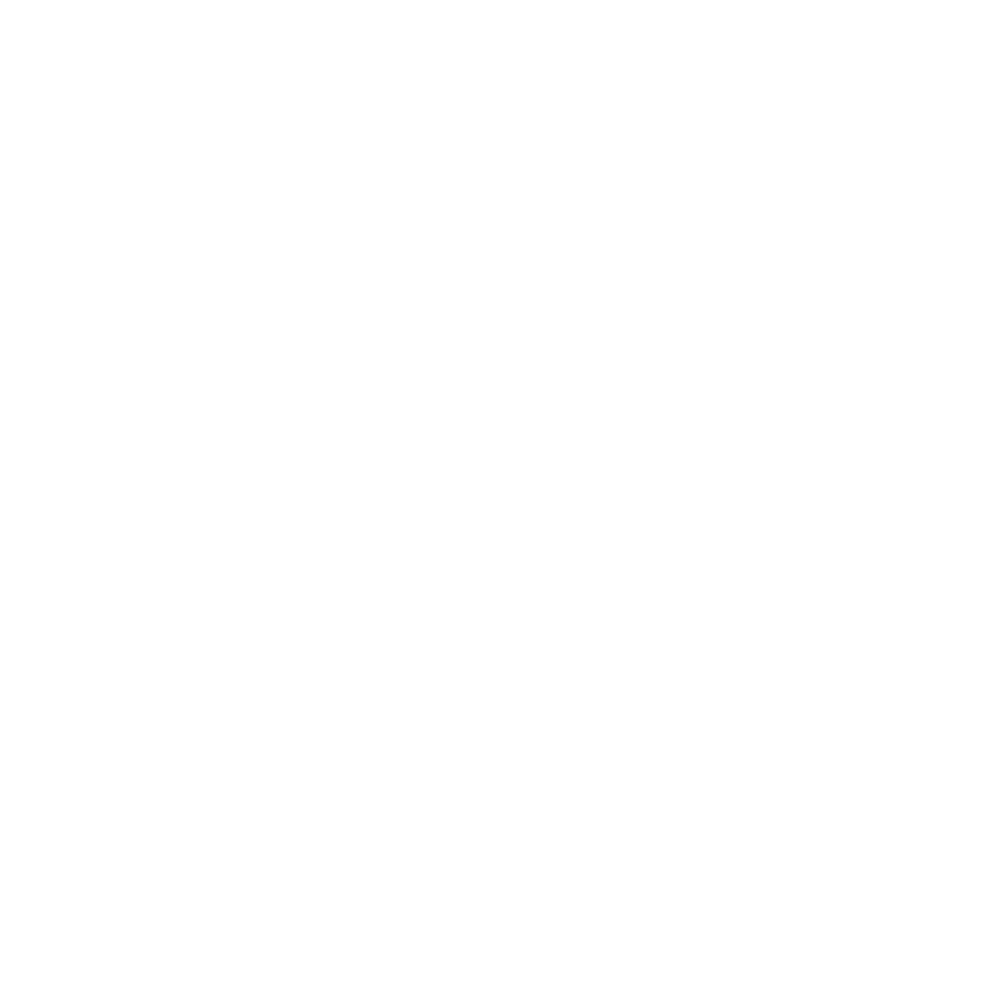
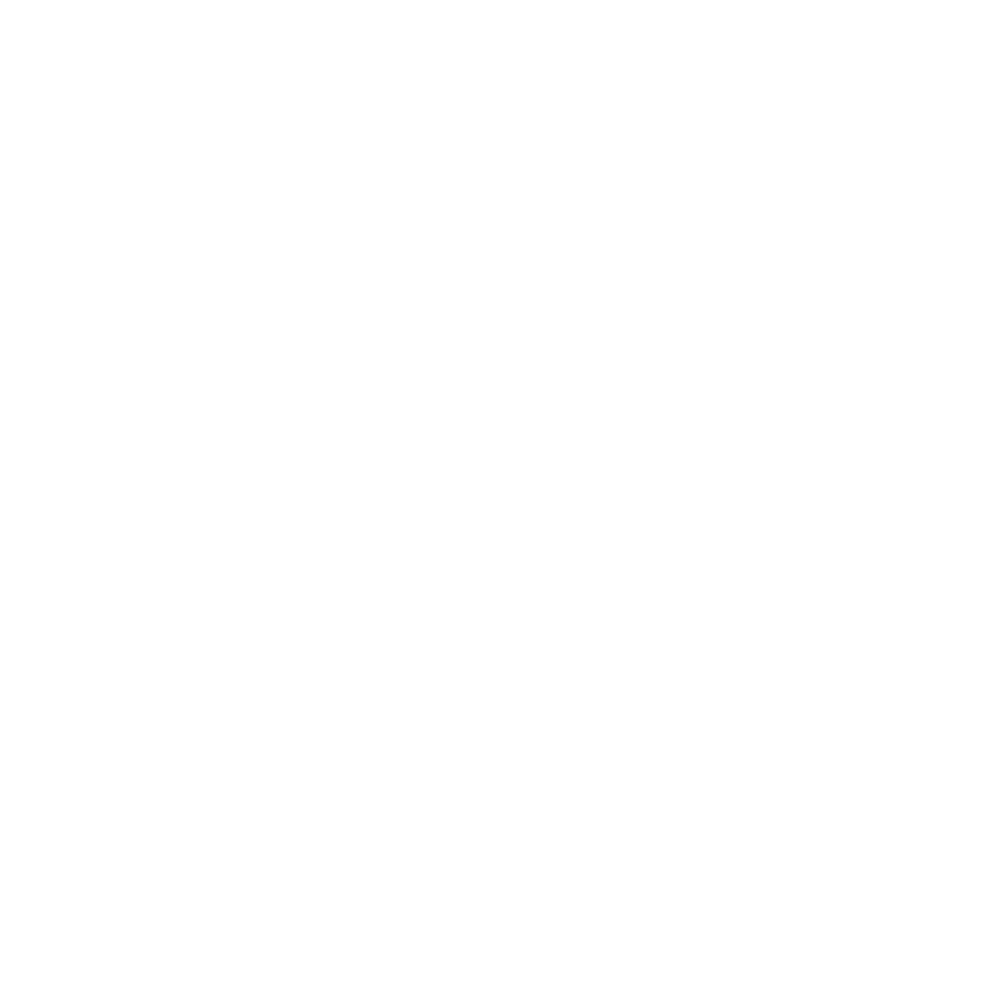
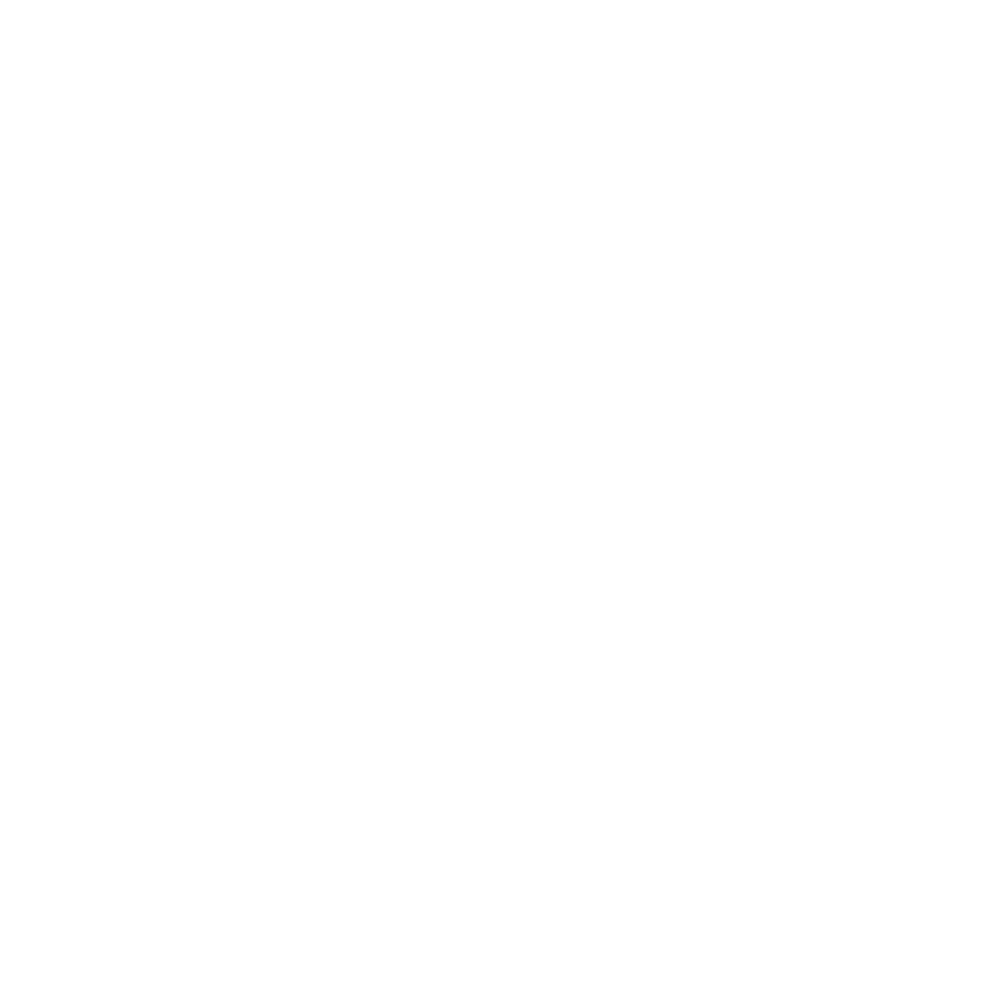
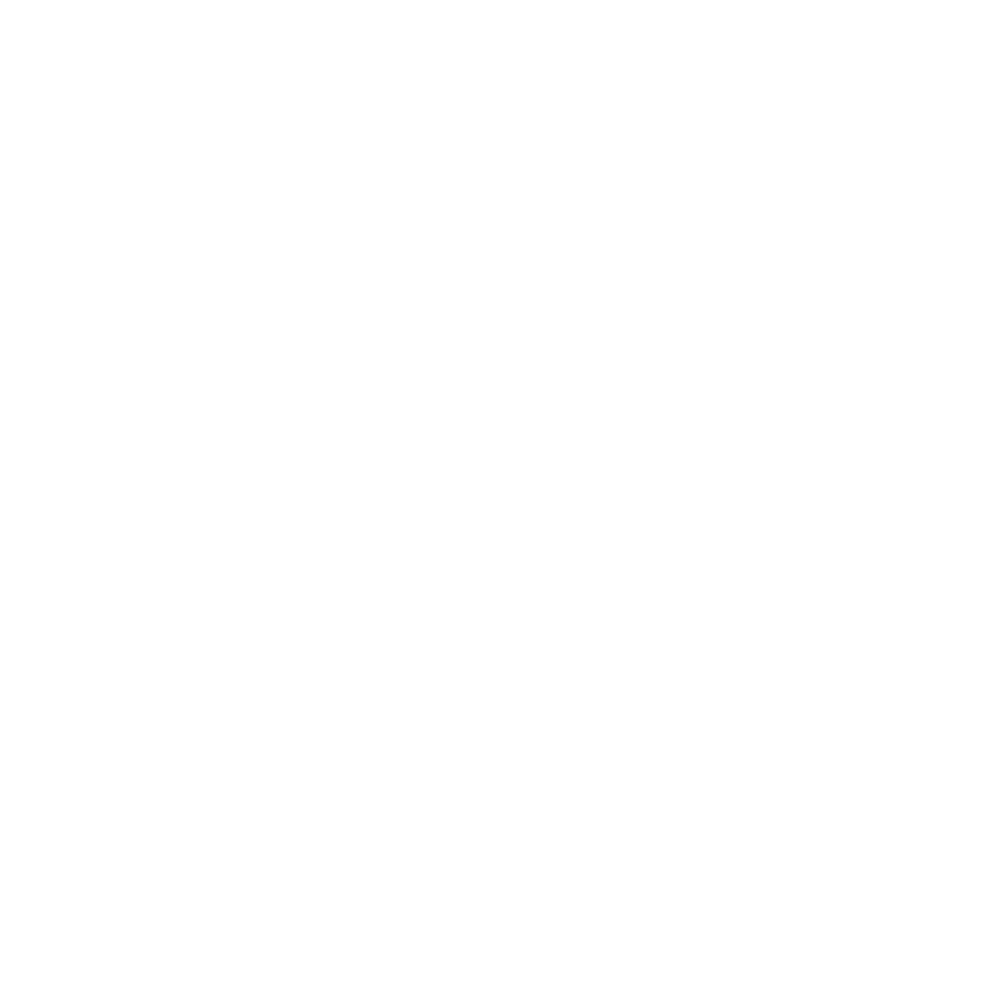
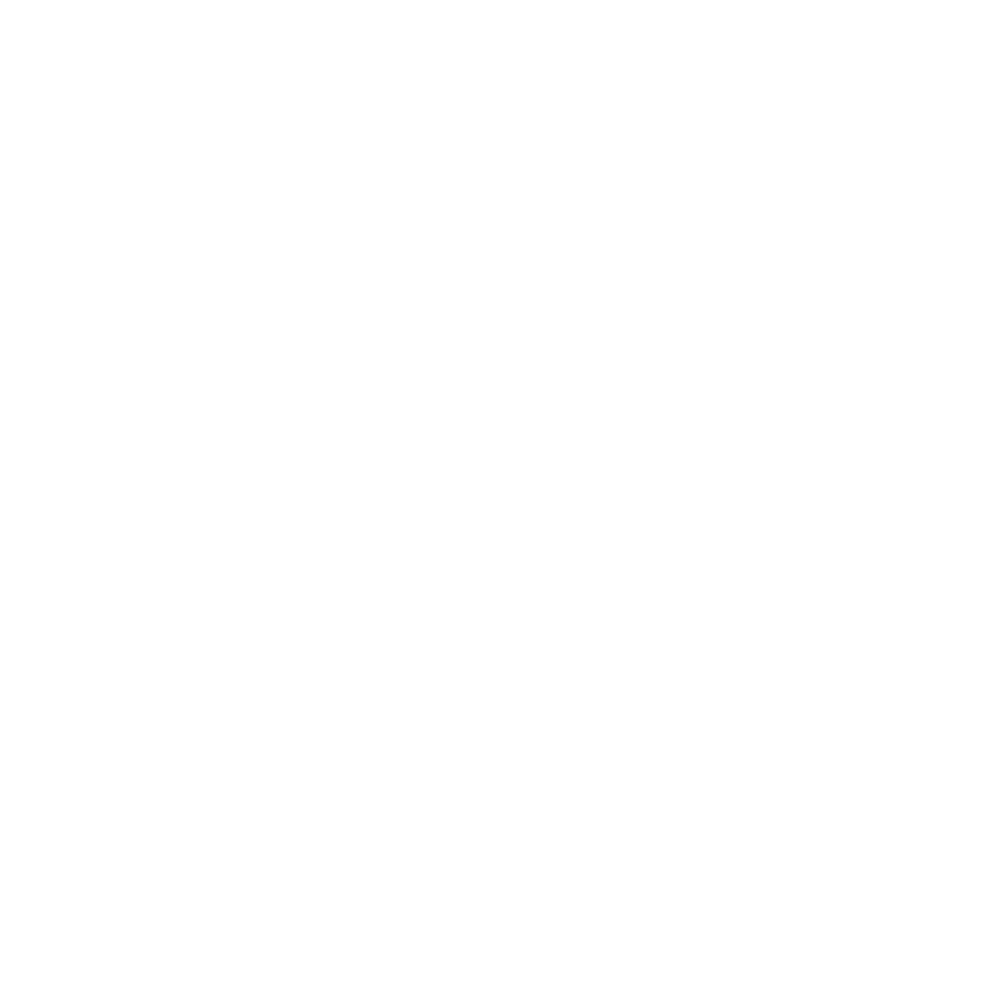
Nutritional assessment of acAN patients encompassed four categories: anthropometric data, biochemical data, clinical data and dietary data. Anthropometric data included height and weight measurement directly before scanning, from which we calculated BMI and BMI standard deviation score (BMI-SDS) as outlined in the main Methods section. Biochemical data included hydration status as gauged by measurements of urine specific gravity from first-morning specimens at room temperature using a hydrometer (Baron *et al.* 2015). Urine specific gravity was normal (n=38; 1.01 [.003]). In a subset of patients, serum leptin values collected immediately prior to scanning, which were assessed using Leptin Human ELISA Kit (BioVendor GmbH; Heidelberg, Germany). Leptin is a sensitive indicator of nutritional status and values in acAN are typically below 2 μg/L (Föcker *et al.* 2011). In the current sub-sample, the mean leptin value in acAN-Tp1 (n=18) was 1.46 (1.56), while it was considerably elevated in acAN-T2 (n=18; 11.18 [7.6]).

Demographic and clinical study data were collected and managed using a secure, web-based electronic data capture tool RedCap (Research Electronic Data Capture; http://www.project-redcap.org; Harris *et al.* 2009).

# SM Results

## SM Descriptive Data

For descriptive data, underlying statistical assumptions for all samples were explored with Histograms, box plots, normal probability plots. Group differences were tested in SPSS 23 (IBM Corp., USA) using independent samples t-tests for the cross-sectional study arm and paired t-tests for the longitudinal study arm.

**SM Table 1:** Demographic variables and clinical measures of the participants in the cross-sectional study arm (acAN-Tp1 and HC). Sample sizes (N), mean value, standard deviation (SD), median (x̅), interquartile range (IQR) and range (R) for each variable are shown. Group differences were tested using independent sample t-tests. Abbreviations: HC, healthy control; acAN-Tp1, acute anorexia nervosa patients at timepoint 1 (baseline); BMI, body mass index; BMI-SDS, BMI standard deviation scores; EDI-2, Eating Disorder Inventory-2; BDI-II, Beck Depression Inventory II; SCL90-R, Symptom-Checklist 90 revised subscale score for anxiety.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable |  | N | Mean | SD | x̅ | IQR | R | *p* |
| Age (years) | acAN-Tp1 | 56 | 15.86 | 2.93 | 15.35 | 3.20 | 16.40 | .556 |
| HC | 56 | 16.19 | 2.89 | 15.85 | 3.57 | 15.50 |
| IQ | acAN-Tp1 | 52 | 112.63 | 11.95 | 112.00 | 21.00 | 49.00 | .703 |
| HC | 56 | 111.84 | 9.44 | 112.00 | 13.00 | 42.00 |
| BMI (kg/m2) | acAN-Tp1 | 56 | 14.66 | 1.34 | 14.43 | 1.71 | 5.63 | <.001 |
| HC | 56 | 20.62 | 2.44 | 20.21 | 3.35 | 11.40 |
| BMI-SDS | acAN-Tp1 | 56 | -3.14 | 1.37 | -2.70 | 1.65 | 6.63 | <.001 |
| HC | 56 | -.03 | -.76 | -.10 | .95 | 3.24 |
| EDI-2 (Total Score) | acAN-Tp1 | 53 | 203.95 | 46.28 | 201.00 | 54.94 | 191.00 | .009 |
| HC | 56 | 144.44 | 30.81 | 138.94 | 45.50 | 126.06 |
| BDI-II (Total Score) | acAN-Tp1 | 56 | 21.23 | 10.92 | 19.45 | 15.75 | 45.00 | <.001 |
| HC | 56 | 6.09 | 5.52 | 5.00 | 6.00 | 25.00 |
| SCL90-R (Anxiety) | acAN-Tp1 | 54 | 1.74 | .74 | 1.50 | .80 | 3.40 | <.001 |
| HC | 55 | 1.26 | .33 | 1.20 | .40 | 1.40 |
| Duration of illness (months) | acAN-Tp1 | 56 | 14.52 | 21.81 | 6.00 | 9.75 | 107.00 | n/a |

**SM Table 2:** Demographic variables and clinical measures in the longitudinal study arm (acAN-Tp1 and acAN-Tp2). Sample sizes (N), mean values, standard deviation (SD), median (x̅), interquartilerange (IQR) and range (R) for each variable are shown. Group differences were tested using paired t-tests.

Abbreviations: acAN-Tp1, acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; BMI, body mass index; BMI-SDS, BMI standard deviation scores; EDI-2, Eating Disorder Inventory-2; BDI-II, Beck Depression Inventory; SCL90-R, Symptom-Checklist 90 revised subscale score for anxiety.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable |  | N | Mean | SD | x̅ | IQR | R | *p* |
| Age (years) | acAN-Tp1 | 44 | 15.40 | 2.28 | 15.00 | 2.88 | 11.20 | <.001 |
| acAN-Tp2 | 44 | 15.64 | 2.27 | 15.20 | 2.87 | 11.00 |
| IQ | acAN-Tp1 | 42 | 113.38 | 11.31 | 112.00 | 23.50 | 44.00 | n/a |
| BMI (kg/m2) | acAN-Tp1 | 44 | 14.85 | 1.19 | 14.86 | 1.61 | 4.98 | <.001 |
| acAN-Tp2 | 44 | 18.72 | 1.10 | 18.83 | 1.79 | 4.14 |
| BMI-SDS | acAN-Tp1 | 44 | -2.85 | 1.03 | -2.62 | 1.52 | 3.90 | <.001 |
| acAN-Tp2 | 44 | -.67 | .61 | -.55 | .91 | 2.91 |
| Leptin | acAN-Tp1 | 18 | 1.47 | 1.56 | .94 | 1.36 | 5.50 | <.001 |
| acAN-Tp2 | 11.18 | 7.60 | 10.85 | 12.67 | 21.92 |
| EDI-2 (Total Score) | acAN-Tp1 | 40 | 207.20 | 43.35 | 207.50 | 51.25 | 191.00 | .120 |
| acAN-Tp2 | 181.23 | 46.30 | 179.17 | 70.17 | 197.00 |
| BDI-II (Total Score) | acAN-Tp1 | 42 | 20.58 | 10.96 | 18.00 | 17.50 | 45.00 | .001 |
| acAN-Tp2 | 10.63 | 7.75 | 10.50 | 11.25 | 30.00 |
| SCL90-R (Anxiety) | acAN-Tp1 | 40 | 1.74 | .77 | 1.45 | .77 | 3.40 | .002 |
| acAN-Tp2 | 1.42 | .42 | 1.35 | .50 | 2.30 |
| Months between scans | n/a | 44 | 2.99 | 1.04 | 2.71 | .94 | 6.34 | n/a |
| Duration of illness (months) | acAN-Tp1 | 44 | 9.80 | 13.10 | 6.00 | 8.00 | 83.00 | n/a |

## SM Cross-sectional and longitudinal comparison of fractional anisotropy

**SM Table 3: A** Cross-sectional comparison of FA: Regions with significantly reduced FA in acAN-Tp1 compared to HC. **B** Longitudinal comparison of FA:Regions with significantly increased FA in acAN-Tp2 compared to acAN-Tp1. **C** Regions with significantly reduced FA in acAN-Tp2 compared to acAN-Tp1. The coordinates are based on the MNI template and belong to the peak voxel of the particular cluster. Regions are based on ‘Juelich Histological Atlas’. For clear arrangement, only clusters with at least 100 voxels contiguity are listed. Abbreviations: FA, fractional anisotropy, acAN-Tp1, acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls; FWE, family-wise error correction; MNI, Montreal Neurological Institute.

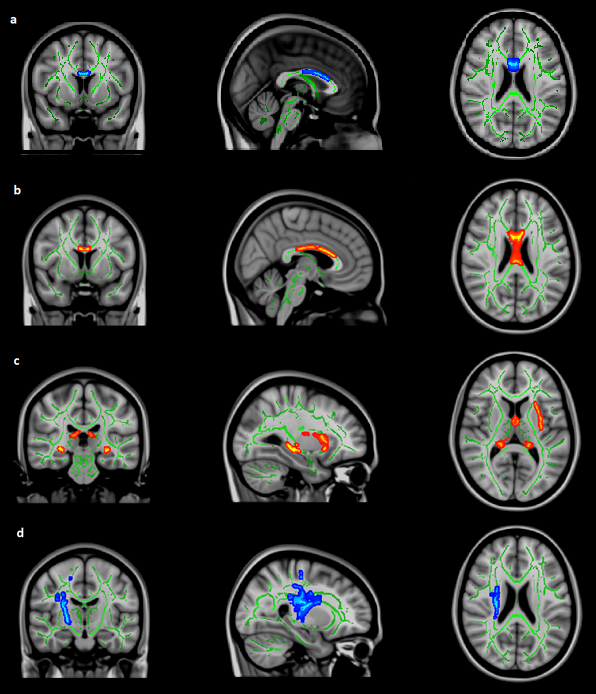
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Region | Cluster size | MNI coordinates (x, y, z) | p (FWE) | T |
| A | Corpus Callosum (body) | 489 | 0, 8, 22 | .014 | 4.00 |
| B | Corpus Callosum (body) | 685 | -3, 4, 23 | .016 | 3.28 |
|  | Fornix, Optic radiation bilateral | 2111 | -26, -15, 20 | <.001 | 3.61 |
| C | Corticospinal tract right | 1801 | 26, -15, 20 | .005 | 2.47 |
|  | Corticospinal tract right | 169 | 22, -20, 61 | .039 | 2.60 |

## SM Cross-sectional and longitudinal comparison of fractional anisotropy with age as nuisance variable

**SM Table 4:** Cross-sectional and longitudinal comparison of FA with age as nuisance variable. Information is presented as in SM Table 3.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Region | Cluster size | MNI coordinates (x, y, z) | p (FWE) | T |
| A | Corpus Callosum (body) | 449 | 0, 8, 22 | .013 | 4.05 |
| B | Corpus Callosum (Body)  Fornix, Optic radiation bilateral | 687  2108 | 4, 6, 23  -28, -24, -9 | .017  <.001 | 3.27  3.62 |
| C | Corticospinal tract right | 1742 | 26, -15, 21 | .005 | 2.50 |
|  | Corticospinal tract right | 109 | 22, -20, 61 | .044 | 3.14 |
|  | Superior longitudinal fascicle right | 109 | 35, -15, 26 | .042 | 2.87 |

**SM Figure 1:** Regions with a significant difference in FA from whole-brain TBSS analysis with age as nuisance variable (p<.05 FWE-corrected). For visualization purposes the suprathreshold clusters were thickened with tbss\_fill (FSL). **a** Reduced FA in acAN-Tp1 compared to HC in the corpus callosum (449 voxels), coordinates (x, y, z in mm): 0, 8, 22; **b** Increased FA in acAN-Tp2 compared to acAN-Tp1 in the corpus callosum (687 voxels), coordinates (x, y, z in mm): 4, 6, 23; **c** Increased FA in acAN-Tp2 compared to acAN-Tp1 in the fornix (2108 voxels), coordinates (x, y, z in mm): -28, -24, 9; **d** Decreased FA in acAN-Tp2 compared to acAN-Tp1 in the right corticospinal tract (1742 voxels, 109 voxels), coordinates (x, y, z in mm): 26, -15, 20. Green: represents major white matter tracts with a minimum FA value of .2 across the sample. Red-Yellow: significant clusters. Peak voxels, t-values and the cluster’s association on atlas regions are in SM Table 4. Abbreviations: FA, fractional anisotropy; TBSS, tract-based spatial statistics (FSL); FWE, family-wise error, acAN-Tp1, acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls; SM, supplementary material.



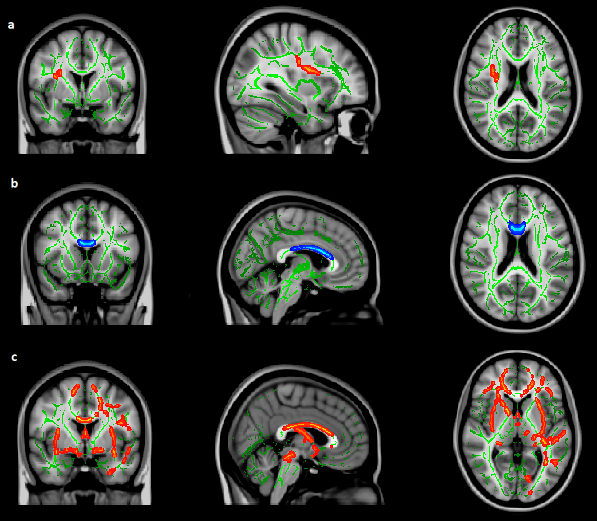
## SM Cross-sectional and longitudinal whole-brain analysis of mean diffusivity

In addition to the fractional anisotropy (FA) analysis, on which we had focused a priori, we conducted a whole-brain analysis of mean diffusivity (MD). Here we followed the same procedure as in our FA approach. Supporting the results in the FA analysis, we found clusters with increased (corpus callosum, 810 voxels) as well as reduced (corticospinal tract right, 377 voxels) MD in acAN-Tp1 compared to HC. These results are largely in line with the findings using FA, since MD is often increased in areas with reduced FA (Feldman *et al.* 2015). In the longitudinal comparison, widespread decreases in MD in acAN-Tp2 were found, with a large cluster encompassing the corpus callosum, fornix, cerebral peduncle left and right, posterior thalamic radiation, external capsule left and right, superior longitudinal fasciculus right, inferior longitudinal fasciculus left, anterior limb of external capsule left and the anterior corona radiata left and right. Although these findings are more widespread compared to our FA approach, the direction of change and the overlap with the brain regions identified in the former analysis can be seen as converging evidence. In line with this, no differences were found between acAN-Tp2 and HC indicating that decreased MD possibly reflects state-related effects of malnutrition rather than trait-related effects.

**SM Table 5: A** Cross-sectional comparison of MD: Regions with significantly increased MD in HC compared to acAN-Tp1. **B** Regions with significantly reduced MD in HC compared to acAN-Tp1. **C** Longitudinal comparison of MD: Regions with significantly reduced MD in acAN-Tp2 compared to acAN-Tp1. The coordinates are based on the MNI template and belong to the peak voxel of the particular cluster. For A and B regions are based on ‘Juelich Histological Atlas’. For C, labeling was performed manually. For clear arrangement, only clusters with at least 100 voxels contiguity are listed. Abbreviations: MD, mean diffusivity; acAN-Tp1, acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls; FWE, family-wise error correction, MNI, Montreal Neurological Institute.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Region | Cluster size | MNI coordinates (x, y, z) | p (FWE) | T |
| A | Corticospinal tract right | 377 | 33, 1, 19 | .035 | 3.67 |
| B | Corpus Callosum (body) | 810 | 5, 15, 20 | .013 | 3.89 |
| C | Corpus Callosum (genu, body),  Fornix (body),  Cerebral peduncle left and right,  Posterior thalamic radiation,  External capsule left and right,  Superior longitudinal fasciculus right,  Inferior longitudinal fasciculus left,  Anterior limb of external capsule left,  Anterior corona radiata left and right | 27349 | 3, 0, 4 | <.001 | 2.24 |
|  | Optic radiation left, Occitipal lobe left | 1273 | -19, -93, -1 | .032 | 2.60 |
|  | Cerebellum right | 431 | 7, -69, -29 | .033 | 3.82 |
|  | Cerebellum left | 332 | -35, -62, -46 | .021 | 4.46 |
|  | Cerebellum left | 282 | -6, -69, -23 | .022 | 4.43 |

**SM Figure 2:** Regions with a significant difference in MD from whole-brain TBSS analysis (p<.05 FWE-corrected). For visualization purposes the suprathreshold clusters were thickened with tbss\_fill (FSL).  
a Increased MD in HC compared to acAN-Tp1 in the right corticospinal tract (377 voxels), coordinates (x, y, z in mm): 33, 1, 19; b Reduced MD in HC compared to acAN-Tp1 in the corpus callosum (810 voxels), coordinates (x, y, z in mm): 5, 15, 20; c Decreased MD in acAN-Tp2 compared to acAN-Tp1 in a cluster encompassing the corpus callosum, fornix, cerebral peduncle left and right, posterior thalamic radiation, external capsule left and right, superior longitudinal fasciculus right, inferior longitudinal fasciculus left, anterior limb of external capsule left and the anterior corona radiata left and right (27349 voxels), coordinates (x, y, z in mm): 3, 0, 4. Green: represents major white matter tracts with a minimum FA value of .2 across the sample. Red-yellow: significant clusters. Peak voxels, t-values and the clusters association on atlas regions can be found in SM Table 5.Abbreviations: FA, fractional anisotropy; TBSS, tract-based spatial statistics (FSL); FWE, family-wise error, acAN-Tp1, acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls; SM, supplementary material.



## SM Correlations with clinical measurements

**SM Table 6**: Spearman correlations between FA values of acAN-Tp1 in significant clusters and clinical variables. No correction for multiple testing was applied. Abbreviations: *r* = Spearman correlation coefficient, \*\* p<.01 (two-sided). \* p<.05 (two-sided); FA, fractional anisotropy; BMI, body mass index; BMI-SDS, BMI standard deviation score; EDI-2, Eating Disorder Inventory-2; BDI-II, Beck Depression Inventory II; SCL90 R, Symptom Checklist 90 R.

|  |  |  |  |
| --- | --- | --- | --- |
|  | FA  Fornix | FA  Corpus Callosum | FA  Corticospinal tract right |
| BMI-SDS  *r*  *p* | -.022  .889 | -.178  .248 | -.037  .810 |
| EDI-2 total score  *r*  *p* | -.256  .110 | -.048  .769 | .082  .615 |
| BDI-II total score  *r*  *p* | -.025  .873 | .144  .357 | -.199  .201 |
| SCL90 R anxiety change score  *r*  *p* | -.005  .974 | -157  .316 | -.040  .800 |

### SM Physical activity

Given the role of the corticospinal tract in motor functioning (Schultz 2001) and that (over-) exercising is common in AN (Gümmer *et al.* 2015), we also explored relationships of FA and hyperactivity as measured with SIAB-EX (How much physical activity (i.e. sports) have you had? In the last three months, did you feel uncomfortable without?; Rated by an expert on a scale ranging from 0 = none to 4 = several times a day). We found that the amount of exercising was reduced at follow-up compared to baseline (n=42, p=.002), but not correlated with baseline FA values in the corticospinal tract (r=.102, p=.515).

## SM Effect of ventricle sizes on fractional anisotropy changes in the fornix

To test the impact of increased ventricular volumes on FA changes in the fornix in our study, we added the relative volume change of the third and the right and left lateral ventricles as a covariate to the model (repeated measurement ANCOVA; Table 7b). Ventricle volumes were computed within FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) which performs cortical reconstruction and segmentation of the subcortical white matter (WM) and deep gray matter (GM) volumetric structures, including ventricles (Fischl *et al.* 2002).

**SM Table 7a**: Pearson correlation between the sum of the right and left lateral and third ventricle volumes with FA values in the fornix at baseline (acAN-Tp1), after partial weight-restoration (acAN-Tp2) and in HC. \*\*\* p<.001 (two-sided). Abbreviations: FA, fractional anisotropy; acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls.

|  |  |  |  |
| --- | --- | --- | --- |
| Ventricle total volume | FA | | |
| acAN-Tp1 | acAN-Tp2 | HC |
| *r*  *p* | -.653\*\*\*  <.001 | -.522\*\*\*  <.001 | -.244  .081 |

**SM Table 7b**: Effect of relative change of ventricle volume from acAN-Tp1 to acAN-Tp2 on FA change in the fornix. We compare the magnitude and significance of the timepoint effect in a repeated measurements ANOVA, not controlling for ventricular volumes (**A**); and in a repeated measurements ANCOVA with relative change of ventricular volumes (sum of the right and left lateral and third ventricle volumes) as covariate (**B**). Abbreviations: FA, fractional anisotropy; acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model | Predictors | *F* | *P* | *Partial η 2*  *(effect size)* |
| A | Timepoint | 153.834 | <.001 | .786 |
| B | Timepoint | 10.110 | .003 | .198 |
| Relative change of ventricle volume | 12.528 | .001 | .234 |

## SM Effect of ventricle sizes on fractional anisotropy changes in the corpus callosum

To test the impact of increased ventricular volumes on FA changes in the corpus callosum in our study, we added the relative volume change of the right and left lateral ventricles as a covariate to the model (repeated measurement ANCOVA, Table 8b). Ventricle volumes were computed within FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) which performs cortical reconstruction and segmentation of the subcortical WM and deep GM volumetric structures, including ventricles (Fischl *et al.* 2002).

**SM Table 8a:** Pearson correlation between the sum of the right and left lateral ventricle volumes with FA values in the corpus callosum at baseline (acAN-Tp1), after partial weight-restoration (acAN-Tp2) and in HC. \*\* p<.01 \* p<.05 (two-sided).Abbreviations: FA, fractional anisotropy; acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls.

|  |  |  |  |
| --- | --- | --- | --- |
| Ventricle total volume | FA | | |
| acAN-Tp1 | acAN-Tp2 | HC |
| *r*  *p* | -.463\*\*  .002 | -.355\*  .019 | .250  .074 |

**SM Table 8b:** Effect of relative change of ventricle volume from acAN-Tp1 to acAN-Tp2 on FA change in the corpus callosum. We compare the magnitude and significance of the timepoint effect in a repeated measurements ANOVA, not controlling for ventricular volumes (A); and in a repeated measurements ANCOVA with relative change of ventricular volumes (sum of the right and left lateral ventricle volumes) as covariate (B). Abbreviations: FA, fractional anisotropy; acute anorexia nervosa patients at timepoint 1 (baseline); acAN-Tp2, acute anorexia nervosa patients at timepoint 2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model | Predictors | *F* | *P* | *Partial η 2*  *(effect size)* |
| A | Timepoint | 59.635 | <.001 | .587 |
| B | Timepoint | 7.156 | .011 | .149 |
| Relative change of ventricle volume | .840 | .365 | .020 |

## SM Corpus callosum volume

**SM Table 9:** Mean values and standard deviation (SD) for each variable are shown. (A) Group differences were tested using independent t-tests. (B) Group differences were tested using paired t-tests.

Abbreviations: acAN-Tp1, acute anorexia nervosa patients at timepoint 1; acAN-Tp2, acute anorexia nervosa patients at timepoint 2; HC, healthy controls.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Mean | SD | *p* |
| A | acAN-Tp1 | 2640.06 | 699.95 | .052 |
| HC | 2919.67 | 741.10 |
| B | acAN-Tp1 | 2664.20 | 703.70 | <.001 |
| acAN-Tp2 | 2830.37 | 681.21 |

## SM Effect of time between scans on longitudinal fractional anisotropy changes

**SM Table 10:** Effect of time (months) between scans from acAN-Tp1 to acAN-Tp2 on FA changes in the fornix, the corpus callosum and the right corticospinal tract. We compare the magnitude and significance of the timepoint effect in a repeated measurements ANOVA, not controlling for time between scans (A); and in a repeated measurements ANCOVA with mean-centered months between scans as covariate (B) respectively for the fornix, the corpus callosum and the right corticospinal tract. Abbreviations: acAN-Tp1, acute anorexia nervosa patients at timepoint 1; acAN-Tp2, acute anorexia nervosa patients at timepoint 2.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Model | Predictors | *F* | *P* | *Partial η 2*  *(effect size)* |
| Increase FA Fornix | A | Timepoint | 151.828 | <.001 | .779 |
| B | Timepoint | 191.903 | <.001 | .820 |
| Months between scans | 12.350 | .001 | .227 |
| Increase FA Corpus Callosum | A | Timepoint | 58.650 | <.001 | .577 |
| B | Timepoint | 57.509 | <.001 | .578 |
| Month between scans | .164 | .688 | .004 |
| Decrease FA Corticospinal tract right | A | Timepoint | 54.650 | <.001 | .560 |
| B | Timepoint | 55.352 | <.001 | .569 |
| Months between scans | 1.553 | .220 | .036 |

## SM Intraclass correlation (ICC) of the longitudinal data

Voxelwise tract-based spatial statistics (TBSS) measurements were reported to be well reproducible (Jovicich *et al.* 2014; Madhyastha *et al.* 2014). We have examined the reproducibility of our FA values of the WM skeleton and calculated an intraclass correlation (ICC; two-way mixed effects model with consistency agreement) from the timepoints acAN-Tp1 and acAN-Tp2 using the toolbox fMRelI (Fröhner *et al.* 2017). The mean value of the ICC=.620 is in the range of the values reported by Madhyastha *et al.* (2014). According to the criteria of Fleiss *et al.* 1986, an ICC between .600 and .750 is considered to reflect good reproducibility (Of note – reproducibility is good despite the considerable treatment effects).

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# Summary of hitherto existing DTI studies in anorexia nervosa (until 12/2017)

**SM Table 11:** Updatedsummary of published DTI studies in AN with samples including patients in the acute phase and healthy controls(until 12/2017; see also King *et al.* 2017). Complete references are provided above.1 denotes studies, that are also listed in SM Table 12. 2 denotes studies, that are also listed in SM Table 13. \* denotes studies that included analyses of WM connectivity. Summaries of main findings are limited to primary analyses of anisotropy/diffusivity and WM connectivity and do not include supplementary analyses of relationships with clinical variables. Data on psychotropic medication and psychiatric comorbidities are given in numbers of AN patients. Abbreviations: acAN, acute, underweight phase AN; EDNOS, eating disorder not otherwise specified; recAN, weight recovered AN; HC, healthy control; DOI, duration of illness; FA, fractional anisotropy; ADC, apparent diffusion coefficient; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity ADHD, attention-deficit hyperactivity disorder; BDD, body dysmorphic disorder; BN, bulimia nervosa; DD, depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; Mal, maltreated participants; noMal, non-maltreated participants.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **sample size** | **AN subtype** | **age ± SD for AN and HC (years)** | **duration of illness±**  **SD (years)** | **medication** | **psychiatric comorbidities (only acAN)** | **time start of**  **realimentation -scanning (only acAN)** | **image acquisition**  **(tesla/ b/ gradient directions/ resolution)** | **white matter volume** | **DTI software** | **Parameters** | **Whole-brain/ROI** |
| Kazlouski *et al.* (2011) | acAN: 16  HC: 17 | mixed | acAN: 23.9±7  HC: 25.1±4 | 7.5±8 | 8 of 16 | 8 (DD) | 1-2 weeks | 3 T, b n/a, 25 directions, 3.5 mm with .5 mm gap | no group difference | SPM, DTIStudio | FA, ADC | Whole-brain FA, ADC analyses |
| **FA:** AN < HC bilateral fimbria-fornix, bilateral fronto-occipital and bilateral posterior cingulum, ADC: AN > HC; in fronto-parietal areas and parieto-occipital areas | | | | | | | | | | | |
| Frieling *et al.* (2012)**1** | acAN: 12  HC: 20  recAN: 9 | restrictive | acAN: 26.8±6.9 recAN: 27.4±5.3  HC: 24.8±2.6 | n/a | n/a | n/a | n/a | 3 T, b=1000 s/mm², 15 directions, 4 mm thickness no gap | n/a | SPM | FA, ADC | Whole-brain FA, ADC analyses |
| **FA:** AN < HC in bilateral posterior thalamic radiation, left mediodorsal thalamus, bilateral posterior coronal radiata, left middle cerebellar peduncle, left superior longitudinal fasciculus. | | | | | | | | | | | |
| Frank *et al.* (2013) | acAN: 19  HC: 22 | mixed | acAN: 15.4±1.4  HC: 14.8±1.8 | n/a | 11 of 19 | 1 (DD)  2 (Anxiety Disorder)  2 (Anxiety Disorder + DD) | min. 1 week | 3 T, b n/a, 25 directions, 3.5 mm thickness with .5 mm gap | WM volume greater in AN than HC in several brain regions | SPM, NordicICE | FA, ADC | Whole-brain FA, ADC analyses |
| **FA**: AN < HC in left fornix, bilateral cingulum, right forcepts major, right superior and left posterior corona radiata. AN > HC in left superior longitudinal fasciculus, bilateral anterior corona radiata and bilateral inferior fronto-occipital fasciculus. **ADC:** AN >HC in left fornix, right corpus callosum, right corticospinal tract, right posterior corona radiata, bilateral corticopontine tract, bilateral superior longitudinal fasciculus. | | | | | | | | | | | |
| Via *et al.* (2014) | acAN: 19 HC: 19 | restrictive | acAN: 28.4±9.6  HC: 28.6±8.6 | 3±3 | 5 of 19 | n/a | Min. 1 week | 1.5 T, b=1000 s/mm², 25 directions, 5 mm thickness no gap | no group difference | FSL, TBSS | FA, MD, AD, RD | Whole-brain analyses for FA and MD, in significant clusters AD and RD values were extracted |
| **FA:** AN < HC in the parietal portion of the superior longitudinal fasciculus and fornix. **MD:** AN > HC in the superior longitudinal fasciculus and fornix. Decreased FA in the superior longitudinal fasciculus was driven largely by increased RD, while increased MD in the fornix was driven by both increased AD and RD. | | | | | | | | | | | |
| Nagahara *et al.* (2014) | acAN: 17  HC: 18 | n/a | acAN: 23.8±6.7  HC: 26.2±5.6 | 5±5 | 6 of 17 | 4 (DD) | n/a | 3 T, b=1000 s/mm², 32 directions, 2 mm thickness no gap | n/a | FSL, TBSS | FA, MD | Whole-brain FA, MD analyses |
| **FA**: AN < HC in left cerebellum. **MD**: AN > HC in the anterior body of the fornix. AN < HC in the corpus callosum and right superior longitudinal fasciculus. Group differences did not remain significant after controlling for medication. | | | | | | | | | | | |  |
| Hayes *et al.* (2015)\* | acAN: 8  HC: 8 | mixed | acAN: 35±11  HC: 36±9 | 16±6 | 8 of 8 | 1 (Anxiety Disorder + DD)  3 (DD + PTSD)  1 (DD + PTSD + OCD)  1 (DD + PTSD + Anxiety Disorder)  1 (DD + BPD + Anxiety Disorder) | n/a | 3 T, b=1000s/mm², 60 directions,  .94 x .94 x 3.0 mm³, n/a | n/a | FSL, 3D Slicer | FA, RD, AD | Focus on subcallosal cingulate-ssociated white matter tracts |
| **FA:** AN < HC in bilateral anterior limb of capsula interna, left inferior fronto-occipital fasciculus, right anterior cingulum (with corresponding decreases in AD and increases in RD). AN > HC in the left fornix crus.  Deterministic multitensor tractography suggested WM connectivity to be increased in prefrontal and left occipitoparietal corticies and decreased in thalamus in AN relative to HC. | | | | | | | | | | | |  |
| Travis *et al.* (2015) | acAN: 15  HC: 15 | restrictive | acAN: 16.6±1.4 HC: 17.1±1.3 | 1±1 | 2 of 15 | n/a | n/a (outpatients) | 3 T, b=2500 s/mm², 96 directions, 2 mm³ isotropic, n/a | n/a | [MrDiffusion](http://white.stanford.edu/newlm/index.php/MrDiffusion) | FA | Diffsuion parameters were extracted from 26 major pathways |
| **FA:** AN < HC in 4 right anterior superior longitudinal fasciculus, bilateral fibra-fornix, motor subdivision of corpus callosum. AN > HC in right anterior thalamic radiation, left anterior superior longitudinal fasciculus. T1 relaxometry also revealed evidence suggestive of reduced myelin content in AN in 11 out of the 26 investigated WM tracts and subdivisions of the corpus callosum. | | | | | | | | | | | |  |
| Pfuhl *et al.* (2016)**1** | acAN: 35  HC: 62  recAN: 32 | mixed | acAN: 16.1±2.8 recAN: 22.5±3 HC: 16.4±2.6 | n/a | none | 2 acAN (DD)  4 recAN (DD)  3 recAN (other) | within 96h | 3 T, b=1300 s/mm², 30 directions, 2.4 mm isotropic no gap | no group difference | FSL, TRACULA | FA, MD, RD, AD | Mean FA, MD, RD and AD values were extracted from 18 WM pathways reconstructed with TRACULA. |
| No group differences in FA, MD, RD, AD after correction for multiple comparisons. | | | | | | | | | | | |
| Cha *et al.* (2016)\*2 | acAN: 22  HC: 18 | mixed | acAN: 19.5±2.42  HC: 20.5±2.95 | n/a | none | 3 (DD)  3 (specific phobia) | min 1 week | 1.5 T, b=800 s/mm², 16 directions, 2 mm isotropic no gap | n/a | FSL, TBSS | FA | FA was first evaluated in whole- brain analyses and in ROI analysis within the  fronto-accumbal pathway |
| **FA**: In the whole brain analyses, no significant differences were found. ROI (fronto-accumbal WM regions) analyses: AN > HC near the lateral orbitofrontal cortex and nucleus accumbens both before and after weight restoration.  Probabilistic tractography suggested increased WM connectivity between nucleus accumbens and lateral orbitofrontal cortex in both hemispheres both before and after weight restoration. | | | | | | | | | | | |
| Vogel *et al.* (2016)2 | acAN: 22  HC: 21 | mixed | acAN: 15±1.6  HC: 15±1.0 | 1±1.1 | 2 of 20 | 1 (DD)  2 (Anxiety Disorder)  1 (Anxiety Disorder + DD) | n/a | 3 T, b=1000 s/mm², 30 directions, Protocol 1: 2 mm³  isotropic, Protocol 2: 2 x 2 mm², 3.5 mm thickness and 10% gap | n/a | FSL, TBSS | FA, MD, RD, AD | Whole-brain FA analyses. In voxels with significant differences, MD, AD, and RD values were extracted. Additionally, the global averages of FA, MD, RD and AD were extracted for all major white matter tracts. |
| **FA**: AN > HC in the bilateral superior corona radiata, anterior corpus callosum, anterior and posterior thalamic radiation, anterior and posterior internal capsule, and the left inferior longitudinal fasciculus at admission using voxelwise TBSS. Elevated FA at admission was associated with reduced MD and RD, but not AD. No group differences were present at discharge using voxelwise TBSS analysis, but FA remained elevated in ROI analysis. | | | | | | | | | | | |
| Canna *et al.* (2017) | acAN: 15  BN: 13  HC: 16 | n/a | acAN: 25.3±1.6  BN: 27.2±2.0 HC: 26:1±3.5 | n/a | none | none | n/a | 3 T, b=1000 s/mm², 16 directions, 2 mm³ isotropic with .4 mm gap | n/a | DTIStudio | FA | Analyses focused only on corpus Callosum |
| **FA:** No group differences were significant. | | | | | | | | | | | |  |
| Frank *et al.* (2016)\* | acAN: 26 BN: 25  HC: 26 | restrictive | acAN: 23.2±5.3  BN: 24.6±4.2 HC: 24.4±3.5 | 7±6 / 7±5 | 16 of 26 | 4 (DD)  5 (Anxiety Disorder) 10 (Anxiety Disorder + DD) | 1-2 weeks | 3 T, b=1000 s/mm², 25 directions, 2.6 mm thickness no gap | n/a | DTIStudio | FA | Analyses focused on fiber paths belonging to a priori-defined brain taste-reward network |
| **FA:** AN < HC: from the left ventral anterior insula/gyrus rectus to ventral striatum, the left posterior insula to middle OFC, the right middle OFC to hypothalamus, the right central nucleus of amygdala to hypothalamus, the left dorsal anterior insula to ventral striatum, the right dorsal anterior insula to gyrus rectus, the bilateral posterior insula to ventral striatum, the left medial OFC to hypothalamus, the right medial OFC to ventral striatum and the left gyrus rectus to PFC.  WM connection strength was increased (AN > HC) in pathways between insula, orbitofrontal cortex and ventral striatum, but decreased (AN < HC) from orbitofrontal cortex and amygdala to hypothalamus. | | | | | | | | | | | |
| Olivo *et al.* (2017)**2** | acAN: 1 EDNOS: 11 HC: 24 | restrictive | acAN: 16  EDNOS: 14.9±1.6 HC: 14.1 | n/a | none | 2 (DD)  1 (Anxiety Disorder+ DD)  2 (DD + PTSD)  1 (DD + OCD) | Upon diagnosis | 3 T, b n/a, 48 directions, 1.75 mm³ isotropic, n/a | n/a | FSL, TBSS | FA, MD, RD, AD | Whole-brain FA analyses. In voxels with significant differences, MD, AD, and RD values were extracted. |
| **FA:** AN/EDNOS < HC at baseline in corpus callosum, corona radiata and posterior thalamic radiation. **RD:** AN/EDNOS < HC at baseline in the same regions. | | | | | | | | | | | |  |
| Kaufmann *et al.* (2017) | acAN: 25 HC: 25 | n/a | acAN: 22.8±4.8  HC: 23.36±3.4 | 6.8±4.9 | 11 of 25 | n/a | min 2 weeks | 3 T, b=1000 s/mm², 64 directions, 2 mm³ isotropic, n/a | no group difference | FSL, TBSS, TRACULA | FA, RD, AD | Analyses focused on the fornix. |
| **FA:** AN < HC: fornix. The group difference was significantly smaller after controlling for ventricular volumes and disappeared completely after correcting for free-water. | | | | | | | | | | | |  |
| Gaudio *et al.* (2017) | acAN: 14  HC: 15 | restrictive | acAN: 15.7±1.6  HC: 16.3±1.5 | .4±.2 | none | none | min 1 week | 1.5 T, b=1000 s/mm², 48 directions, 2.5 mm thickness no gap | no group difference | FSL, TBSS | FA, MD, RD, AD | Whole-brain analyses of FA, MD, AD and RD. |
| **FA:** AN < HC in the left anterior and superior corona radiata and left superior longitudinal fasciculus. **AD:** AN < HC in the superior longitudinal fasciculus bilaterally and the left superior and anterior corona radiata. No group differences in RD or MD. | | | | | | | | | | | |  |
| Hu *et al.* (2017) | acAN: 8  HC: 14 | restrictive | acAN: 17.6±2.2  HC: 19.1±3.1 | n/a | n/a | none | min 1 week | 3 T, b=1000 s/mm², 44 directions, 3 mm thickness, no gap | n/a | SPM, DTIStudio | FA | Whole-brain analyses |
| FA: AN < HC in the left superior frontal gyrus, medial frontal gyrus, anterior cingulate cortex, middle frontal gyrus, inferior frontal gyrus, thalamus and bilateral insula | | | | | | | | | | | |  |

**SM Table 12:** Updatedsummary of published DTI studies in AN with samples including patients recovered from AN and healthy controls (until 12/2017; see also King *et al.* 2017). For table information, see SM Table 11.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **sample size** | **AN subtype** | **age ± SD (years)** | **duration of illness**  **± SD** | **medication** | **psychiatric comorbidities (only acAN)** | **Weight recovered since (months)** | **image acquisition**  **(tesla/ b/ gradient directions/ resolution)** | **white matter volume** | **DTI software** | **Parameters** | **Whole-brain/ROI** |
| Frieling *et al.* (2012) | recAN: 9  HC: 20  acAN: 12 | restrictive | acAN: 26.8±6.9 recAN: 27.4±5.3  HC: 24.8±2.6 | n/a | n/a | n/a | n/a | 3 T, b=1000 s/mm², 15 directions, 4mm thickness no gap | n/a | SPM | FA, ADC | Whole-brain analyses for FA, ADC |
| **FA:** no significant differences between acAN and recAN. | | | | | | | | | | | | |
| Yau *et al.* (2013) | recAN: 12  HC: 10 | restrictive | recAN: 28.7±7.9  HC: 26.7±5.4 | 68±62.5 (months) | none | none | 26.22±18.23 | 3 T, b=1000 s/mm², 55 directions, 2.5 mm isotropic, n/a | n/a | FSL | FA, MD, RD, AD | Whole-brain analyses for FA and MD, in significant clusters AD and RD values were extracted |
| **FA:** no group differences. MD: recAN < HC in left superior frontal WM including corona radiata (superior and posterior), corpus callosum (body and bilateral splenium), posterior limb of capsula interna, left superior longitudinal fasciculus, left posterior cingulum, precuneus and superior parietal WM, left dorsal cingulum, right precuneus and posterior corona radiata, right posterior cingulum and posterior corona radiata. In all of these regions, AD and/or RD was reduced in AN relative to HC. | | | | | | | | | | | |
| Shott *et al.* (2016) | recAN: 24 HC: 24 | restrictive | recAN: 30.3±8.1  HC: 27.4±6.3 | 70.2±62.2 (months) | 6 of 24 | 3 (DD),  4 (Anxiety Disorder) 2 (Anxiety Disorder + DD) | 94.8±72.1 | n/a, b=1000 s/mm², 25 directions, 2.6 mm thickness, no gap | no group difference | FSL TBSS, (Probtrackx for fiber tracking) | FA, MD, RD, AD | FA, additionally, extraction of diffusion values in reward circuit. |
| **FA:** AN < HC in anterior coronata radiata, external capsule, cerebellum, corpus callosum, anterior thalamic radiation, inferior fronto-occipital and unicate fasciculus.  Probabilistic tractography suggested increased WM connectivity between bilateral insula and ventral striatum, left insula and middle orbitofrontal cortex and right insula to gyrus rectus and medial orbitofrontal cortex. | | | | | | | | | | | |
| Pfuhl *et al.* (2016) | acAN: 35  HC: 62  recAN: 32 | mixed | acAN: 16.1±2.8 recAN: 22.5±3 HC: 16.4±2.6 | n/a | none | 2 of 35 (acAN)  7 of 32 (recAN) | min 6 months | 3 T, b=1300 s/mm², 30 directions, 2.4 mm isotropic no gap | no group difference | FSL, TRACULA | FA, MD, RD, AD | Mean FA, MD, RD and AD values were extracted from 18 WM pathways were reconstructed with TRACULA. |
| No group differences in FA, MD, RD, AD after correction for multiple comparisons. | | | | | | | | | | | |
| Bang *et al.* (2017) | recAN: 21  HC: 21 | Mixed | recAN: 27.62±5.06  HC: 26.10±4.75 | 33.90  ± 27.75 (months) | 3 of 21 | n/a | 53.60±42.80 | 3 T, b=1000 s/mm2, 32 directions, 2 mm isotropic, n/a | n/a | FSL, TBSS | FA, MD, RD, AD | Whole-brain analyses for FA, MD, AD, RD |
| No group differences found. | | | | | | | | | |  |  |  |

**SM Table 13:** Updatedsummary of published DTI studies in AN including longitudinal samples (until 12/2017; see also King *et al.* 2017). For table information, see SM Table 11.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year** | **sample size** | **AN subtype** | **age ± SD (years) (AN/HC)** | **duration of illness**  **± SD (years)** | **medication** | **psychiatric comorbidities (only acAN)** | **Time between scans** | **image acquisition**  **(tesla/ b/ gradient directions/ resolution)** | **white matter volume** | **DTI software** | **Parameters** | **Whole-brain** |
| Cha *et al.* (2016) | acAN: 22  HC: 18 | mixed | acAN: 19.5±2.42  HC: 20.5±2.95 | n/a | none | 3 (DD)  3 (specific phobia) | 47.6±10.13 (weeks) | 1.5 T, b=800 s/mm², 16 directions, 2mm isotropic no gap | n/a | FSL, TBSS | FA | FA was first evaluated in whole-brain analyses and in ROI analysis within the  fronto-accumbal WM. |
| **FA**: no FA differences were found in whole brain analyses and ROI (fronto-accumbal WM regions) analyses before and after weight restoration. | | | | | | | | | | | |
| Vogel *et al.* (2016) | acAN: 22  HC: 21 | mixed | acAN: 15±1.6,  HC: 15±1.0 | 1±1.1 |  | 1 (DD)  2 (Anxiety Disorder)  1 (Anxiety Disorder + DD) | 20.38±6.72 (weeks) | 3 T, b=1000 s/mm², 30 directions, Protocol 1: 2mm³  isotropic | n/a | FSL, TBSS | FA, MD, RD, AD | ROI-analyes, resulting frim significant differences in the cross-sectional study (see SI Table 5) |
| **FA:** AN > HC No group differences were present at discharge compared to HC using voxelwise TBSS analysis, but FA remained elevated in ROI analysis. | | | | | | | | | | | |
| Olivo *et al.* (2017) | acAN: 1  EDNOS: 11  HC: 24 | restrictive | acAN:16  EDNOS: 14.9±1.6 HC:14.1 | n/a | none | 2 (DD)  1 (Anxiety Disorder+ DD)  2 (DD + PTSD)  1 (DD + OCD) | 12 months | 3 T, b n/a, 48 directions, 1.75 3 Tmm³ isotropic, n/a | n/a | FSL, TBSS | FA, MD, RD, AD | Whole-brain FA analyses. In voxels with significant differences, MD, AD, and RD values were extracted. |
| No group differences were found. | | | | | | | | | | | |

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