Journal of Psychiatric Research 57 (2014) 26–33

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Predicting clinical outcome using brain activation associated with set-shifting and central coherence skills in Anorexia Nervosa

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ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form
16 June 2014
Accepted 17 June 2014

Keywords:
Anorexia Nervosa
Neuroimaging
Set-shifting
Central coherence

ABSTRACT

Background: Patients with Anorexia Nervosa (AN) have neuropsychological deficits in Set-Shifting (SS) and central coherence (CC) consistent with an inflexible thinking style and overly detailed processing style, respectively. This study investigates brain activation during SS and CC tasks in patients with AN and tests whether this activation is a biomarker that predicts response to treatment..

Methods: FMRI data were collected from 21 females with AN while performing an SS task (the Wisconsin Card Sort) and a CC task (embedded figures), and used to predict outcome following 16 weeks of treatment (either 16 weeks of cognitive behavioral therapy or 8 weeks cognitive remediation therapy followed by 8 weeks of cognitive behavioral therapy).

Results: Significant activation during the SS task included bilateral dorsolateral and ventrolateral prefrontal cortex and left anterior middle frontal gyrus. Higher scores on the neuropsychological test of SS (measured outside the scanner at baseline) were correlated with greater DLPFC and VLPFC/insula activation. Improvements in SS following treatment were significantly predicted by a combination of low VLPFC/insula and high anterior middle frontal activation (R squared = .68, p = .001). For the CC task, visual and parietal cortical areas were activated, but were not significantly correlated with neuropsychological measures of CC and did not predict outcome.

Conclusion: Cognitive flexibility requires the support of several prefrontal cortex resources. As previous studies suggest that the VLPFC is important for selecting context-appropriate responses, patients who have difficulties with this skill may benefit the most from cognitive therapy with or without cognitive remediation therapy. The ability to sustain inhibition of an unwanted response, subserved by the anterior middle frontal gyrus, is a cognitive feature that predicts favorable outcome to cognitive treatment. CC deficits may not be an effective predictor of clinical outcome.

1. Introduction

Anorexia Nervosa (AN) is a life-threatening psychiatric disorder with an estimated prevalence of .48–.7% in female patients (Hoek and Hoeken, 2003). AN is characterized by cognitive distortions about weight and appearance, severe weight loss, minimization of health and emotional problems, and significant co-morbid psychiatric disorders (Association AP, 2013; Godart et al., 2002; Holtkamp et al., 2005). Unfortunately, AN is challenging to treat, with few evidenced based interventions, particularly for adults with an enduring form of the disorder (Berkman et al., 2007; Hay and Pubmed Partial STitle, 2013; Hay et al., 2012). Currently, cognitive interventions such as cognitive behavioral therapy (CBT) are recommended for adults with AN; however, fewer than 35% achieve remission with this treatment (Hay et al., 2012; Pike et al., 2004; Fairburn et al., 2014).

Because of the severe health-related consequences as well as societal costs of persistent AN (Golden et al., 2003; Arcelus et al., 2011; Crow and Nyman, 2004; Streigel-Moore et al., 2000) it is important to identify clinical markers or biomarkers to guide treatment selection. Recent studies suggest possible neuroimaging biomarkers for selecting treatment for other psychiatric disorders, including major depressive disorder, wherein subgenual cingulate

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http://dx.doi.org/10.1016/j.jpsychires.2014.06.013
0022-3956/

activation predicts response to CBT (Siegle et al., 2012), visual cortex activation predicts response to scopolamine (Furey et al., 2013) and insula metabolism differentially predicts response to CBT versus escitalopram (McGrath et al., 2013). For patients suffering from panic disorder with agoraphobia, a negative functional connectivity between the anterior cingulate and amygdala at pretreatment predicts favorable response to CBT (Lueken et al., 2013). Although prospective studies are needed to determine the utility of these biomarkers for individual patients, the use of neuroimaging biomarkers to predict response to specific treatments is a potential translational use of neuroimaging.

Thus far, no treatment predictor biomarkers have been proposed for AN. However, candidate biomarkers might be identified by examining the brain circuitry underlying the cognitive inefficiencies reported in AN (Tchanturia et al., 2012a; Fonville et al., 2013). AN is associated with a specific neuropsychological profile, including impaired set shifting (e.g., inflexibility and perseveration) and weak central coherence (exaggerated focus on detail to the neglect of the whole) (Tchanturia et al., 2012b, 2001, 2002, 2004; Holliday et al., 2006; Lock et al., 2011; Roberts et al., 2007; Benson et al., 2010; Harrison et al., 2010). This cognitive style appears to be heritable, persists after recovery, and is seen in relatives without AN (Fossella et al., 2003; Treasure, 2007; Wade and Bulik, 2007; Grice et al., 2002). Cognitive inefficiencies are likely to interfere with the ability of a patient to acquire and to use concepts taught in psychotherapy, particularly cognitive therapies (Baldock and Tchanturia, 2007). Therefore, examining neural correlates of these cognitive processes could identify a biomarker related to treatment response. The purpose of the current study is to describe neural correlates of cognitive inefficiencies in adults with AN, and examine their relationship to treatment outcome after cognitive therapy.

Brain circuitry underlying cognitive function in patients with AN has been investigated in a few studies. Abnormal structure and function has been reported in the anterior cingulate cortex (ACC), prefrontal cortex, insula, and striatum (Wagner et al., 2007; Muhlau et al., 2007; Uher et al., 2005, 2004; Uher, 2001) regions associated with executive function, interoception, and behavioral inhibition. Zastrow and colleagues reported hypoactivation of the ACC and striatum compared to controls, but exaggerated activation in prefrontal and parietal supervisory regions during a target detection task (Zastrow et al., 2009). In another study, blood flow in the superior frontal gyrus was positively correlated with accuracy on a Stroop task requiring response flexibility in patients with AN (Ferro et al., 2005). Taken together this preliminary evidence supports the view that neural correlates of cognitive processes such as SS and CC can be identified in patients with AN and may be useful as a biomarker to predict treatment response.

The current study investigates the neural basis of cognitive inefficiencies in AN, and tests whether neural correlates of these processes are related to treatment outcome. We hypothesized that evidence of greater inefficiencies in CC and SS as evidenced by low activation in key areas of the prefrontal cortex would lead to poorer outcomes from cognitive treatment.

2. Methods

2.1. Participants

Participants were recruited from among those participating in an NIH-funded treatment study (Lock et al., 2013). Twenty-three female participants gave informed consent as approved by the Stanford University Institutional Review Board. Participants were between 16 and 35 years old and met DSM-IV criteria for AN as assessed by the Eating Disorder Examination (EDE) (Cooper and Fairburn, 1987). Participants were required to be medically stable for outpatient treatment as determined by their physician (Golden et al., 2003). All participants reported no history of learning disability or head injury and met safety criteria of the MRI scan environment.

2.2. Measures of symptom severity and comorbid disorders

As part of the clinical trial associated with this project, participants were assessed at baseline and end of treatment (EOT), which was 16 weeks after baseline. At both assessment times, subjects completed the EDE (Cooper and Fairburn, 1987; Fairburn and Cooper, 1993) to measure severity of ED symptoms and the Beck Depression Inventory (Beck, 1987; Beck et al., 1988) to measure symptoms of depression. Comorbid diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS (Kaufman et al., 1997)) for participants under 18 years old, and the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) for those over 18 years old.

2.3. Neuropsychological measures

Standard neuropsychological tests of SS and CC abilities were completed outside the scanner at baseline and EOT. To assess SS, we used the Stroop subtest of the Delis-Kaplan Executive Functioning System (Delis et al., 2001), as this is a classic measure of response shifting that is different from the task administered in the scanner. The scaled score was used for correlations with activation at baseline, and the difference in raw scores was used to assess change from baseline to EOT. To measure CC ability, we administered the Rey–Osterrieth Complex Figure Test (Osterrieth, 1944), as this is a standard measure of detailed perceptual processing. We correlated both the Style and Coherence scores with brain activation at baseline, and computed outcome as the difference between baseline and EOT.

2.4. Treatments

The treatment protocols used in the RCT from which the participants in this study were drawn are described in detail in a previous publication (Lock et al., 2014). Participants received either 16 weeks of CBT ($N = 10$) or 8 weeks of cognitive remediation therapy (CRT) followed by 8 weeks of CBT ($N = 11$). CBT is a standard treatment offered to address the behavioral and cognitive distortions in eating disorders and has been used in several randomized clinical studies for adults with AN (Pike et al., 2004; Fairburn et al., 2014). Cognitive Remediation Therapy (CRT) for AN is a novel cognitive therapy that was developed to address the cognitive style specifically associated with AN (Tchanturia and Lock, 2011). CRT for AN was derived in part from cognitive re-training therapies developed for patients with traumatic brain injury (Malia et al., 1995). There were no outcome differences between the randomized groups at week 16 on clinical measures related to eating psychopathology (e.g., BMI, EDE) in the previously published RCT (Lock et al., 2014).

2.5. Neuroimaging scan Acquisition

All imaging data were acquired within the first 2 weeks of therapy using a 3.0 T General Electric MR750 scanner (gehealthcare.com) housed in the Lucas Imaging Center, using an 8-channel head coil. FMRI scans used a spiral-in/out pulse sequence (Glover and Lai, 1998) with the following parameters: 30 axial slices (3 mm thick, 1 mm skip) parallel to the AC–PC line and covering the whole brain; TR = 2000 ms, TE = 30 ms, flip angle = 90°, 1