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RESEARCH LETTER

MR spectroscopy in HIV and stimulant dependence

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INTRODUCTION

HIV infection and abuse of central nervous system (CNS) stimulants are both associated with brain damage and dysfunction. CNS stimulant overdose can lead to microinfarction, hemorrhagic lesions, and vasculitis (Bostwick, 1981; Cahill et al., 1981), and may impact frontostriatal systems. Investigations of HIV-infected (HIV+) individuals have demonstrated deficits in attention, speed of information processing, motor functioning, executive functioning, and learning efficiency. These deficits are consistent with frontostriatal involvement (Heaton et al., 1995; Martin, 1994). Given the rise in AIDS cases attributable to drug use at a time when the number of AIDS cases due to sexual transmission is stable or declining, it is critical to determine if drug use, especially CNS stimulants, potentiates HIV-related neuronal injury.

Magnetic resonance spectroscopy (MRS) provides a noninvasive approach to examine brain metabolites. Robust reductions in N-acetylaspartate (NAA), a putative marker of neuronal integrity, have been demonstrated in HIV+ individuals (Chong et al., 1994). Lowered NAA has also been related to poorer neuropsychological functioning in HIV+ groups (Meyerhoff, et al., 1997) and other brain disorders such as traumatic brain injury (Friedman, et al., 1998). Increases in choline (Cho) and myo-inositol (mI) have also been noted (Fründ et al., 1997; Laubenberger et al., 1996). Choline is a constituent of myelin and a precursor of acetylcholine. Increases in choline may reflect cell membrane degradation and ultimately demyelination, as seen in plaques of individuals with multiple sclerosis. Myo-inositol is found primarily in glial cells and is commonly elevated in neurodegenerative diseases such as Alzheimer's disease, Creutzfeld-Jakob disease, and alcoholism. In addition, mI is elevated in hy-perosmolar conditions including diabetes, renal failure, and hypernatremia. Elevations in mI may be the result of proliferation of glial cells following neuronal injury or death, enzymatic abnormalities in the phosphoinositide cycle, or osmoregulation of cells to maintain cell volume and protect protein structure. Chang et al. (1997) found increased creatine (Cr) in the white matter of abstinent stimulant users, but no proton MRS studies have examined the burden of both HIV infection and CNS stimulant dependence on neuropsychological performance.

This preliminary study utilized MRS to examine the additive effects of HIV infection and stimulant dependence on frontostriatal circuitry. HIV+ stimulant dependent individuals (HIV+/STIM+) were predicted to evidence decreased NAA compared to controls (HIV−/STIM−), and HIV+ nonusers (HIV+/STIM−). Seronegative stimulant dependent individuals (HIV−/STIM+) were predicted to fall at intermediate levels. Elevations in Cho and mI were expected in the HIV+/STIM+ group reflecting abnormalities in cellular integrity with smaller increases in HIV+/STIM− and HIV−/STIM+. Finally, consistent with the report by Chang et al. (1997), elevated Cr was predicted in the white matter of stimulant abusing groups.

METHODS

Research Participants

Seven HIV+/STIM+, 5 HIV+/STIM−, 3 HIV−/STIM+ and 5 HIV−/STIM− participants were recruited and tested at the San Diego HIV Neurobehavioral Research Center. Demographic characteristics of the groups are presented in Table 1. Participants with history of schizophrenia or other severe psychiatric disorder, opportunistic infection of the brain, HIV associated dementia, or head injury with a loss of consciousness greater than 30 min were excluded. Stimulant dependence was assessed using the Structured Clinical Interview for DSM–IV. One participant in the HIV−/

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Table 1. Demographic characteristics of participants by HIV and stimulant dependence status

	HIV−		HIV+	
Participant characteristic	STIM− ($N = 5$)	STIM+ ($N = 3$)	STIM− ($N = 5$)	STIM+ ($N = 7$)
Age (years)	43.0	39.3	40.4	42.3
SD	(8.9)	(6.5)	(6.3)	(7.7)
Education (years)	14.4	13.7	12.8	12.6
SD	(0.9)	(0.6)	(1.3)	(1.1)
Sex (% male)	80.0	33.3	80.0	57.1
Ethnicity (% non-White)	40.0	66.7	60.0	71.4
CD4 cell count	—	—	238.9	361.9
SD			(200.6)	(244.1)
% AIDS			80%	57%

STIM+ group met criteria for alcohol dependence. Two participants (1 in each STIM+ group) met criteria for marijuana dependence. All participants received comprehensive neuropsychological testing, with subsequent clinical ratings as described previously (Heaton et al., 1995).

Procedure

Spectra were acquired using a General Electric 1.5-T scanner (Signa 4.8) at the VA San Diego Healthcare System. Single voxel PRESS (TE 35 ms, TR 1.5 s) with voxels of interest in the anterior cingulate gyrus (20 × 20 × 20 mm), right anterior centrum semiovale (20 × 20 × 20 mm), and the right caudate nucleus (15 × 15 × 15 mm). Anatomic placement of the voxels was performed using T1-weighted axial and coronal localizers. The frontal lobe measures were based on 128 acquisitions, whereas 256 acquisitions were used for the caudate due to its smaller size.

Spectra were eddy current corrected, apodized, zero-filled, automatically phased followed by touch-up phasing, and referenced to creatine. Absolute quantitation techniques were employed to eliminate difficulty in interpretation of metabolite ratios and to provide a means of cross-study comparison. Absolute metabolite concentration was determined by scaling the signal to the transmitter gain and *a priori* calibration of signal at various coil loads using a phantom. For absolute calculations, institutional units of each metabolite were scaled to millimoles per liter of brain volume to conform with values reported for controls (Kreis et al., 1993).

RESULTS

In the predominantly gray matter region of the anterior cingulate gyrus, NAA was found to differ significantly between groups [$F(3,14) = 4.06$, $p < .05$]. Tukey follow-up tests for all pairwise comparisons revealed significantly lower NAA in the anterior cingulate gyrus of the HIV+/STIM+ compared to the HIV−/STIM− group. Less extreme reductions were evident among HIV+/STIM− and HIV−/STIM+ participants compared to HIV−/STIM− participants (see Figure 1). A similar, although not statistically significant, pattern of results was found in the predominantly white matter region of the anterior centrum semiovale [$F(3,14) = 0.91$, $p = .46$]. In the caudate, however, there was a trend toward lower NAA for only the two STIM+ groups [$F(3,9) = 3.53$, $p = .06$]. Reliable differences in Cho, Cr and mI were not observed.

Given the significant findings described above for the anterior cingulate gyrus, correlations were calculated between ratings of neuropsychological impairment (as described by Heaton et al., 1995) and NAA level in the anterior cingulate gyrus. One-tailed tests were performed, as poorer neuropsychological performance was predicted in participants with lower NAA levels. Statistically significant correlations were found for the following neuropsychological domains: abstraction–cognitive flexibility ($r = -.50$, $p = .01$); attention–concentration ($r = -.50$, $p = .01$); complex perceptual–motor ($r = -.40$, $p = .04$); learning ($r = -.38$, $p = .05$); sensory ($r = -.43$, $p = .03$); and global neuropsychological functioning ($r = -.38$, $p = .05$). The correlations for the verbal, memory, and motor domains were not statistically significant.

DISCUSSION

These preliminary data raise the possibility that stimulant dependence may potentiate HIV related neuronal injury, and that this damage is related to neuropsychological functioning. Specifically, NAA measured in the anterior cingulate gyrus was lowest in HIV+/STIM+, highest in HIV−/STIM−, and at intermediate level in HIV+/STIM− and HIV−/STIM+. We cannot determine whether this neuronal injury is reversible, perhaps reflecting dendritic changes, or irreversible, reflecting neuronal death. Only stimulant dependence seemed to be related to the level of NAA in the caudate nucleus. Although small sample size precludes speculating on regional differences in HIV and stimulant effects, this is consistent with animal studies of methamphetamine and cocaine that have demonstrated damage to this structure. Contrary to prediction, Cho and mI were not different between groups. Studies with larger samples will be necessary to determine whether the types of cell membrane changes reflected by elevations in Cho and mI are not present in HIV+/STIM+ groups, or whether our study simply lacked adequate power to detect them.

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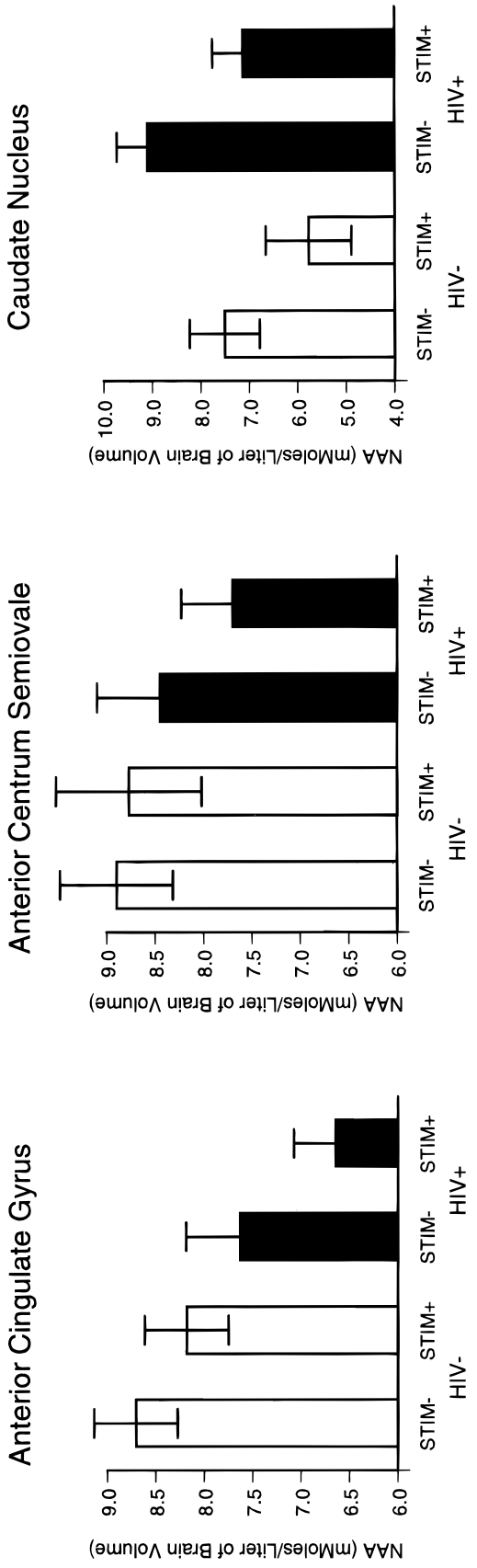

Fig. 1. N-acetylaspartate concentrations in anterior cingulate gyrus, anterior centrum semiovale, and caudate nucleus by HIV and drug status. Error bars represent *SEM*.

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