Title: Neuroanatomical correlates of temperament and cognitive function in women with and without anorexia nervosa

Authors: Amy E. Miles, PhD [a,b], Allan S. Kaplan, MD, MSc [a,b,c] & Aristotle N. Voineskos, MD, PhD [a,b,c,d]

Affiliations:

[a] Centre for Addiction and Mental Health, Toronto, ON, Canada

[b] Institute of Medical Science, University of Toronto, Toronto, ON, Canada

[c] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[d] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada

Corresponding Author: Amy E. Miles

Email: amy.miles@camh.ca

Phone: 416 535 8501 ext 30426

Mail: Centre for Addiction and Mental Health, 250 College Street, Room 647, Toronto, Ontario, Canada, M5T 1R8

ABSTRACT

Temperamental characteristics and cognitive processing deficits have been identified as potential endophenotypes of anorexia nervosa (AN), but their neuroanatomical correlates have not been thoroughly assessed. Therefore, we aim to systematically and comprehensively examine relationships among empirically-derived measures of clinical and cognitive function and distinct indices of cortical surface architecture and white matter microstructure in women at various stages of and with varying risk factors for AN. Neuroimaging and assessment data was collected from women with acute AN (n = 24), women with remitted AN (n = 24), unaffected sisters of women with acute or remitted AN (n = 12), and unrelated healthy control women (n = 12). T1 and diffusion-weighted MRI data was acquired on a 3T scanner with 60 gradient directions, and it was processed with Freesurfer and FSL Tract-Based Spatial Statistics. Separate linear regressions were used to test relationships among six clinical components ("eating, weight, and shape concern"; "neuroticism and attachment insecurity"; "reward sensitivity"; "general cognitive impairment"; "cognitive inflexibility"; "perfectionism") and vertex-wise, cortex-wide thickness (CT) and surface area (CSA) and voxel-wise, brain-wide fractional anisotropy (FA) and mean diffusivity (MD). Threshold-free cluster enhancement was applied to t-statistic images, and significance was determined using permutation testing. We detected significant associations between "neuroticism and attachment insecurity" and vertex-wise CSA in the left and right insula (left, r = -0.617; right, r = -0.614), and we detected significant associations between "general cognitive impairment" and voxel-wise FA and MD in the corpus callosum and corona radiata (FA, r = -0.561; MD, r = 0.512). We did not detect significant associations between "eating, weight, and shape concern", "reward sensitivity", "cognitive inflexibility", or "perfectionism" and vertex/voxel-wise CT, CSA, FA, or MD. Cortical surface area and white matter microstructure are relatively heritable phenotypes that develop in childhood and adolescence, and variations therein could give rise to temperamental characteristics and cognitive processing deficits that persist in adulthood and increase susceptibility to psychopathology characteristic of AN.

INTRODUCTION

Anorexia nervosa (AN) is a complex psychiatric disorder, the diagnostic hallmark of which is persistent restriction of energy leading to severely low body weight (for a review, see Treasure et al., 2015). AN is typically diagnosed during adolescence, and it disproportionately impacts women. In the absence of evidence-based treatments, prognosis is relatively poor; fewer than half of patients achieve sustained recovery and one in ten dies by suicide or from medical consequences of AN.

Despite strong evidence of heritability and consistent identification of temperamental and cognitive risk factors (e.g. neuroticism and inflexibility), neuroanatomical correlates of AN are poorly understood, and assessment thereof is complicated by starvation-driven pathophysiology, effects of which cannot be readily distinguished from premorbid differences in brain structure (Bulik et al., 2006; Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Walsh & Devlin, 1998). Nevertheless, structural magnetic resonance imaging (MRI) studies in AN provide preliminary evidence of variations in cortical surface architecture and white matter microstructure that are common to acute and remitted patients and independent of disease state, and these phenotypic differences could contribute to disease vulnerability (Miles, Kaplan, French, & Voineskos, 2018; Miles, Voineskos, French, & Kaplan, 2018).

In order to gain additional information about the developmental origins and clinical significance of observed variations in brain structure, we aim to explore relationships among measures of clinical and cognitive function, derived from a comprehensive assessment battery, and distinct indices of cortical surface architecture and white matter microstructure. Because we aim to assess brain-based vulnerability dimensionally, our sample includes women with acute AN, women with remitted AN, unaffected sisters of women with acute or remitted AN, and unrelated healthy control women. By including unaffected sisters, we glean potentially relevant information about genetic contributions to phenotypic differences while buffering against confounding effects of lifetime malnutrition. Likewise, by including women with remitted AN, we glean potentially relevant information about resilience factors that contribute to good outcome from AN.

Although this study is exploratory, we have several preliminary hypotheses. First, we expect to observe significant, negative associations between disorder-specific psychopathology and site-specific cortical thickness, a dynamic phenotype that remains susceptible to environmental modulation across the lifespan (Tamnes et al., 2013; Wenger et al., 2012). Second, we expect to observe significant, negative associations between temperamental risk factors for AN and site-specific cortical surface area, a heritable phenotype that develops in early life and remains relatively stable thereafter (Lilenfeld et al.,

2006; Panizzon et al., 2009; Raznahan et al., 2011). Third, we expect to observe significant, negative associations between cognitive risk factors for AN and site-specific white matter integrity, a heritable phenotype that develops in childhood and adolescence and has been implicated in cognition and learning (Fields, 2008; Holliday et al., 2005; Lebel et al., 2012; Voineskos, 2015). These hypotheses are consistent with reported associations between drive for thinness and extrastriate cortical thickness (King et al., 2015), neuroticism and prefrontal-temporal cortical surface area (Riccelli et al., 2017), and cognitive impairment and site-specific white matter integrity (Peters et al., 2014; Voineskos et al., 2012) in clinical and non-clinical samples.

METHODS AND MATERIALS

Sample Recruitment

The current sample included 72 volunteers: 24 women with acute AN, 24 women with remitted AN, 12 unaffected sisters of women with acute or remitted AN, and 12 unrelated healthy control women. All participants were female, aged 18 to 48, and medically fit for imaging. None had a current substance use disorder or a history of psychosis, severe head trauma, or neurological problems.

AN patients and healthy controls were recruited from university campuses and hospital and community-based clinics in the Greater Toronto Area. Participants assigned to the acute AN group met the following criteria: current AN diagnosis and BMI < 18.0 kg/m2. Participants assigned to the remitted AN group met the following criteria: past AN diagnosis; BMI > 18.5 kg/m2, as maintained for twelve consecutive months; and abstinence from bingeing, purging, and restrictive eating, as maintained for twelve consecutive months. Healthy controls met the following criteria: BMI > 18.5 kg/m2 and BMI < 30.0 kg/m2 and no lifetime psychiatric history.

Participants with acute or remitted AN were asked to provide study information to their sisters, and those who replied were screened for eligibility: BMI > 18.5 kg/m2 and BMI < 30.0 kg/m2 and no lifetime eating disorder diagnosis.

The study was approved by the Centre for Addiction and Mental Health Research Ethics Board, and all participants gave written informed consent.

Clinical Assessment

A comprehensive clinical battery was used to assess participants. As part of this battery:

(1) a semi-structured interview, administered by the first author, was used to collect demographic and clinical information;

(2) the Structured Clinical Interview for Diagnosis, Research Version (SCID-I/P: First, Spitzer, Gibbon, & Williams, 2002), modified to reflect guidelines from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013), was used to confirm AN diagnosis, screen for psychosis and substance use, and report comorbid anxiety and mood disorders;

(3) the Eating Disorder Examination Questionnaire, Version 6.0 (EDE-Q 6.0: Fairburn & Beglin, 2008) was used to assess restraint, eating concern, weight concern, shape concern, and global symptom severity;

(4) the Eating Disorder Inventory-3 (EDI-3: Garner, 2004) was used to assess drive for thinness, bulimia, body dissatisfaction, low self-esteem, personal alienation, interpersonal insecurity, interpersonal alienation, interoceptive deficits, emotional dysregulation, perfectionism, asceticism, and maturity fears;

(5) the NEO Personality Inventory-Revised (NEO PI-R: Costa & McCrae, 1992) was used to assess neuroticism;

(6) the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ: Torrubia, Ávila, Moltó, & Caseras, 2001) was used to assess sensitivity to punishment and sensitivity to reward;

(7) the State-Trait Anxiety Inventory (STAI: Spielberger & Gorsuch, 1983) was used to assess state anxiety and trait anxiety; and

(8) the WCST-64: Computer Version 2-Research Edition (WCST-64:CV2: Kongs, Thompson, Iverson, & Heaton, 2000) was used to assess total errors, perseverative responses, perseverative errors, non-perseverative errors, and conceptual level responses.

Assessment scales were selected to reflect a wide range of clinical and cognitive deficits frequently associated with AN.

Image Acquisition and Processing

MRI data was collected on a 3T scanner (Echospeed; General Electric Medical Systems) at the Centre for Addiction and Mental Health. High-resolution 3D T1-weighted structural scans were acquired using a fast-spoiled gradient-recalled echo sequence with the following parameters: TE = 3ms; TR = 8.2ms; TI = 650ms; $\alpha = 8°$; FOV = 24cm; NEX = 1; 0.9mm isotropic voxels, no gap. Sixty diffusion-weighted (b = 1000 s/mm2) and five baseline scans (b = 0 s/mm2) were acquired using an echo planar imaging sequence with dual spin-echo and the following parameters: TE = 88 ms; TR = 8800ms; FOV = 256mm; 128x128 encoding steps; 2.0mm isotropic voxels, no gap.

Image processing and analysis, described in detail elsewhere (Miles, Kaplan, French, & Voineskos, 2018; Miles, Voineskos, French, & Kaplan, 2018), was carried out with tools from the Freesurfer

Software Suite (http://surfer.nmr.mgh.harvard.edu, version 6.0.0) and FMRIB Software Library (https://fsl.fmrib.ox.ac.uk, version 5.0.10). For T1-weighted data, key steps included preprocessing, tissue classification, cortical surface reconstruction, and vertex-wise estimation of cortical thickness (CT) and cortical surface area (CSA). For diffusion-weighted data, key steps included preprocessing, tensor fitting, white matter skeletonisation, and voxel-wise estimation of fractional anisotropy (FA) and mean diffusivity (MD).

Dimension Reduction and Feature Extraction

Dimension reduction and feature extraction were performed with principal components analysis (PCA) followed by varimax rotation. In brief, this involved: centering, scaling, and transforming raw data; performing PCA and selecting components for rotation based on $\lambda > 1$; rotating components; and extracting standardized scores ("clinical component scores") for further analysis.

Regression Analyses

Relationships among clinical component scores and vertex-wise, cortex-wide CT and CSA and voxel-wise, brain-wide FA and MD were tested with separate linear regressions. Threshold-free cluster enhancement was applied to t-statistic images, and significance was determined using permutation testing with 10,000 repetitions and a Bonferroni-adjusted threshold (pFWER < .05). The latter technique has been described in detail by Lett et al. (2017). Because age was not significantly associated with clinical component score, it was not included as a nuisance variable.

Post hoc correlation analyses confirmed relationships among clinical component scores and cluster means, and separate univariate analyses of covariance, controlling for age (CT, FA, MD) or age and intracranial volume (CSA), were used to test main effect of group.

Statistical analyses were performed with RStudio (RStudio Team, version 0.99.489) and the TFCE_mediation toolbox (https://github.com/trislett/TFCE_mediation).

RESULTS

Sample Characteristics

Sample characteristics are summarized in Table 1, and AN patients and healthy controls are described in detail elsewhere (Miles et al., 2018).

Neuroimaging and assessment data was collected from twelve unaffected sisters. As anticipated, these participants reported significantly less clinical and cognitive impairment than their sisters with acute AN (n = 8) or remitted AN (n = 4). Contrary to expectation, however, they did not report significantly more clinical and cognitive impairment than unrelated healthy control women.

AN patients with sisters who agreed to participate did not differ significantly from AN patients without sisters or with sisters who declined participation. This was true for each of the following variables: disease subtype, current and lowest BMI, age-adjusted illness duration, lifetime depression diagnosis, and lifetime anxiety-spectrum diagnosis.

Varimax-Rotated Principal Components

Six components accounted for 84% of variance in the original dataset. These components are summarized in Table 2.

The following scales loaded prominently onto clinical component #1 ("eating, weight, and shape concern"), which explained 29% of variance: global symptom severity (0.917), shape concern (0.893), weight concern (0.870), drive for thinness (0.851), eating concern (0.837), restraint (0.835), and body dissatisfaction (0.756).

The following scales loaded prominently onto clinical component #2 ("neuroticism and attachment insecurity"), which explained 18% of variance: interpersonal insecurity (0.801), interpersonal alienation (0.737), neuroticism (0.688), trait anxiety (0.658), low self-esteem (0.658), sensitivity to punishment (0.648), and personal alienation (0.646).

The following scales loaded prominently onto clinical component #3 ("reward sensitivity"), which explained 11% of variance: sensitivity to reward (0.745), maturity fears (0.664), and emotional dysregulation (0.632).

The following scales loaded prominently onto clinical component #4 ("general cognitive impairment"), which explained 11% of variance: non-perseverative errors (0.937), conceptual level responses (-0.912), and total errors (0.903).

The following scales loaded prominently onto clinical component #5 (“cognitive inflexibility”), which explained 9% of variance: perseverative errors (0.927) and perseverative responses (0.920).

The following scales loaded prominently onto clinical component #6 (“perfectionism”), which explained 5% of variance: perfectionism (0.879).

Regression Results

We tested relationships among clinical component score and vertex/voxel-wise CT, CSA, FA, and MD in a sample of women with and without AN, including unaffected sisters. In doing so, we detected the following associations, depicted in Figures 1 and 2.

Clinical component #2 (“neuroticism and attachment insecurity”) was a significant predictor of vertex-wise CSA in two clusters covering 1956 mm2 in the left insula, inferior frontal gyrus, and lateral orbitofrontal cortex (cluster #1, pFWER = .010) and 1216 mm2 in the right insula, inferior frontal gyrus, and lateral orbitofrontal cortex (cluster #2, pFWER = .023). Post hoc analyses confirmed these relationships (cluster #1, $t = -6.270$, $p < .001$; cluster #2, $t = -6.217$, $p < .001$) and revealed strong correlations between clinical component score and cluster-wise CSA (cluster #1, $r = -.617$, $p < .001$; cluster #2, $r = -.614$, $p < .001$). Clinical component #2 was a non-significant predictor of vertex/voxel-wise CT, FA, and MD.

Clinical component #4 (“general cognitive impairment”) was a significant predictor of voxel-wise FA in one cluster covering 29.4% of the white matter skeleton and including substantial portions of the corpus callosum, corona radiata, internal capsule, posterior thalamic radiation, superior longitudinal fasciculus, and external capsule (cluster #3, pFWER = .004), and it was a significant predictor of voxel-wise MD in a partially-overlapping cluster covering 10.1% of the white matter skeleton and including substantial portions of the body and splenium corpus callosum, posterior and superior corona radiata, posterior thalamic radiation, and superior longitudinal fasciculus (cluster #4, pFWER = .011). Again, post hoc analyses confirmed these relationships (cluster #3, $t = -5.419$, $p < .001$; cluster #4, $t = 4.774$, $p < .001$), and they revealed strong correlations between clinical component score and cluster-wise FA or MD (cluster #3, $r = -.561$, $p < .001$; cluster #4, $r = .512$, $p < .001$). Clinical component #4 was a non-significant predictor of vertex-wise CT and CSA.

Clinical component #1 (“eating, weight, and shape concern”), clinical component #3 (“reward sensitivity”), clinical component #5 (“cognitive inflexibility”), and clinical component #6 (“perfectionism”) were non-significant predictors of vertex/voxel-wise CT, CSA, FA, and MD.

Main Effect of Group

We detected a significant main effect of group on clinical component #1 (“eating, weight, and shape concern”), clinical component #2 (“neuroticism and attachment insecurity”), clinical component #6 (“perfectionism”), and cluster-wise CSA (clusters #1, #2).

We did not detect a significant main effect of group on clinical component #3 (“reward sensitivity”), clinical component #4 (“general cognitive impairment”), clinical component #5 (“cognitive inflexibility”), or cluster-wise FA or MD (clusters #3, #4).

Results are summarized in Table 3.

DISCUSSION

We tested relationships among empirically-derived measures of clinical and cognitive function and distinct indices of cortical surface architecture and white matter microstructure in a sample of women with and without AN, including unaffected sisters. As anticipated, we detected significant associations between temperamental characteristics associated with AN ("neuroticism and attachment insecurity") and site-specific cortical surface area, and we detected significant associations between cognitive processing deficits associated with AN ("general cognitive impairment") and site-specific white matter microstructure. Contrary to expectation, however, we did not detect a significant association between clinical hallmarks of AN ("eating, weight, and shape concern") and site-specific cortical thickness.

Interpersonal Difficulties and Insular Cortical Surface Area

The observed relationship between clinical component #2 ("neuroticism and attachment insecurity") and cortical surface area in the bilateral insula, a crucial hub of interoceptive processing frequently implicated in AN (for a review, see Nunn, Frampton, Fuglset, Törzsök-Sonnevend, & Lask, 2011), could have significant implications for disease vulnerability and manifestation. This is particularly true given the observed effect of group; in each case, group means were most extreme in women with acute AN, least extreme in unrelated healthy control women, and more extreme in women with remitted AN than unaffected sisters. This pattern mirrors that of cumulative risk and indicates a potential link between cortical surface area, a highly heritable phenotype that develops in early-life, and temperamental features that increase vulnerability to AN (Bulik et al., 2006; Jang, Livesley, & Vemon, 1996; Panizzon et al., 2009).

The insula is a highly interconnected relay for affective, cognitive, and homeostatic inputs from distributed regions implicated in self-referential processing and reward and reinforcement (Nieuwenhuys, 2012). As such, site-specific reductions in cortical surface area could give rise to network-wide disruption that manifests as neuroticism and attachment insecurity. Dysregulation consistent with this hypothesis has been reported in patients with acute and remitted AN; specifically, altered resting-state functional connectivity between the insula and default mode network and thalamus has been observed in the former group, and altered structural connectivity between the insula and ventral striatum and orbitofrontal cortex has been observed in the latter group (Boehm et al., 2014; Ehrlich et al., 2015; Shott et al., 2016).

Site-specific reductions in cortical surface area could also contribute to neuroticism and attachment insecurity by influencing monoamine function. Significant interrelationships among insula cortical surface area, dopamine beta-hydroxylase (DBH) polymorphism, and novelty seeking were reported in healthy adults, and insula cortical surface area appeared to partially mediate the association between DBH and novelty seeking in this group (Li et al., 2015). Given evidence of low novelty seeking and dopaminergic perturbation in AN (Fassino et al., 2002; Kaye, Frank, & McConaha, 1999), further exploration of the link between insula morphometry, monoamine function, and reward processing is warranted.

General Cognitive Impairment and Diffuse White Matter Microstructure

We observed significant relationships between clinical component #4 ("general cognitive impairment"), a measure of insight and concept formation, and distinct indices of white matter microstructure in major association, commissural, and projection tracts. These tracts connect widespread cortical and subcortical regions implicated in visual attention, working memory, and response selection (Mori et al., 2008), and compromised integrity thereof could disrupt coordinated information flow necessary for complex processing.

Although deficits in cognitive performance and white matter microstructure have been reported in AN (Galimberti et al., 2013; Monzon, Hay, Foroughi, & Touyz, 2016), group was not a significant predictor of clinical component score or cluster-wise FA or MD. Likewise, despite reports of cognitive decline and white matter impairment in aging (Voineskos et al., 2012), age was not a significant predictor of clinical component score ($t = 1.208$, $p = 0.231$) or cluster-wise MD ($t = 1.788$, $p = 0.079$), and it was only weakly associated with cluster-wise FA ($r = -0.282$, $p = 0.022$). As such, our findings indicate a brain-behavior link that is independent from phenotype-specific risk or age effects.

AN rarely manifests in isolation (Herzog, Keller, Sacks, Yeh, & Lavori, 1992), and a substantial proportion of participants reported a lifetime diagnosis of major depression (acAN, 83.3%; recAN, 37.5%) or anxiety-spectrum disorder (acAN, 62.5%; recAN, 62.5%; sibAN, 16.7%). Deficits in cognitive performance and white matter microstructure have also been reported in these groups (Hammar & Årdal, 2009; Purcell, Maruff, Kyrios, & Pantelis, 1998; Zarei et al., 2011; Zhu et al., 2011), suggesting that we may have captured a brain-behavior link associated with vulnerability to one or more of these disorders or to psychopathology in general. Further research is needed to explore this possibility.

Limitations and Future Directions

We tested relationships among composite measures of clinical and cognitive function and distinct neuroanatomical phenotypes in women at various stages of and with varying risk factors for AN. With fewer than one-hundred participants, we may have been underpowered to detect subtle brain-behavior relationships. Likewise, by testing associations across subjects, rather than within groups, we may have failed to detect brain-behavior relationships that are unique to acutely-ill patients. As such, replication in a larger sample, including an equal number of unaffected sisters and healthy controls, is warranted, as is replication in a separate sample of underweight patients. Ideally, the former would also include women with anxiety or depression but not AN, and the latter would test mediation models designed to examine the impact of BMI and illness duration.

Despite limitations in sample size and composition, this study makes several important contributions to our understanding of brain-behavior relationships in women with and without AN, including unaffected sisters. First, it suggests that site-specific variations in cortical surface area, a highly heritable phenotype that develops in childhood, could influence temperament and psychosocial function and contribute to AN vulnerability. Second, it provides evidence of a link between site-specific white matter impairment, a moderately heritable phenotype that develops in childhood and adolescence, and deficits in cognitive performance that manifest in a range of psychiatric disorders.

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TABLE 1 SAMPLE CHARACTERISTICS

[insert table here]

Demographic and clinical characteristics and group differences therein.

[a] data presented as frequency counts or mean (standard deviation); [b] determined using $p_{FWER} < 0.05$; [c] includes selective serotonin reuptake inhibitors and atypical antipsychotics; [d] includes generalized anxiety disorder, obsessive compulsive disorder, panic disorder, and post-traumatic stress disorder; acAN = acute anorexia; AN-BP = binge-purge subtype; BMI = body mass index; EDE-Q = Eating Disorder Examination Questionnaire, Version 6.0; EDI-3 = Eating Disorder Inventory-3; FWER = family-wise error-corrected; HC = healthy control; NEO PI-R = NEO Personality Inventory-Revised; recAN = remitted anorexia; sibAN = unaffected sister; SPSRQ = Sensitivity to Punishment and Sensitivity to Reward Questionnaire; STAI = State-Trait Anxiety Inventory; WCST-64:CV2 = WCST-64: Computer Version 2-Research Edition

TABLE 2 VARIMAX-ROTATED COMPONENTS

[insert table here]

Rotated variable loadings (largest outlined) and component summary statistics.

EDE-Q = Eating Disorder Examination Questionnaire, Version 6.0; EDI-3 = Eating Disorder Inventory-3; NEO PI-R = NEO Personality Inventory-Revised; SPSRQ = Sensitivity to Punishment and Sensitivity to Reward Questionnaire; SS = sum of squares; STAI = State-Trait Anxiety Inventory; WCST-64 = WCST-64: Computer Version 2-Research Edition

TABLE 3 MAIN EFFECT OF GROUP

[insert table here]

Varimax-rotated clinical component scores, cluster means, and group differences therein.

Data presented as mean (standard deviation). [a] determined using $p_{FWER} < 0.05$; [b] adjusted for age (FA, MD) or age and total intracranial volume (CSA); acAN = acute anorexia; CSA = cortical surface area; FA = fractional anisotropy; FWER = family-wise error-corrected; HC = healthy control; MD = mean diffusivity; recAN = remitted anorexia; sibAN = unaffected sister

FIGURE 1 REGRESSION RESULTS, CLINICAL COMPONENT #2

[insert figure here]

Regions in which clinical component #2 ("neuroticism and attachment insecurity") is a significant predictor of cortical surface area: (A) cluster #1: left hemisphere, 1956 mm^2, p_{FWER} = 0.010, peak in insular cortex; (B) cluster #2: right hemisphere, 1216 mm^2, p_{FWER} = 0.023, peak in insular cortex

CSA = cortical surface area; FWER = family-wise error-corrected

FIGURE 2 REGRESSION RESULTS, CLINICAL COMPONENT #4

[insert figure here]

Regions in which clinical component #4 ("general cognitive impairment") is a significant predictor of white matter microstructure: (A) cluster #3: 37,759 voxels, p_{FWER} = 0.004, peak in body corpus callosum; (B) cluster #4: 13,030 voxels, p_{FWER} = 0.011, peak in right posterior corona radiata

FWER = family-wise error-corrected

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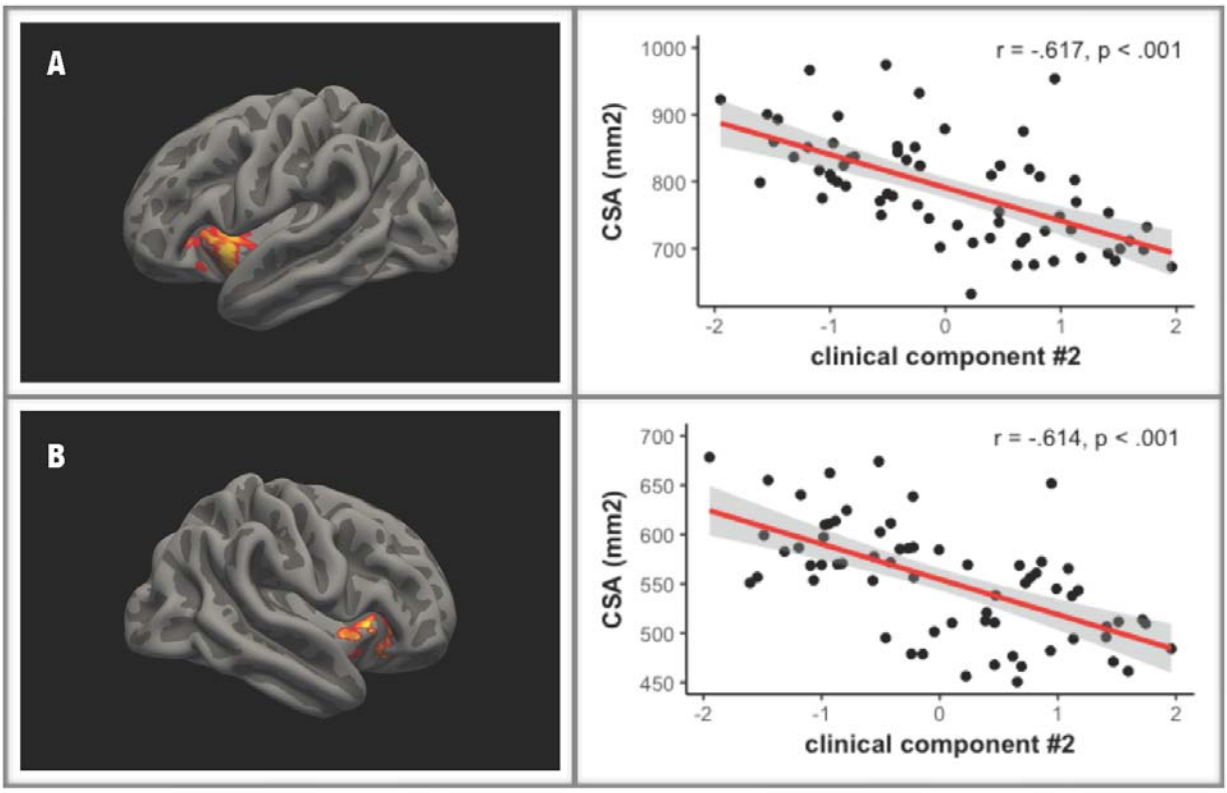
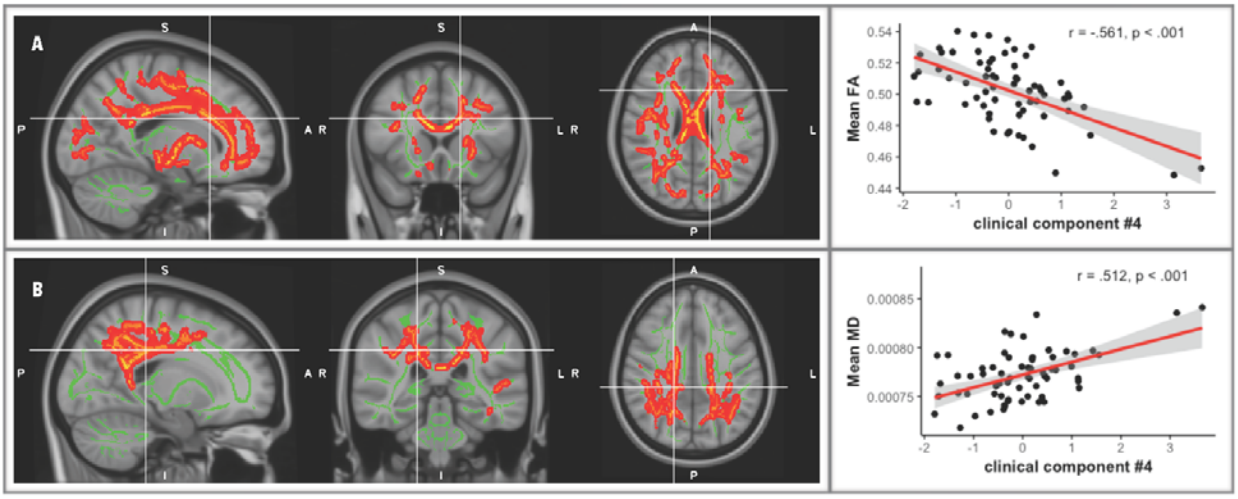

A
r = -.617, p < .001
CSA (mm2)
1000
900
800
700
-2
-1
0
1
2
clinical component #2
B
r = -.614, p < .001
CSA (mm2)
700
650
600
550
500
450
-2
-1
0
1
2
clinical component #2


A
S
P
A R
I
S
L R
I
A
L
P
r = -.561, p < .001
Mean FA
0.54
0.52
0.50
0.48
0.46
0.44
-2
-1
0
1
2
3
clinical component #4
B
S
P
A R
I
S
L R
I
A
L
P
r = .512, p < .001
Mean MD
0.00085
0.00080
0.00075
-2
-1
0
1
2
3
clinical component #4

	acAN (1)	recAN (2)	sibAN (3)	HC (4)	F	Sig.	Comp. [b]
Interview data [a]							
N	24	24	12	12	–	–	–
Age, years	29.2 (8.1)	27.0 (6.3)	31.6 (7.3)	27.2 (7.4)	1.239	0.302	–
BMI, kg/m^2	16.0 (1.3)	20.8 (1.8)	22.7 (6.9)	21.9 (3.2)	15.718	< .001	1 < 2, 3, 4
Education, age-adjusted years	15.0 (0.3)	15.9 (0.3)	16.3 (0.5)	16.6 (0.5)	3.345	0.024	1 < 4
Illness duration, age-adjusted years	12.3 (1.0)	9.5 (1.0)	–	–	3.820	0.057	–
Race, white:non-white	22:2	19:5	12:0	8:4	6.653	0.084	–
Handedness, right:left	23:1	20:4	12:0	11:1	3.818	0.282	–
AN subtype, restricting:binge-purge	9:15	17:7	–	–	4.112	0.043	1 > 2 (AN-BP)
Current medication, yes:no [c]	16:8	9:15	2:10	0:12	18.133	< 0.001	1 > 4
Lifetime anxiety, yes:no [d]	15:9	15:9	2:10	0:12	19.688	< 0.001	1, 2 > 4
Lifetime depression, yes:no	20:4	9:15	0:12	0:12	34.759	< 0.001	1 > 2, 3, 4

	Clinical component #					
	1	**2**	**3**	**4**	**5**	**6**
Variable loadings						
EDE-Q Restraint	0.835	0.170	0.158	0.232		
EDE-Q Eating Concern	0.837	0.305	0.293			
EDE-Q Shape Concern	0.893	0.333				0.131
EDE-Q Weight Concern	0.870	0.345		0.116		0.114
EDE-Q Global	0.917	0.308	0.158	0.119		
EDI-3 Drive for Thinness	0.851	0.293		0.147	0.133	0.110
EDI-3 Bulimia	0.590	0.130	0.563		0.246	-0.210
EDI-3 Body Dissatisfaction	0.756	0.411				
EDI-3 Low Self Esteem	0.580	0.658	0.255		0.109	
EDI-3 Personal Alienation	0.495	0.646	0.463	0.106		
EDI-3 Interpersonal Insecurity	0.362	0.801				-0.117
EDI-3 Interpersonal Alienation	0.284	0.737	0.259		0.119	0.214
EDI-3 Interoceptive Deficits	0.495	0.518	0.325		0.268	0.184
EDI-3 Emotional Dysregulation	0.245	0.390	0.632	0.112	0.243	
EDI-3 Perfectionism	0.174	0.152		-0.152		0.879
EDI-3 Asceticism	0.500	0.330	0.342		0.229	0.456
EDI-3 Maturity Fears	0.239	0.237	0.664	0.190	0.149	
STAI State Anxiety	0.551	0.502	0.443			
STAI Trait Anxiety	0.542	0.658	0.365			0.138
NEO PI-R Neuroticism	0.458	0.688	0.441			
SPSRQ Sensitivity to Punishment	0.391	0.648		0.134		0.259
SPSRQ Sensitivity to Reward			0.745		-0.229	0.364
WCST-64 Total Errors				0.903	0.290	
WCST-64 Perseverative Responses				0.313	0.920	
WCST-64 Perseverative Errors				0.304	0.927	
WCST-64 Nonperseverative Errors	0.158			0.937		-0.105
WCST-64 Conceptual Level Responses	0.129			-0.912	-0.326	
Summary statistics						
SS loading	7.905	4.968	3.002	2.953	2.302	1.430
Proportional Variance	0.293	0.184	0.111	0.109	0.085	0.053
Cumulative Variance	0.293	0.477	0.588	0.697	0.783	0.836

	acAN (1)	recAN (2)	sibAN (3)	HC (4)	F	Sig.	Comp. a
Clinical component scores							
#1: "eating, weight, and shape concern"	0.69 (0.65)	-0.13 (1.20)	-0.75 (0.43)	-0.63 (0.45)	9.764	0.000	1 > 2, 3, 4
#2: "neuroticism and attachment insecurity"	0.51 (0.87)	0.05 (0.97)	-0.51 (0.59)	-0.77 (1.07)	5.774	0.002	1 > 3, 4
#3: "reward sensitivity"	-0.02 (1.35)	0.15 (0.89)	-0.13 (0.69)	-0.13 (0.39)	0.272	0.846	--
#4: "general cognitive impairment"	0.20 (1.33)	-0.13 (0.77)	-0.10 (0.76)	-0.23 (0.72)	0.607	0.613	--
#5: "cognitive inflexibility"	0.23 (0.76)	-0.12 (1.37)	0.10 (0.63)	-0.39 (0.78)	0.951	0.422	--
#6: "perfectionism"	-0.17 (1.03)	0.46 (0.90)	-0.64 (0.78)	-0.17 (0.76)	3.976	0.012	2 > 3
Covariate-adjusted cluster means b							
CSA (mm^2), cluster #1	759.0 (15.1)	791.6 (15.5)	815.1 (22.9)	842.1 (26.6)	3.133	0.032	1 < 4
CSA (mm^2), cluster #2	521.8 (10.1)	559.7 (10.4)	573.0 (15.3)	605.6 (17.8)	6.830	0.000	1 < 3, 4
FA, cluster #3	0.498 (0.004)	0.503 (0.004)	0.510 (0.006)	0.506 (0.007)	0.871	0.461	–
MD, cluster #4	0.000780 ± 5	0.000773 ± 5	0.000757 ± 8	0.000768 ± 9	2.345	0.082	–