Regional Cerebral Blood Flow After Recovery from
Anorexia or Bulimia Nervosa

Guido K. Frank, MD1,2
Ursula F. Bailler, MD1,3
Carolyn C. Meltzer, MD1,4
Julie C. Price, PhD5
Chester A. Mathis, PhD5
Angela Wagner, MD6
Carl Becker, BS5
Walter H. Kaye, MD1*

ABSTRACT
Objective: Abnormalities of regional cerebral blood flow (rCBF) have been found in individuals who are ill with anorexia (AN) or bulimia nervosa (BN). Little is known about whether rCBF normalizes after recovery from AN and BN.

Method: Eighteen control women (CW), 10 recovered restricting type AN, 8 recovered AN with a binging history, and 9 recovered BN participants without a history of AN were studied using positron emission tomography and [15O]water in order to assess rCBF.

Results: Partial volume corrected rCBF values in cortical and subcortical brain regions were similar between groups. Neither current body mass index nor age correlated with rCBF values.

Conclusion: The results from this study indicate that rCBF normalizes with long-term recovery. Thus, altered rCBF is unlikely to confound functional imaging studies in AN or BN after recovery. © 2007 by Wiley Periodicals, Inc.

Keywords: anorexia nervosa; bulimia nervosa; cerebral blood flow; brain

Introduction
Anorexia (AN) and bulimia nervosa (BN) are severe psychiatric disorders1 that are associated with physiological abnormalities of most organ systems during the ill state. Resting regional cerebral blood flow (rCBF), a marker for baseline brain function,2 is altered in ill AN and BN. That is, studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) found either unilateral or bilateral reduction of rCBF in women ill with AN3–8 in frontal, temporal, and parietal regions. Women ill with BN had increased frontal cortical resting rCBF, which fluctuated in relation to food restriction and binging behavior.9,10

To avoid the possible confounding effect of starvation and emaciation, we have been studying individuals who are long-term remitted from AN and BN (REC AN or REC BN). These individuals have normal weight and nutrition, but often continue to have mild to moderate persistent dysphoric mood and behavioral symptoms that are also present in childhood before the onset of AN or BN.11 Numerous studies found that REC AN and BN have altered serotonin or dopamine function on PET imaging or altered response to stimuli on functional magnetic resonance imaging (fMRI).12–14 Thus, it is possible that symptoms after recovery from weight loss and normalization of caloric intake reflect traits that contribute to vulnerabilities to developing AN or BN.

It is not clear whether rCBF normalizes after recovery from AN, as different studies show both normalization5 and failure to normalize.7 Moreover, few studies were stratified by restricting and binging/purging type of AN. Naruo et al. found reduced rCBF in the anterior cingulate in restricting type AN, which seemed to persist with weight recovery.6,15 Our group found normal rCBF in BN after long-term recovery16; however, to our knowl-
edge, no studies have investigated AN after long-term recovery.

Our group recently published normal brain volume measures for gray and white matter in long-term recovered AN and BN participants compared with controls,17 indicating a normalization of structural brain compared with the ill state.18 In this study, we investigated rCBF of long-term recovered AN and BN participants.

Analysis methods in receptor imaging studies aim to correct for nonspecific binding and blood flow, but fMRI usually does not have a baseline blood flow measure. It is important to characterize rCBF in REC AN and BN in order to determine whether altered rCBF confounds the interpretation of PET and fMRI results.

Method

Ten recovered restricting type AN (RRAN), 8 recovered AN with binging history (RBAN), and 9 recovered BN (RBN) participants were recruited, all women. RRAN never had BN, and BN participants never had AN (DSM-IV). To be considered “recovered,” participants had to, for at least 6 months before the study: (1) maintain a weight above 90% average body weight; (2) have regular menstrual cycles; (3) have not binged, purged, or engaged in restrictive eating patterns. Eighteen healthy control women (CW) were recruited who had no history of an eating disorder or any psychiatric, major medical, or neurologic illness. Detailed methods have been published previously.19 All participants underwent magnetic resonance (MR) imaging prior to PET-scanning. PET-scanning was performed during the first 10 days of the follicular menstrual cycle phase. [15O]water was used as radiotracer. Participants were positioned in a Siemens HR+PET scanner (CTI PET Systems, Knoxville, TN). Following 12 mCi [15O]water bolus intravenous injection (automated injection system), 20-frame dynamic PET-scanning in three-dimensional imaging mode was acquired over 3 min. Arterial blood samples were obtained (6 ml/min), and radioactive events were detected with dual 50 mm × 25 mm BGO scintillation crystals and blood was monitored over 210 s. Regions of interest (ROIs) were hand drawn on the coregistered MR images and applied to the dynamic PET data to generate time-activity curves.16

The [15O]water data were analyzed using a one-tissue two-compartment model in which blood flow was measured as the clearance of [15O]water from blood to brain (K2, ml min\(^{-1}\) ml\(^{-1}\)) while accounting for arterial input function timing delays.20 rCBF was assessed on a regional basis via regional K2 values. PET data were initially analyzed without and then with partial volume correction21 in order to correct for potential brain volume differences.

SPSS software was used for statistical analyses.22 Because of small sample sizes, between-group comparisons were made using the nonparametric four-group comparison Kruskal–Wallis Test. Correlations were examined with Spearman correlation coefficients (p). All values are expressed as mean ± standard deviation. Statistical significance was defined as p < 0.05.

Results

Groups were similar in age (CW, 26 ± 6; RRAN, 24 ± 5; RBAN, 28 ± 7; RBN, 24 ± 5 years), and lifetime high body mass index (BMI) (CW, 23 ± 2; RRAN, 22 ± 3; RBAN, 24 ± 2; RBN, 25 ± 2). RRAN (20 ± 2) had significantly lower current BMI compared with CW (22 ± 2, p = 0.02) and RBN (23 ± 3, p = 0.02), but similar compared with RBAN (21 ± 2). Lifetime low BMI was higher in CW (20 ± 1) compared with RRAN (14 ± 2, p < 0.001), RBAN (15 ± 2, p < 0.001), and RBN (19 ± 1, p < 0.01), as well as higher in RBN compared with RRAN (p < 0.001) and RBAN (p < 0.001). RRAN were recovered for 41 ± 26, RBAN for 24 ± 13, and RBN for 18 ± 10 months. Five CW, 2 RRAN, 1 RBAN, and 1 RBN were on birth control pills at the time of the study. All RBAN had a history of regular binging and associated purging. Among RRAN, six had a history of purging, but no binging lifetime.

rCBF was similar across groups in the analysis without partial volume correction (data not shown). Similarly, partial volume corrected data were not significantly different between groups: Table 1 shows regional rCBF data, and Figure 1 shows exemplary scatterplots for selected regions. No statistical relationship was found between current BMI and rCBF. Length of recovery correlated negatively with rCBF for most ROIs in the RBN cohort, but this was significant only for the occipital cortex (p = −0.8, p = 0.04); no significant correlation was found in the other eating disordered (ED) groups individually or in ED participants combined. Past low BMI in RRAN was positively related to rCBF in the lateral (r = 0.8, p = 0.003) and medial orbitofrontal (p = 0.8, p = 0.005), mesial (p = 0.6, p = 0.05) and lateral temporal (p = 0.7, p = 0.03), parietal (p = 0.7, p = 0.02) and sensorimotor cortex (p = 0.8, p = 0.01).

Conclusion

This study found normal rCBF in RRAN, RBAN, and RBN after long-term recovery compared
with healthy CW. It is well known that ill and short-term recovered AN and BN have brain volume abnormalities, which return to normal with long-term recovery. Our study suggests that a similar normalization phenomenon occurs with rCBF. It is important to note that the participants in our study had been at stable weight and normalized nutrition for more than 6 months. Other studies of AN individuals soon after weight recovery have found unilateral temporal lobe hypoperfusion or reduced temporo-parietal and orbitofrontal perfusion. Normalization of rCBF appears to lag behind weight recovery: ill AN had bilateral cortical hypoperfusion that normalized after 3 months of remission, and weight recovery in AN was shown to be associated with increases in rCBF. In summary, rCBF returns to normal with long-term recovery, and it is unlikely that altered rCBF contributes to altered serotonin or dopamine function or to stimulus-specific fMRI brain activation in recovered AN or BN individuals.

A previous study from our group found a negative correlation of rCBF with length of recovery in a separate cohort of RBN participants. In the current study, only the occipital cortex showed a significantly negative correlation with rCBF in RBN, although most other regions showed a non-significant negative correlation (data not shown). The participants in the previous study had a longer length of recovery (57 ± 45 months), but it is not known whether this accounts for those findings. No significant correlations of length of recovery and rCBF were found within the other ED groups or when taking all ED participants together.

Curiously, past low lifetime BMI was associated with current rCBF in only RRAN but no other group. The small number of participants makes drawing conclusions from this finding problematic, and the meaning is not clear. Thus, this finding needs to be replicated before the implication of a potential “scar” can be determined.

The major limitation of this study is the small sample size. However, participants were carefully selected, assessed during relative hormonal stability, and grouped by ED subtype. Furthermore, although brain volumes are normal in ED participants after recovery, altered gray matter volume could still change rCBF results. The raw data did not show group differences, and we then applied a partial volume correction algorithm to correct for potential group differences. Still, rCBF was similar across groups. This indicates both similar rCBF as well as a lack of partial volume effects after long-term recovery. Lastly, nonparametric tests, which include all four groups, each of small size, may be insufficiently powered to detect group differences. However, additional individual two-group comparisons (Mann–Whitney, data not shown)

### TABLE 1. Regional cerebral blood flow (rCBF) across subject groups

<table>
<thead>
<tr>
<th>Region</th>
<th>CW (n = 18)</th>
<th>RRAN (n = 10)</th>
<th>RBAN (n = 8)</th>
<th>RBN (n = 9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>0.55 (0.1)</td>
<td>0.54 (0.1)</td>
<td>0.56 (0.1)</td>
<td>0.66 (0.2)</td>
<td>.20</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>0.55 (0.2)</td>
<td>0.56 (0.1)</td>
<td>0.51 (0.1)</td>
<td>0.64 (0.2)</td>
<td>.24</td>
</tr>
<tr>
<td>Subgenual cingulate cortex</td>
<td>0.56 (0.1)</td>
<td>0.57 (0.1)</td>
<td>0.54 (0.1)</td>
<td>0.62 (0.2)</td>
<td>.73</td>
</tr>
<tr>
<td>Pregenual cingulate cortex</td>
<td>0.57 (0.1)</td>
<td>0.58 (0.1)</td>
<td>0.55 (0.1)</td>
<td>0.66 (0.2)</td>
<td>.51</td>
</tr>
<tr>
<td>Middle striatum</td>
<td>0.38 (0.1)</td>
<td>0.39 (0.1)</td>
<td>0.38 (0.1)</td>
<td>0.64 (0.1)</td>
<td>.38</td>
</tr>
<tr>
<td>Lateral orbitofrontal cortex</td>
<td>0.67 (0.2)</td>
<td>0.64 (0.1)</td>
<td>0.68 (0.1)</td>
<td>0.70 (0.2)</td>
<td>.91</td>
</tr>
<tr>
<td>Lateral temporal cortex</td>
<td>0.56 (0.1)</td>
<td>0.57 (0.1)</td>
<td>0.56 (0.1)</td>
<td>0.59 (0.2)</td>
<td>.65</td>
</tr>
<tr>
<td>Mesial temporal cortex</td>
<td>0.47 (0.1)</td>
<td>0.47 (0.1)</td>
<td>0.45 (0.1)</td>
<td>0.55 (0.2)</td>
<td>.51</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>0.66 (0.2)</td>
<td>0.69 (0.2)</td>
<td>0.64 (0.1)</td>
<td>0.70 (0.2)</td>
<td>.59</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>0.61 (0.1)</td>
<td>0.57 (0.1)</td>
<td>0.62 (0.2)</td>
<td>0.67 (0.2)</td>
<td>.60</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>0.63 (0.2)</td>
<td>0.60 (0.1)</td>
<td>0.56 (0.1)</td>
<td>0.65 (0.2)</td>
<td>.56</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>0.65 (0.1)</td>
<td>0.63 (0.1)</td>
<td>0.64 (0.1)</td>
<td>0.68 (0.2)</td>
<td>.93</td>
</tr>
<tr>
<td>Sensorimotor cortex</td>
<td>0.55 (0.1)</td>
<td>0.52 (0.1)</td>
<td>0.53 (0.1)</td>
<td>0.60 (0.2)</td>
<td>.60</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.59 (0.1)</td>
<td>0.59 (0.1)</td>
<td>0.59 (0.1)</td>
<td>0.66 (0.2)</td>
<td>.59</td>
</tr>
</tbody>
</table>

CW, control women; RRAN, recovered restricting type anorexic women; RBAN, recovered binge eating/purging type anorexic women; RBN, recovered bulimic women; p, value based on Kruskal–Wallis nonparametric test.

a Values are mean (SD).

b p values are nonsignificant.
did not show significant rCBF differences compared with CW. Most studies in the past have used SPECT, but PET signal quantification is considered more reliable.28

In conclusion, rCBF is normal in long-term recovered AN and BN. It is therefore unlikely that rCBF confounds task-related functional neuroimaging studies in this subject population.

We thank Tyson Oberndorfer, M.S. and Katherine Plotnicov, Ph.D. for their editorial assistance.

References

19. Frank G, Bailer UF, Henry S, Drevets W, Meltzer CC, Price JC, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission to-
mography and $^{[11]}\text{C}]\text{raclopride}. \text{Biol Psychiatry} 2005;58:908–912.


