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Abnormal white matter properties in adolescent girls with anorexia nervosa

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ABSTRACT

Anorexia nervosa (AN) is a serious eating disorder that typically emerges during adolescence and occurs most frequently in females. To date, very few studies have investigated the possible impact of AN on white matter tissue properties during adolescence, when white matter is still developing. The present study evaluated white matter tissue properties in adolescent girls with AN using diffusion MRI with tractography and T1 relaxometry to measure R1 (1/T1), an index of myelin content. Fifteen adolescent girls with AN (mean age = 16.6 years ± 1.4) were compared to fifteen age-matched girls with normal weight and eating behaviors (mean age = 17.1 years ± 1.3). We identified and segmented 9 bilateral cerebral tracts (18) and 8 callosal fiber tracts in each participant's brain (26 total). Tract profiles were generated by computing measures for fractional anisotropy (FA) and R1 along the trajectory of each tract. Compared to controls, FA in the AN group was significantly decreased in 4 of 26 white matter tracts and significantly increased in 2 of 26 white matter tracts. R1 was significantly decreased in the AN group compared to controls in 11 of 26 white matter tracts. Reduced FA in combination with reduced R1 suggests that the observed white matter differences in AN are likely due to reductions in myelin content. For the majority of tracts, group differences in FA and R1 did not occur within the same tract. The present findings have important implications for understanding the neurobiological factors underlying white matter changes associated with AN and invite further investigations examining associations between white matter properties and specific physiological, cognitive, social, or emotional functions affected in AN.

1. Introduction

Anorexia nervosa (AN) is a serious eating disorder with high mortality (Arcelus et al., 2011). It is characterized by weight loss, cognitive distortions about shape and weight, and medical complications affecting almost every organ system (American Psychiatric Association, 2013). The onset of AN is typically in adolescence and the prevalence among girls is higher than the prevalence among boys (American Psychiatric Association, 2013). In recent years, the role of neurobiology of AN has become increasingly important for understanding the etiology and complications of the condition.

Structural brain changes have been identified in low weight patients with AN, and include reduced brain volume in both gray and white matter structures and enlarged lateral ventricles (Boghi et al., 2011; Castro-Fornieles et al., 2009; Golden et al., 1996; Hoffman et al., 1989; Katzman et al., 1996, 1997; Kingston et al., 1996; Muhlau et al., 2007; Roberto et al., 2011; Swayze et al., 1996, 2003). While the etiology of these changes has not yet been elucidated, decreased brain volumes observed in AN may, in part, reflect reductions in white matter volume that occur secondary to reductions in myelin content from the effects of malnutrition (Swayze et al., 2003). White matter, which is comprised of myelin-wrapped axons, continually develops throughout the second and third decades of life (Yakovlev and Lecours, 1967). Myelin is composed of various types of lipids and may therefore be particularly vulnerable to injury from malnutrition in AN during adolescence (Giedd, 2008). The impact of AN on white matter microstructure during adolescence has not been well characterized. We address this issue in the present study by exploring whether white matter tissue properties differ in a sample of adolescent girls with AN as compared to an age-matched sample of girls of normal weight and eating behaviors. To achieve this overall aim, we used two advanced structural neuroimaging techniques for assessing white matter microstructure: diffusion

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MRI (dMRI) analyzed with tractography and a novel quantitative magnetic resonance imaging (qMRI) method for measuring T1 relaxometry, R1 (1/T1), reflecting myelin content (Mezer et al., 2013).

Diffusion MRI is currently the most common structural neuroimaging method for assessing white matter changes associated with clinical conditions, such as AN. Diffusion MRI is most frequently analyzed using voxel-based or tractography approaches (Feldman et al., 2010). The predominate measure derived from dMRI to index white matter microstructure is fractional anisotropy (FA). FA serves as an index for the degree of water diffusion in a single direction in relation to diffusion in the perpendicular directions and is represented as a scalar value from 0 to 1 (Basser and Jones, 2002). In white matter regions in which fibers are coherently organized in a single direction, higher FA is typically associated with favorable neurobiological factors, such as increased myelination, greater axonal count, and higher axonal density (Basser and Pierpaoli, 1996; Beaulieu, 2002). However, in white matter regions of multiple fiber directions, FA in isolation is highly challenging to interpret (De Santis et al., 2014; Jeurissen et al., 2013; Jones and Cercignani, 2010).

Using voxel-based dMRI, several studies have observed decreased FA in adults with AN as compared to normal weight control adult subjects. Regions for decreased FA have been observed in distributed cortical white matter brain areas, including the bilateral fimbria-fornix, fronto-occipital fasciculus, posterior cingulate (Frank et al., 2013; Kazlouski et al., 2011), superior and posterior corona radiata (Frank et al., 2013; Frieling et al., 2012), optic radiations (Frieling et al., 2012), and the superior longitudinal fasciculus (Frieling et al., 2012; Via et al., 2014). However, not all studies of AN observe changes in FA (Yau et al., 2013). Failure to find group differences may be related to the biology of AN, such as stage of recovery following treatment (Yau et al., 2013), but may also reflect limitations in voxel-based methods for analyzing dMRI data (Jones and Cercignani, 2010), or difficulty detecting group FA differences with small sample sizes (De Santis et al., 2014). To our knowledge, only a single study has examined diffusion property changes associated with AN during adolescence (Frank et al., 2013). We require further studies of adolescents with AN to gain deeper understanding for whether changes in white matter properties during adulthood reflect persistent structural differences inherent to AN neuropathology beginning in adolescence, late alterations in tissue microstructure during adulthood, compensatory processes secondary to physiological manifestations of AN, or a combination of these possibilities. For this study, we chose to analyze dMRI data with tractography, an analytic approach that provides greater anatomical precision for identifying the specific white matter pathways and tract locations responsible for group differences than voxel-based approaches.

White matter tissue microstructure can also be examined using quantitative MRI approaches for measuring R1 (1/T1). R1 is a direct measure of the longitudinal relaxation rate of water protons in a magnetic field (Tofts, 2003). Rates of R1, measured in units of 1/s, are most affected by the amount of tissue contained within a voxel. Consequently, voxels comprised of mostly water typically have much slower R1 rates (~0.25/s) than voxels containing higher proportions of tissue (up to ~1.2/s). R1 rates are also sensitive to the biophysical characteristics of specific tissue types, particularly those affected by the presence of myelin (Bottomley et al., 1984; Kucharczyk et al., 1994; Mansfield, 1982; Rooney et al., 2007). In white matter, variations in myelin content account up to ~90% of R1 (Stuber et al., 2014), suggesting that R1 may be a useful proxy for tissue myeloarchitecture. R1 has also been shown to be directly related to tissue concentrations of iron (Stuber et al., 2014). Oligodendrocytes, the cells responsible for myelination within the central nervous system, are the predominant iron-containing cells of the brain (Connor and Menzies, 1996). Taken together, these features make R1 an important complement to diffusion measures, such as FA, which are indirect and open to multiple biological interpretations. Advances in qMRI methods now allow for the measurement of R1 with clinically-feasible scan times (Lutti et al., 2010; Mezer et al., 2013; Yarnykh, 2010). Techniques for mapping R1 have been combined with dMRI to assess changes in white matter tissue composition in relation neurological disorders known to affect myelin, such as multiple sclerosis (Mezer et al., 2013), and to dissociate among biological processes contributing to white matter changes observed during development and aging (Yeatman et al., 2014). To our knowledge, the present study is the first to employ both dMRI and R1 mapping techniques to evaluate white matter tissue properties in AN during adolescence. Using these two measures, we expected to gain further insight into white matter differences associated with AN that would not be distinguished with dMRI alone.

Based on the evidence described above, we hypothesized that, compared to controls, adolescent girls with AN would show evidence for decreased FA and decreased R1 in multiple white matter tracts. In particular, we expected to observe evidence for white matter property differences within pathways observed in previous dMRI studies to demonstrate differences in diffusion measures, including the fimbria-fornix, the inferior fronto-occipital, cingulate, and superior longitudinal fasciculus. Decreased FA in combination with decreased R1 would most likely reflect changes in white matter microstructure related to decreased myelin content. Findings from these analyses would contribute substantially to understanding neurobiological basis of white matter changes that have been previously observed in adult studies of AN. Documenting changes in white matter in girls with AN may prove important for understanding symptoms of the condition, including changes in physiological, cognitive, social, or emotional functions.

2. Materials and methods

2.1. Participants

Sixteen adolescent females between the ages of 14–18 years who met DSM-IV diagnostic criteria for AN (American Psychiatric Association, 2000), were recruited from the outpatient program of Lucile Packard Children's Hospital Stanford to participate in the study. At the time of MRI scanning, all AN participants were being treated medically as outpatients, were of low weight, but had stable vital signs. Inclusion criteria were low weight (<85% of expected body weight for age and height), endorsement of fear of gaining weight or becoming fat, body image distortion, and amenorrhea of greater than 3 months duration. Fifteen group age-matched controls were recruited from the community and from the Teen and Young Adult Clinic at Stanford to serve as controls. Inclusion criteria for controls were normal weight and no evidence of medical or psychiatric illness. Exclusion criteria included primary amenorrhea, and any contraindications to MRI scanning, such as metal heart valves, piercings, implants or jewelry that could not be removed. Based on these exclusion criteria, one AN subject with primary amenorrhea had to be excluded from the original AN group ($n = 16$) and the present analyses. Thus, the final number of participants analyzed for the AN group was 15 and for the control group 15. All AN subjects were of the restricting sub-type. Two AN subjects were on selective serotonin reuptake inhibitors, one on sertraline and one on fluoxetine. Subjects and controls were offered a monetary incentive for participation. This study was approved by the Institutional Review Board (IRB) at Stanford University. Written informed consent was obtained from each subject and a parent when the subject was a minor. Assent was obtained for those under the age of 18 years.

2.2. Clinical protocol

All study participants underwent a brief structured interview to confirm eligibility and to ensure subjects did not meet exclusion criteria. For those with AN, highest weight, lowest weight, current weight, rate of weight loss and duration of amenorrhea (in months) were recorded. The diagnosis of AN was confirmed by a board certified child psychiatrist. A neuroradiologist (MS) blind to the subjects' medical diagnosis, examined the high resolution T1-weighted scans collected as part of