Impact of cocaine use on brain metabolism: hypoactivity, dose dependence, and relationship to cognitive ability

Peiying Liu[1], Bryon Adinoff[2,3], Carol Tamminga[2], Francesca Filbey[4], and Hanzhang Lu[1]

[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [2]*Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, United States,* [3]*VA North Texas Health Care System, Dallas, Texas, United States,* [4]*Center For Brain Health, University of Texas at Dallas, Dallas, Texas, United States*

INTRODUCTION: Long-term use of cocaine is known to negatively impact neural systems, but the nature of these changes is not fully elucidated. Previous literature has focused on BOLD fMRI (1), resting-state connectivity (2), and cerebral blood flow (CBF) (3) to characterize these deficits, but their relationship to neural function is indirect at best. The brain's energy "budget", denoted by cerebral metabolic rate of oxygen ($CMRO_2$), is thought to be a more direct index of neural activity. Unfortunately, *in vivo* measurement of $CMRO_2$ has proved challenging and no techniques were previously available to determine this parameter on a routine basis. Recently, we have developed an MRI method that can provide non-invasive (no exogenous agent), fast (<5 min), and reliable (coefficient of variation, CoV<3%) estimation of global $CMRO_2$ on a standard 3T system (4-6). In the present study, we applied this technique to examine the impact of long-term cocaine use on brain oxygen metabolism during early abstinence. We sought to answer three questions: 1) is $CMRO_2$ in cocaine-addicted patients significantly different from that in healthy controls? 2) is there a relationship between the length of usage and the severity of metabolic deficit? 3) does the degree of $CMRO_2$ deficit predict cognitive ability on an individual basis?

METHODS: *Participants:* 13 cocaine-addicted subjects (all males, age 46.6±6.9 y, range 30-54 y) and 13 healthy controls (all males, age 44.7±6.0 y, range 33-53 y) participated in this study. Cocaine-addicted subjects had a primary DSM-IV diagnosis of cocaine dependence and cocaine was their lifetime drug of choice. Their averaged lifetime use of cocaine was 4187.5±2808.3 days, ranging from 317 to 8896 days. They were scanned between 14-28 days of their last use of cocaine. The 14-28 day time frame avoided 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. The cocaine-addicted subjects were also given a Wechsler Test of Adult Reading (WTAR) test, from which a Full-Scale IQ was obtained. *$CMRO_2$ measurement:* The MRI scans were done on a Philips 3T. $CMRO_2$ of each subject was measured using a method described previously (4-6). Briefly, global $CMRO_2$ (in unit of μmol O_2/min/100g brain tissue) was quantified based on arterio-venous difference in oxygen content (known as the Fick principle), i.e., $CMRO_2=CBF\times(Y_a-Y_v)\times C_a$, where CBF was measured by phase-contrast MRI at the feeding arteries of the brain, Y_a is the arterial blood oxygenation assumed to be 98%, Y_v is the venous oxygenation and was determined using a novel TRUST MRI technique (7), and C_a is a constant representing the capacity of blood to carry O_2 and was assumed to be 8.97μmol O_2/100ml blood (8). The scan duration of a complete set of $CMRO_2$ measurement was 4.5 min. *Statistic analysis:* Group comparisons between the cocaine-addicted subjects and healthy controls were conducted using the Student t tests. Next, within the addicted group, dose-response relationship was examined by calculating the cross-correlation between days of lifetime cocaine use and $CMRO_2$ after correcting for age effects. The potential of metabolism biomarker in predicting cognitive ability was evaluated by the correlation between WTAR Full-Scale IQ and $CMRO_2$ in the addicted group. Finally, causal modeling, a theoretical framework widely used in psychological sciences (9), was used to test the hypothesis that $CMRO_2$ is a mediator of the relationship between cocaine usage and IQ.

RESULTS and DISCUSSION: Fig. 1 shows representative images of phase-contrast MRI and TRUST MRI. Group comparison results between cocaine-addicted subjects and healthy controls are shown in Fig. 2. As can be seen, the addicted group had significantly lower $CMRO_2$ (p=0.015), suggesting that long-term use of cocaine reduced overall neural activity. This metabolic difference was accompanied by a decrease in CBF (p=0.023, Fig. 2). Furthermore, based on the finding that the oxygen extraction fraction (indicated by Y_v) was unchanged comparing the addicts group to the controls (p=0.90, Fig. 2), we concluded that the causal direction is such that lower metabolism resulted in a lower CBF (via neurovascular coupling) rather than the reverse, because Y_v would have been decreased should the reverse be true (as in the case of other conditions such as stroke) (10).

Fig. 3a shows that, within the addicted group, $CMRO_2$ is negatively correlated with the days of lifetime cocaine use. That is, the more days that an individual has used cocaine in his life, the lower his $CMRO_2$ will be, which likely indicates more disruption in brain function.

Comparing $CMRO_2$ to WTAR Full-Scale IQ across addicted individuals, a positive correlation (Fig. 3b) was observed, suggesting that the metabolism index is of predictive value for cognitive ability in cocaine users. With the two correlations described above, one would also expect that the days of lifetime use and IQ would be correlated. However, this relationship was found to be weaker (cc=-0.36, p=0.23). Moreover, causal modeling suggested that this link was not direct and was instead mediated by the $CMRO_2$ changes. In other words, the causal relationship among the variables appears to be cocaine consumption → reduced brain metabolism → reduced IQ.

In summary, the present work represents the first study, to our knowledge, to measure brain oxygen metabolism in cocaine-addicted patients. We found a significant reduction of whole-brain $CMRO_2$ in cocaine users, the degree of which was significantly correlated with the total number of days of their chronic cocaine use. Our results further suggested that levels of $CMRO_2$ can predict cognitive ability of the individual. Although a global measure at present, quantitative evaluation of $CMRO_2$ may be a promising marker in drug addiction and treatment assessment.

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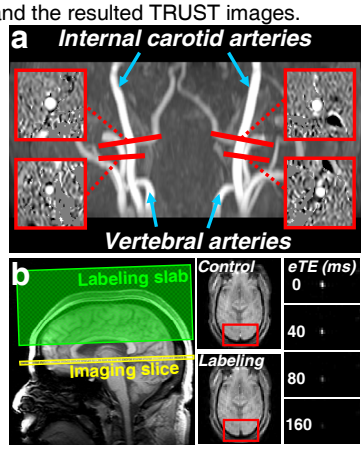
Fig. 1: MR images from a representative subject. (a) Positioning and the resulted phase-contrast images. (b) Positioning and the resulted TRUST images.



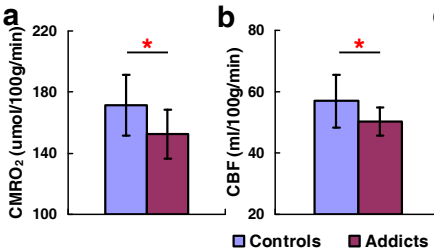


Fig. 2: Results of group comparisons between cocaine addicted subjects and healthy controls. (a) Comparison of $CMRO_2$ between the two groups. (b) Comparison of CBF between the two groups. (c) Comparison of Y_v between the two groups. N = 13 in both groups. Red stars indicate significant difference between the two groups ($p < 0.05$ using two tail t test).

Fig. 3: Results of $CMRO_2$ correlation analysis in cocaine-addicted subjects. (a) Scatter plot between $CMRO_2$ and days of lifetime cocaine use. (b) Scatter plot between $CMRO_2$ and WTAR Full-Scale IQ score. Each dot represents one subject. Black line indicates linear fitting line. N = 13.