NeuroImage: Clinical 4 (2014) 615–622

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

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

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ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form 2 April 2014
Accepted 5 April 2014

Keywords:
Anorexia nervosa
Functional connectivity
Effective connectivity
Resting-state fMRI

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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2213-1582/$ - see front matter
http://dx.doi.org/10.1016/j.nicl.2014.04.002

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,