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Spatial Inhibition and the Visual Cortex: A Magnetic Resonance Spectroscopy Imaging Study

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Abstract

Introduction—Deficits in processing spatial information have been observed in clinical populations who have abnormalities within the dopamine (DA) system. As psychostimulants such as methamphetamine (MA) are particularly neurotoxic to the dopaminergic system it was of interest to examine the performance of MA-dependent individuals on a task of spatial attention.

Method—51 MA-dependent subjects and 22 age-matched non-substance abusing control subjects were tested on a Spatial Stroop attention test. MR Spectroscopy (MRS) imaging data were analyzed from 32 MA abusers and 13 controls.

Results—No group differences in response time or accuracy emerged on the behavioral task with both groups exhibiting equivalent slowing when the word meaning and the spatial location of the word were in conflict. MRS imaging data from the MA abusers revealed a strong inverse correlation between NAA/Cr ratios in the primary visual cortex (PVC) and Spatial interference ($p=0.0001$). Moderate inverse correlations were also seen in the anterior cingulate cortex (ACC) ($p=0.02$). No significant correlations were observed in the controls, perhaps due to the small sample of imaging data available ($n=13$).

Discussion—The strong correlation between spatial conflict suppression and NAA/Cr levels within the PVC in the MA-dependent individuals suggests that preserved neuronal integrity within the PVC of stimulant abusers may modulate cognitive mechanisms that process implicit spatial information.

Keywords

Visual Cortex; Methamphetamine; MRS; spatial attention; Stroop; substance abuse

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Introduction

Distinct pathways within the cerebral cortex have been proposed to modulate different types of information in both humans and non-human primates (Ungerleider & Haxby, 1994). Single-cell recordings of neurons in the dorsal pathways of non-human-primates show preferential activation to spatial information, while neurons in more ventral pathways fire rapidly when responding to non-spatial or object information (Scalaidhe, Wilson, & Goldman-Rakic, 1999; Wilson, Scalaidhe, & Goldman-Rakic, 1993). The identification of separate pathways in the processing of spatial location versus objects has evolved in great part from the patient literature (Kolb & Whishaw, 1995). Patients with lesions involving the parietal cortex exhibit deficits in spatial orientation (e.g., Balint's syndrome, neglect) whereas patients with lesions involving the inferior temporal cortex exhibit object-based deficits such as object agnosia (the inability to recognize objects) and prosopagnosia (the inability to recognize faces) (for a review; (Salo & Robertson, 2003). This dissociation between the "what" and "where" pathways has also been supported by patterns of performance on behavioral tasks (Egley, Driver, & Rafal, 1994; Smith, Jonides, & Koeppe, 1996) and human neuroimaging studies (Haxby et al., 1991; Jonides et al., 1993). Although there is abundant evidence from the neurological literature for deficits in processing both object and spatial information, there is perhaps more evidence of spatial processing deficits in psychiatric populations, especially those with abnormalities within the dopamine (DA) system (e.g., schizophrenia patients). (C.S. Carter et al., 1996; Gold, Wilk, McMahon, Buchanan, & Luck, 2003; Park & Holzman, 1992, 1993; Schwartz, Satter, O'Neill, & Winstead, 1989).

The role of DA in the processing of spatial information has also been investigated in studies that employ DA agonists in healthy populations (Clark, Geffen, & Geffen, 1986a, 1986b, 1987a, 1987b, 1989). Given that psychostimulants such as methamphetamine (MA) are particularly neurotoxic to the dopaminergic system (Davidson, Lee, & Ellinwood, 2005; Nordahl, Salo, & Leamon, 2003; Quinton & Yamamoto, 2006; Volkow, Chang, Wang, Fowler, Ding et al., 2001; Volkow, Chang, Wang, Fowler, Leonido-Yee et al., 2001), it was of interest to examine cognitive performance on a test of spatial response conflict in a group of MA-dependent individuals. Based on our previous findings of abnormal Stroop word-based attention in MA-dependent individuals (Salo et al., 2007; Salo et al., 2002; Salo, Ursu, Buonocore, Leamon, & Carter, 2009), we wanted to test whether these deficits would extend to tasks of spatial attention.

The majority of studies that have examined domain specific processing in both human and non-human primates have employed explicit tests of attention and working memory. Attention studies have compared behavioral data and patterns of cortical activation when a person is consciously attending to the physical properties of the stimuli versus when a person is attending to its spatial location (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990, 1991). Similarly, domain specific memory studies have compared both performance and brain activation patterns when subjects are required to remember the spatial location of an object or conversely to store in memory the constituent features of the target stimulus (Jonides et al., 1993; Postle, Awh, Jonides, Smith, & D'Esposito, 2004; Smith et al., 1996). Given the findings from the literature that have documented spatial processing deficits in patients with damage involving the DA system (Clark et al., 1987b, 1989; Goldman-Rakic & Selemon, 1997), we hypothesized that MA-dependent individuals would exhibit performance deficits on a task of spatial attention compared to controls.

In order to test these hypotheses, we administered a Spatial Stroop task to a group of MA-dependent subjects and non-substance abusing controls. The Spatial Stroop task measures the ability to ignore spatial context that is task-irrelevant (See Methods section for task

details). In contrast to the traditional word-based Stroop task (MacLeod, 1991), the subjects are not explicitly instructed to ignore the irrelevant stimulus dimension, but are simply instructed to read the word in front of them, regardless of where it appears on the screen. We predicted that the MA abusers would show increased location-based interference/conflict (i.e., slower reaction times; (RT) when the word meaning and spatial location were in conflict compared to the controls. In addition, as single-voxel MRS imaging data were available on 32 of the 51 MA-dependent subjects and 13 of the 22 controls we also sought to determine if any relationship existed between spatial inhibition and metabolite values. MRS data were collected in two midline brain regions; the Rostral Anterior Cingulate Cortex (ACC) and the medial Primary Visual Cortex (PVC). The ACC voxel was chosen due to its rich DA innervation and its link to higher-level attentional processes such as conflict resolution and behavioral control (M. M. Botvinick, Braver, Barch, Carter, & Cohen, 2001; M. M. Botvinick, Cohen, & Carter, 2004; C. S. Carter et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000). The PVC was chosen as a control region due to less DA innervation (Eberling et al., 2002) and the lack of imaging findings linking the PVC to tasks of response conflict (M. Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; M. M. Botvinick et al., 2001; Kerns et al., 2004). Based on our previous findings, we predicted lower NAA/Cr levels in the MA abusers within the ACC, but not in the PVC (Nordahl et al., 2005; Nordahl et al., 2002; Salo et al., 2007). We also predicted that increased RT interference/conflict on the Spatial Stroop task would correlate with lower ACC- NAA/Cr metabolite ratios in the MA abusers (Salo et al., 2007), but not with metabolite ratios in the PVC, a region that receives relatively little dopamine innervation (Eberling et al., 2002; Hall et al., 1994). Based on our previous study we did not predict any significant correlations in the control group (Salo et al., 2007).

Methods

Subjects

Two groups were studied: 51 MA-dependent subjects and 22 age-matched non-substance abusing control subjects.¹ The controls were recruited from the local community and were screened to exclude any history of substance abuse/dependence. The MA abusers were recruited from substance abuse treatment centers and residential housing programs in the Sacramento area and met DSM-IV criteria for lifetime MA dependence determined from the Structured Clinical Interview (SCID) (First, Spitzer, Gibbon, & Williams, 1995). Random urine screens were performed at the referring sites.² For the MA subjects, inclusion criteria were 1) lifetime diagnosis of MA dependence according to DSM-IV criteria; 2) age range between 18 and 55 years.

Controls met the same criteria as the patients, except for the history of MA dependence. Exclusion criteria for both groups were: 1) substance dependence other than MA (except nicotine) within the past year; 2) alcohol abuse/dependence 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); 5) reported history of a seropositive test for HIV; 6) severe hepatic, endocrine, renal disease, or history of loss of consciousness of over 30 min; and 7) compound skull fracture or clear neurological sequelae of head trauma. All subjects who underwent scanning were screened for any contraindications that would preclude MRI procedure. All subjects

¹The cognitive data has not been published previously, however a subset of the MRS imaging data from 14 of the methamphetamine abusers and 7 of the controls was reported in our previous study (Salo et al., 2007).

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

signed informed consent approved by the University of California, Davis Institutional Review Board and were paid a modest stipend for their participation in the study.

On average, the controls and MA abusers did not differ in age [$F(1, 71) = .33, p = 0.57$], but did differ in years of education [$F(1, 71) = 9.74, p = 0.003$]. All MA abusers had been drug abstinent a minimum of 3 weeks. Substance use characteristics of the MA abusers are outlined in Table 1.

Spatial Stroop Attention Test

Apparatus—Stimuli were presented on a 14" VGA color monitor. A desktop personal computer (PC) controlled stimuli presentation and data collection. Voice responses were recorded via a voice-operated relay interfaced to the microcomputer.

Stimuli—The words "UP" and "DOWN" were displayed in black font against a white background in a top, central or bottom position within a rectangular box on the screen. The incongruent stimuli were created by trials in which the word and the position of the stimuli were in conflict (i.e., the word "UP" displayed in the bottom of the rectangle and the word "DOWN" displayed in the upper position of the rectangle). The congruent stimuli were created by trials in which the word and the position of the stimuli matched (the word "UP" displayed in the top of the rectangle and the word "DOWN" displayed in the lower position of the rectangle). The neutral stimuli consisted of the words "UP" and "DOWN" displayed in the central position within the rectangle. Each letter within the stimulus words was upper case and subtended 1 degree vertically. The width of each word display varied as a function of the word presented (range 2 – 4 letters: approx 1.1 – 3.2 visual degrees).

Procedure

Participants were instructed to read the word that appeared within the rectangular box. Responses were recorded via a vocal response. They were given instructions to discourage a speed-accuracy tradeoff in that they were instructed to respond as quickly as possible without making too many errors. Each trial began with a fixation point of 500 msec followed by a 10000 msec stimulus duration on the screen. The onset of the subject's voice triggered the voice-operated relay switch (recorded by the computer to the nearest msec). The experimenter typed in the first letter to record the subject's response. The fixed time interval between the subjects' response and the next trial was 988 msec. There was one practice block of 32 trials and one block of 108 data trials. The data from the practice block were not included in the analysis.

Magnetic Resonance Spectroscopy [MRS] 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 N-acetyl-aspartate (NAA), choline (Cho), and creatine (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).

Sagittal Scout Sequence—The midsagittal slice of a sagittal Fast Spin Echo (FSE) 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.

Axial-Oblique 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.

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 NAA (2.02 ppm), Cr (3.03 ppm), and Cho (3.21 ppm) were easily identified in all of the spectra.

Placement of Voxels

Anterior Cingulate Cortex (ACC)—The ACC voxel (Fig. 2a) was sampled 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 (PVC)—The PVC voxel (Fig. 2b) was sampled at 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.

Data Analysis

Spatial Stroop Attention Test—Median RTs for correct responses for every condition were computed for each subject.³ Analysis of variance procedures (ANOVA) for repeated measures were used to analyze the data in a 2 × 3 mixed ANOVA with group as a between subjects factor (MA subjects vs controls) and wordtype (incongruent vs congruent vs neutral) as within subjects variables. To calculate Spatial Stroop Conflict effects the median RT of all congruent trials was subtracted from the median RT of all incongruent trials. To calculate Stroop Interference the median RT of all neutral trials was subtracted from the

³Analysis of mean values revealed similar results.

median RT of all incongruent trials. Incorrect responses were not included within the analysis of variance for RT. Further analyses examined error responses between groups. Planned comparisons of Spatial Conflict (incongruent minus congruent) and Spatial Interference (incongruent minus neutral) were performed across all subjects. All values presented are two-tailed unless otherwise specified.

MRS Analysis—Quantitative analysis was performed at the console 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.

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, Satlin, Yurgelun-Todd, & Renshaw, 1997). Utilizing information from brain segmentation, the Cr values for the ACC-voxel and the ACC-PVC-voxel were adjusted to control for cerebral spinal fluid (CSF) fraction.

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 CSF (Cohen et al., 1992; Pfefferbaum, Adalsteinsson, Spielman, Sullivan, & Lim, 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 Proton Density (PD) 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 image⁴

Results

Spatial Stroop Reaction Time Analyses

Analyses revealed a main effect of Stroop wordtype (Incongruent, Congruent and Neutral) [$F(2,142) = 65.15$, $p < 0.0001$], but no interaction between group and wordtype [$F(2,142) = 0.28$, $p = 0.76$]. Planned comparisons revealed that RT Conflict (incongruent vs congruent) and RT interference (incongruent vs neutral) did not differ significantly between the MA abusers and controls on spatial conflict: [$F(1,71) = .13$, $p = 0.72$] or spatial interference: [$F(1,71) = .48$, $p = 0.50$]. No other main effects or interactions reached significance. Power analyses revealed that the failure to detect group differences was not due to insufficient sample size.

⁴WM-GM separation is based on PD image only, not a sum of T2 and PD image

Error Analyses

Although error trials were not included in the RT analyses, further analyses examined accuracy patterns. Analyses revealed a main effect of wordtype [$F(2,100) = 40.51$, $p = 0.0001$] in that all groups made significantly more errors in the incongruent condition (13%) than in either the neutral condition (2%) or the congruent condition (1%). No other effects were significant. Analyses revealed no evidence of a speed-accuracy trade-off in either group (MA abusers; $r = .21$, $p > 0.05$, controls: $r = .34$, $p > 0.05$).

Imaging Results

The creatine values did not differ between the 32 MA abusers and the 13 controls in either the ACC or the PVC (ACC, $F(1,43) = 0.15$, $p = 0.70$; PVC, $F(1,41) = 0.82$, $p = 0.37$).⁵ Utilizing information from the segmented regions the Cr values were adjusted to control for CSF signal. No group differences were observed for the adjusted Cr values (ACC, $F(1,43) = 0.05$, $p = 0.83$; PVC, $F(1,41) = 0.01$, $p = 0.96$) (See Table 3). There were significantly lower values for the ACC-NAA/Cr in the MA abusing subjects compared with the controls [ACC-NAA/Cr $F(1,43) = 5.51$, $p = 0.02$]. Group differences in ACC-Cho/NAA and Cho/Cr values did not reach significance; [ACC-Cho/Cr: $F(1,42) = 0.05$, $p = .82$; ACC-Cho/NAA: $F(1,42) = 1.64$, $p = 0.21$]. Group differences for NAA/Cr endured when education [$p = 0.02$] was employed as a covariate. No group differences were observed in the PVC [NAA/Cr: $F(1,42) = 0.15$, $p = 0.71$; Cho/Cr: $F(1,39) = 0.01$, $p = 0.94$; Cho/NAA: $F(1,38) = 0.0001$, $p = 0.98$].⁶ Power analyses revealed that the lack of group metabolite differences within the PVC was not due to insufficient sample size.

Correlations with Cognitive Measures and Metabolite Levels

A significant correlation was observed between both Spatial Stroop Conflict (incongruent minus congruent) and Spatial Stroop Interference (incongruent minus neutral) and PVC-NAA/Cr levels in the MA abusers. Greater conflict and interference effects were associated with lower NAA/Cr levels in the PVC [Interference; $r = -.64$; $p = 0.0001$; Conflict; $r = -.44$; $p = 0.01$]. A significant negative correlation was also observed for interference and NAA/Cr levels in the ACC [Interference; $r = -.40$; $p = 0.02$] and approached significance for conflict [$r = -.33$; $p = 0.063$]. Given the pattern of correlation with both regions, we tested for statistical differences between the slopes of the two regions (ACC and PVC) with both Spatial Conflict and Interference costs and found that neither differed significantly [$p > .05$]. Perhaps given the small sample of imaging data ($n = 13$), none of the correlations reached statistical significance in the controls in either region.

Discussion

This study extends our previous work that examined the relationship between neurometabolites and word-based conflict (Salo et al., 2007). In contrast to our previous findings of increased word-based Stroop interference in MA-dependent individuals, we observed no group differences on a measure of location-based Stroop conflict between MA abusers and non-substance using controls (Salo et al., 2002). These behavioral findings suggest that spatial inhibitory processes may be intact in MA abusers and may reflect a relative sparing of the dorsal or “where” pathways that modulate performance on a location-based behavioral task such as employed in the current study. Similar results have been published in some (Bisagno, Ferguson, & Luine, 2002; Schroder, O'Dell, & Marshall, 2003), but not all animal studies with dissociations in performance between object and spatial tasks

⁵MRS data from 21 of the MA abusers have been previously reported (Salo et al., 2007). None of the cognitive data have been previously published.

⁶PVC metabolites were missing for 1 MA abuser and 1 control; PVC-choline values were missing for 2 MA abusers.

(Simoes et al., 2007). Furthermore, the fact that Spatial Interference correlated with MRS metabolites in the ACC as well as in the PVC suggests that the ability to resolve spatial conflict may depend in part on medial-frontal systems similar to word conflict suppression.

Although both the spatial and the word Stroop tasks engage an automatic response to a pre-potent mechanism via either the semantics of the word stimulus or the spatial location of the word, there may be key differences between the two tasks. One possibility is that the Spatial Stroop task taps into more implicit processes. In contrast to the word Stroop task, in which the subjects are explicitly told to actively suppress a pre-potent response (i.e., word-reading), the Spatial Stroop task requires only that the participants read the word on the screen. It is also possible that a combination of factors (i.e., the implicit nature of the task and processing of spatial information) may have contributed to the lack of group differences and the preserved attentional performance in the MA abusers. Studies from the neurological literature suggest that preserved implicit representation of space may be mediated in part by the visual cortex. In studies of patients with partial visual cortex ablation, it has been shown that the subjects can respond to spatial locations that are below the level of conscious awareness in that they orient their eyes to a spatial location that they cannot identify (Kentridge & Heywood, 2000; Kentridge, Nijboer, & Heywood, 2008). Another body of literature has examined the role of posterior brain regions in modulating implicit spatial attention by studying patients with bilateral parietal lobe lesions (Balint's patients). Although Balint's patients have no explicit representation of space and cannot tell you "where" something is, they perform normally on the same Stroop Spatial task used in this current study (Robertson, Treisman, Friedman-Hill, & Grabowecky, 1997). In other words they show slowing to words in the display when they are in conflict with their spatial location (i.e., the word "UP" displayed in the bottom of the rectangle). Thus collectively, these data suggest that implicit spatial encoding may be mediated by posterior brain regions, including the parietal and visual cortex.

Finally, another potential reason for the lack of group differences on the Spatial Stroop Task is task difficulty. It is possible that location conflict may be less pre-potent than word reading and that on a task that requires cognitive control to overcome a pre-potent response, word reading is more difficult to suppress. Thus the Spatial Stroop task employed in this current study may have been a less difficult task for the participants compared to the Word Stroop task. A post-hoc analysis of a subset of subjects who performed both tasks revealed that the magnitude of interference on the Stroop Word-color task was indeed greater (MA abusers = 155 ms; Ctls = 125ms) compared to Spatial Stroop interference (MA abusers = 35 ms; Ctls = 29ms). A similar comparison from a subset of subjects who ran both tasks revealed a greater conflict error rate (9%) on the Stroop Word task compared to the Spatial Stroop task (4%). Thus there is some evidence that the Stroop Word task was indeed more challenging for both groups of subjects.

Exposure to high doses of MA can cause long-term changes in the dopaminergic system (Ricaurte, Guillery, Seiden, Schuster, & Moore, 1982; Ricaurte, Sabol, & Seiden, 1994; Ricaurte, Seiden, & Schuster, 1984; Wagner et al., 1980) and alterations in NAA/Cr have been reported in relatively DA rich regions (i.e., ACC and PFC) of MA abusers (Ernst, Chang, Leonido-Yee, & Speck, 2000; Nordahl et al., 2005; Taylor, Alhassoon, Schweinsburg, Videen, & Grant, 2000). In contrast, the PVC regions may be less vulnerable to the neurotoxic effects of MA upon dopamine neurons, given that the PVC receives less DA innervation (Hall et al., 1994; Nordahl et al., 2005; Nordahl et al., 2002). It should be acknowledged however that both noradrenergic and serotonergic fibers innervate complementary layers within the PVC (Morrison, Foote, Molliver, Bloom, & Lidov, 1982).

As recent studies have shown that lower values of NAA correlate directly with lower ATP values (Manji, Moore, Rajkowska, & Chen, 2000), NAA can be regarded as a marker of neuronal viability & metabolism (Grachev, Kumar, Ramachandran, & Szeverenyi, 2001; Ohrmann et al., 2004; Tsai & Coyle, 1995). Given that levels of NAA have been found to correlate with measures of selective attention in other studies (Grachev et al., 2001) our data suggest that relative preservation of neurochemical integrity in posterior regions such as the PVC may allow MA abusers to efficiently process spatial information, at least on the task employed in the current study. Other MRS studies have reported significant correlations with measures of visual inhibition and visual cortex metabolites in patients with schizophrenia (Yoon et al., 2010).

Limitations

To minimize the possibility that group differences were due to pre-existing abnormalities in the MA subjects, we excluded those who had non-drug-related Axis I disorders. We studied subjects whose primary drug of choice was MA and excluded subjects with recent abuse/dependence of other drugs. Post hoc analyses revealed no differences in metabolite values or behavioral performance between those subjects with a past history of dependence on other drugs versus those subjects with no polydrug dependence. Although, we acknowledge that word-displays are not equivalent to the complex nature of environmental events that substance abusers encounter in their everyday lives, the use of targeted tasks of cognition allows one to dissociate the component processes of attention. (Posner, 1986; Posner, Snyder, & Davidson, 1980). Furthermore, as the single-voxel MRS approach does not allow one to sample the entire brain, it is possible that other brain regions may have correlated with our behavioral task. Although previously published structural imaging studies in MA abusers have not reported volumetric differences in the PVC or the rostral ACC sampled here, we cannot rule out that structural changes following long-term MA abuse may have contributed to the neurochemical patterns reported in this study (Berman, O'Neill, Fears, Bartzokis, & London, 2008). In addition, the lack of significant correlations in the control group may have due to small sample of controls that had both behavioral and imaging studies.

Conclusion

This current study links neurochemical levels in posterior brain regions, such as the PVC, with performance on a task of spatial attention, and provides an important direction for our imaging work in substance abusers. As addiction may represent abnormal stimulation of some normal processes coupled with pathological functioning of others, the dissociation of component processes of attention is essential to identify which processes are intact versus those which are dysfunctional. Few studies have systematically examined implicit processing of basic visual information as a contributing factor to drug seeking behavior. Given the importance of associated memories in addiction (Vorel, Liu, Hayes, Spector, & Gardner, 2001), the finding that implicit processes are intact in long-term MA abusers (Jasiukaitis & Fein, 1999; Ray & Bates, 2006; Salo et al., 2008) suggests that systems supporting processing of basic visual perceptual information may be intact in persons who abuse substances. Studies that provide increased knowledge about the basic cognitive mechanisms underlying behaviors that may promote and sustain substance use will constitute an important contribution to the neuroscience of drug addiction.

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Figure 1.
Spatial Stroop Experiment Stimuli Display

2A. Anterior Cingulate Cortex Voxel

2B. Primary Visual Cortex Voxel

Figure 2.
Magnetic Resonance Spectroscopy (MRS) Single Voxel Placement

Figure 3. Representative anterior cingulate cortex (ACC) spectra from one control subject (3a) and one methamphetamine abuser (3b).

Figure 4.
Representative primary visual cortex (PVC) spectra from one control subject (4a) and one methamphetamine abuser (4b).

Figure 5.
Group Differences in Reaction Time (RT) performance on Spatial Stroop Task

R =0.64; p=.0001

Figure 6.
Correlation between Spatial Stroop Interference and NAA/Cr Levels in the Primary Visual Cortex

R =0.40; p= 0.02

Figure 7.
Correlation between Spatial Stroop Interference and NAA/Cr Levels in the Anterior Cingulate Cortex

Table 1

Demographic Characteristics of Study Participants

	Methamphetamine Abusers (n =51)	Non-Substance Using Controls (n =22)
Age, y, mean (SD)	38.2 (8.2)	39.5 (10.3)
Females	37	9
Subject's education, y, mean (SD)	12.9 (1.5)	14.3 (2.2) [†]
NART	106.9 (5.8)	113.6 (8.3) [†]
Right-handed	46	21
MA Use Variables		
Duration, y, mean (SD)	13.3 (7.3)	
Months Abstinent, mean (SD)	25.1 (31.01)	
Age of first use, y, mean (SD)	19.5 (6.9)	
Tobacco smokers	39	8
Past Alcohol Dependence	18	
Past Cocaine Dependence	13	
Past Cannabis Abuse	18	

[†] Significantly different from control group

Table 2

Median Reaction Times and Accuracy Rates for Trial conditions Across Groups

	M (SD)	M (SD)	M (SD)	
MA Abusers	<u>Incongruent</u>	<u>Congruent</u>	<u>Neutral</u>	<u>Conflict Errors</u>
	543.4 (94.9)	527.3 (92.1)	508.7 (91.2)	.05 (0.2)
Controls	<u>Incongruent</u>	<u>Congruent</u>	<u>Neutral</u>	<u>Conflict Errors</u>
	503.0 (59.6)	488.8 (61.3)	474.0 (61.3)	.01 (0.01)

Table 3

Magnetic Resonance Spectroscopy (MRS) metabolite values for 32 Methamphetamine (MA) abusers and 13 Controls.

Mean, (SD)	Methamphetamine Abusers (n =32)	Controls (n =13)
ACC-NAA/Cr	1.65 (0.23) [†]	1.82 (0.19)
ACC-Cho/Cr	1.30 (0.22)	1.31 (0.22)
ACC-Cho/NAA	0.79 (0.14)	0.73 (0.13)
PVC- NAA/CR	2.01 (0.27)	2.04 (0.28)
PVC- Cho/CR	0.65 (0.10)	0.65 (0.14)
PVC- Cho/NAA	0.33 (0.05)	0.33 (0.07)

[†] Significantly different from Controls, $p < .05$