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Brain volume reduction predicts weight development in adolescent patients with anorexia nervosa

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ABSTRACT

Background: Acute anorexia nervosa (AN) is associated with marked brain volume loss potentially leading to neuropsychological deficits. However, the mechanisms leading to this brain volume loss and its influencing factors are poorly understood and the clinical relevance of these brain alterations for the outcome of these AN-patients is yet unknown.
Methods: Brain volumes of 56 female adolescent AN inpatients and 50 healthy controls (HCs) were measured using MRI scans. Multiple linear regression analyses were used to determine the impact of body weight at admission, prior weight loss, age of onset and illness duration on volume loss at admission and to analyse the association of brain volume reduction with body weight at a 1-year follow-up (N = 25).
Results: Cortical and subcortical grey matter (GM) and cortical white matter (WM) but not cerebellar GM or WM were associated with low weight at admission. Amount of weight loss, age of onset and illness duration did not independently correlate with any volume changes. Prediction of age-adjusted standardized body mass index (BMI-SDS) at 1-year follow-up could be significantly improved from 34% of variance explained by age and BMI-SDS at admission to 47.5–53% after adding cortical WM, cerebellar GM or WM at time of admission.
Conclusion: Whereas cortical GM changes appear to be an unspecific reflection of current body weight ("state marker"), cortical WM and cerebellar volume losses seem to indicate a longer-term risk (trait or "scar" of the illness), which appear to be important for the prediction of weight rehabilitation and long-term outcome.

1. Introduction

Anorexia nervosa (AN) is an eating disorder that is characterised by low body weight, fear of gaining weight and body-image distortion (American Psychiatric Association, 2000). AN is the third most common chronic illness in adolescence and is associated with a high psychological and social burden for both patients and society. Its aetiology and pervasive factors are complex and involve environmental, psychological and neurobiological factors, which makes AN difficult to understand and treat (Herpertz-Dahlmann, 2015). The way that AN interacts with the still developing brain and the substantial brain volume decrease that accompany AN are not well understood (Van den Eynde et al. 2011; Titova et al., 2013; Seitz et al., 2014). We currently do not know what causes this brain volume loss nor whether it influences the prognosis. Testing the influence of brain volume changes on the AN prognosis using

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longitudinal data could help us to identify important biological markers for the progression of the disease (Garrett et al., 2014).

A significant global loss of brain volume in AN, regarding both grey matter (GM) and white matter (WM), has been identified in several studies including two recent meta-analyses that studied 126 and 214 patients, respectively (Titova et al., 2013; Seitz et al., 2014). Several studies have shown the potential clinical significance of acute volume loss in the brains of patients with AN at admission, such as altered visuospatial functioning (Castro-Fornieles et al., 2009), reduced perceptual organisation and reasoning (McCormick et al., 2008) and increased drive for thinness (Joos et al., 2010). However, these findings have to be regarded as preliminary, as other studies did not find correlations between brain volume changes and clinical measures (Chui et al., 2008; Amianto et al., 2013; Fonville et al., 2013).

As the peak onset period for AN is during adolescence (Herpertz-Dahlmann, 2015) and the brain shows large developmental changes at this age, it seems important to study adolescent patients with AN. Also, global GM loss was particularly pronounced in adolescence with an average reduction of 10.8% vs 3.1% in adults (Seitz et al., 2014) which might point to a more vulnerable GM during development. Some brain regions might be more susceptible to semi-starvation in AN (Muhlau et al., 2007; Joos et al., 2011), a systematic comparison of regional brain volumes affected in adolescents and adults has been compiled by van den Eynde et al. (Van den Eynde et al., 2012).

GM in the brain contains neurons with their dendrites, axons and synapses as well as supporting glial tissue. GM volume is known to slowly decrease in volume after childhood, thought to represent pruning processes selecting the most relevant neural networks. WM mostly consists of axonal projections and their surrounding myelin sheaths, together with myelin-producing oligodendrocytes and supporting glia. WM volume has been shown to increase until the mid-twenties supporting prolonged maturation (Lenroot and Giedd, 2006; Shaw et al., 2008).

The mechanisms of brain volume reduction in AN are largely unknown. As there is significant volume recovery upon weight rehabilitation and no increase in apoptotic markers (Ehrlich et al., 2008; Mainz et al., 2012), neuronal cell death is unlikely, as are colloidal/osmotic water shifts that would be expected to rather increase brain volume than be responsible for shrinkage. More likely, human post-mortem studies (Neumärker et al., 1997; Benitez-Bribiesca et al., 1999) and animal studies (Leuba and Rabinowicz, 1979; Garcia-Ruiz et al., 1993) point to reduced neuronal and glial cell sizes as well as fewer dendrites and synapses in GM. Reduced and belated myelination as well as lower lipid content seem to be the cause of volume loss in malnourished mice in WM (Yusuf et al., 1981). Importantly, the factors that influence brain volume changes in AN remain unclear. One study found a correlation between global GM volume at admission and the body mass index (BMI) (Katzman et al., 1996). Several studies found that regional GM changes correlated with BMI, e.g. GM changes in the hypothalamus (Boghi et al., 2011) and the right frontal and temporal cortical structures (Brooks et al., 2011; Amianto et al., 2013); GM changes in the cingulum correlated with lowest lifetime BMI (Muhlau et al., 2007). Still, other studies did not find any correlations of GM changes with BMI (Joos et al., 2010; Fonville et al., 2013). The amount of weight loss prior to admission was associated with global GM loss in one small study (Bomba et al., 2013). Apart from weight and the severity of weight loss, the chronicity of the illness may have an impact on brain volume changes that occur during acute starvation. Indeed, two studies have shown the effects of illness duration on cerebellar and metencephalic GM volume reduction in adults with AN (Boghi et al., 2011; Fonville et al., 2013). In adolescents with AN, this matter has not been investigated to date. Finally, the age of onset could be an important factor for brain volume loss that is due to AN. However, correlations with age of onset have not been found to date (e.g. Fonville et al., 2013). In sum, the decisive factors that influence brain volume loss in AN remain largely unclear.

All of the prior results on the clinical significance of brain volume changes in AN refer to cross-sectional correlations at the time-point of admission. Papers that analyse the predictive power of brain volume loss in AN regarding clinical prognosis and weight gain are lacking thus far. One study on a similar subject indicates volume normalisation in the cingulate cortex during treatment to predict the clinical 1-year outcome of adult patients with AN (McCormick et al., 2008). We could not identify other studies that used longitudinal clinical data and included MRI images at baseline for the prediction of clinical prognosis.

Our study aimed to analyse brain volume changes in a large group of adolescents with AN and age- and sex-matched controls, to answer the following questions:

1. Are the brain volume changes that are associated with adolescent AN influenced by absolute weight at admission, prior weight loss, duration of the illness or age of onset?
2. Do brain volumes at admission help predict body weight, as one of the most important clinical outcome measures (Kaplan et al., 2009) at a 1-year follow-up?

2. Methods and materials

2.1. Participants

Fifty-eight adolescent female patients with AN, based on the DSM-IV criteria (American Psychiatric Association, 2000), and 51 age-matched and sex-matched healthy controls (HCs) were recruited. MRI images of sufficient quality could be obtained for 56 patients and 50 HCs, and data for these participants were included in this study. The patients with AN were consecutively recruited at the eating disorder unit of the department for child and adolescent psychiatry, Aachen RWTH University Hospital. Exclusion criteria included a history of psychosis, a history of substance abuse and an IQ below 80. The HC group was recruited via flyers and newspaper advertisements that did not refer to the aims of the study. The exclusion criteria for the healthy controls were any psychiatric diagnoses and an IQ that was below 80. Data at admission from 18 patients with AN and 19 HCs had been previously analysed by our group (Mainz et al., 2012). The severity of the eating disorder symptoms of the participants was assessed using the Eating Disorder Inventory-II (EDI-II). The Beck Depression Inventory-II (BDI-II) and the Spence Children Anxiety Scale (SCAS) were used to document depressive and anxious symptomatology. Age-adjusted, standardised body mass index (BMI-SDS) was calculated using the Kromeyer-Hausschild normative data-set of German youth (Kromeyer-Hauschild et al., 2001), the latter transformation being necessary when studying adolescents with AN as their normal BMI is expected to rise with age (Herpertz-Dahlmann, 2015). Two patients were taking Olanzapine and three diazepam and one both medications at admission, none were taking serotonine reuptake inhibitors.

Treatment of patients followed a multi-modal approach (Herpertz-Dahlmann et al., 2014) with a target weight of 15th–20th BMI percentile, the mean duration of illness prior to admission was 11.4 months, with an average age of onset of 14.5 years. A stepped-care approach of inpatient and daypatient treatment of on average 16.6 ± 6.6 weeks was continued by outpatient treatment until follow-up at one year. 77.3% of the patients reached at least the 10th BMI percentile at discharge from hospital, the cut-off for a diagnosis of AN, while 56.5% were above the 10th BMI