Alterations in cerebral physiology in women suffering from anorexia nervosa

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INTRODUCTION: Anorexia nervosa (AN) is a fatal psychiatric disorder characterized by restricted eating, a pursuit of thinness, and obsessive fears of becoming fat. Early research focused primarily on associations between this aberrant behavior and psychosocial functions of the patients, but recent neuroimaging studies have identified both anatomical and functional differences in the brain in these patients. A better understanding of physiological changes in AN patients may help provide a brain-specific health marker (rather than inferring from BMI), guide treatment, and predict risk for future conditions. In this report, we conducted a thorough study on cerebral physiological status in current AN (CAN) and recovered AN (RAN) patients using several advanced MRI methods. We separately examined the changes due to chronic starvation and those due to neuro-psychiatric abnormality. Since the effects of starvation are expected to be global, we used whole brain measures of four markers, including total oxygen delivery to brain tissue, cerebral blood flow (CBF), oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygenation (CMRO2). We expected a neuropsychiatric abnormality to be focal. Thus we used voxel-by-voxel measurement of resting CBF.

METHODS: EXPERIMENT A total of 12 CAN patients (age 28.3±8.9), 11 RAN patients (age 30.1±8.1), and 20 healthy controls (CN) (age 26.9±6.4) were examined on a 3T system (Philips). All participants were females. Body mass index (BMI) in the CAN group was 17.5±1.5, which was significant lower than CN (BMI 23.0±2.7) ($p<0.001$) and RAN group (BMI 22.4±2.4) ($p<0.001$). All RAN subjects had maintained a stable weight with BMI greater than 18.5 for at least two years, demonstrating a consistent weight-recovery from the disease. All CAN subjects had a history of one year or more at a BMI < 18.5 but had not lost weight (2 kgs or more) during the two months preceding the scan. *Global CBF* was measured by phase-contrast (PC) MRI at the feeding arteries of the brain (Fig. 1a). Global cerebral venous oxygenation (Yv) was determined using a novel TRUST MRI technique (Fig. 1b), from which *OEF* was calculated as 0.98-Yv (assuming an arterial oxygenation, Ya, of 0.98). *Oxygen delivery* to the brain was estimated as CBFxYaxCa, where Ca is a constant representing the capacity of blood to carry O2 which varied based on different hematocrit values. *Global CMRO2* (in units of μmol O2/min/100g brain tissue) was quantified based on arterio-venous difference in oxygen content (known as the Fick principle), i.e., CMRO2= CBF x (Ya-Yv) x Ca. The total scan duration of these global measurements was 4 min. *Regional CBF* was measured with a pseudo-continuous ASL (PCASL) sequence with following parameters: TR/TE=4260/14ms, label duration=1650ms, post label delay=1525ms, 29, 5mm thick axial slices, duration 5 min 40 sec. DATA ANALYSIS:The data were processed with previously established procedures. The physiological markers were compared across groups with an ANOVA test. If a main effect was observed, follow-up t-tests were performed to examine the differences between two groups. For ASL data, we used voxel-based analysis to detect any clusters with a significant effect. A threshold of $P<0.005$ and minimum cluster size of 250 voxels were used.

RESULTS AND DISCUSSION: Global physiological markers are plotted in Fig. 2. Comparing CAN patients to controls, there was no difference in blood supply (i.e. CBF) to the brain (Fig. 2a). But the amount of oxygen delivered to the brain was 7.6% lower ($p=0.047$) in the CAN group. This is attributed to a lower level of hematocrit in CAN patients. The average hematocrit values in CAN (from all patients who were hospitalized) were 35.7%, which was considerably lower than typical female hematocrit of 40%. This is known to be caused by anemia associated with starvation (5). OEF and CMRO2 in CAN patients did not show significant differences from controls, suggesting that the brain was able to adapt to reduced oxygen delivery and maintain a normal brain activity during the starvation. Surprisingly, more physiological differences were observed when comparing the RAN patients to the controls. In the RAN group, CBF was 11% lower ($p=0.03$) than the control group (Fig. 2a). Accordingly, the amount of oxygen delivery to the brain was also lower than the control group, despite their long-term normal BMI values. The brain's activity in RAN patients appears to be similar to that in controls, as indicated by an equivalent CMRO2. However, this was achieved by an increased oxygenation extraction fraction (OEF) (by 15%, $p=0.02$). That is, since less blood arrives at the brain, the brain takes a larger fraction of the oxygen from the incoming blood in order to keep the total oxygen molecules extracted the same. Regional CBF: We further verified that reduced CBF in the RAN group is widespread across the brain. Lobe-by-lobe analysis of absolute CBF revealed significant reduction of CBF in frontal ($p=0.02$), parietal ($p=0.006$), temporal ($p=0.03$), and occipital ($p=0.04$) lobes. To evaluate focal changes that might be caused by neuropsychiatric abnormalities, we factored out the global effect by dividing the voxel-wise CBF value by the whole-brain averaged CBF value, resulting in a relative CBF (rCBF) map. Lower rCBF was observed in the medial frontal lobe of the RAN patients (Fig. 3). No regions were detected when using RAN>CN comparison.

In summary, the present work conducted a systematic study on potential physiological deficits in currently-ill and long term weight-recovered anorexia patients. It appears that, due to starvation and anemia, the currently-ill patients receive reduced oxygen delivery to the brain. The brain appears to compensate for this small reduction in oxygen and overall neural activity is preserved. For the recovered patients, although their BMI and hematocrit have returned to normal, their brain physiology has not. Specifically, they still receive less blood supply to the brain and extract a larger fraction of oxygen from incoming blood to meet their metabolic demand. Although this does not appear to affect the neural activity at their current age (as shown by intact CMRO2), this chronic insufficiency in blood supply may increase their risk for ischemic attack, vascular diseases, or dementia in the future. Therefore, if our results can be verified by further studies, medications to increase brain's blood supply may be considered in these patients. Finally, we observed that medial frontal region showed an excessive reduction in CBF beyond the extent of the whole brain, which may be due to suppressed neural activity in these regions.

REFERENCES: 1) Kaye et al. Nat Rev Neurosci, 10, 573 (2009); 2) Xu et al. J Cereb Blood Flow Metab, 31, 58 (2011); 3) Lu et al. MRM, 60, 357 (2008); 4) Yezhuvath et al. Neurobiol. of Aging, 33, 75 (2012); 5) Rieger et al. Am J Psychiatry, 8,135 (1978)

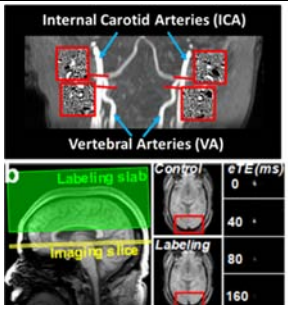

Fig. 1. CMRO2 technique; a) Phase contrast technique applied at arteries feeding into brain, b) TRUST MRI applied at the sagittal sinus

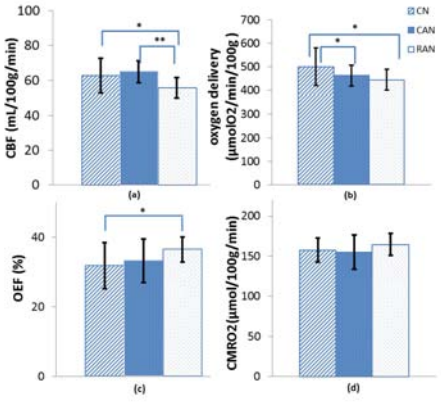

Fig. 2. Group comparison of CBF(a), oxygen delivery in the brain(b), OEF(c) and CMRO2(d) . (* $p<0.05$, ** $p<0.005$)

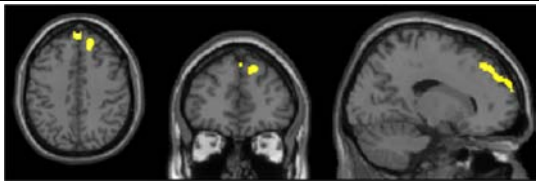

Fig. 3. CBF results: Regions in yellow color show lower rCBF in RAN compared to CN ($p=0.005$, extent 250 voxels).