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Aberrant network integrity of the inferior frontal cortex in women with anorexia nervosa

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ABSTRACT

Neuroimaging studies investigating the neural profile of anorexia nervosa (AN) have revealed a predominant imbalance between the reward and inhibition systems of the brain, which are also hallmark characteristics of the disorder. However, little is known whether these changes can also be determined independent of task condition, using resting-state functional magnetic resonance imaging, in currently ill AN patients.
Therefore the aim of our study was to investigate resting-state connectivity in AN patients ($n = 12$) compared to healthy athlete ($n = 12$) and non-athlete ($n = 14$) controls. For this purpose, we used degree centrality to investigate functional connectivity of the whole-brain network and then Granger causality to analyze effective connectivity (EC), to understand directional aspects of potential alterations.
We were able to show that the bilateral inferior frontal gyrus (IFG) is a region of special functional importance within the whole-brain network, in AN patients, revealing reduced functional connectivity compared to both healthy control groups. Furthermore, we found decreased EC from the right IFG to the midcingulum and increased EC from the bilateral orbitofrontal gyrus to the right IFG. For the left IFG, we only observed increased EC from the bilateral insula to the left IFG.
These results suggest that AN patients have reduced connectivity within the cognitive control system of the brain and increased connectivity within regions important for salience processing. Due to its fundamental role in inhibitory behavior, including motor response, altered integrity of the inferior frontal cortex could contribute to hyperactivity in AN.

1. Introduction

Anorexia nervosa (AN) is an eating disorder that tends to begin during adolescence in women and is characterized by relentless pursuit to lose weight, mostly by self-starvation, and distorted body image (APA, 2000), as well as high mortality rates (Zipfel et al., 2000). Nonetheless, a large number of AN patients benefit from treatments offered in specialized eating disorder centers (Zipfel et al., 2013b). Besides food restriction, physical hyperactivity is another frequent puzzling symptom in AN patients that is poorly understood, but plays a central role in the pathogenesis and progression of the disorder (Hebebrand and Bulik, 2011). AN patients with hyperactivity show poorer recovery rates, higher rates of relapse, longer periods of hospitalization (Carter et al., 2004; Casper and Jasbine, 1996; Strober et al., 1997) and increased energy requirements (Zipfel et al., 2013a). Thus, it has been recommended to include hyperactivity as part of the core psychopathology of AN (Hebebrand and Bulik, 2011).

Until today, the etiology of AN is still largely unknown and mechanisms that maintain the disorder remain poorly understood (Kaye et al., 2013). Hence advances in neuroimaging techniques have become increasingly important for understanding the pathophysiology of AN. These studies revealed a predominant imbalance between the reward and inhibition systems of the brain, which are hallmark characteristics of the disorder. Recovered AN patients show increased dopamine receptor availability (Frank et al., 2005) and also functional magnetic resonance imaging (fMRI) studies point to dopamine dysfunction by discovering hypoactivity of striatal regions in response to pleasurable stimuli (Kaye et al., 2009). This resulted in the notion that AN patients suffer from general anhedonia unable to experience pleasure.

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However this view was challenged by Fladung et al. (2010) showing increased activity in the reward system in response to visual stimuli depicting underweight women. In response to food stimuli, previous studies have also frequently reported heightened salience processing in AN resulting in an increased response in the insula and orbitofrontal cortex (OFC) (Frank et al., 2012; Uher et al., 2004) and dorsolateral prefrontal cortex (Brooks et al., 2011; Brooks et al., 2012a).

When challenging cognitive control, reduced prefrontal cortex (PFC) activity has mostly been revealed in AN patients compared to healthy controls (Lock et al., 2011; Oberndorfer et al., 2011). But again when using stimuli with inherent rewarding properties for AN patients, as physical activity stimuli, we were able to show enhanced attentional engagement towards these stimuli (Giel et al., 2013)and increased PFC activity when challenging inhibitory control (Kullmann et al., 2013a; Zastrow et al., 2009).

These studies indicate that mesolimbic reward activations in conjunction with PFC activations are highly dependent on the task and stimuli. A unique advantage provided by resting-state fMRI is that it allows examining task-independent activations. The importance of studying intrinsic brain networks has been illustrated by altered functional connectivity in several different medical conditions such as schizophrenia (Meda et al., 2009), depression (Greicius et al., 2007) and Alzheimer's disease (Greicius et al., 2004). Recently, it has also been discovered that obesity is related to prominent alterations in resting-state and task-based functional networks mainly in prefrontal regions (Garcia-Garcia et al., 2012; Kullmann et al., 2012; Kullmann et al., 2013b). Furthermore, latest studies have evaluated resting-state functional connectivity in AN patients and those recovered from the disease. Favaro et al. (2012) evaluated exclusively the organization of visuospatial and somatosensory brain areas, revealing hypoconnectivity within these networks. In recovered AN patients, on the other hand, increased resting-state functional connectivity was identified in the default mode network, important for self-referential processing and cognitive control (Cowdrey et al., 2012). Interestingly, McFadden et al. (2013) observed reduced resting-state functional connectivity in the default mode network of currently ill AN patients suggesting state-dependent abnormalities. However, they observed reduced functional connectivity in both AN patients and recovered women within the anterior cingulate cortex of the salience network (McFadden et al., 2013). These studies used independent component analyses to investigate functional connectivity in AN, by identifying separable sets of brain regions or networks (Cole et al., 2010). Graph theory based network measures, on the other hand, characterize functional connectivity within the whole-brain network, taking into account a given region's relationship to the whole brain (Bullmore and Sporns, 2009). Degree centrality (DC) is a graph theory based network analysis to assess the centrality or functional importance, such that the complexity of the whole-brain network can be captured as a whole (Zuo et al., 2012). Since the neural mechanisms underlying the disorder in AN are poorly understood and multiple brain systems are affected, we used DC to analyze functional connectivity within the whole-brain network. However, to investigate the directional aspect of possible alterations, we used the Granger causality analysis (GCA), which is a statistical method originally used in the field of economics to assess directional influences between simultaneously recorded time series (Granger, 1969; Zhou et al., 2009). GCA has meanwhile been widely applied to reveal causal effects amongst brain regions by using time-prediction between BOLD fMRI series (Ding et al., 2006; Jiao et al., 2011; Qi et al., 2013; Stephan and Roebroeck, 2012; Uddin et al., 2009; Zhou et al., 2011).

To further delineate the neurobiological profile of AN, we sought to identify in this study brain regions that show altered functional connectivity within the whole-brain network in currently ill AN patients using degree centrality (DC) and then use GCA to analyze effective connectivity to understand the directional aspect of these alterations.

We evaluated resting-state connectivity in AN patients compared to two healthy control groups, displaying different levels of physical activity: healthy non-athletes (HC) and healthy athletes (HCA). Based on the extensive exercise in both AN and HCA groups, we predicted a similar connectivity pattern in sensorimotor brain regions between AN and athletes, while we hypothesized that the connectivity pattern of the prefrontal and striatal regions should be quite distinctive between athletes and AN patients.

2. Materials and methods

2.1. Participants

Twelve female individuals with AN (mean BMI 15.5 ± 1.5 kg/m^2; mean age 23.3 ± 4.7 years) and twenty-six age-matched healthy female participants of normal weight were recruited for this study. Participants' characteristics have been described in detail in a recent publication (Kullmann et al., 2013a) (Table 1). AN patients were recruited in the Department of Psychosomatic Medicine and Psychotherapy at the University Hospital of Tübingen. We used the Eating Disorder Examination (EDE) to diagnose eating disorder and the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I (Fairburn and Cooper, 1993; Wittchen et al., 1997) to diagnose comorbid Axis I disorders in patients. Patients were excluded from the study for the following reasons: body mass index (BMI) < 12 kg/m^2, intake of neuroleptics or benzodiazepines, a primary obsessive–compulsive or affective disorder, psychosis, bipolar disorder and substance abuse or addiction according to DSM-IV.

Twenty-six age-matched healthy female participants of normal weight were recruited through local advertisement for two healthy control groups. One control group consisted of healthy athletes (HCA, 12 participants; mean BMI 22 ± 1.9 kg/m^2; mean age 24.1 ± 3.2 years), required to perform competitively exercise in an endurance sport of at least 5 h a week for at least 1 year. The other control group consisted of healthy non-athletes, only included when performing casual physical exercise (HC, 14 participants; mean BMI 21.4 ± 1.5 kg/m^2; mean age 24.6 ± 2.9 years). As assessed by the SCID-I, the healthy female participants had no history of an eating disorder or any other psychiatric, serious medical or neurological diseases and were not on any psychoactive medication. The local medical faculty's ethics committee approved the study. Written informed consent was obtained from all participants after complete description of the study to the participants.

Participants completed several self-report assessments as recently reported (Kullmann et al., 2013a). Of special importance to this study are questionnaires related to eating disorder symptoms (Eating Disorder Inventory-2 [EDI-2]) (Garner, 1991; Paul and Thiel, 2005), reward sensitivity and behavioral inhibition (behavioral activation/inhibition system [BAS/BIS]) (Gray, 1970; Strobel et al., 2001) and excessive exercise (Commitment to Exercise Scale [CES]) (Davis et al., 1993). Participants had a standardized breakfast (staff supervised) 1 h before the fMRI measurement, consisting of a bread roll with butter, jam or honey and herbal tea. In addition hunger was assessed by a 10 cm visual analogue scale ranging from 0 cm [not hungry at all] to 10 cm [strongest feeling of hunger] just before the fMRI measurement. All fMRI measurements were performed between 9 and 11 am.

2.2. Data acquisition

Whole-brain functional magnetic resonance imaging (fMRI) data was obtained by using a 3.0 T scanner (Siemens Tim Trio, Erlangen, Germany). Functional data were collected by using echo-planar imaging sequence: TR = 3 s, TE = 30 ms, FOV = 192 mm^2, matrix 64 × 64, flip angle 90°, voxel size 3 × 3 × 3 mm^3, slice thickness 3 mm, and the images were acquired in an interleaved order. Each brain volume comprised 47 axial slices and each functional run contained 200 image volumes, resulting in a total scan time of 10.06 min. In addition,

Table 1
Participants' characteristics.

	Female anorexia nervosa patients (AN) ($n = 12$)		Female non-athletes (HC) ($n = 14$)		Female athletes (HCA) ($n = 12$)		Analysis			
Characteristic	M	SD	M	SD	M	SD	F	df	p	Post-hoc difference
Age (years)	23.3	4.7	24.6	2.9	24.1	3.2	.379	35	.687	–
Current BMI (kg/m^2)	15.5	1.5	21.4	1.5	22.0	1.9	57.87	35	<.001	AN < HCA, HC
Leptin (ng/dl)	0.7	0.4	5.89	3.2	4.46	3.6	10.691	34	<.001	AN < HCA, HC
Hunger rating (cm)	0.5	0.7	0.7	0.7	1.0	1.3	1.07	35	.352	–
CES	6.5	2.6	4.12	1.9	5.55	1.6	4.329	35	.021	AN > HC
BAS	3.1	0.4	3.18	0.4	3.24	0.2	.455	35	.638	–
BIS	3.5	0.5	2.98	0.4	2.83	0.5	7.247	35	.002	AN > HCA, HC
Depression score	11.3	4.5	1.8	1.5	1.8	1.9	44.512	35	<.001	AN > HCA, HC
State anxiety score	61.0	10.4	31.9	6.7	32.7	5.6	56.198	35	<.001	AN > HCA, HC
EDI-2 EDEQ	309.8 3.43	54.68 1.46	186.57	36.92	194.08	54.68	32.127	35	<.001	AN > HCA, HC
Vigorous activity (h/week)	10.51	13.21	6.87	2.21	3.08	3.1	2.98	35	0.06	AN > HC

Data are presented as mean ± SD. = p-Values for comparison of unadjusted data by ANOVA. AN: Anorexia nervosa patient; HC: healthy non-athlete control group; HCA: healthy athlete control group; BIS: behavioral inhibition system; BAS: behavioral activation system; CES: Commitment to Exercise Scale; EDI-2: Eating Disorder Inventory; EDEQ: Eating Disorder Examination Questionnaire.

high-resolution T1 weighted anatomical images (MPRage: 176 slices, matrix: 256 × 240 × 192, 1 × 1 × 1 mm^3) of the brain were obtained. All participants were instructed not to focus their thoughts on anything in particular and to keep their eyes closed during the resting state MR acquisition.

2.3. Data preprocessing

Preprocessing was carried out by using Data Processing Assistant for Resting-State fMRI (DPARSF) (Chao-Gan and Yu-Feng, 2010) (http://www.restfmri.net) which is based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (Song et al., 2011) (REST, http://www.restfmri.net). Functional images were realigned and co-registered to the T1 structural image. The anatomical image was normalized to the Montreal Neurological Institute (MNI) template using DARTEL, and the resulting parameter file was used to normalize the functional images (voxel size: 3 × 3 × 3 mm^3). Finally the normalized images were smoothed with a three-dimensional isotropic Gaussian kernel (FWHM: 6 mm). A temporal filter (0.01–0.08 Hz) was applied to reduce low frequency drifts and high frequency physiological noise. Nuisance regression was performed using white matter, CSF, and the six head motion parameters as covariates. No participant had head motion with more than 2.0 mm maximum displacement or 2.0° of any angular motion.

2.3.1. Degree centrality analysis

In the present study, we used network degree centrality to identify regions of high connectivity by mapping the degree of functional connectivity across the brain (Buckner et al., 2009; Zuo et al., 2012). Degree centrality is defined by the number of edges connecting to a node. For a weighted graph, as used in this study, it is the weighted sum of positive correlations by requiring each connection's statistical significance to exceed a threshold of $p < 0.001$. Subject-level Z-score maps were created by subtracting the mean degree centrality value for the entire brain from each voxel and by dividing the corresponding standard deviation. Degree centrality has been shown to represent the most local and directly quantifiable centrality measure and has been widely used to examine node characteristics of intrinsic network connectivity (for review see Zuo et al., 2011). The degree centrality maps were transferred to z values for group comparisons.

2.3.1.1. Statistical analysis: degree centrality

The degree centrality maps were entered into SPM8 for group comparison. One-way ANOVA with group as the between subject factor was used to examine differences between AN patients, HCA and HC. All group tests were thresholded at $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons.

2.3.2. Effective connectivity analysis

Effective connectivity was analyzed by Granger causality as described previously (Qi et al., 2013) using REST-GCA in the REST toolbox (Zang et al., 2012). Based on the results of the degree centrality analysis we selected the seed regions, which showed significant differences between AN patients and the control groups (left and right inferior frontal gyrus; MNI coordinates (x, y, z) ±48, 9, 24). Effective connectivity was calculated between the reference time series of the seed region (right and left inferior frontal gyrus, respectively), defined as x, and the time series of each voxel within the whole brain, defined as y. The direct influence of x on y ($F_{x\to y}$) and y on x ($F_{y\to x}$) was calculated voxel by voxel across the whole brain. The residual-based F was normalized (F') and standardized to Z scores for each voxel ($Z_{x\to y}$ and $Z_{y\to x}$, subtracting the global mean F' values, divided by the standard deviation) (Zang et al., 2011).

2.3.2.1. Statistical analysis: effective connectivity from and to the inferior frontal gyrus

Granger causality maps were obtained for each seed region for each direction ($Z_{x\to y}$ and $Z_{y\to x}$) for both AN patients and healthy controls (HCA and HC). These Granger causality maps were entered into SPM8 for group comparison. Separate one-way ANOVAs with group as the between subject factor were used to examine differences between AN patients, HCA and HC for each direction and seed (left and right IFG) separately. All group tests were thresholded at $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons.

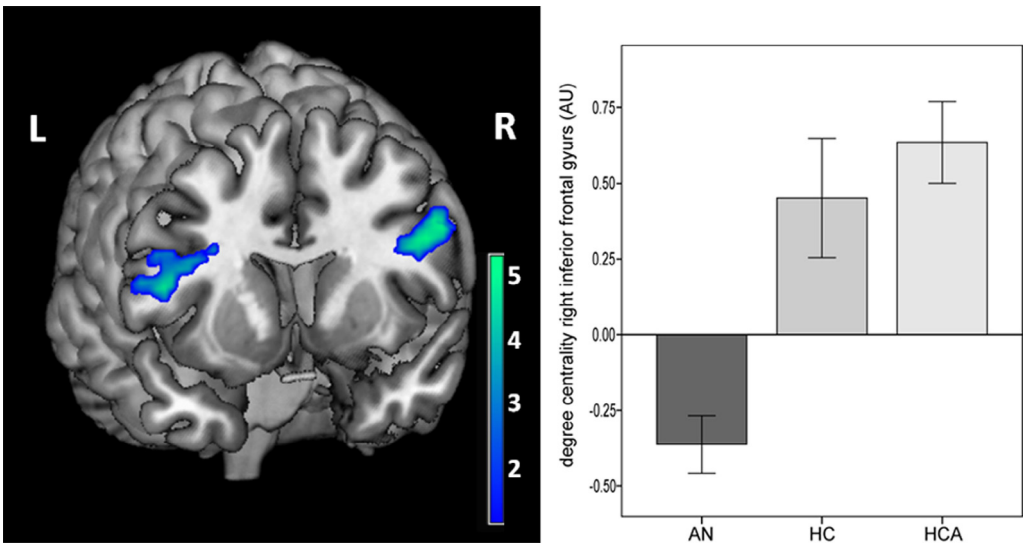

Fig. 1. Decreased functional connectivity in the inferior frontal gyrus measured by degree centrality in anorexia nervosa patients compared to healthy controls ($p < 0.05$, FWE corrected) (AN: anorexia nervosa; HC: healthy non-athlete controls; HCA healthy athlete controls).

Table 2
Altered effective connectivity in anorexia nervosa patients compared to healthy controls from and to the inferior frontal gyrus (IFG).

Regions	Hem	BA	MNI (mm) (x, y, z)	Size	*T* value*
Increased effective connectivity to the right IFG					
Medial frontal orbital gyrus	Bilateral	47	0, 36, −18	48	5.6
Decreased effective connectivity from the right IFG					
Midcingulum	Bilateral	24	±3, 12, 33	52	4.22
Increased effective connectivity to the left IFG					
Insula	Left	13	−39, −15, 12	49	4.53
Insula	Right	13	39, 0, −3	19	4.15

*$p < 0.05$, family wise error corrected for multiple comparisons.

Pearson correlations (two-sided) were calculated between behavioral measurements and degree centrality and effective connectivity measures (6 brain regions; 8 behavioral measurements) for each group separately and over the whole group ($p < 0.001$, Bonferroni corrected) using SPSS (version 20; IBM Corporation, Armonk, NY).

3. Results

3.1. Resting-state functional connectivity in anorexia nervosa and healthy controls

Degree centrality was used to measure voxel-wise network centrality. Specifically, we found reduced degree centrality within the bilateral inferior frontal gyrus (IFG) (MNI coordinates (x, y, z) ±48, 9, 24; $t_{max} = 4.74$; $p < 0.05$ FWE-corrected for multiple comparisons) (Fig. 1) in AN patients compared to healthy controls. No significant differences were observed between HC and HCA ($p > 0.05$, FWE-corrected).

3.2. Effective connectivity from and to the inferior frontal gyrus

Compared with healthy controls, patients with AN showed decreased effective connectivity from the right IFG to the midcingulum (Table 2; Fig. 2A; $p < 0.05$, FWE corrected).

From the bilateral OFC to the right IFG, AN patients showed increased effective connectivity compared to healthy controls (Table 2; Fig. 2A); and from the bilateral insula cortex to the left IFG AN patients showed increased effective connectivity compared to healthy controls (Table 2; Fig. 2B).

No significant differences were observed between HC and HCA ($p > 0.05$, FWE-corrected).

3.3. Correlation results

After correcting for multiple comparisons, we only found, in AN patients, a significant negative correlation between the degree centrality of the right IFG with vigorous physical activity ($r = -0.764$, $p = 0.001$).

For the whole group, we found a significant negative correlation between the degree centrality of the left IFG and state anxiety score ($r = -0.519$, $p = 0.001$) and for the right IFG with the depression sum score ($r = -0.528$, $p = 0.001$) and state anxiety score ($r = -0.521$, $p = 0.001$). For the differential effective connectivity patterns, our analyses revealed positive correlations between the increased effective connectivity from the orbital frontal cortex to the right IFG and the depression sum score ($r = 0.657$, $p < 0.001$), state anxiety score ($r = 0.593$, $p < 0.001$), and the Eating Disorder Inventory ($r = 0.509$, $p = 0.001$). For the decreased effective connectivity from the right IFG to the midcingulum, we found negative correlations with the depression sum score ($r = -0.516$, $p = 0.001$) and state anxiety score ($r = -0.628$, $p < 0.001$). And for the increased effective connectivity from the insula cortex to the left IFG, we found a positive correlation with the depression sum score ($r = -0.569$, $p < 0.001$), state anxiety score ($r = -0.521$, $p = 0.001$) and the Eating Disorder Inventory ($r = 0.549$, $p < 0.001$).

Additionally, significant correlations, uncorrected for multiple comparisons, are reported in Supplementary Table 1.

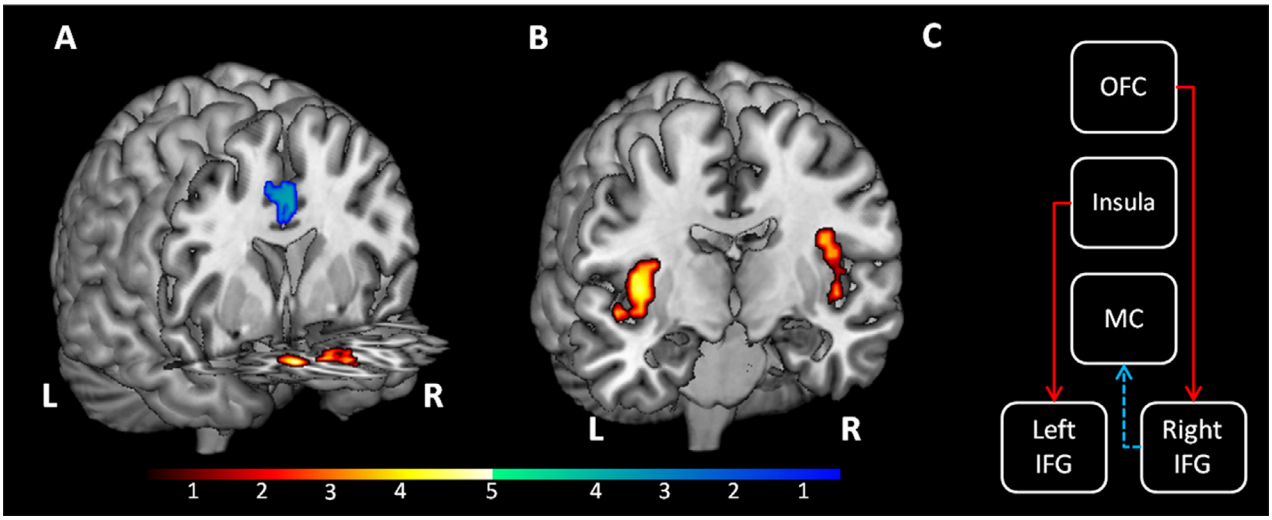

Fig. 2. Altered effective connectivity from and to the IFG in anorexia nervosa compared to healthy controls. (A) Increased effective connectivity from the bilateral OFC (red) to the right IFG and decreased effective connectivity from the right IFG to the midcingulum (blue) ($p < 0.05$, FWE corrected). (B) Increased effective connectivity from the bilateral insula (red) to the left IFG ($p < 0.05$, FWE corrected). (C) Schematic overview of changes in effective connectivity measured by Granger causality in anorexia nervosa patients compared to healthy controls. The red arrows indicate increased effective connectivity from the insula and OFC to the IFG; the blue arrow indicates decreased effective connectivity from the IFG to the MC in AN patients compared to healthy controls (IFG: inferior frontal gyrus, MC: midcingulum; OFC: orbitofrontal cortex).

4. Discussion

This is the first study, to our knowledge, investigating whole-brain resting-state functional and effective connectivity alterations in currently ill AN patients compared to healthy controls. Using degree centrality, we were able to show that the bilateral IFG is a region of special functional importance in AN patients revealing reduced functional connectivity. To further investigate the influence of directionality, we applied GCA to evaluate changes in effective connectivity. AN patients showed reduced effective connectivity from and increased effective connectivity to the IFG. Specifically, we were able to show decreased effective connectivity from the right IFG to the midcingulum and increased effective connectivity from the bilateral OFC to the right IFG in AN compared to healthy controls. For the left IFG, we only observed increased connectivity from the bilateral insula to the left IFG in AN compared to healthy controls. Of note, scores reflecting vigorous physical activity in AN patients correlated with connectivity patterns of the right IFG.

The major region affected by AN is the inferior frontal cortex, which is a key area for executive functions, encompassing multiple high level processes to control and organize other cognitive operations. Inhibition of inappropriate behaviors, for instance, is one critical component of cognitive control and especially the right IFG, as found in our study, is of special importance for inhibitory control of motor responses (Asahi et al., 2004; Duann et al., 2009). Imaging studies in AN have found, when challenging cognitive control, reduced prefrontal activity in AN patients compared to healthy controls (Lock et al., 2011; Oberndorfer et al., 2011). While these studies have shown that AN patients need less inhibitory resources to maintain behavioral performance, we were able to show in a recent study that in response to stimuli depicting physical activity AN patients need more inhibitory resources to maintain behavioral performance, resulting in hyperactivation of the prefrontal cortex. These results suggest that physical activity stimuli might place an increased demand on the inhibitory control system in AN patients (Kullmann et al., 2013a). Similarly, processing of food in AN goes along with increased prefrontal activations, which has been speculated to impinge on cognitive control over food consumption (Brooks et al., 2011; Brooks et al., 2012a).

In the current study, we were able to observe a significant relationship between vigorous physical activity and altered network integrity of the right IFG. Particularly AN patients displayed hyperactivity, ranging from lengthy walks to vigorous exercise. Our results indicate that the more vigorous AN patients exercise the stronger the reduction of the functional connectivity in the IFG. Since the IFG is pivotal for inhibitory behavior, including motor response, altered integrity within the whole-brain network could contribute to hyperactivity symptoms in AN. However, we cannot disentangle, in this cross sectional study, whether hyperactivity is a cause or effect of the altered connectivity pattern. Yet, there are multiple hypotheses trying to explain the role of hyperactivity in AN. Some approaches conceptualize it as a secondary order symptom to deliberately lose weight (Bruch, 1962). However, in many cases hyperactivity has been shown to precede food restriction (Davis et al., 2005). Evolutionary approaches, on the other hand, consider hyperactivity as a primary reinforcer by increasing foraging during food restriction (Fessler, 2002; Scheurink et al., 2010). Furthermore, exercise can also be considered as a coping strategy to compensate anxiety and depression (Brewerton et al., 1995; Penas-Lledo et al., 2002), which is elevated in AN patients, or as a thermoregulatory behavior (Carrera et al., 2012).

The Granger causality analysis revealed altered effective connectivity patterns between the IFG and the midcingulum, OFC and insula. The former is part of the cingulate cortex, which is especially known for its functional heterogeneity subdivided in several distinct regions. The midcingulum is central to skeletomotor regulations (Vogt et al., 1992) on top of its role in cognitive tasks, especially related to attention (Torta and Cauda, 2011). In terms of connectivity, the midcingulum has been shown to be part of a network including the thalamus, midbrain, and anterior insular cortex (Torta and Cauda, 2011). Together these regions belong to the so called core network recruited by cognitive demanding tasks controlling goal-directed behavior (Dosenbach et al., 2006; Dosenbach et al., 2007; Seeley et al., 2007). There is growing evidence that the core network can be divided into two distinct subnetworks for salience processing and executive control (Seeley et al., 2007). The anterior cingulate cortex and anterior insula respond to personal salience including motivational, emotional or cognitive tasks by integrating sensory data (Bush et al., 2000; Critchley, 2005), as for example processing taste reward (Keating et al., 2012), while the prefrontal cortex is exceedingly involved in cognitive control operating on identified salience by directing attention towards relevant stimuli (Seeley et al., 2007). Of note, within the

resting-state salience network, McFladden and colleagues identified the anterior cingulate cortex as a possible trait-related biomarker due to the reduced functional connectivity in AN patients and recovered women (McFadden et al., 2013). In our study, we postulate that the reduced IFG functional and effective connectivity to the midcingulum may lead to a dysfunctional inhibitory response directing attention away from food and lowering the drive to approach food. Whether this is associated with an increased or decreased PFC activation during cognitive demanding tasks probably depends on the input the IFG receives from the insula and OFC. The latter is crucially involved in reward processing and is part of the secondary gustatory cortex (Rolls et al., 1990). As a multisensory neural node, the insular cortex integrates perception, emotion, interoceptive awareness, cognition, and gustation (Frank et al., 2013; Nunn et al., 2008), the anterior part of the insular cortex is also recognized, amongst other functions, as the primary gustatory cortex (Rolls, 2005; Yaxley et al., 1988). Previous studies have frequently reported heightened salience processing in AN patients resulting in an increased response to food cues in the insula and OFC (Frank et al., 2012; Uher et al., 2004) and altered effective connectivity to food cues between the insula and IFG (Kim et al., 2012). This imbalanced convergence on the insula has been proposed to increase the experience of anxiety and fear, mostly on the monitoring of the bodily states (Brooks et al., 2012b). Concomitantly, we observed a heightened effective connectivity from the insula and OFC to the IFG, which could induce an overregulated inhibitory system in order to restrict the stronger interceptive response evoked by salient stimuli.

Even though both the AN and HCA groups displayed intensive exercise, we found no similarities in functional and effective connectivity. Both control groups revealed the same connectivity pattern. This is probably related to the fact that the main regions consistently involved in altered cerebral function in AN are the frontal and cingulate cortex as well as striatal regions (Kaye et al., 2009; Pietrini et al., 2011) and not sensorimotor areas. However when challenging inhibitor control with physical activity stimuli, we were able to show a similar sensorimotor response in athletes and AN patients (Kullmann et al., 2013a).

A limitation of our study is the small sample size making this study a preliminary study that needs further replication. Hence, differences in functional and effective connectivity can also be due to comorbidities associated with AN, as depression and anxiety. Also, we could not differentiate restricting versus purging subgroups due to the small sample size. Further studies are needed to evaluate differences between these subtypes with respect to hyperactivity and brain function.

Taken together, AN patients showed reduced connectivity within the cognitive control system of the brain and increased connectivity within regions important for salience/reward processing. These results are also consistent with clinic findings showing aberrant cognitive control and overregulation (Tchanturia et al., 2004; Vitousek and Manke, 1994).

Disclosures

None of the authors declares a conflict of interest.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nicl.2014.04.002.

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