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Resting state functional connectivity in anorexia nervosa

Andrea Phillipou [a,b,c,*], Larry Allen Abel [a], David Jonathan Castle [b,d,e], Matthew Edward Hughes [f], Richard Grant Nibbs [f], Caroline Gurvich [g], Susan Lee Rossell [d,f,g]

[a] Department of Optometry & Vision Sciences, The University of Melbourne, Melbourne, VIC, Australia
[b] Department of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia
[c] Department of Mental Health, The Austin Hospital, Melbourne, VIC, Australia
[d] Department of Psychiatry, St Vincent's Hospital, Melbourne, VIC, Australia
[e] Faculty of Health Sciences, Australian Catholic University, Melbourne, VIC, Australia
[f] Brain and Psychological Sciences Research Centre, Swinburne University of Technology, Melbourne, VIC, Australia
[g] Monash Alfred Psychiatry Research Centre, Monash University and The Alfred Hospital, Melbourne, VIC, Australia

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ABSTRACT

Anorexia Nervosa (AN) is a serious psychiatric illness characterised by a disturbance in body image, a fear of weight gain and significantly low body weight. The factors involved in the genesis and maintenance of AN are unclear, though the potential neurobiological underpinnings of the condition are of increasing interest. Through the investigation of functional connectivity of the brain at rest, information relating to neuronal communication and integration of information that may relate to behaviours and cognitive symptoms can be explored. The aim of this study was to investigate functional connectivity of the default mode network, and sensorimotor and visual networks in AN. 26 females with AN and 27 healthy control participants matched for age, gender and premorbid intelligence underwent a resting state functional magnetic resonance imaging scan. Default mode network functional connectivity did not differ between groups. AN participants displayed reduced functional connectivity between the sensorimotor and visual networks, in comparison to healthy controls. This finding is discussed in terms of differences in visuospatial processing in AN and the distortion of body image experienced by these individuals. Overall, the findings suggest that sensorimotor and visual network connectivity may be related to visuospatial processing in AN, though, further research is required.

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1. Introduction

Anorexia Nervosa (AN) is a psychiatric condition characterised by significantly low body weight and a fear of weight gain. A disturbance in the experience of one's own body weight or shape is a core feature of the illness (American Psychiatric Association, 2013). AN has a mortality rate among the highest of any mental illness (Harris and Barraclough, 1998; Sullivan, 1995), thus, it is critical to gain a better understanding of the neurobiological basis of the illness which currently remains unclear. The potential neurobiological underpinnings of AN have typically been investigated with the use of functional magnetic resonance imaging (fMRI), in which brain states evoked during an experimental and a control condition are compared, with the aim of elucidating task-specific activations. Recently, however, researchers have begun to investigate synchronous brain activity at rest to examine 'functional connectivity' between brain regions. The term 'functional connectivity' is used to signify the correlation of activity time courses between brain regions. The examination of functional connectivity at rest provides information about neuronal communication in the brain, and how integration of information may relate to behaviour (Van Den Heuvel and Hulshoff Pol, 2010).

A number of resting state networks describing anatomically distinct but functionally connected brain regions have been identified using fMRI. Of particular interest has been the default mode network, a network which is active when no cognitive tasks are undertaken, but whose activity is suspended during goal-directed behaviour (Raichle et al., 2001). Differences in default mode network connectivity, particularly reduced connectivity within the network, have been reported in a number of psychiatric illnesses, including schizophrenia (Rotarska-Jagiela et al., 2010), bipolar disorder (Öngür et al., 2010), major depressive disorder (Bluhm et al., 2009), obsessive compulsive disorder (Jang et al., 2010) and autism spectrum disorder (Monk et al., 2009). These findings have suggested that altered functional connectivity within this network may contribute to the clinical phenomenology and/or cognitive symptoms experienced in these conditions.

* Correspondence to: Department of Mental Health, St Vincent's Hospital, Fitzroy, VIC 3065, Australia.
E-mail address: ap@unimelb.edu.au (A. Phillipou).

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Differences in default mode network connectivity have also been implicated in AN. The default mode network is thought to be involved in self-referential processing (Buckner et al., 2008), a process found to be particularly disturbed in AN (Phillipou et al., 2015a). Specifically, AN has been linked to poor self-esteem (Geller et al., 2000), disturbed body image of oneself but not others (Phillipou et al., 2016), and disruptions in the processing of one's own face and one's own emotions (Phillipou et al., 2015a). The default mode network also consists of a number of brain areas which have been reported to display atypical task-based activity in AN (see Phillipou et al. (2014) for a review). A number of recent studies have reported differences between AN and healthy individuals in resting state default mode network connectivity utilising a number of different methods. Using a seed-based method, Lee et al. (2014) reported stronger activity between the dorsal anterior cingulate cortex and both the precuneus and retrosplenial cortex, which positively correlated with scores on a body shape questionnaire. Employing independent components analysis (ICA) on the other hand, Cowdrey et al. (2012) reported increased functional connectivity between the default mode network, and a region of the right precuneus near the border of the posterior cingulate gyrus and the DLPFC/inferior frontal gyrus in recovered AN participants. In a separate study, Boehm et al. (2014) found increased functional connectivity of the anterior insula within the default mode network in ill AN compared to healthy controls; whereas McFadden et al. (2014) reported decreased precuneus activity in ill AN, but no difference in recovered AN compared to controls. The study by McFadden et al. (2014), however, involved participants undertaking a reward task during the scan, thus not reflecting default mode network functional connectivity when at rest. Although the current findings of default mode network connectivity in AN are heterogeneous, they suggest that altered functional connectivity of this network exists in AN. Further, altered connectivity of the default mode network may reflect atypical self-focused ruminations when at rest and during active performance.

A range of other networks have also been studied in AN. In particular, Favaro et al. (2012) investigated the medial, lateral and ventral visual networks, as well as the somatosensory network, in groups of recovered and currently ill AN, and healthy individuals. These networks were examined to explore visuospatial and somatosensory processing in AN. Given the distorted processing of body image in this condition, functional connectivity of these brain regions may provide insight into why these patients do not perceive their body sizes accurately. In the study by Favaro et al. (2012), both AN groups showed areas of decreased connectivity in the ventral visual network, a network involved in the “what?” pathway of visual perception (i.e. regions involved in spatial memory and representation). In addition, increased coactivation in the left superior parietal cortex was found, including the somatosensory and premotor cortices of the somatosensory network in ill but not recovered AN. This study also reported poorer visuospatial performance in AN, demonstrated by poorer visual memory and lower central coherence on the Rey-Osterrieth complex figure test, which correlated with the two connectivity differences. The authors argued that a failure to integrate visual and somatosensory perceptual information may underlie body image disturbance in AN, but they did not directly examine this hypothesis. Thus, this was a specific goal of this study and was investigated by examining the functional connectivity within and between the sensorimotor and visual networks.

The aim of the current study was to investigate resting state functional connectivity in AN in networks related to the phenomenology of the condition, i.e. self-referential processing (default mode network) and body image (sensorimotor and visual networks). As the study aimed to investigate differences in functional connectivity between different areas within and between networks, a seed-driven approach was utilised in which the correlation of time courses is analysed between different pre-defined brain regions. In relation to the default mode network, AN participants were expected to display increased functional connectivity as has been reported in the only previous studies examining this network at rest in AN. Related to the findings of poor visuospatial task performance and the body image distortion experienced by individuals with AN, they were hypothesised to show reduced connectivity between somatosensory and visual areas of the sensorimotor and visual networks, relative to healthy individuals. An additional aim of the study was to investigate whether functional connectivity between these networks was correlated with performance on two visuospatial tasks, the Brief Visuospatial Memory Test – Revised (BVMT-R™) and the Wechsler Memory Scale (WMS®-III): Spatial Span task. Performance on these measures was hypothesised to positively correlate with functional connectivity of the sensorimotor and visual networks.

2. Methods

This study was approved by the human research ethics committees at The University of Melbourne, Swinburne University of Technology, The Melbourne Clinic, The Austin Hospital and St Vincent's Hospital; all in Melbourne, Australia. Written informed consent was obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.1. Participants

Participants were 26 right-handed females with AN and 27 right-handed healthy controls (HC) matched for age and premorbid intelligence quotient (IQ). HCs were recruited through public advertisements, whereas AN participants were recruited through public advertisements; the Body Image and Eating Disorders Treatment and Recovery Service at the Austin and St Vincent's Hospitals; and The Melbourne Clinic.

All participants were English speaking and had no history of significant brain injury or neurological condition. Controls were required to have no history of an eating disorder or other mental illness; they were also required to not be taking any medications apart from hormonal contraceptives (11 HC participants were taking hormonal contraceptives). AN participants were stable on their medications for one month and were instructed to continue with these as normal, which were: selective serotonin reuptake inhibitors (11), atypical antipsychotics (12), benzodiazepines (6), serotonin-noradrenaline reuptake inhibitors (3), hormonal contraceptives (3), melatonergic antidepressants (3), noradrenergic and specific serotonergic antidepressant (1) and cyclopyrrolones (1). Of the 26 patients, seven were medication-free, five were taking one type of medication, eight were taking two types of medications, five were taking three different medication types, and one patient was on four different types of medication. The combination of medications varied between patients.

The Mini International Neuropsychiatric Interview, 5.0.0 (MINI) (Sheehan et al., 1998) was used to screen participants for major Axis I psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). It was also used to confirm diagnoses of AN from their primary physician (i.e. psychiatrist or psychologist), with the exception of the amenorrhoea criterion which is no longer included in the current DSM-5. AN was required to be the primary diagnosis of the AN group. AN

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