MRI assessment of cerebral oxygen metabolism in cocaine-addicted individuals: hypoactivity and dose dependence

Peiying Liua,b*, Hanzhang Luab, Francesca M. Filbeyc, Carol A. Tammingab, Yan Cao and Bryon Adinoffb,e

INTRODUCTION

Cocaine is one of the most reinforcing and addictive drugs of abuse. Long-term cocaine consumption has been shown to reduce cognitive function and increase the risk for stroke, suggesting that cocaine use may have a negative impact on both neural and vascular components of the brain (1,2). Imaging techniques that are sensitive to combined effects of neural and vascular deficits, such as cerebral blood flow (CBF) measured by arterial-spin-labeling MRI, resting-state functional connectivity MRI, and task-evoked fMRI, have been widely used in studies of cocaine-addicted individuals (3–6). However, a common limitation of many of these studies is that it is difficult to precisely interpret these changes, as a reduction in blood flow could be either due to a dysfunction in cerebral vascular system or a lower metabolic demand by the neural tissues. Therefore, a better understanding of pathophysiology associated with cocaine addiction requires the use of imaging techniques that are capable of disentangling the vascular and tissue alterations. The goal of the present study is to specifically examine the tissue metabolic rate in cocaine-addicted individuals using a novel MRI method.

Brain metabolic rate, denoted by cerebral metabolic rate of oxygen (CMRO2), represents the amount of oxygen consumed by the brain per unit time and is thought to be a more direct index of the aggregated neural activity, compared with CBF or blood-oxygenation-level dependent (BOLD) contrast imaging measures. However, the in vivo measurement of CMRO2 has proven challenging. For decades, the CMRO2 measurement has been considered the “niche market” of positron emission tomography (PET), but the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers, and the PET measurement requires an on-site cyclotron, the injection/infusion/inhalation of 15O-labeled radiotracers.

Keywords: cocaine addiction; cerebral metabolic rate of oxygen; MRI; brain functions

Abbreviations used: CMRO2, cerebral metabolic rate of oxygen; CBF, cerebral blood flow; PET, positron emission tomography; PC, phase contrast; TRUST, TR, relaxation under spin tagging; ETE, effective echo time; Tsp, time of repetition; Tep, echo time; Tinv, time of inversion; VA, vertebral artery; FOV, field of view; ROI, region of interest; SD, standard deviation; rsFC, resting state functional connectivity.

*Correspondence to: P. Liu, Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA.
E-mail: peiying.liu@utsouthwestern.edu

a P. Liu, H. Lu
Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

b P. Liu, H. Lu, C. A. Tamminga, B. Adinoff
Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

c F. M. Filbey
Center For Brain Health, University of Texas at Dallas, Dallas, TX, USA

d Y. Cao
Department of Mathematical Sciences, University of Texas at Dallas, Richardson, TX, USA

e B. Adinoff
VA North Texas Health Care System, Dallas, TX, USA

Received: 23 October 2013, Revised: 16 February 2014, Accepted: 13 March 2014, Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/nbm.3114
an arterial line for dynamic blood sampling (7). Other possible techniques, such as $^{13}$C or $^{17}$O nuclear resonance spectroscopy methods (8,9), also involve exogenous tracers and complex procedures. Therefore, there has not been a clinically practical technique to determine this important parameter.

Recently, our laboratory has developed an MRI method that provides a non-invasive (no exogenous agent), fast (<5 min), and reliable (coefficient of variation < 4%) estimation of global CMRO2 on a standard 3T system (10,11). In this method, CMRO2 is calculated from CBF, arterial oxygenation ($Y_a$) and venous oxygenation ($Y_v$) using the Fick principle of arteriovenous difference, where whole-brain CBF was measured by phase-contrast (PC) MRI (12) and $Y_v$ was measured by a $T_2$-relaxation-under-spin-tagging (TRUST) MRI technique that was developed in our laboratory (13,14). The TRUST technique has been validated in humans against a gold-standard pulse oximetry method (15), and the PC MRI has previously also been validated under both in vitro and in vivo conditions (16,17). This novel CMRO2 technique has been used to detect CMRO2 changes in normal aging (18), multiple sclerosis (19), and Alzheimer’s disease (20).

In the present study, we applied this novel technique to examine the impact of long-term cocaine use on brain oxygen metabolism during early abstinence. We sought to answer the following two questions. (1) Is CMRO2 in cocaine-addicted patients significantly different from that in healthy controls? (2) Is there a relationship between the duration of cocain use and CMRO2?

**MATERIALS AND METHODS**

**Participants**

Thirteen male cocaine-addicted subjects (age 46.6 ± 6.9 years) and 13 healthy male controls (age 44.4 ± 6.0 years) were studied. The control subjects had no past or present history of substance use disorder. The cocaine-addicted participants had a primary DSM-IV diagnosis of cocaine dependence and cocaine was their lifetime drug of choice. They were hospitalized as soon as possible after their last reported use of cocaine and remained in a structured, residential unit until study completion. Abstinence was verified throughout residential treatment by urine drug screens. The MRI study was performed between 14 and 28 days following their last cocaine use. The 14–28 day time frame was chosen to avoid the rapid fluctuations in neural activity that occur within the first few days of cocaine abstinence as well as the more gradual changes that may develop with extended abstinence (21). This time frame also allows the dissipation of withdrawal symptoms such as anxiety and sleep disturbance, which are no longer present two weeks after the cessation of cocaine use. The study was approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and the VA North Texas Health Care System.

**CMRO2 measurement using MRI**

The MRI scans were performed on a standard 3T MR scanner (Philips Medical Systems, Best, The Netherlands). CMRO2 of each subject was measured using a method described previously (10,11). Briefly, global CMRO2 (in units of $\mu$mol O$_2$/min/100 g brain tissue) was quantified based on arteriovenous difference in oxygen content (Fig. 1), i.e., $\text{CMRO2} = \text{CBF}(Y_a - Y_v)\text{C}_h$, where CBF is measured by PC MRI at the feeding arteries of the brain (12), $Y_a$ is the arterial blood oxygenation, assumed to be 98% (22), and $\text{C}_h$ is a constant representing the capacity of blood to carry O$_2$ and was assumed to be 8.56 $\mu$mol O$_2$/ml blood (23). The most challenging component, venous oxygenation ($Y_v$), is measured by a novel TRUST MRI technique that was recently developed and validated in our laboratory (13,15). TRUST MRI utilizes the spin-tagging principle on the venous side to separate out the pure venous blood signal by subtracting the labeled image from the control image. The venous blood signal is modulated with different $T_2$ weightings using various numbers of flow-insensitive $T_2$-preparation pulses. The monoexponential fitting of the blood signal to the $T_2$-preparation duration (termed effective echo time, $eT_2$) then gives the $T_2$ value of the venous blood, which is further converted to $Y_v$ via the well-known relationship between blood $T_2$ and oxygenation (15,24).

The total scan duration of a complete set of CMRO2 measurements was 4.5 min, including an axial 3D time-of-flight angiogram to visualize the feeding arteries of the brain for PC MRI slice positioning (Fig. 2(a)), a TRUST scan to measure the venous oxygenation at the superior sagittal sinus, which is the major draining vein of the brain (Fig. 2(b)), and four PC MRI scans corresponding to the four feeding arteries of the brain: left internal carotid artery, right internal carotid artery, left vertebral artery (VA) and right VA, respectively (Fig. 2(a)) (11). The slice positioning and imaging parameters followed the optimized protocols established earlier (11). Specifically, the time-of-flight angiogram was positioned with the top of the slab at the level of the bottom of the pons, with the following imaging parameters: $T_{ip}/T_{fl}/\text{flip angle} = 20 \text{ ms}/3.45 \text{ ms}/18^\circ$, field of view (FoV) = $160 \times 160 \times 70.5 \text{ mm}^3$, voxel size = $1.0 \times 1.0 \times 1.5 \text{ mm}^3$, number of slices = 47, one 60 mm saturation slab positioned above the imaging slab, scan duration = 1.4 min. The TRUST sequence was positioned to be parallel to the anterior-commissure posterior-commissure line with a distance of 20 mm from the sinus confluence, with the following imaging parameters: $T_{ip} = 3000 \text{ ms}$, $T_{fl} = 1200 \text{ ms}$, voxel size = $3.44 \times 3.44 \times 5 \text{ mm}^3$, four $eT_2$ values of 0, 40, 80, and 160 ms, $T_{CPMG} = 10 \text{ ms}$, scan duration = 1.2 min. The four PC MRI slices were placed perpendicular to the target vessels at the level of the foramen magnum, with the following imaging parameters: single slice, voxel size = $0.5 \times 0.5 \times 5 \text{ mm}^3$, FoV = $200 \times 200 \times 5 \text{ mm}^3$, maximum velocity encoding = 80 cm/s, non-gated, four averages, scan duration of one PC MRI scan is 0.5 min.

**Data processing**

Data processing of TRUST and PC MRI followed methods used previously using custom-written Matlab scripts (10,11). Briefly,
LONG-TERM COCAINE USE AFFECTS CEREBRAL METABOLISM

The total blood flow of all four feeding arteries was normalized by calculating the cross-correlation between years of lifetime use and CMRO2. A potential interaction effect between age and years of cocaine use was also examined by including the interaction term as an additional regressor in the linear model. A p value less than 0.05 was considered statistically significant. A p value between 0.05 and 0.1 was considered a trend of difference.

RESULTS

There was no significant difference in age (p = 0.23) or race (p = 0.42) between the control group and cocaine-addicted group (Table 1). For the cocaine-addicted subjects, the average lifetime use of cocaine was 11.5 ± 7.7 years, ranging from 0.9 to 24.4 years. Six of the cocaine-addicted participants had a co-morbid active diagnosis of alcohol dependence and one participant had co-morbid cannabis and opioid dependence. Ten of the cocaine-addicted subjects were also light (<10 cigarettes/day) or moderate (<25 cigarettes/day) smokers.

The cocaine-addicted participants showed a significantly lower CMRO2 relative to controls (p = 0.031, Fig. 3(a)). This metabolic difference was accompanied by a trend of decrease in CBF (p = 0.058, Fig. 3(b)). Venous oxygenation did not differ between the two groups (p = 0.96, Fig. 3(c)). Data of individual subjects are shown in Table 2. Gray/white matter volume ratios were comparable between the two groups (1.26 ± 0.08 versus 1.24 ± 0.15, p = 0.92). Thus, the lower CMRO2 in cocaine-addicted subjects cannot be attributed to the possibility that their brains contain more white matter.

Within the cocaine-addicted participants, the dose–response relationship between CMRO2 and cocaine use was examined by calculating the cross-correlation between years of lifetime cocaine use and CMRO2. CMRO2 negatively correlated with years of lifetime cocaine use (r = −0.55, p = 0.05) (Fig. 3(d)). That high resolution T$_2$-weighted magnetization-prepared rapid gradient-echo image using the software FSL (FMRIB Software Library, Oxford University). Specifically, FSL-BET was first applied to perform skull stripping on the T$_1$ image of the brain. Then FSL-FAST was used to segment the brain 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 (25). Normalizing the total blood flow to the brain’s parenchyma volume yields the unit volume CBF (in ml/100 g/min), which has accounted for brain volume differences across subjects and groups.

Statistical analysis

Group comparisons between the cocaine-addicted subjects and healthy controls were conducted. Since distribution of the CMRO2, CBF and Y$_v$ values within each group were found to be non-Gaussian according to the Kolmogorov–Smirnov test, the group comparisons were conducted using the Mann–Whitney U test. Within the addicted group, linear regression between the years of lifetime cocaine use and CMRO2 was performed after correcting for the effects of normal aging. The age effect was determined by linear regression of age and CMRO2 in the control group, assuming the age effect on CMRO2 is the same for both groups and is independent of the cocaine effect on CMRO2. In a separate analysis, multiple regression was performed on data from all 26 subjects, in which CMRO2 was used as the dependent variable and age and years of cocaine use were independent variables. A potential interaction effect between age and years of cocaine use was also examined by including the interaction term as an additional regressor in the linear model. A p value less than 0.05 was considered statistically significant. A p value between 0.05 and 0.1 was considered a trend of difference.

Figure 2. MR images of the CMRO2 measurement from a representative subject. (a) Positioning and the resulting PC images of the four feeding arteries of the brain, i.e. left and right internal carotid arteries, and left and right vertebral arteries. The four PC MRI scans (red bars) are positioned perpendicular to the respective feeding arteries. (b) Positioning and the resulting TRUST images. The imaging slice (yellow box) was positioned to be perpendicular to the superior sagittal sinus. The TRUST technique utilizes the spin-tagging principle with the labeling slab (green box) on the venous side (above the imaging slice). Subtraction of the control and labeled images yields pure blood signal in sagittal sinus, which is then subject to increasing T$_2$ weightings. The monoexponential fitting of the blood signal to the T$_2$-preparation duration (e$^{-T_2}$) then gives the T$_2$ value of the venous blood. As blood T$_2$ has a well-known relationship with the oxygenation level of the blood, the estimated venous T$_2$ can be converted to Y$_v$.

for TRUST MRI data, after motion correction and pairwise subtraction between control and labeled images, a preliminary region of interest (ROI) was manually drawn to include the superior sagittal sinus, and the top four voxels with the highest intensity within the ROI were chosen for spatial averaging. The averaged venous blood signals for each e$^{-T_2}$ were then fitted to a monoexponential function to obtain T$_2$. T$_2$ was in turn converted to Y$_v$ via a calibration plot obtained by in vitro bovine blood experiments. For PC MRI data, an ROI was manually drawn on the magnitude image of each PC MRI scan by tracing the boundary of the targeted artery. The rater was blinded to the subject category prior to ROI drawing. The phase signals, i.e. velocity values, within the mask were summed to yield the blood flow of each artery. We point out that, although this analysis involves subjective delineation of ROIs, previous methodological studies have shown that the inter-rater reliability of the flow results was relatively high, with an R$^2$ of 0.994, which is largely attributed to the high flow velocities in these major arteries (11). The total blood flow of all four feeding arteries was normalized to the brain’s parenchyma volume, which was estimated from

Copyright © 2014 John Wiley & Sons, Ltd. wileyonlinelibrary.com/journal/nbm
is, the more years of cocaine use, the lower the CMRO2. Multiple regression analysis in all subjects using both age and years of cocaine use as regressors confirmed that years of cocaine use was significantly correlated with CMRO2 ($t = 2.78, p = 0.01$).

No interaction between age and years of cocaine use on CMRO2 was observed ($t = 0.67, p = 0.51$).

In the cocaine-addicted group, the six subjects with alcohol dependence did not significantly different from the non-alcohol-dependent participants in years of lifetime cocaine use ($t = 0.93, p = 0.37$) or CMRO2 ($t = 1.08, p = 0.30$). Group differences (control versus cocaine-dependent participants) in CMRO2 persisted when the participant with active cannabis and opiate dependence was excluded ($t = 2.15, p = 0.04$). Considering cocaine-addicted participants as three subgroups, based upon the intensity of cigarette smoking (non-smoker, $n = 3$; light ($\leq 10$ cigarette/day), $n = 6$, and moderate $ (>10$ but $ \leq 25$ cigarette/day), $n = 4$), yielded no significant difference in CMRO2 between groups by analysis of variance ($F = 1.74, p = 0.23$).

### DISCUSSION

The present study examined the effect of long-term cocaine use on CMRO2 using a non-invasive MRI technique. A significant reduction in global CMRO2 was observed in cocaine-addicted participants relative to healthy controls and this reduction was significantly correlated with years of cocaine use. These findings suggest that the long-term use of cocaine reduces overall neural activity.

**Pathophysiological considerations**

For the control subjects, we obtained the averaged value of $169.06 \mu$mol/100 g/min, $55.75$ ml/100 g/min and $61.85\%$ for CMRO2, CBF and $Y_v$, respectively. In a previous study of normal aging with 232 subjects (18), the CMRO2, CBF and $Y_v$ at the age of 44.4 years was shown to be $170.44 \mu$mol/100 g/min, $56.15$ ml/100 g/min and $60.78\%$, respectively. Therefore, the physiologic values we obtained from the control subjects are consistent with the normal values at this age range.

There exists very limited literature on energy metabolic changes in cocaine-addicted patients. We are not aware of any studies that quantified oxygen metabolic rate in this condition. One laboratory has examined glucose metabolism in long-term cocaine users previously. Volkow et al. (26) reported a 9% decrease in glucose metabolism in dorsal medial and dorsal lateral prefrontal cortices of cocaine-dependent participants with an average cocaine use of 3.3 years. As these brain regions represent no more than 10% of the whole brain volume, this would translate to a global glucose metabolism reduction of just 1%. Therefore, our observed 9.8% reduction in global CMRO2 in cocaine-addicted participants suggests that long-term cocaine use might affect the functional integrity of the brain in a broader manner, unrestricted to the fronto-limbic–striatal regions that have been the primary focus of cocaine addiction literature. It is possible that there exist sub-threshold brain regions in the...
previous studies in which the metabolic deficit did not reach statistical significance. It is also important to note that, from a metabolic pathway point of view, oxygen metabolism is expected to provide a more accurate marker for the brain’s energy consumption than glucose metabolism (27,28). This is because glucose phosphorylation represents an early step in the metabolic pathway and it does not necessarily correlate with the amount of adenosine triphosphate generated, when for example lactate is produced by the brain or some of the intermediate metabolites are diverted to neurotransmission pathways (29).

Previous studies reported that chronic cocaine users have significant CBF decrease in a few brain regions including frontal, periventricular and temporal-parietal areas (30,31). In our study, the whole-brain CBF in cocaine-addicted patients showed a trend of difference ($p=0.058$) compared to that in healthy controls, but it did not reach significance. This is probably due to the small sample size in our study. The observation that the reduction in CMRO2 was accompanied by a decrease in CBF in the presence of unaltered oxygen extraction fraction led us to hypothesize that the metabolic reduction may be initiated by cocaine’s vasoconstriction effects. Cocaine modulates vascular tone through its effect on calcium channels or monoamine reuptake of smooth muscle cells (32,33). Cocaine could also induce toxicity to vascular endothelium and subsequently impair endothelium-dependent vasorelaxation, which, in turn, may contribute to vasospasm (34). Chronic hypoperfusion secondary to these effects (35) may suppress neuronal activity and/or cause neuronal toxicity, resulting in an attenuated global CMRO2. This process may underlie the increased risk of ischemic stroke associated with cocaine use (32). Although cocaine-induced vasospasm is relatively transient, repeated cocaine-induced attenuation in CMRO2 may alter the baseline brain activity more permanently. For example, significant cerebral hypoperfusion has been reported in cocaine-addicted patients even after 6 months of abstinence (30). Therefore, whereas cerebral artery vasospasm has been posited as the etiology underlying persistently diminished CBF in individuals chronically exposed to cocaine (32,35), the same process may explain the associated CMRO2 deficit.

Reduced CMRO2 is in agreement with previous findings of diminished resting state functional connectivity (rsFC) in brain networks of long-term cocaine users (3). Consistent with our observation that lower CMRO2 correlates with increased cocaine use, decreased rsFC also correlated with increased lifetime cocaine use (3). Global hypometabolism in cocaine-dependent individuals might also affect global brain functions, such as attention. Attention, which contains a variety of subcomponent processes involving relatively global brain processes, is perhaps the most well-documented deficit in cocaine-dependent individuals (36).

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Age (years)</th>
<th>Cocaine use (years)</th>
<th>Total blood flow (ml/min)</th>
<th>CBF (ml/100 g/min)</th>
<th>$Y_v$ (%)</th>
<th>CMRO2 ($\mu$mol/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>38</td>
<td>—</td>
<td>919.03</td>
<td>71.74</td>
<td>71</td>
<td>165.85</td>
</tr>
<tr>
<td>C2</td>
<td>39</td>
<td>—</td>
<td>809.99</td>
<td>63.12</td>
<td>70</td>
<td>151.33</td>
</tr>
<tr>
<td>C3</td>
<td>43</td>
<td>—</td>
<td>589.22</td>
<td>51.32</td>
<td>58</td>
<td>175.75</td>
</tr>
<tr>
<td>C4</td>
<td>46</td>
<td>—</td>
<td>774.98</td>
<td>63.27</td>
<td>71</td>
<td>146.26</td>
</tr>
<tr>
<td>C5</td>
<td>53</td>
<td>—</td>
<td>619.82</td>
<td>55.52</td>
<td>60</td>
<td>180.63</td>
</tr>
<tr>
<td>C6</td>
<td>39</td>
<td>—</td>
<td>695.14</td>
<td>50.56</td>
<td>66</td>
<td>138.52</td>
</tr>
<tr>
<td>C7</td>
<td>47</td>
<td>—</td>
<td>713.10</td>
<td>55.54</td>
<td>64</td>
<td>161.68</td>
</tr>
<tr>
<td>C8</td>
<td>46</td>
<td>—</td>
<td>898.81</td>
<td>64.05</td>
<td>69</td>
<td>159.05</td>
</tr>
<tr>
<td>C9</td>
<td>48</td>
<td>—</td>
<td>787.52</td>
<td>58.37</td>
<td>56</td>
<td>209.92</td>
</tr>
<tr>
<td>C10</td>
<td>51</td>
<td>—</td>
<td>523.03</td>
<td>43.91</td>
<td>48</td>
<td>187.97</td>
</tr>
<tr>
<td>C11</td>
<td>52</td>
<td>—</td>
<td>568.31</td>
<td>46.40</td>
<td>54</td>
<td>174.79</td>
</tr>
<tr>
<td>C12</td>
<td>33</td>
<td>—</td>
<td>629.27</td>
<td>48.84</td>
<td>54</td>
<td>190.31</td>
</tr>
<tr>
<td>C13</td>
<td>42</td>
<td>—</td>
<td>736.39</td>
<td>51.97</td>
<td>63</td>
<td>155.75</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.4 ± 6.0</td>
<td>—</td>
<td>712.66 ± 124.06</td>
<td>55.74 ± 8.06</td>
<td>61.85 ± 7.50</td>
<td>169.06 ± 20.00</td>
</tr>
</tbody>
</table>

| P1             | 48          | 9.71                | 618.69                    | 50.40             | 64       | 146.71                    |
| P2             | 53          | 15.76               | 481.10                    | 46.63             | 67       | 123.78                    |
| P3             | 30          | 3.74                | 721.10                    | 57.88             | 64       | 168.51                    |
| P4             | 50          | 23.29               | 578.79                    | 51.17             | 68       | 131.45                    |
| P5             | 54          | 12.90               | 636.07                    | 49.41             | 62       | 152.31                    |
| P6             | 49          | 18.46               | 661.97                    | 54.85             | 66       | 150.28                    |
| P7             | 48          | 24.37               | 604.01                    | 48.65             | 60       | 158.30                    |
| P8             | 49          | 11.11               | 582.13                    | 43.71             | 58       | 149.70                    |
| P9             | 47          | 2.93                | 509.03                    | 43.20             | 56       | 155.34                    |
| P10            | 36          | 9.29                | 687.04                    | 53.68             | 67       | 142.49                    |
| P11            | 51          | 0.87                | 625.62                    | 45.37             | 58       | 155.38                    |
| P12            | 50          | 13.94               | 685.91                    | 54.38             | 64       | 158.30                    |
| P13            | 41          | 2.77                | 719.28                    | 53.96             | 57       | 189.41                    |
| Mean ± SD      | 46.6 ± 6.9  | 11.5 ± 7.7          | 623.90 ± 74.03            | 50.25 ± 4.61      | 62.38 ± 4.17 | 152.46 ± 16.12          |

$p$ = 0.23

C indicates control subjects, P indicates cocaine-addicted subjects.
Although the present study has focused on the brain, it is important to point out that blood flow to the brain is also influenced by the cardiovascular function of the individual. In particular, cocaine is known to increase heart rate and blood pressure while decreasing myocardial contractility and ejection fraction. Thus, it is possible that reduced CBF observed in this study can be partly attributed to the effect of cocaine on cardiac function. An examination of cardiac output and its relationship with CBF would be useful to provide insight into this question.

Technical considerations

In this study, CMRO2 is written in μmol O2 per 100 g brain tissue per minute, accounting for brain volume. Thus, the observed group differences in CMRO2 cannot be explained by brain size difference across participants and groups. Furthermore, the observation that the gray/white matter volume ratio was not significantly different between the groups suggests that the CMRO2 differences were not simply reflecting cortical atrophy (relative to white matter). A potential confound in the CMRO2 quantification was our assumption that the arterial oxygen saturation, \( Y_o \), was 98% for both the healthy control and cocaine-addicted participants. However, cocaine-addicted participants might have a lower \( Y_o \) due to possible complications in their lung function caused by cocaine use (37). We therefore tested the impact of the assumption of \( Y_o \) on our general conclusion by using a lower \( Y_o \), e.g. 96%, in our CMRO2 calculation for the cocaine-addicted participants. It was found that, using the lower \( Y_o \), the difference between the cocaine-addicted group and the controls became more significant (\( p = 0.002 \)). Therefore, the metabolic deficit observed in the present study cannot be attributed to a \( Y_o \) difference between the groups. In fact, the current results may have underestimated the extent of the deficit.

A methodological strength of the present study is that the CMRO2 measurement was performed non-invasively without injecting any exogenous tracers or blood sampling. Therefore, the measurement was performed when the participant was awake and under minimal stress, which are important for assessment of functional physiological parameters. Furthermore, this method can be completed within 5 min on a standard 3T system, which are useful features for clinical applicability. Finally, our earlier technical studies have suggested that the test–retest reproducibility of this CMRO2 technique might be superior to that of the PET methods (11).

Limitation

An important limitation of the present CMRO2 technique is the lack of spatial resolution. Thus, it is unclear whether the diminished CMRO2 is present throughout the brain or distributed focally in a few brain regions. It is also possible that certain regions may manifest hyperactivity. As technical development of regional CMRO2 measurement gains sufficient success, it would be important to reproduce these findings in a future study. The present study is also limited by its small sample size. However, the statistical significance shown by the present data suggest that the robustness of the measurement technique may have helped the detection of the group effect in the small sample size. Another limitation is that the nicotine use in the control group does not match that in the cocaine-addicted group. Although there has not been clear evidence that nicotine consumption would affect baseline CMRO2, this factor should be considered. Finally, this study lacks evaluation in females, which should be investigated in future work.

CONCLUSION

The present study suggests that cocaine results in a reduction in the brain’s oxygen metabolism and the MRI measure of CMRO2 provides a sensitive marker in evaluating this deficit. Furthermore, the degree of the metabolic dysfunction appears to be dependent on the length of cocaine use. These findings, if replicated in larger cohorts, may offer an important approach in assessing the neurotoxic effects of cocaine and offer new targets to mitigate the long-term effects of cocaine.

Acknowledgements

We thank the staff of Homeward Bound, Inc., and the Substance Abuse Team at the Dallas VA Medical Center for their support in the screening and recruitment of study participants. This study was funded by NIH R01 DA023203 (BA), NIH R01 MH084021 (HL), NIH R01 AG042753 (HL), NIH R01 NS067015 (HL), NIH R21 NS078656 (HL) and NIH UL1TR000451.

REFERENCES

2. Yang S, Salmeron BJ, Ross TJ, Xi ZX, Stein EA, Yang Y. Lower gluta-
5. Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoxia in cocaine users during a GO–NOGO task as revealed by event-


