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Larger hippocampus size in women with anorexia nervosa who exercise excessively than healthy women

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ABSTRACT

Exercise has been shown to increase hippocampal volume in healthy older adults. Observations from animal models of diabetes and hypertension suggest that the combination of exercise and caloric restriction may exert greater neuroprotection in the hippocampus than either behavior alone. Yet, in humans, the effects of exercise and caloric restriction on the hippocampus are not known. We measured the volume of the hippocampus prior to clinical treatment in women with anorexia nervosa (AN) who were restricting calories and engaging in excessive exercise, women with AN who did not exercise excessively, and healthy women who did not engage in either behavior. Women with AN were also examined longitudinally (once weight was restored and 6 months later). In the present report, we found that women with AN engaged in caloric restriction and excessive exercising prior to clinical treatment had larger hippocampal volumes than healthy comparison women. After weight restoration, women with AN who had engaged in food restriction and excessive exercise prior to treatment had hippocampal volumes similar to that of women with AN who only engaged in caloric restriction. These results advance the field by showing for the first time that hippocampal volume may be increased by exercise alone or exercise interacting with food restriction in AN.

1. Introduction

The hippocampus is a brain structure that continues to undergo structural changes during adulthood (Erickson et al., 2011; Herting and Nagel, 2012). Six months of aerobic exercise (i.e., walking) increased the volume of the hippocampus in previously sedentary older adults (Erickson et al., 2011). Similar results have been found in animal research (e.g., mice; Biedermann et al., 2012; Fuss et al., 2014). Furthermore, reduced caloric intake can promote neurogenesis in the hippocampus of mice (Lee et al., 2002). A large multisite study in humans has begun to investigate the extent to which caloric restriction affects indicators of the aging process, such as cardiovascular risk markers, neuroendocrine function, and cognitive decline in healthy adults (Stewart et al., 2013).

Animal studies have examined the combined effects of caloric restriction and exercise on the hippocampus. Engaging in *both* caloric restriction and exercise produced greater neuroprotective effects on the hippocampus in adult rats than rats only engaging in one of these behaviors (Kishi and Sunagawa, 2012; Santin et al., 2011; Stranahan et al., 2009). However, there is also evidence that food restriction paired with free access to wheel running can lead to severe starvation and death (i.e., rat models of activity-based anorexia, see Richter et al. (2014), Routtenberg and Kuznesof (1967), Dwyer and Boakes (1997) and Aoki et al. (2012)). Stark differences in outcome may be related to the amount of time that animals are allowed for wheel running (Naylor et al., 2005; Droste et al., 2003), whereby mice allowed to run for 9 days showed increased neurogenesis in the hippocampus, but a running period of 24 days showed a 50% reduction in neurogenesis relative to controls. At this stage, the combined effects of engaging in both caloric restriction and exercise on hippocampal volume in humans are not known.

A unique opportunity to examine the effects of caloric restriction and exercise in humans may be found in studying individuals

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with anorexia nervosa (AN) because they have severely reduced caloric intake and many engage in excessive exercise while starved. Specifically, 40% to 80% of individuals with AN engage in excessive exercise while drastically reducing their caloric intake (Davis et al., 1997). The study of these behaviors in AN has additional clinical relevance because eating disorders have the highest mortality rates among all mental illnesses (Sullivan, 1995), and 30% of patients with AN relapse after hospital discharge (Strober et al., 1997). The present study is a report on the extent to which *combined* exercise and caloric restriction affect hippocampal volume. The degree to which hippocampal volume predicts clinical outcome in patients with AN is also investigated.

2. Methods

2.1. Participants

2.1.1. Women with anorexia nervosa (AN)

Women with a diagnosis of AN ($n=36$) were recruited from the inpatient eating disorders unit of the University of Iowa Hospitals and Clinics (UIHC) between 2009 and 2012. The AN diagnosis was determined by board certified psychiatrists using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000).

The UIHC inpatient eating disorders unit consists of daily cognitive-behavioral therapy (CBT) groups and individual therapy, supervised eating, occupational and recreational therapy, as well as physician supervision. Following inpatient treatment, patients frequently transition to the UIHC Psychiatric Partial Hospital (PPH), a structured day therapy program that provides services including meal and snack supervision, group therapy, occupational and recreational therapy, and dietary guidance. In an effort to reassess AN participants upon completion of maximal weight restoration, AN participants completed repeat testing either at the time of discharge from the inpatient unit or, when applicable, at the time of discharge from the PPH.

Twenty-nine AN participants (81%) completed repeat testing upon weight restoration and these participants are the focus of this study. Of these, 25 (86%) had transitioned to the PPH prior to repeat testing. Repeat testing typically occurred after body weight was restored to a body mass index (BMI) of ≥ 18.5 kg/m. However, two AN participants did not meet this threshold ($M=20.3$, S.D.$=1.3$, range$=17.1–22.6$). Repeat testing occurred, on average, 2.7 days after the last day of treatment.

2.1.2. Healthy women

Age-matched normal comparison women ($n=20$) were recruited through advertisements in the Iowa City, IA area and did not have current or lifetime histories of any major psychiatric diagnoses, including eating disorders, as established through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, 1997). These participants did not engage in severe caloric restriction or frequent excessive exercising as measured by the eating disorder symptoms questionnaires and questionnaire-derived exercise assessment, respectively.

2.2. Measures

2.2.1. Questionnaire assessment

2.2.1.1. Exercise assessment. Categorization of frequent excessive exercise was defined as scores of 10 or greater on item 18 of the Eating Disorder Examination Questionnaire (EDE-Q; Fairburn, 1994), "Over the past 28 days, how many times have you exercised in a 'driven' or 'compulsive' way as a means of controlling your weight, shape or amount of fat, or to burn off calories?" and/or endorsement of at least three of the exercise-specific rituals defined by the Yale–Brown–Cornell Eating Disorder Scale (YBC-EDS); (Mazure et al., 1994). These rituals included items such as, "need to exercise after meals" or, "need to exercise in a specific way and/or at a specific time." In other words, these participants exercised frequently in a manner that was driven, intense, and had compulsive qualities.

2.2.1.2. Clinical outcome. Outcome was assessed 6 months after patients' weight had been restored by a modified version of the LIFE II scale (Keller et al., 1987; Warshaw et al., 2001), called the LIFE-EAT II scale. Specifically, the Psychiatric Status Rating subscale was used to measure AN symptom severity. A patient was designated as in remission if the score on this scale was between 1 and 3, including complete and partial recovery. This signifies that individuals did not meet full criteria for AN and were within 10% of ideal body weight. Relapse was categorized by scores of 4–6 on this scale, indicating marked, definite, or definite severe symptoms of AN.

2.2.1.3. Clinical, cognitive, and personality measures. The Eating Attitudes Test (EAT) (Garner et al., 1982) and the Eating Disorder Inventory 3 (EDI-3) (Garner et al., 1983) measure eating disorder symptomatology and tendencies towards perfectionism. The perfectionism scale measures, "self-oriented perfectionism," reflecting rigorous personal standards for performance and "socially prescribed perfectionism," indicating performance demands emanating from pressures from parents and teachers. Perfectionism may play an important role in the maintenance of eating disorder symptoms. The YBC-EDS scale (Mazure et al., 1994) assessed obsessions and compulsions related to eating disorder symptoms. Depression was measured using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Full scale intelligence quotient (FSIQ) was assessed by the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) (Wechsler, 2008). Scores are reported in Table 1.

2.2.2. Structural neuroimaging

2.2.2.1. Neuroimaging parameters. Magnetic resonance imaging (MRI) scans were obtained using a Siemens 3T Trio scanner (Siemens Medical Solutions, Erlangen, Germany) and T1- and T2-weighted images were collected. T1 images were collected using a coronal 3D MP-RAGE sequence (slice thickness$=1$ mm, TR$=2530$ ms, TE$=2.8$ ms, TI$=1100$ ms, NEX$=1$, number of echoes$=1$, flip angle$=10°$, FOV$=256\times256\times256$ mm^3, Matrix$=256\times256\times256$). T2 scans were acquired using a coronal 2D TSE sequence (slice thickness$=1.5$ mm, TR$=9910$ ms, TE$=12$ ms, NEX$=1$, number of echoes$=10$, FOV$=256\times256$ mm^2, Matrix$=256\times256$).

2.2.2.2. Neuroimaging analysis. The University of Iowa AutoWorkup (Pierson et al., 2011) was used to process the MRI scans. This involves an automated procedure in BRAINS image analysis software (Magnotta et al., 2002) and artificial neural networks (Powell et al., 2008). Total regional brain volume which included the sum of the gray and white matter volume (but not cerebral spinal fluid, CSF) of the right and left side of each brain region was computed for the hippocampus, caudate, and putamen (Fig. 1). Total gray and white matter volume of the brain (but not CSF) was also measured and used as a covariate in analyses of regional brain volume to account for individual differences in brain size. Once the AutoWorkup procedure was completed, the scans were examined for correct realignment, co-registration, tissue classification, and accuracy of brain and subcortical structures. Only participants that passed inspection for all of these variables were included in the study.

The hippocampus, putamen, and caudate regions also underwent close visual inspection, following similar procedures to Aylward et al. (2012). The hippocampus was manually edited where necessary (by reviewers blind to diagnosis), according to the methods of Pantel et al. (2000). The putamen's border with the globus pallidus was manually edited where necessary (also blind to diagnosis) using methods described by Ward et al. (2001).

2.2.2.3. Analyses. We investigated how caloric restriction and previous exercise during the month prior to beginning clinical treatment affected hippocampal volume and clinical outcome by examining 29 women with AN in comparison to 20 healthy women (matched in age) with no history of major psychiatric diagnoses (see Table 1). Patients with AN were examined longitudinally, first when they were engaging in caloric restriction immediately prior to beginning their clinical treatment (starvation phase), again when their weight had been restored (weight restoration phase), and finally 6 months after their weight had been restored to determine short term clinical outcome (outcome). We used structural MRI to measure gray and white matter brain volumes in the hippocampus and two comparison regions, the caudate and putamen. Because a severe reduction of caloric intake is a primary symptom of AN, all patients in the AN group were categorized as engaging in caloric restriction. The exercise group was defined as frequent and excessive exercise which included 10 or more instances of 'driven' or 'compulsive' exercise within the past 28 days and/or endorsement of at least three exercise-specific rituals, such as needing to exercise immediately after meals (see Section 2.2).

Based on these criteria, participants were divided into three subgroups: CR+EX (individuals with AN participating in both exercise and caloric restriction), CR (individuals with AN only engaged in caloric restriction), and NC (normal comparison women participating in neither frequent excessive exercise nor caloric restriction). We hypothesized that the largest hippocampal volumes would be found in the CR+EX subgroup, with the next largest in the CR group, and the smallest in the NC group.

2.2.2.3.1. Group differences in brain volume. Total brain volume (the summation of total gray and white matter volume in the brain) was compared in the AN group versus the NC group using a *t*-test. To account for individual differences in brain volume, subsequent analyses used total brain volume as a covariate. Regional brain differences between the AN and NC groups in the hippocampus, caudate, and putamen were examined using a MANCOVA. The dependent variables included regional brain volumes (hippocampus, caudate, or putamen), the independent variable was participant group (AN, NC), and the covariate was total brain volume.

Differences in regional hippocampal volume during the starvation phase were examined in the CR+EX, CR, and NC groups using an ANCOVA with LSD planned