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Reduced Functional Connectivity in the Thalamo-Insular Subnetwork in Patients With Acute Anorexia Nervosa

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Abstract: The neural underpinnings of anorexia nervosa (AN) are poorly understood. Results from existing functional brain imaging studies using disorder-relevant food- or body-stimuli have been heterogeneous and may be biased due to varying compliance or strategies of the participants. In this study, resting state functional connectivity imaging was used. To explore the distributed nature and

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complexity of brain function we characterized network patterns in patients with acute AN. Thirty-five unmedicated female acute AN patients and 35 closely matched healthy female participants underwent resting state functional magnetic resonance imaging. We used a network-based statistic (NBS) approach [Zalesky et al., 2010a] to identify differences between groups by isolating a network of interconnected nodes with a deviant connectivity pattern. Group comparison revealed a subnetwork of connections with decreased connectivity including the amygdala, thalamus, fusiform gyrus, putamen and the posterior insula as the central hub in the patient group. Results were not driven by changes in intranodal or global connectivity. No network could be identified where AN patients had increased coupling. Given the known involvement of the identified thalamo-insular subnetwork in interoception, decreased connectivity in AN patients in these nodes might reflect changes in the propagation of sensations that alert the organism to urgent homeostatic imbalances and pain-processes that are known to be severely disturbed in AN and might explain the striking discrepancy between patient's actual and perceived internal body state. *Hum Brain Mapp 36:1772–1781, 2015.*

Key words: fMRI; connectivity; network; posterior insula; thalamus

INTRODUCTION

Anorexia nervosa (AN) is a severe eating disorder that predominantly begins during early adolescence in females. Patients deprive themselves of food despite starvation, suffer severe body image distortions and often have a lack of insight about being ill. Mortality rates are among the highest in psychiatry [Steinhausen, 2002]. Despite high genetic heritability estimates [Kaye et al., 2009], our knowledge of the biological underpinnings of this devastating illness is very limited [Kaye et al., 2011, 2013a]. The use of modern noninvasive neuroimaging techniques may allow a deeper understanding of AN [Kidd and Steinglass, 2012].

However, compared to other neuropsychiatric disorders, neuroimaging research in AN has only recently gained momentum. Existing studies, which are often limited by small sample sizes, have focused on executive functioning [Kullmann et al., 2013; Lock et al., 2011; Sato et al., 2013; Wierenga et al., 2014; Zastrow et al., 2009] or the processing of food/taste and other appetitive stimuli [Bischoff-Grethe et al., 2013; Brooks et al., 2012; Holsen et al., 2014; Oberndorfer et al., 2013a; Wagner et al., 2007, 2008]. Results suggest that patients may have an altered sensitivity for sensory-interoceptive and/or reward processes as well as an impaired awareness of homeostatic needs [Kaye et al., 2013b].

To date, only very few studies have tried to characterize functionally synchronized brain activity in AN. Functional connectivity magnetic resonance imaging (fcMRI) measures the temporal correlation of neural activity via the blood oxygen level-dependent (BOLD) signal between different brain regions [Biswal et al., 1995]. Functional connectivity is typically determined while the participant is resting, since regions that are functionally related or coactivated during a cognitive task, tend to be temporally correlated at rest [Beckmann et al., 2005; Smith et al., 2009]. Groups of temporally correlated regions can be determined using independent component analysis (ICA) or seed based connectivity analysis [Cole et al., 2010] and are termed resting-state networks. A major advantage of resting state compared to task-based fMRI lies in it's lack of any domain bias, that is at the same time, a variety of functional networks with individual contribution to the complexity of the disorder can be observed. Moreover, potential bias due to patients' strategy to perform certain tasks can be limited by the minimum task requirement to lie still and not fall asleep.

In patients with AN, two groups of researchers [Cowdrey et al., 2014; Lee et al., 2014] reported increased functional connectivity between midline brain structures (dorsal anterior cingulate cortex (dACC), precuneus, retrosplenial cortex) and within the default mode network, respectively, when compared to healthy controls (HC). The latter finding is in line with results from an ICA-based resting state study that we have published very recently [Boehm et al., 2014]. Another study [Favaro et al., 2012] found decreased connectivity within a ventral visual network in AN. Decreased connectivity in AN was also found for connections originating from the dorsal putamen [Favaro et al., 2014].

Instead of focusing on the connectivity of certain regions of interest (ROI) or components, recent studies have tried to model the brain as a complex network [Bassett et al., 2009; Bullmore and Sporns, 2009; Zalesky et al., 2010a], that is, as a graph whose nodes are interconnected by edges. The nodes commonly comprise a large number of structurally or functionally defined regions across the whole brain while the edges are the structural or functional connections between these regions [Bullmore and Bassett, 2011]. The advantage of such a mathematical framework is that it allows considering changes in the relationship between multiple regions in the context of whole-brain networks [Zalesky et al., 2010a].

To determine differences in network connectivity patterns between patients with acute AN and pairwise matched female HC we used a network-based statistic

(NBS) approach [Zalesky et al., 2010a]. NBS identifies differences between groups by isolating interconnected nodes with a deviant connectivity pattern (subnetworks) and thus provides information about whole-brain topology of complex networks. Previous studies in patients with major depressive disorder, schizophrenia and amyotrophic lateral sclerosis have used NBS to identify impaired network topology [Bai et al., 2012; Verstraete et al., 2011; Zalesky et al., 2011; Zhang et al., 2011].

METHODS

Participants

The sample consisted of 70 female volunteers: 35 acute AN (12–23 years old) and 35 pairwise matched, female HC (12–23 years old). AN participants were recruited from specialized eating disorder programs of a university child and adolescent psychiatry and psychosomatic medicine department and underwent magnetic resonance imaging (MRI) within 96 h after beginning behaviorally-oriented nutritional rehabilitation programs. This sample overlaps with another recently published resting state study using a strictly hypothesis-driven ICA approach [Boehm et al., 2014].

All participants were diagnosed using the expert version of a semistructured research interview, the Structured Interview for Anorexia and Bulimia Nervosa for DSM-IV (SIAB-EX, [Fichter and Quadflieg, 1999], see also Supporting Information (SI) 1.2) and AN had to have a BMI below the 10^{th} age percentile (if younger than 15.5 years) or a BMI below 17.5 kg/m^2 (if older than 15.5 years) [Hebebrand et al., 2004; Kromeyer-Hauschild, 2001] and no recent weight gain. Within the AN group, 32 (94.1%) of the patients were of the restrictive and 2 (5.9%) of the binge/purging subtype; 4 (11.4%) had comorbid psychiatric disorders (5.7% depressive disorders including dysthymia, 2.9% anxiety disorder, and 2.9% obsessive compulsive disorder). HC participants had to be of normal weight, eumenorrhoeic and without any history of psychiatric illness. We applied several additional exclusion criteria for each group (see Supporting Information 1.1) — most importantly a history of bulimia nervosa or "regular" binge eating, psychotropic medications within 4 weeks prior to the study, substance abuse and neurologic or medical conditions. Case-control age-matching was carried out using the Munkres algorithm [Munkres, 1957] resulting in a maximum difference of 0.9 years between the individuals within one pair.

This study was approved by the local Institutional Ethics Review Board, and all participants (and their guardians if underage) gave written informed consent.

Clinical Measures

To complement the information obtained with the clinical interviews, eating disorder-specific psychopathology was assessed with the German version of the Eating Disorders Inventory (EDI-2, [Paul, 2005]). Here we use a summary score representing "core" symptoms that was estimated by averaging across the following three subscales: "drive for thinness," "body dissatisfaction," and "bulimia." Intelligence quotient (IQ) was assessed with a short version of the German adaption of the Wechsler Adult Intelligence Scale [von Aster et al., 2006] for participants aged 16 years and older or a short version of the German adaption of the Wechsler Intelligence Scale for Children [Petermann and Petermann, 2008] for participants aged 15 years or younger.

Data Acquisition

Images were acquired between 8 and 9 in the morning after an overnight fast using standard sequences with a 3 T MRI scanner (TRIO; Siemens, Erlangen, Germany) equipped with a standard head coil (Supporting Information 1.3 for details). During fMRI participants were instructed to lie still with closed eyes without falling asleep.

Preprocessing of Imaging Data

Functional and structural images were processed using SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/) within the Nipype framework (http://nipy.sourceforge.net/nipype/, [Gorgolewski et al., 2011]). The slice time corrected functional data were realigned and registered to their mean. The realigned files were coregistered to the subject's structural brain image. A DARTEL template was created using structural images from all subjects [Ashburner, 2007]. The EPI volumes were then normalized to MNI space using the DARTEL template and corresponding flow field. The resulting data were smoothed with an isotropic 8 mm FWHM Gaussian kernel.

We evaluated the quality of the fMRI data by manual inspection and using artifact detection tools [Whitfield-Gabrieli et al., 2009]. Volumes that exceed an intensity threshold of three standard deviations (SD) or a threshold of 2 mm normalized movement in any direction were classified as outliers (motion-outlier: AN: 0.31 ± 0.87 HC: 0.97 ± 2.67; intensity-outlier: AN: 1.5 ± 2.37 HC: 2.38 ± 2.85); the two groups did not differ regarding numbers of motion- and intensity-outliers (motion-outlier: $t(68)=1.38$; $P=0.17$; intensity-outlier: $t(68)=1.38$; $P=0.17$).

Using the DPARSF toolbox [Chao-Gan and Yu-Feng, 2010], implemented in MATLAB, temporal filtering between 0.01 and 0.08 Hz was applied. Then white matter and cerebrospinal fluid signal were regressed out. ROI were identified using a modified version of the AAL atlas [Tzourio-Mazoyer et al., 2002] with 104 ROIs including a more fine-grained parcellation in the superior frontal gyrus, insula, anterior cingulate cortex (ACC) and temporo-parietal junction as described previously

TABLE I. Basic demographic and clinical variables

	AN		HC		Test statistics		
	Mean	SD	Mean	SD	*t*	df	*P*
Age	16.10	2.56	16.16	2.64	−0.09	68	0.927
BMI	14.78	1.26	20.81	2.72	−11.91	68	<0.001
Minimal lifetime BMI	14.42	1.28	19.87	2.35	−11.98	66	<0.001
IQ	111	11	112	10	−0.36	68	0.720
Parental SES	3.77	0.81	4.34	0.80	−2.97	68	0.004
Handedness score	0.51	2.06	1.77	3.60	−1.79	68	0.077
EDI-2 core subscales	71.34	20.46	50.15	16.76	4.62	68	<0.001
EDI-2 Drive for thinness	27.00	8.90	14.56	7.03	6.36	65	<0.001
EDI-2 Body dissatisfaction	33.27	10.02	24.94	9.51	3.52	66	0.001
EDI-2 Bulimia	10.79	5.28	10.31	3.07	0.46	67	0.645
Leptin (in ng/ml)	1.32	1.56					

BMI and minimal lifetime BMI are displayed but statistical comparisons are based on BMI-SDS values to ensure comparability across age (see Supporting Information 1.4). BMI, body mass index; EDI-2, Eating disorder inventory, version 2; SCL-90-R GSI, Revised symptom checklist 90 global symptom score. IQ was assessed with a short version of the German adaption of the Wechsler Adult Intelligence Scale (von Aster et al., 2006) for participants aged 16 years and older or a short version of the German adaption of the Wechsler Intelligence Scale for Children (Petermann and Petermann, 2008) for participants aged 15 years or younger. Group differences were tested using with Student's *t*-tests using SPSS v21.0 (SPSS, Chicago, Illinois).

([Borchardt et al., 2014; Lord et al., 2012], see also Supporting Information Table I for details). Mean time courses across voxels in each ROI were extracted and undirected correlation matrices were constructed by calculating Pearsons product moment correlation coefficients between each pair of time courses.

Network Based Statistics

NBS is a method for identifying a statistically significant cluster of connections revealing differences between two groups. Such a subnetwork is identified using a one-sided t-statistic, which may either reveal reduced (AN < HC) or increased (AN > HC) functional connectivity. NBS returns a single p-value, which represents the likelihood that the subnetwork is due to a true effect in the data. This approach measures the entire cluster of returned connections, but does not identify the contribution of each component independently.

NBS is computed using the following steps, (1) Identify all ROI that are reduced in one specific group beyond a particular T value. (2) Select the largest contiguous cluster of these connections, and (3) validate the effect against surrogate data sets. To validate that the resulting subnetwork is not due to a random effect, group membership is resampled 5,000 times. The returned subnetwork is statistically significant at a family wise error (FWE) corrected value of $P < 0.05$. Although the network needs to be considered as a whole, the extent of the returned network can be varied using a network threshold parameter. Basically, this adjusts the extremity of deviation in a connection between groups required, before it is considered for inclusion in the NBS result. This technique has been described and validated in depth by [Zalesky et al., 2010a].

NBS results can depend on the underlying atlas used to parcellate the brain and how to obtain an optimal parcellation of the brain into meaningful regions remains an open issue [Sporns, 2011; Wig et al., 2011; Zalesky et al., 2010a, b]. To test the reproducibility of our findings we performed NBS using a variety of different parcellation templates comprising the original AAL template displaced by 1.5, 4.5, or 20 millimeters along a randomly generated vector for each region and evaluated the emerging changes at a $t=4$ (see also [Cocchi et al., 2012]). Any portion of a displaced region lying outside the brain volume was omitted. Effects of displacement were evaluated with four independent parcellation templates generated for each displacement magnitude.

Intranodal Homogeneity

To test, whether changes in interregional connectivity (such as identified with NBS) can be explained by differences regional connectivity [Zalesky et al., 2012] we estimated Kendall's coefficient concordance (KCC) for all voxels within each node implicated in the subnetwork (identified by NBS at $t=4$) as a measure of regional homogeneity (ReHo). The preprocessing steps were identical to the ones for NBS and individual KCC (with values from 0 to 1) were estimated using the DPARSFA software [Chao-Gan and Yu-Feng, 2010]. Group comparisons were performed using Student's *t*-tests and associations between KCC of a specific node and inter-regional connectivity (from the NBS analysis) for connections between this node

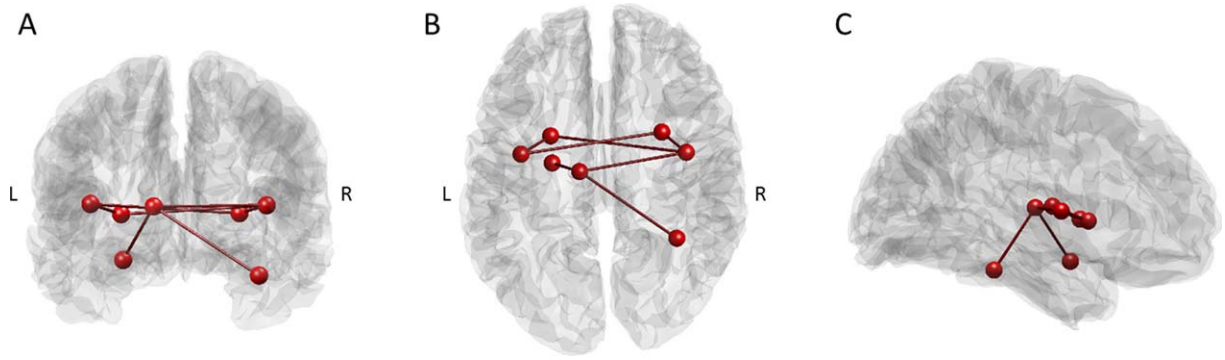

Figure 1.
Subnetwork of nodes with reduced connectivity in patients with AN-identified using NBS: back view (**A**), top view (**B**), and side view (**C**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and other nodes were estimated using Pearson correlations coefficients [Zalesky et al., 2012].

RESULTS

Sample Characteristics

There were no differences in age, IQ, or handedness score between the pairwise matched groups of AN and HC. However, as expected AN had a significantly lower BMI and lower minimal lifetime BMI. Furthermore AN had significantly higher eating disorder symptom scores as well as very low plasma leptin levels (normal range for young females is around 8.5 ± 0.9 ng/ml; Table I).

Network Analysis

NBS was performed in both directions. That is, to look for a subnetwork in the AN cohort that is stronger than in HC and vice versa. When considering the direction HC > AN, a subnetwork of connections was found that survived FWE corrected statistical testing. This subnetwork survived FWE correction at multiple network thresholds between 2 and 4 with highly significant results ($P < 0.027$ or below for all tested network thresholds) with the strongest alterations forming a tightly interconnected subnetwork of 7 nodes ($P = 0.017$). The regions involved in this largely subcortical network were the amygdala (left), thalamus (left), fusiform gyrus (right), bilateral putamen and posterior insula (Fig. 1, Table II). No network was found at any network threshold for the AN > HC, showing no consistent increase in functional connectivity in any network in AN patients.

TABLE II. Connections identified by NBS at threshold = 4

Region A	Region B
Amygdala Left	Thalamus Left
Fusiform Right	Thalamus Left
Putamen Left	Post Insula Left
Putamen Right	Post Insula Left
Putamen Left	Post Insula Right
Putamen Right	Post Insula Right
Thalamus Left	Post Insula Right

All connections are undirected.

To ensure the reduced subnetwork in AN was not due to globally altered correlations of the BOLD time series between the various brain regions we estimated average correlation coefficients across all (modified) AAL nodes per participant similar to [Lord et al., 2012]. No group difference was observed (for HC mean=0.372, SD=0.123; for AN mean=0.321, SD=0.120; t=1.851, df=68, P =0.0685), however, when restricting this analysis to connections identified in the NBS, the mean correlation coefficients were significantly reduced in AN (for HC mean=0.127, SD=0.043; for AN mean=0.072, SD=0.051; t=14.950, df=68, P =5*10 e −6).

Next we assessed the extent of overlap between the significant HC > AN subnetwork identified with the NBS across the original and displaced parcellation templates to test the reproducibility of our results. Displacement of all nodes by 1.5 mm along randomly generated vectors revealed that the HC > AN subnetwork remained very stable (one new edge between fusiform and posterior insula in 75% of the models). Displacing by 4.5 mm resulted on average in 0.75 new nodes and 1.75 new edges while a displacement by 20 mm resulted on average in 2.75 new nodes and 3 new edges.

Finally, associations between connectivity and clinically relevant variables were explored. We extracted correlation coefficients from the original correlation matrices for each of the seven connections comprising the implicated subnetwork at t=4 (Amygdala Left - Thalamus Left, Fusiform Right - Thalamus Left, Putamen Left - Post Insula Left, Putamen Right - Post Insula Left, Putamen Left- Post

Insula Right, Putamen Right - Post Insula Right, Thalamus Left - Post Insula Right) in each participant. We tested for associations with age, BMI-SDS, the three EDI-2 subscales ("drive for thinness," "body dissatisfaction," and "bulimia") as well as the EDI-2 core summary measure and the duration of the current AN episode (in months). Pearson correlation analyses were carried out independently in each participant group and did not yield any statistically significant results.

Intranodal Homogeneity

It has been suggested that changes in inter-regional functional connectivity occur in the context of some global and/or local alterations in neural dynamics [Cocchi et al., 2012; Zalesky et al., 2012]. In our study, there were no significant differences in intranodal connectivity between AN and HC as measured by ReHo (KCC; Supporting Information Table II). Next, we tested whether there are associations between KCC of a specific node and connectivity values (in the connectivity matrix underlying the NBS analysis) for connections between this node and other nodes (using Pearson correlations coefficients). Replicating [Zalesky et al., 2012] we found significant positive associations (low - medium sized effects), that is, there was a robust link between regionally localized homogeneity and inter-regional connectivity of the same brain region. However, this relationship was similar for both, AN and HC (see Supporting Information Table 3).

DISCUSSION

In a comparatively large sample of young unmedicated acute AN and pairwise matched HC we found a robust subnetwork of brain regions clustered around the posterior insula that showed a marked decrease in synchronized activity in the patient group. Of note, we only found a subnetwork with reduced connectivity estimates, while no subnetwork could be identified where AN patients had increased coupling.

This finding extends results from a relatively small number of previous resting state functional connectivity studies in AN using more conventional techniques. Favaro et al., reported decreased temporal coherence in a visual ventral network in AN using ICA and, using seed-based analysis in a largely overlapping partially medicated adult sample, decreased functional connectivity of the putamen with the contralateral putamen, cingulate gyrus, amygdalae, and precentral gyrus [Favaro et al., 2012, 2014]. Using the dACC as an a priori seed region, Kim et al. [Kim et al., 2012] found decreased connectivity of this region with the DLPFC in medicated adult AN patients. However, two of the aforementioned studies also found increased coupling in AN – namely between dACC and retrosplenial cortex/precuneus [Kim et al., 2012] as well as in a somatosensory network [Favaro et al., 2012]. Furthermore, several studies have used ICA to target potential changes in the default mode network. While recovered AN participants were reported to show increased default mode network connectivity [Cowdrey et al., 2014], this was not confirmed in another study that investigated connectivity during a conditioned stimulus task [McFadden et al., 2014]. In parallel to the NBS approach described in this manuscript, we have also used ICA to target the default mode network and a few select other well-characterized resting state networks in AN in a more hypothesis-driven way [Boehm et al., 2014]. Interestingly, we found the anterior insula to be more strongly connected to the default mode network in patients with acute AN (and increased functional connectivity within the fronto-parietal network).

These studies have all focused *a priori* on specific known resting state networks or considered connectivity from a few predetermined seed regions. Instead, NBS allowed us to isolate a set of interconnected regions (i.e., a subnetwork) based on information about whole-brain functional organization without any *a priori* assumptions [Zalesky et al., 2010a] while applying very conservative measures to control for false positive effects due to multiple testing.

Hidden in the Sylvian fissure and interconnected with a large number of cortical areas the insula is a brain region thought to be implicated in a range of different functions including sensory perception (gustatory, olfactory, visual, auditory, and tactile inputs), the subsequent integration of exteroceptive and interoceptive information, cognition and emotion [Craig, 2009; Erberich et al., 2006; Kurth et al., 2010; Menon and Uddin, 2010]. The insula also has a remarkably high base rate of activation and considerable functional heterogeneity [Duncan and Owen, 2000; Nelson et al., 2010; Yarkoni et al., 2011]. Functional parcellation studies of the insula provide evidence for distinct subregions. While the ventroanterior and dorsoanterior regions are associated with chemosensory [Pritchard et al., 1999], socioemotional [Chang et al., 2011; Sanfey et al., 2003], and higher cognitive processing respectively [Dosenbach et al., 2006; Eckert et al., 2009], the posterior insula region is associated with pain and sensorimotor processing [Craig, 2002; Wager and Barrett, 2004]. According to a recent study the latter posterior region is functionally connected to supplementary motor area and somatosensory cortex as well as posterior temporal lobes right hippocampus, and rostral ACC [Chang et al., 2013; Deen et al., 2011].

Based on Damasio's somatic marker hypothesis [Damasio, 1996] in which emotional states result from the fast and unconscious processing of exteroceptive and interoceptive sensory data – insular dysfunction, or the dysfunction of networks passing through the insula, has been repeatedly suggested as a core factor in AN etiology. More specifically it has been proposed that impaired integration of visual and body perception with feelings/emotions and the inhibition of higher cognitive processes may account for the striking symptomatology of AN [Nunn et al., 2008, 2011]. In line with that, a relatively large proportion of neuroimaging

studies in AN have yielded differential neural responses in this region. Studies on food cue-reactivity reported either insula hypo- [Gizewski et al., 2010; Holsen et al., 2012] or hyperactivity (Gizewski et al., 2010; Oberndorfer et al., 2013a) in patients with AN compared to HC. Two studies reported decreased insula responses to the oral application of sucrose as well as water in AN [Oberndorfer et al., 2013b; Wagner et al., 2008]. However, using a multimodal paradigm insula hyperactivation in AN was reported in response to aversive gustatory taste [Cowdrey et al., 2011]. Studies on body image processing in AN have yielded equally mixed results with either reduced [Sachdev et al., 2008] or increased [Friederich et al., 2010; Mohr et al., 2010] insula responses during the rating of thin self-images or when contrasting the viewing of self versus nonself-images. Our own ICA-based study (see above, [Boehm et al., 2014]) and a recent pilot study (12 AN patients) combining reduced degree centrality (defined by the number of edges connecting to a node, i.e., brain voxel) and a techniques targeting changes in effective connectivity also provides evidence for altered resting state functional connectivity of the insula in AN [Kullmann et al., 2014]. Furthermore, changes in structural connectivity in AN as measured by diffusion tensor imaging are also in line with disturbances of brain networks involved in proprioception and the integration of visual information — processes that are essential for the representation of the body self-image [Frieling et al., 2012; Via et al., 2014].

While most of the aforementioned functional studies have not differentiated between anterior and posterior insular cortex or not targeted an insular subregion, pain stimuli can be used to specifically probe the posterior insula, which is thought to function as the primary interoceptive cortex [Craig, 2002, 2011]. Two studies have used heat pain in patients with AN and found decreased posterior insula responses during stimulation [Bar et al., 2013; Strigo et al., 2013]. Since the insular cortex is well-connected to the thalamus, amygdalae and basal ganglia [Augustine, 1996; Craig, 2011] reduced posterior insular responses are well in line with our own connectivity results and might lead to a relative insensitivity to pain, an established phenomenon in AN [de Zwaan et al., 1996; Lautenbacher et al., 1991; Raymond et al., 1999]. According to Craig, homeostatic afferent representations of the physiological condition of the body ascend from the spinal cord and brain stem via a pair of specific subnuclei in the thalamus to the posterior and midinsula [Craig, 2011]. Reduced connectivity in a subnetwork consisting of the thalamus, basal ganglia, amygdala, fusiform gyrus (including the fusiform body area) and the posterior insula (as the major hub) may thus reflect the altered calibration of signals such as pain, body size and hunger and subsequently contribute to abnormal cognitive-affective and behavioral responses such as excessive physical activity. Within this framework, the finding from our recently published ICA-based study in the same group of AN patients [Boehm et al., 2014] can be interpreted: Increased connectivity between the default-mode network and the anterior insula, a subregion associated with socioemotional [Chang et al., 2011; Sanfey et al., 2003] and higher cognitive processing [Dosenbach et al., 2006; Eckert et al., 2009], may be a compensatory response to dysconnectivity in the afferent thalamus - posterior insular network identified using NBS. However, more studies are needed to substantiate this hypothesis.

Finally, reduced interregional connectivity in AN could not be explained by local neural dynamics or abnormalities in global signal. There were no group differences in intranodal homogeneity of BOLD fluctuations. Further, although we could replicate previous findings showing that intranodal homogeneity of a ROI predicts connectivity between the very same node and other nodes across the brain [Zalesky et al., 2012]; this mechanism was the same for patients and HC. Likewise, there were no group differences in correlation coefficients averaged across all nodes of the modified AAL template [Lord et al., 2012]. Thus we are confident that dysconnectivity in a thalamo-insular subnetwork is indeed a specific finding which may be related to the pathophysiology of AN even though we did not find any direct linear correlations between the degree of self-reported symptoms and reduced connectivity in this network.

Limitations

Our study has to be seen in the light of the following limitations. First, properties of graph networks may be influenced by its density, chosen parcellation scheme, and the image preprocessing steps [Bassett et al., 2006; Braun et al., 2012; Liang et al., 2012; Zalesky et al., 2010b]. For these reasons, the current results may be restricted to the parameters and settings used (which were all common and comparable to similar studies). To address this issue, the regions of our modfied AAL template were displaced to introduce random variability in regional demarcations. The abnormal subnetwork in AN remained remarkably robust when applying small changes to the atlas template. However, with increasing spatial displacement of the atlas an increasing number of new nodes and edges were detected. Thus, our results seem to be both, robust to minor inaccuracies during realignment and registration but also specific to the original brain regions. Second, during resting-state data acquisition participants were required to close their eyes which may lead to different levels of wakefulness. Since we did not monitor respiration or heart rate during scanning we cannot account fluctuations in wakefulness which may have influenced resting-state dynamics [Tagliazucchi and Laufs, 2014]. Third, determining whether changed brain functioning is a consequence or a potential antecedent of pathologic eating behavior is one of the most difficult questions in the field of eating disorder research [Frank, 2013]. More resting state connectivity studies in long-term recovered AN patients are needed to disentangle trait and state effects. However, strengths of the current study include the large sample size, the fact that all participants were young and unmedicated, the short duration of illness (reducing effects

of chronic illness), the homogeneity of the sample (94% restrictive AN subtype) and the fact that time of scanning and food intake were experimentally controlled.

CONCLUSION

Taken together, results from this study suggest decreased connectivity in a thalamo-insular subnetwork in patients with AN. This network is believed to be crucial for the propagation of sensations that alert the organism to urgent homeostatic imbalances and pain – a process that is known to be severely disturbed in AN. A lack of or erroneous interoceptive feedback might contribute to the striking discrepancy between their actual and perceived internal body state. Future studies are needed to test whether biofeedback and modern invasive or noninvasive brain stimulation techniques may potentially be of use to improve interoception by modulating activity and connectivity in the thalamo-insular brain network.

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