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Cerebral perfusion differences in women currently with and recovered from anorexia nervosa

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ABSTRACT

Anorexia nervosa is a serious psychiatric disorder characterized by restricted eating, a pursuit of thinness, and altered perceptions of body shape and size. Neuroimaging in anorexia nervosa has revealed morphological and functional alterations in the brain. A better understanding of physiological changes in anorexia nervosa could provide a brain-specific health marker relevant to treatment and outcomes. In this study, we applied several advanced magnetic resonance imaging (MRI) techniques to quantify regional and global cerebral blood flow (CBF) in 25 healthy women (HC), 23 patients currently with anorexia (AN-C) and 19 patients in long-term weight recovery following anorexia (AN-WR). Specifically, CBF was measured with pseudo-continuous arterial spin labeling (pCASL) MRI and then verified by a different technique, phase contrast (PC) MRI. Venous T_2 values were determined by T_2 relaxation under spin tagging (TRUST) MRI, and were used to corroborate the CBF results. These novel techniques were implemented on a standard 3T MRI scanner without any exogenous tracers, and the total scan duration was less than 10 min. Voxel-wise comparison revealed that the AN-WR group showed lower CBF in bilateral temporal and frontal lobes than the AN-C group. Compared with the HC group, the AN-C group also showed higher CBF in the right temporal lobe. Whole-brain-averaged CBF was significantly decreased in the AN-WR group compared with the AN-C group, consistent with the PC-MRI results. Venous T_2 values were lower in the AN-WR group than in the AN-C group, consistent with the CBF results. A review of prior work examining CBF in anorexia nervosa is included in the discussion. This study identifies several differences in the cerebral physiological alterations in anorexia nervosa, and finds specific differences relevant to the current state of the disorder.

1. Introduction

Anorexia nervosa is a serious psychiatric disorder characterized by calorie restriction leading to significant weight loss, fear of weight gain, and a disturbance in body-image (American Psychiatric Association, 1994). The precise etiology of anorexia nervosa is still unknown, but many factors are thought to contribute to anorexia, including genetic, neural, psychological, and social (Garfinkel and Garner, 1983; Bulik et al., 2008; Kaye et al., 2011; Brown and Keel, 2012; Scott-Van Zeeland et al., 2014). Unfortunately, the success of treatments is very limited, with nearly 5% of patients dying from the disorder, the highest mortality rate for any mental illness (Hoek, 2006; Bulik et al., 2008). A better understanding of the physiological characteristics of brain function in anorexia nervosa may assist in understanding both the causes and consequences of the illness.

Cerebral microvasculature abnormalities may play a significant role in the psychiatric disorders (West, 2007). It is plausible that abnormalities in microvasculature can result in functional deficits because of the coupling between neuronal activity and blood oxygen consumption (Roy and Sherrington, 1890; Kuschinsky, 1991). The most common techniques used to detect this abnormality are to measure brain perfusion and metabolic parameters by nuclear medicine techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Techniques based on magnetic resonance imaging (MRI) are more attractive for psychiatric research because they provide both noninvasive and reproducible measures of cerebral microvasculature (Theberge, 2008). Several studies have shown agreement between MRI-based physiological studies and nuclear medicine studies (Liu et al., 2012; Zimny et al., 2015). Arterial spin labeling (ASL) MRI relies on the use of magnetically tagged or labeled blood as an endogenous tracer that does not involve any injection of MRI contrast agent, making it more convenient for subjects. In recent years, it has been used to study several psychiatric diseases, such as schizophrenia (Risterucci et al., 2005; Ota et al., 2014), depression (Doraiswamy et al., 1999; Clark et al., 2001, 2006a, 2006b),

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dementia (Du et al., 2006; Hayasaka et al., 2006), and addictions (Gazdzinski et al., 2006; Clark et al., 2007).

Anorexia nervosa is associated both with medical complications (Garfinkel and Garner, 1983; Michell and Crow, 2006) and disturbances of brain function (Bailer and Kaye, 2011; Kaye et al., 2011). As such, cerebral vasculature changes may be particularly important in anorexia nervosa, and cerebral blood flow (CBF) might provide a measure of the severity of brain dysfunction occurring in patients with anorexia. Physiological brain differences in anorexia nervosa have been investigated in studies using nuclear medicine-based techniques, with largely heterogeneous results (Gordon et al., 1997; Kuruoglu et al., 1998; Naruo et al., 2001; Råstam et al., 2001; Takano et al., 2001; Chowdhury et al., 2003; Kojima et al., 2005; Lask et al., 2005; Key et al., 2006; Matsumoto et al., 2006; Frank et al., 2007; Yonezawa et al., 2008; Komatsu et al., 2010; Frampton et al., 2011). A review of this literature is included in the discussion and summarized in Table 1.

Here, we applied pseudo-continuous arterial spin labeling (pCASL) as well as other advanced MRI techniques to obtain rapid, non-invasive measures of cerebral physiological parameters, including CBF and venous T_2 values, markers of blood oxygenation. Further, we compared these parameters among subjects with a current diagnosis of anorexia nervosa (AN-C), subjects in long-term weight recovery from anorexia nervosa (AN-WR), and healthy women (HC) to determine if cerebral physiological characteristics differed during different stages of the disorder.

2. Methods

2.1. Participants

Subjects came to an initial screening appointment to provide written informed consent to participate in this study. The Health Insurance Portability and Accountability Act compliant protocol was approved by the University of Texas Southwestern Institutional Review Board, and written informed consent was obtained from all participants. A total of 67 female subjects, between 18 and 47 years of age were included. All subjects were interviewed using the Structured Clinical Interview for DSM-IV disorders (SCID-RV) to confirm the history of anorexia nervosa in the AN-C ($n=23$) and AN-WR ($n=19$) groups, and the absence of current or past eating disorders in the HC group ($n=25$). All subjects in the AN-C group had met the DSM-IV criteria for anorexia nervosa within the previous 12 months, and were required to be at a stable or increasing weight (no weight loss exceeding 2 kg in preceding 8 weeks). Many of these subjects (16 of 23) had completed an intensive treatment program or partial hospital program for anorexia nervosa within the previous 12 weeks. All subjects in the AN-WR group had met the DSM-IV criteria for AN previously but had maintained a healthy weight, defined as a minimal body-mass index (BMI) greater than or equal to 19.0 kg/m^2, for at least 2 years. No participants met criteria for any psychotic disorders, for bipolar disorder, or for a history of a traumatic brain injury. Clinician-administered quantitative assessments of depression (Quick Inventory of Depression, Clinician-Report), and anxiety (Structured Inventory of Generalized Hamilton Anxiety Symptoms, SIGH-A) were obtained. The Eating Attitudes Test-26 was used to assess current disordered eating behaviors in all three groups (Table 2). The participants did not have any safety contraindications for MRI such as metal implants, pacemaker, neurostimulator, body piercings, or claustrophobia.

2.2. General MRI procedures

All experiments were conducted on a 3T MR system (Philips Healthcare, Best, The Netherlands). The body coil was used for radiofrequency transmission, and an eight-channel sensitivity encoding (SENSE) head coil was used for receiving (Dai et al., 2008; Aslan and Lu, 2010). A 3D T_1-weighted magnetization-prepared-rapid-acquisition-of-gradient-echo (MPRAGE) scan was performed for anatomical reference and the estimation of brain volume. The MPRAGE sequence used the following imaging parameters: repetition time (TR) of 8.1 ms, echo time (TE) of 3.7 ms, flip angle (FA) of 12°, shot interval of 2100 ms, inversion time (TI) of 1100 ms, voxel size of $1\times1\times1$ mm^3, 160 slices with a sagittal slice orientation, and total scan duration of 3 min 57 s.

2.3. Pseudo-continuous arterial spin labeling (pCASL) MRI methods and analysis

The pCASL MRI method was used to obtain regional CBF values and to evaluate regional heterogeneity of CBF change (Aslan and Lu, 2010). Forty pairs of control and labeled images were acquired using a multi-slice echo-planar imaging (EPI) acquisition. Imaging parameters for pCASL experiments were as follows: single-shot gradient-echo EPI, field of view (FOV)$=240\times240$ mm^2, matrix$=80\times80$, voxel size$=3\times3$ mm^2, 29 slices acquired in ascending order, thickness$=5$ mm, labeling duration 1650 ms, post-labeling delay 1525 ms, TR/TE$=4205/13.81$ ms, FA$=90°$, and scan duration$=5$ min 40 s.

The pCASL control and labeled images were realigned using Statistical Parametric Mapping software (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK, www.fil.ion.ucl.ac.uk/spm) running in MATLAB (Mathworks, Natick, MA). The CBF map was calculated using a perfusion kinetic model similar to that described by Thomas et al. (2013). For the normalization, MPRAGE images were first segmented to gray matter, white matter and cerebrospinal fluid (CSF) in SPM. Next, the gray matter images were spatially normalized to the gray matter template of the Montreal Neurological Institute (MNI) atlas and applied to the CBF maps. CBF maps were smoothed with a full-width at half-height (FWHH) of 8 mm to reduce noise. A whole brain mask was applied to CBF maps to exclude out-of-brain voxels.

For CBF map analysis, a whole brain voxel-wise analysis of variance (ANOVA) and follow-up post-hoc t-tests were conducted in SPM5 to compare data across all three groups. Maps were thresholded using a voxel height of $P<0.005$ and extent of 256 voxels, which corresponded to a cluster-$P_{\text{FWE-Corrected}}<0.001$ according to the "3d clustersim" function in AFNI. Region of interest (ROI) analysis on the CBF map was performed using in-house MATLAB scripts. ROIs in different brain lobes were defined from the clusters that showed a significant group difference in the voxel-wise comparison within each lobe. Anatomical masks of major brain lobes were generated by Automated Anatomical Labeling (AAL) software, and were defined in the MNI template space. If an isolated significant cluster was observed in a lobe, the cluster was defined as the functional ROI of this lobe and was applied to the CBF map. If multiple clusters were observed within one lobe, the clusters were combined into one functional ROI of this lobe, and applied to the CBF maps.

2.4. Phase-contrast MRI methods and analysis

Phase-contrast (PC) flow velocity MRI (Fig. 1) was used to measure the whole-brain, global CBF (Liu et al., 2013). Time-of-flight angiogram was performed before the PC flow measurements to obtain the anatomical information of the feeding arteries of the brain. The slice positioning and imaging parameters followed the optimized protocols established earlier (Liu et al., 2013), as follows: TR/TE/flip angle$=23$ ms/3.45 ms/18°, field of view (FOV) $=160\times160\times70.5$ mm^3, voxel size$=0.3\times0.3\times1.5$ mm^3, number of slices$=47$, one 60 mm saturation slab positioned above the imaging slab, and scan duration$=1.4$ min. Since the brain is supplied exclusively by four arteries, left and right internal carotid arteries (ICAs) and left and right vertebral arteries (VAs), we performed four PC-MRI scans, with each scan targeting one specific feeding artery. An automatic algorithm was applied to determine PC-MRI slice positioning of the targeting arteries (Liu et al., 2014). Imaging parameters of PC MRI were as follows: one slice, FOV$=200\times200\times5$ mm^3, voxel size$=0.5\times0.5\times5$ mm^3, 4 averages, maximum velocity encoding$=80$ cm/s, and scan duration$=0.5$ min for one PC scan. An ROI was then drawn on each of the four arteries based on the magnitude image (Aslan et al., 2010). The ROI mask was applied to the velocity map, and the integration of the velocity within the ROI (i.e., velocity × area) yielded CBF in units of ml/min. To obtain a unit volume CBF value in order to account for brain volume, we use software FSL (FMRIB Software Library, Oxford University, UK) to segment the high-resolution T_1 image into gray matter, white matter and cerebrospinal fluid. The brain's parenchyma volume was given by the sum of gray and white matter volumes, and converted to the weight of the brain by assuming a parenchyma density of 1.06 g/ml (Herscovitch et al., 1985). The CBF (in ml/100 g/min) was normalized to unit volume to account for differences in brain volume across subjects.

2.5. T_2-relaxation under-spin-tagging (TRUST) MRI methods and analysis

The T_2-relaxation under-spin-tagging (TRUST) MRI technique (Fig. 2) provides a measure of whole-brain venous blood T_2 values (Lu and Ge, 2008; Ge et al., 2012; Lu et al., 2012). Venous blood T_2 is a surrogate marker of blood oxygenation, which is thought to be tightly coupled to blood flow (Liu et al., 2013), and should provide results comparable to both the pCASL and PC-MRI CBF techniques. In the TRUST approach, pure venous blood signal was first isolated from the superior sagittal sinus (SSS) by subtracting the labeled image from the control image (Lu and Ge, 2008) (Fig. 2A). The venous blood signals were then fitted to a monoexponential function to obtain T_2 (Fig. 2B). The imaging parameters were as follows: voxel size $3.44\times3.44\times5$ mm^3, TR$=3000$ ms, TI$=1022$ ms, four effective TEs$=0$, 40, 80, and 160 ms, labeling thickness$=100$ mm, gap$=22.5$ mm, and scan duration$=1.2$ min. This procedure did not use any exogenous tracers.

2.6. Statistical analysis of whole-brain CBF values

A one-way ANOVA was conducted to identify significant differences between the means of three independent groups for the whole-brain CBF values ($P<0.05$).