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Extended findings of Brain Metabolite Normalization in MA-Dependent Subjects Across Sustained Abstinence: A Proton MRS Study

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Abstract

Objective—The goal of the present study was to extend our previous findings on long-term methamphetamine (MA) use and drug abstinence on brain metabolite levels in an expanded group of MA-dependent individuals.

Methods—Seventeen MA abusers with sustained drug abstinence (1 year to 5 years), 30 MA abusers with short-term drug abstinence (1 month to 6 months) and 24 non-substance using controls were studied using MR spectroscopy (MRS). MRS measures of NAA/Cr, Cho/Cr and Cho/NAA were obtained in the anterior cingulate cortex (ACC) and in the primary visual cortex (PVC).

Results—ACC-Cho/NAA values were abnormally high in the short-term abstinent group compared to controls [$F(1,52)=18.76$, $p<0.0001$]. No differences were observed between controls and the long-term abstinent group [$F(1,39)=0.97$, $p=0.97$]. New evidence of lower ACC-NAA/Cr levels were observed in the short-term abstinent MA abusers compared to controls [$F(1,52)=23.05$, $p<0.0001$] and long-term abstinent MA abusers [$F(1,45)=7.06$, $p=0.01$]. No differences were observed between long-term abstinent MA abusers and controls [$F(1,39)=0.48$, $p=0.49$].

Conclusions—The new findings of relative NAA/Cr normalization across periods of abstinence suggest that adaptive changes following cessation of MA abuse may be broader than initially thought. These changes may contribute to some degree of normalization of neuronal function in the ACC.

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Keywords

Methamphetamine; imaging; MRS; NAA; Cho; anterior cingulate cortex

1. Introduction

In the past decade the use of the stimulant methamphetamine (MA) has increased in the general population, with worldwide abuse of amphetamines surpassing that of cocaine and opiates combined (Nations, 2004). It is now estimated that approximately 5% of the adult population in the United States have used MA on at least one occasion with worldwide use estimated to be 33 million users (Roehr, 2005). The statistics on the growing pandemic of MA abuse are overwhelming and include the following: 1) admissions to substance abuse treatment programs with MA as the primary substance increased 332% from 1996 to 2006, with essentially all states reporting increases (DHHS, 2008); 2) emergency room admissions related to MA use have doubled during the period of 1994 to 2002 (SAMSHA, 2004); and 3) several acts of national legislation, such as the Comprehensive Methamphetamine Control Act of 1996 and the Methamphetamine and Club Drug Anti-Proliferation Act of 2000, have focused specifically on the growing problem of MA abuse throughout the United States (Justice, 2005). The highly addictive nature of MA, as well as its preferential action on the dopamine (DA) system that can produce psychotic symptoms, makes MA a major public and mental health concern in the 21st century.

MA has multiple mechanisms by which it exerts its neurotoxicity (Davidson et al., 2001; Seiden and Ricaurte, 1987). Acute administration of MA increases extracellular DA levels via the reverse transport of DA and also by the displacement of DA from vesicular stores (Liang and Rutledge, 1982; Sulzer et al., 1993). The displaced monoamine is then oxidized and converted to reactive oxygen species which ultimately contribute to necrotic cell death (Davidson et al., 2001). The lipophilic nature of MA allows it to penetrate cellular membranes and disrupt the electrochemical gradient of key organelles such as mitochondria resulting in neurotoxicity driven by apoptosis (Cadet et al., 2003; Davidson et al., 2001; Seiden and Sabol, 1996). The excitatory neurotransmitter glutamate may also play a role in MA-induced neurotoxicity with acute administrations of MA producing marked and prolonged increases in glutamate release (Ohmori et al., 1996). Hence DA, glutamate, and perhaps nitric oxide may all play a role in the neurotoxic effects of MA on the both the DA and 5-HT systems (Abekawa et al., 1994).

Recent animal and human studies suggest that neuronal changes associated with long-term MA use may not always be permanent but may partially recover with prolonged abstinence (Ernst and Chang, 2008; Melega et al., 1996; Volkow et al., 2001a; Wang et al., 2004). A series of Positron Emission Tomography (PET) studies have tracked neuronal changes as a function of MA abstinence in human MA abusers. One PET study reported evidence of sustained striatal DA transporter (DAT) abnormalities in long-term MA-dependent subjects who had remained abstinent for approximately 3 years (McCann et al., 1998). In contrast, other longitudinal PET studies have reported evidence of both striatal DAT normalization in detoxified MA-dependent subjects (Volkow et al., 2001a; Volkow et al., 2001b) and normalized thalamic metabolism following protracted abstinence (> 12 mos) (Wang et al., 2004).

A small set of studies have employed magnetic resonance spectroscopy (MRS) techniques to track neuronal changes linked to drug abstinence in chronic MA abusers. A recent study followed 12 MA-dependent subjects longitudinally and found that after five months of drug abstinence changes in frontal gray matter glutamate+ glutamine (GLX) correlated inversely

with the duration of abstinence (Ernst and Chang, 2008). In another MRS study of 30 abstinent MA abusers, a strong positive correlation was observed in the mid-frontal gray matter and time drug abstinent (Sung et al., 2007). In our previously published MRS study of 24 MA-dependent subjects we reported evidence of relative Cho/NAA normalization across periods of abstinence in the rostral ACC. Thus the collective MRS findings suggests that following cessation of MA abuse, adaptive changes may occur, that contribute to some degree of normalization of neuronal structure and function in select brain regions (Ernst and Chang, 2008; Nordahl et al., 2005). Recent published work from our research group suggest that these changes may also be linked to improvements in cognitive function (Salo et al., 2009).

1.1 Study Rationale

The goal of the present study was to combine our previously published MRS data with new data collected on the same GE scanner in order to extend our findings to a larger sample. In this increased sample of 47 MA-abusers, we tested the hypothesis that short-term abstinent MA-abusers would exhibit abnormally low ratios of ACC-NAA/Cr and abnormally high ACC-Cho/Cr or ACC-Cho/NAA ratios, compared with both controls and long-term abstinent MA-abusers. Low ACC-NAA/Cr ratios and high ACC-Cho/Cr or Cho/NAA ratios would be consistent with neuronal changes or overt damage with increased membrane turnover in the ACC, respectively. No group differences were predicted in the primary visual cortex (PVC), a region that receives relatively little DA innervation (Hall et al., 1994).

2. Methods

2.1 Subjects

Two groups were studied: 47 MA-abusers and 24 matched control subjects¹. The MA-abusing group was recruited from six substance abuse treatment centers (one inpatient clinic and five outpatient clinics) and met DSM-IV criteria for lifetime MA dependence determined from the Structured Clinical Interview (SCID) (First et al., 1995). Random urine screens were performed at the referring sites.² For analysis the MA-abusers were divided into two groups: 1) 17 long-term abstinent MA-abusers (1 year to 5 years) and 2) 30 short-term abstinent MA-abusers (1 month to 6 months). There were no significant differences in age [$F(1,45)=0.01$, $p=0.99$], education [$F(1,45)=2.92$, $p=0.09$], estimates of IQ [$F(1,45)=2.73$, $p=0.11$], years of MA use [$F(1,45)=0.01$, $p=0.95$] or age at first MA use [$F(1,45)=0.34$, $p=0.56$] between short and long-term abstinent MA-abusers.

On average the controls and the combined short and long-term abstinent MA groups differed in age [$F(1,69)=4.27$, $p=0.04$], estimates of premorbid intelligence (Nelson, 1982) [$F(1,66)=10.57$, $p=0.002$] and years of education [$F(1,69)=21.38$, $p<0.001$]. For the MA-abusing subjects, inclusion criteria were 1) lifetime diagnosis of MA dependence according to DSM-IV criteria; 2) age range between 18 and 52 years.

Exclusion criteria for the MA group were: 1) substance dependence other than MA (except nicotine) within the past year; 2) alcohol abuse within the past 5 years; 3) treatment or hospitalization for non-drug related DSM-IV Axis I psychiatric disorders; 4) medical or neurological illness or trauma which would affect the CNS (e.g., stroke or seizure disorder);

¹24 of the MA subjects and 13 of the Controls were scanned in the previous study. Nordahl, T.E., Salo, R., Natsuaki, Y., Galloway, G.P., Waters, C., Moore, C.D., Kile, S., Buonocore, M.H., 2005. Methamphetamine users in sustained abstinence: a proton magnetic resonance spectroscopy study. *Archives of General Psychiatry* 62, 444–452..

²Drugs screened in the random urine toxicology included: alcohol, amphetamine, methamphetamine, MDMA, cocaine, benzodiazepines, barbiturates, THC, morphine, codeine, hydro- and oxycodone

5) severe hepatic, endocrine, renal disease, or history of loss of consciousness of over 30 min; 6) compound skull fracture or clear neurological sequelae of head trauma; and 7) metal implant or any other indication that would preclude MRI procedure. The controls were recruited from the local community. Controls met the same criteria as the MA-abusers, except for the history of MA dependence. After complete description of the study to the subjects, written informed consent was obtained.

2.2 MRS Procedure

Image Acquisition: Single voxel 1H-MRS and structural MRI scans were acquired with a neuro-optimized 1.5T GE Signa NV/i MRI system (GE Healthcare, Waukesha, WI), with LX 9.1M4 operating system software. Proton MRS-measurements of interest were NAA, Cho, and Cr. Voxels of interest were the ACC and PVC, both regions containing predominately gray matter. NAA values were expressed as ratios of Cr, whereas Cho values were expressed as ratios of both Cr and NAA (Bottomley, 1987)

2.2.1 Sagittal Scout Sequence—The midsagittal slice of a sagittal Fast Spin Echo sequence (TR=2500 ms, TE=85 msec, slice thickness=3 mm, skip 1.5 mm, NEX=1, time<2 min) was acquired to orient slices of subsequent scans with the AC-PC line.

2.2.2 Axial-Oblique Fast Spin Echo [FSE] Sequence—19 axial oblique slices (FOV=24 cm, 256 × 256 matrix, TR=3500, TE=17/115, echo train length=20, slice thickness=5 mm, skip=0 mm, NEX=2) were acquired. These images covered the entire brain and permitted selection of the voxels for MRS.

2.2.3 Single Voxel MRS—Localized brain spectra were collected using a long TE point-resolved spectroscopy (PRESS) sequence (Bottomley, 1987) (Probe/SV, GE Healthcare, Waukesha, WI). The following acquisition parameters were used: Psd: PROBE-P, Orientation: Axial-Oblique (AC-PC Line), TE: 144 ms, TR: 1500 ms, Number of spectral points: 2048, Spectral Bandwidth: 2500 Hz, Total number of repetitions: 128, Phase Cycling: 8, Center Frequency: Water, Extended Dynamic Range: On, Water Suppression Optimization: On, Spatial saturation pulses: On, Scan Time: 4 min 54 seconds. In the PRESS sequence, prior to collection of the 128 spectra, 8 baseline reference spectra are acquired without excitation pulses, followed by 16 spectra without water suppression. Two cm × 2 cm in plane and 1 cm thick voxels were sequentially placed using the a priori rules in the ACC and the control region, the PVC (see below). Pre-scanning was performed prior to each MRS scan that included an automated first-order shimming procedure within the defined voxel, and an automated RF pulse flip angle optimization procedure for optimal water suppression (PROBE/SV Manual, GE Healthcare, Waukesha, WI).

The 128 water-suppressed spectra were averaged, baseline corrected, phase corrected, and apodized to form the spectra from which spectral peaks and areas were derived by separate analysis of the individual resonances. The average water signal from the 16 non-water suppressed spectra served as reference for an initial phase correction applied to each of the 128 water-suppressed spectra, and subsequent local phase correction was applied to align each metabolite signal along the in-phase (real part of complex spectra) direction. Metabolite peaks N-acetyl-aspartate (2.02 ppm), creatine (3.03 ppm), and choline (3.21 ppm) were easily identified in all of the spectra.

2.2.4 Placement of Voxels—Anterior Cingulum: The ACC voxel (Fig. 1) was placed at the midline and included samples from both left and right hemispheres. This voxel abutted upon the anterior portion of the corpus callosum posteriorly. The caudate was well formed visually at this level but the sampling was near the superior portion of the putamen, at a

level with dense striatal connections. The sampling of the ACC contained the terminal portion of axons synapsing in the ACC, including the neuropil, which is primarily gray matter.¹⁵

Primary Visual Cortex: This voxel (Fig. 2) was sampled in the midline and included tissue from both the left and right occipital hemispheres. The placement of the sample was anterior nearly to the point of sampling some ventricle in order to ensure exclusion of signal from posterior scalp lipids. This voxel was acquired at a level sufficiently inferior so that the superior portion of the voxel did not sample parietal cortex.

2.2.5 Segmentation of ACC and PVC Voxels—Fully automated brain segmentation procedures were performed to separate the axial slices into the 3 components: white matter (WM), gray matter (GM), and cerebral spinal fluid (CSF) (Cohen et al., 1992; Pfefferbaum et al., 1999). Similar to the segmentation algorithm described by others (Cohen et al., 1992; Pfefferbaum et al., 1999), our algorithm was based on the short echo ([PD] or Proton Density) and the long echo (T2) MRI images (or dual-echo FSE images) of the same slice location. The CSF-brain tissue separation was performed similar to Cohen et al. by using intensity-shifted T2 image subtracted by PD image (Cohen et al., 1992). This “image math” technique (e.g. image subtraction) was applied to further enhance the CSF separation in the T2 image 3.

2.3 MRS Analysis

Quantitative analysis was performed on each resonance (Cho, Cr, and NAA) separately using analysis software (GE Healthcare, Waukesha, WI) on the MRI system. The analysis was done using only the real part of the spectra. A narrow frequency window was set around the residual water resonance and each of the metabolite resonances. Each resonance was apodized to effect line width normalization based on the width of the Cr resonance, and to effect a line shape transformation from a Lorentzian to a Gaussian distribution. By normalizing the line widths, direct measurement of the heights of the processed resonances was then equivalent to measuring areas under the unprocessed resonances. Each processed resonance was then curve fit to a Gaussian using the Marquardt-Levenberg method (Marquardt, 1963). The maximum value of the Gaussian fit was taken as the relative metabolite concentration, from which NAA/Cr, Cho/Cr, and Cho/NAA ratios were computed.

2.4 Statistical Analysis

Only MRS data with adequate quality of shim (main field inhomogeneity < 6 ppm) were included for statistical analysis. For group comparisons, absolute Cr values were examined for the primarily gray regions, the ACC and PVC. These absolute Cr values were divided into the respective metabolites as a part of the normalization process (Frederick et al., 1997). Utilizing information from brain segmentation, the Cr values for the ACC-voxel and the ACC-PVC-voxel were adjusted to control for CSF fraction. Utilizing linear multiple regression we examined correlations between relative metabolites, years of usage, and months of abstinence in the MA-abusers. In addition, non-parametric correlational techniques were employed, to examine the relationship between years of usage and relative metabolites separately for each of the two MA-abusing groups.

³WM-GM separation is based on PD image only, not a sum of T2 and PD image

3. Results

3.1 Group Differences in Regional Metabolite Values

The absolute Cr values did not differ between the MA-abusers and the control group in the ACC [$F(1,69)=0.09$, $p=0.77$] or in the PVC [$F(1,66)=0.20$, $p=0.66$].⁴ Utilizing information from the segmented regions the Cr values were adjusted to control for CSF signal. No group differences were observed for the adjusted ACC-Cr values [$F(1,69)=0.04$, $p=0.85$] or in the PVC-Cr [$F(1,66)=0.14$, $p=0.71$]. Consistent with our previous findings, there was a significant interaction between group and normalized ACC-Cho/NAA values [$F(2,68)=11.15$, $p<0.0001$]. Planned comparisons revealed that the ACC-Cho/NAA values were statistically lower in the long-term abstinent MA-abusers compared to the short-term abstinent MA-abusers [$F(1,45)=12.96$, $p=0.0008$] but did not differ from controls [$F(1,39)=0.01$, $p=0.97$]. There was also a significant interaction between group and ACC-NAA/Cr values [$F(2,68)=8.99$, $p=0.0003$]. Planned comparisons revealed that ACC-NAA/Cr values were significantly higher in the long-term abstinent MA-abusers compared to the short-term abstinent MA-abusing subjects [$F(1,45)=7.06$, $p=0.01$] but did not differ significantly from controls [$F(1,39)=0.48$, $p=0.49$]. Group differences were observed for Cho/NAA levels within the primary visual cortex [$F(2,54)=3.77$, $p=0.03$] but not for NAA/Cr and Cho/Cr [NAA/Cr: $F(2,64)=2.52$, $p=0.09$; Cho/Cr: $F(2,54)=0.69$, $p=0.50$]. It should be noted however that PVC-Cho values were missing from 4 controls and 10 MA abusers, thus statistical results on PVC-Cho values may not be reliable. All of the above results endured when age was employed as a covariate. Figure 3 here

3.2 Metabolite Correlations with Years of Use, Length of Remission, and Metabolites

Using regression analyses for the combined MA subject groups we examined the relationship between months of abstinence, years of usage, and relative metabolites. Months of abstinence correlated positively with both ACC-NAA/Cr ratios ($t=2.29$, $p=0.03$) and inversely with ACC-choline ratios (Cho/NAA ($t=-2.36$, $p=0.02$)). Years of usage correlated positively with ACC-Cho/NAA ($t=2.14$, $p=0.04$) but not with ACC-NAA/Cr [$t=-0.89$, $p=0.38$]. In contrast to our previous findings, a significant positive correlation emerged for months of abstinence and PVC-NAA/Cr [$t=2.06$, $p=0.05$].

Spearman correlations were carried out to examine the relationship between metabolite ratios and years of use separately in the two MA-abusing groups. Among the long-term abstinent MA-abusers significant correlations were observed between years MA use and ACC-Cho/NAA levels [ACC Cho/NAA: $p=0.02$] but not with the other metabolites [ACC NAA/Cr: $p=0.42$; ACC Cho/Cr: $p=0.12$]. Among the short-term MA-abusers no significant correlations were observed between years MA use and any of the ACC metabolite values [ACC-NAA/Cr: $p=0.94$; ACC Cho/Cr: $p=0.20$; ACC Cho/NAA: $p=0.26$]. No significant correlations were observed in the PVC - NAA/Cr metabolites in either group of MA-abusers.

3.3 Gender Analyses

The male and female MA-abusers did not differ significantly in age [$F(1,45)=0.14$; $p=0.71$]; education [$F(1,45)=0.25$; $p=0.62$], NART score [$F(1,45)=0.23$; $p=0.63$] or age of first MA use [$F(1,45)=1.07$; $p=0.31$]. Although not statistically significant, the male MA-abusers had significantly longer periods of MA use (mean =14.9 years) compared to the female MA-abusers (mean =10.6 years) [$F(1,45)=2.80$; $p=0.10$]. There were also differences that approached trend significance in the time period of drug abstinence with the female MA-

⁴PVC Creatine values were missing from one control and two MA subjects.

abusers reporting longer periods of MA abstinence (mean=24.65 months) compared to shorter period in the male abusers (mean =10.17 months) [$F(1,45)=3.45$; $p=0.06$]. This is consistent with higher percentage of females (76%) than males (24%) in the long-term abstinent group. No statistically significant gender differences were observed in any of the ACC metabolites [NAA/Cr: $F(1,45)=1.30$; $p=0.26$; Cho/Cr: $F(1,45)=0.01$; $p=0.96$; Cho/NAA: $F(1,45)=0.54$; $p=0.247$]. No gender differences were observed in PVC-NAA/Cr levels [NAA/Cr: $p=0.20$]. 5

4. Discussion

The data in this study extend our previous findings of partial metabolite normalization as a function of drug abstinence (Nordahl et al., 2005). With the increased statistical power in the current study we were able to confirm our previous finding of Choline normalization as a function of drug abstinence within the ACC, but were also able to detect evidence of ACC-NAA/Cr normalization. In our previous paper we proposed a model which suggested that in the first 8 months following MA exposure three processes may contribute to elevated Cho levels: 1) Release of choline-containing compounds associated with acute damage to membrane, 2) gliosis, and 3) membrane biosynthesis (Nordahl et al., 2005). The time course of this regeneration phase, which includes reactive gliosis, increased membrane turnover, and axonal sprouting, may provide one explanation for our elevated Cho findings in MA-abusers in early remission (1 to 6 months). We proposed that at longer remission periods less membrane synthesis and turnover would occur, thus potentially explaining the normalized relative choline values measured in the affected regions. Given these new findings of partial normalization of ACC-NAA/Cr levels we are now proposing that in addition to the reduction in membrane synthesis and turnover across sustained periods of drug abstinence collateral events also occur that impact the NAA/Cr levels within the ACC region.

As NAA is synthesized within the mitochondria and decreases in NAA correlate with reductions in ATP, NAA can be regarded as a marker of neuronal viability that is related to the energy metabolism of the neuron (Grachev et al., 2001; Moffett et al., 2007; Ohrmann et al., 2004; Tsai and Coyle, 1995). This hypothesis is supported by animal studies of traumatic brain injury (TBI) in which acute declines in NAA levels were paralleled by decreases in ATP levels (Signoretti et al., 2001; Tavazzi et al., 2005). In these same TBI studies concomitant increases in NAA were also observed over extended periods of recovery suggesting that NAA levels can recover following neural insult that does not involve substantial or permanent brain dysfunction (Moffett et al., 2007; Signoretti et al., 2001; Tavazzi et al., 2005). Furthermore NAA levels have been shown to recover in periods of disease remission such as multiple sclerosis (Arnold et al., 1990; Narayanan et al., 2001). As it is thought that one of the neurotoxic mechanisms by which MA damages the brain is by disrupting the electrochemical gradient within the mitochondrion (Davidson et al., 2001), it is reasonable to speculate that the ability of MA to disrupt mitochondrion function may be one mechanism by which NAA concentrations are lowered. It is also noteworthy that in previous studies NAA/Cr within the ACC, and not Cho/NAA values correlated with measures of cognition (Grachev et al., 2001; Salo et al., 2009). Thus one possibility may be that alterations in Cho levels may represent a short-term pattern of response to neuronal injury and not sustained neural changes that support cognitive regulation (Nordahl et al., 2005; Pennypacker et al., 2000).

⁵Group analyses on metabolite differences were also carried out on the female abusers alone (Short-term abstinent = 15; Long-term abstinent = 13). The p values were very similar to those of the combined male and female sample.

4.1 Limitations

To minimize the possibility that group differences were due to pre-existing abnormalities in the MA-abusers, we excluded those who had non-drug-related Axis I disorders. To reduce the potential effects of other drugs of abuse, we studied subjects whose primary drug of choice was MA and whose alcohol abuse was greater than 5 years prior to time of study. It is also possible that chronic tobacco use may potentiate the affects of MA by degrading the ability of the brain to metabolize DA (Brody et al., 2004). Post-hoc analyses failed to reveal differences in any of the ACC or PVC metabolite values between the MA-abusers who were cannabis (n=31) or tobacco smokers (n=37) versus those who were non-smokers in this sample. Although group differences were observed for Cho/NAA levels within the PVC, we recognize that missing PVC-Cho data may have limited our ability to reliably measure metabolite patterns in the PVC, an area that has not shown group differences in our previous studies. And finally, as this study was cross-sectional in design, there may be selection differences between those subjects who are sampled in first six months of abstinence and those who were sampled at a later stage of abstinence.

4.2 Summary

Some studies have found persistent neuronal terminal abnormalities as a result of long-term MA use, whereas others have reported evidence of normalization following extended periods of abstinence (Ernst and Chang, 2008; Nordahl et al., 2005; Volkow et al., 2001a; Volkow et al., 2001b; Wang et al., 2004). The findings within the present study suggest that adaptive changes, as evidenced by Cho/NAA ratios and concomitant increases in NAA/CR, may occur across periods of extended drug abstinence. Our findings of normalization may be more reflective of women as our sample contained a large percentage of females in the long-term abstinent group. However post-hoc analyses carried out on the female sample revealed similar results to the combined sample of males and females. The exact role of NAA within the human brain is still unknown, but recent studies suggest its role as a marker of both neuronal health and viability (Moffett et al., 2007). Combined with recent published evidence of improved cognitive function across periods of drug abstinence (Salo et al., 2009), these findings have profound implications for clinical treatment settings as they suggest that positive changes may occur when individuals remain drug abstinent. Furthermore, the timeline of these findings (i.e., more than 12 months) suggest that neurometabolites within the brain and cognitive function may not show signs of normalization until an extended period of one year or longer. Furthermore, the fact that increased power was needed to observe changes in some neurochemicals (NAA/Cr) suggests that some adaptive changes may be more difficult to detect than others. More research is needed utilizing a longitudinal design to elucidate the mechanisms underlying these adaptive changes.

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Figure 1.
Anterior Cingulate Cortex (ACC) Voxel

Figure 2.
Primary Visual Cortex (PVC) Voxel

Figure 3.
Anterior Cingulate Metabolite Levels Across Periods of Methamphetamine Abstinence

Table 1

	Control Subjects (n =24)	Short-term Abstinent (n =30)	Long-term Abstinent (n =17)
Age, y, mean (SD)	32.13 (7.9)	36.33 (9.02) [†]	36.35 (6.83) [†]
Females	12	15	13
Subject's education, y, mean (SD)	15.54 (2.87)	13.37 (1.50) [†]	12.53 (1.81) [†]
NART	112.24 (6.32)	108.30 (5.50) [†]	105.59 (5.23) [†]
Right-handed	22	29	15
MA Use Variables			
Duration, y, mean (SD)		11.88 (7.75)	12.03 (6.62)
Mos Abstinent, mean (SD)		2.85 (1.69)	46.94 (27.60) ^{††}
Age of first use, y, mean (SD)		20.23 (6.20)	19.12 (6.53)
Tobacco smokers	4	23	14
Cannabis Users	0	15	13
Cocaine Users	0	7	8
MDMA users	0	4	0

[†]Significantly different from control group

^{††}Significantly different from Short-term Abstinent group

Table 2

	Control Subjects (n =24)	Short-term Abstinent (n =30)	Long-term Abstinent (n =17)
ACC-NAA/Cr	1.80 (0.17) ^{††}	1.57 (0.17)	1.75 (0.29) ^{††}
ACC-Cho/NAA	0.72 (0.11) ^{††}	0.85 (0.11)	0.72 (0.13) ^{††}
ACC-Cho/Cr	1.29 (0.21)	1.33 (0.18)	1.24 (0.22)
PVC-NAA/CR	2.05 (0.21)	1.99 (0.31)	2.18 (0.25) ^{††}
PVC-Cho/NAA	0.32 (0.05)	0.34 (0.05)	0.29 (0.05) ⁶
PVC-Cho/CR	0.66 (0.10)	0.67 (0.12)	0.63 (0.08)

[†]Significantly different from Short-term Abstinent and Distant Abstinent, $p < .0001$

^{††}Significantly different from Short-term Abstinent, $p < .01$

⁶PVC-Cho values were missing from 4 controls and 10 MA abusers, thus statistical results on PVC-Cho values may be unreliable.