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Functional interactions of HIV-infection and methamphetamine dependence during motor programming

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Abstract

Methamphetamine (METH) dependence is frequently comorbid with HIV infection and both have been linked to alterations of brain structure and function. In a previous study, we showed that the brain volume loss characteristic of HIV infection contrasts with METH-related volume increases in striatum and parietal cortex, suggesting distinct neurobiological responses to HIV and METH (Jernigan et al., 2005). fMRI has the potential to reveal functional interactions between the effects of HIV and METH. In the present study, 50 participants were studied in four groups: an HIV+ group, a recently METH dependent group, a dually affected group, and a group of unaffected community comparison subjects. An fMRI paradigm consisting of motor sequencing tasks of varying levels of complexity was administered to examine blood oxygenation level dependent (BOLD) changes. Within all groups, activity increased significantly with increasing task complexity in large clusters within sensorimotor and parietal cortex, basal ganglia, cerebellum, and cingulate. The task complexity effect was regressed on HIV status, METH status, and the HIVxMETH interaction term in a simultaneous multiple regression. HIV was associated with less complexity-related activation in striatum, whereas METH was associated with less complexity-related activation in parietal regions. Significant interaction effects were observed in both cortical and subcortical regions; and, contrary to expectations, the complexity-related activation was less aberrant in dually-affected than in single-risk participants, in spite of comparable levels of neurocognitive impairment among the clinical groups. Thus, HIV and METH dependence, perhaps through their effects on dopaminergic systems, may have opposing functional effects on neural circuits involved in motor programming.

Keywords

FMRI; neuroimaging; dopamine; drug abuse

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1. Introduction

The rates of comorbid methamphetamine (METH) dependence and HIV infection are high as METH use is a risk factor for HIV infection and dependence is frequent among HIV-infected individuals (Woody et al., 1999) Both HIV and METH have been associated with mild-to-moderate neurocognitive impairment (Heaton et al., 2010; Heaton et al., 2004; Nordahl et al., 2003; Sacktor et al., 2002; Scott et al., 2007; Simon et al., 2010; Woods et al., 2005), with particular effects on executive functions, episodic memory, and psychomotor skills (Heaton et al., 2010; Scott et al., 2007) Comorbid HIV and METH may have additive adverse neurocognitive effects (Rippeth et al., 2004), particularly among immunosuppressed individuals (Carey et al., 2006). It has been suggested that the cellular basis for the additive effects of HIV and METH may, at least in part, be related to loss of calbindin and parvalbumin interneurons in the frontal cortex (Chana et al., 2006). Structural MRI studies suggest that HIV-related neurodegenerative changes result in volume loss in white matter, basal ganglia, and cortical structures (Archibald et al., 2004; Jernigan et al., 1993) as well as the cerebellum (Becker et al., 2011; Klunder et al., 2008; Sullivan et al., 2011). Methamphetamine dependence (METH) has also been associated with volume changes on MRI; however both increased striatal (Chang et al., 2005a; Jernigan et al., 2005) and parietal cortex (Chang et al., 2005a; Jernigan et al., 2005) volumes, and decreased gray matter volume in cingulate, limbic, and hippocampal regions (Thompson et al., 2004) have been reported. METH-related volume increases may represent compensatory neuroplastic responses to drug exposure, or inflammatory responses to METH-induced neural injury (Chang et al., 2005a; Jernigan et al., 2005). While the effects of HIV and METH are distinct and sometimes opposing, some additive effects have been reported using MR spectroscopic imaging. These include reductions in N-acetyl aspartate (NAA) and creatine in the basal ganglia, reductions in NAA in frontal white and gray matter, and *myo*inositol increases in the frontal white matter (Chang et al., 2005b).

Strong evidence links METH to damage within dopamine circuits. METH exposure in rodents has been linked with numerous changes in brain function and structure, including reduction of striatal and frontocortical dopamine transporters (DAT) (Robinson and Kolb, 1997), production of compensatory neuroplastic changes in the striatum (Robinson and Kolb, 1999), stimulation of microglial and astrocytic activation in striatum and parietal cortex (Thomas et al., 2004), and alteration of levels of parietal lobe NMDA receptors on glutamatergic neurons (Eisch et al., 1996; LaVoie et al., 2004; Pu et al., 1996). PET studies of METH dependent participants have also revealed alterations in both striatal and parietal lobe structures. Depletion of striatal DAT and reduced striatal metabolism have been observed; however global cerebral metabolism was shown to be increased in recovering methamphetamine abusers, and this increase was disproportionately due to a relative increase in parietal cortex, the severity of which predicted performance on a motor task (Volkow et al., 2001).

Given the prominence of HIV-related damage in striatum, several investigators have examined dopaminergic markers in this population as well (see Ferris et al. (2008), for review). Wang et al. (2004) observed reduced striatal DATs in participants with HIV-related dementia and DAT reduction was correlated with higher plasma HIV viral load. Decreased CSF dopamine (DA) has been reported in HIV+ individuals (Berger et al., 1994), and HIV-related dementia has been associated with reduced CSF homovanillic acid (Larsson et al., 1991) which is associated with dopamine levels in the brain. In postmortem material, HIV was associated with decreased DA levels throughout the basal ganglia and substantia nigra, and areas with highest levels of HIV-1 RNA exhibited the most severe reductions in DA (Kumar et al., 2009), suggesting that HIV may bear a direct relationship to dopamine reductions.

In summary, motor systems in the brain, and particularly dopaminergic circuits, are altered by both HIV and METH, and it is possible that comorbid HIV and METH could produce functional interactions in motor systems. Prior research indicates that alterations in brain metabolism and brain structures in dually affected groups are the result of unique, sometimes opposing effects in basal ganglia and parietal brain regions, but their impact on measures of brain functioning is less clear. It is possible that the combined exposure to HIV and METH could yield a pattern of alterations that reflect interactions rather than additive effects. We designed a motor switching task designed to probe the fronto-striatal circuit and sensorimotor functions to explore this. We hypothesized that functional interactions of HIV and METH would be detectable in the pattern of activity evoked by an fMRI paradigm designed to measure brain response to increasing motor task complexity. Using a cued motor programming task, we compared 4 patient groups, with and without a history of METH and HIV exposure, to identify the main effects of these factors and their interactive effects. We expected to see changes in the fronto-striatal system in both HIV and METH groups. Based on our previous structural findings we predicted that group effects of task-related BOLD effects would yield a relative reduction in activation in basal ganglia structures in HIV and reductions in parietal cortex activation in METH, while the dually exposed group would exhibit changes in both regions that would be disproportionately greater than expected from additive effects (i.e., significant interaction effects).

2. Methods

2.1. Participants

Participants were fifty volunteers recruited from the HIV Neurobehavioral Research Program (HNRP) at the University of California, San Diego as part of NIDA-funded Program Project focused on central nervous system effects of HIV and METH. The current sample was comprised of participants from 4 groups: community controls with neither of the risk factors, a group with HIV only, a group with a history of METH dependence only, and a group who were both HIV+ and recently METH dependent. HIV serological status was determined by enzyme linked immunosorbent assays (ELISA) plus a confirmatory test. METH participants met Diagnostic and Statistical Manual of Mental Disorders Version IV (DSM-IV; American Psychiatric Association, 1994) criteria for lifetime substance dependence, with methamphetamine abuse criteria met within the previous 18 months, as determined by the Composite International Diagnostic Interview (CIDI) and also must have been abstinent from METH for a minimum of 10 days confirmed by urine toxicology. Additional exclusion criteria for both METH groups included meeting DSM-IV criteria for the following: alcohol dependence within the last year; other drug dependence within 5 years of the evaluation; abuse within the year prior to the evaluation of drugs other than methamphetamine (e.g., cocaine, opioids); a remote (i.e., > 5 years) but significant history of alcohol or other drug dependence. Given the high frequency of comorbid alcohol or marijuana abuse and marijuana dependence in methamphetamine users, individuals with such histories were not excluded from either study group. Participants with a history of METH dependence were primarily recruited from drug treatment programs in the San Diego area, while those participants without a history of METH abuse were recruited from the larger San Diego community through the use of flyers and advertisements at community events. All participants gave written consent prior to enrollment and again prior to the MRI procedure. All procedures were approved by the Human Research Protection Program of the University of California, San Diego.

2.2. Demographics

The four groups were well matched on age, and years of education, although they were somewhat different in ethnicity. The control group (seronegative, METH negative) included

fewer Caucasian participants relative to the other 3 groups (Table 1). All participants except one subject in the METH group were male. The control group also had significantly higher scores on cognitive indices relative to each of the other groups (p<.05) based on the average T-score from the neurobehavioral assessment (Table 1). Histories (Hx) of other abuse or dependence to other drugs, lifetime major depression and attention hyperactivity disorder are also reported in Table 1.

The HIV and dually affected HIV/METH groups did not differ significantly on nadir CD4 T-4 cells, current CD4 T-4 cells, estimated years of infection, or HIV viral load in either plasma or CSF (p > .10). The two METH groups did not differ significantly on estimated total quantity of METH use, recency of use, or on age at first use (p > .10), although there was a tendency for the METH-only group to report more drug use both in quantity and duration (see Table 2). Both METH groups had higher rates of nicotine use and the METH only group smoked considerably more (quantity and duration) than smokers in the other groups.

2.3. Procedures

Participants were referred for neuroimaging after a detailed medical, psychiatric and substance use history was obtained, a neuromedical examination was performed (including a lumbar puncture and blood draw), and a neuropsychological battery was administered (see Rippeth et al., 2004). Substance use and psychiatric diagnoses were obtained from the CIDI. Methamphetamine use characteristics (i.e., lifetime amount used in grams, total duration of use, age at first use, and recency of use) were obtained via a semi-structured timeline follow-back interview (see Rippeth et al., 2004, for more detail).

Subjects were prescreened for MRI safety and then further screened in detail by the neuroimaging investigators for metal or other exclusions for MRI. Subjects were given a urine toxicology screen (Rapid Response, BTNX Inc.) at the scanner and were excluded from the study if they were positive for stimulants including amphetamine, methamphetamine, or cocaine. Six subjects were excluded due to positive urine toxicology. There were 3 from the METH only group, 2 from the dually affected group and one HIV subject. Data from two additional subjects in the METH only group were excluded because of severe motion artifacts.

2.3.1. Behavioral paradigm—The paradigm was presented using E-prime presentation software (Psychological Software Tools, Pittsburgh, PA) and responses were recorded on a Lumina 4-button optical response system (Cedrus, San Pedro, CA) held in the right hand. The task required visually-cued switching between motor subtasks, each of which required subjects to press the response buttons in a particular sequence. The subtasks varied in motor complexity and included 1) tapping a single key repeatedly with the index finger (i.e., 1,1,1,1,1,..., where the index finger is finger 1); 2) pressing four sequential keys in a repeating sequence with the four fingers in order (1,2,3,4,1,2,3,4.); 3) pressing the four keys in an alternating finger pattern (1,3,2,4,1,3,2,4,...); or 4) resting the hand. The cue stimuli were single words (TAP, SEQUENCE, ALTERNATE, REST) presented visually on a back projection screen. Cues were present continuously throughout the 7-minute task, but changed in a pseudorandom order at intervals varying in duration from 3 to 9 seconds. Each subtask was presented for equal amounts of time during the task and each subject got the cues in exactly the same order. Blocks of motor sequence cues were interleaved with blocks of rest. Thus subjects were required to switch tasks at frequent, and unpredictable, intervals. Participants were told to execute the subtask sequences as quickly as possible without making mistakes.

Participants were trained on the behavioral paradigm immediately prior to the imaging exam, and were required to demonstrate accurate performance for a minimum of two complete cycles through the 3 motor subtasks. During imaging, examiners viewed the responses on a display in the observation room to verify that the tasks were being executed correctly. Behavioral data were further examined to ensure no more than 2 of the subtask trials were performed incorrectly. No subjects were excluded on this basis.

Following the fMRI paradigms subjects were asked to lie still and view nature scenes while the imaging exam was completed. The behavioral data collected via E-prime were scored for total number of presses during each of the subtask conditions and examined for general accuracy as described above.

This paradigm was chosen because it may reflect changes in complex patterns of motor shifting. It reliably activates the fronto-striatal regions as well as the sensorimotor association areas that were implicated in structural studies of HIV and METH.

2.3.2. Imaging parameters—Imaging was performed on a 3T GE Excite system with an 8 channel head coil at the UCSD Center for Functional Magnetic Resonance Imaging. The fMRI sequence was a whole brain sagittal gradient recalled sequence with 36 slices collected from left to right, 140 epochs, repetition time (TR)=3 ms, slice thickness of 4mm, and 25 cm FOV. The corresponding field maps were 36 sagittal 2dflash slices collected from left to right. Structural images were collected for localization and included a 3D sagittal SPGR volume, with slice thickness 1.2 mm, echo time (TE) =3 ms, and TR=7 ms.

2.3.3. Individual BOLD data processing—FMRI data were processed and analyzed with Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). The first 2 TRs were eliminated to exclude time before stabilization. Remaining images were corrected for motion across time using the section that required the least rotation, and epochs with significant motion remaining were detected by visual inspection and removed. The images were then unwarped using field maps with software developed by the UCSD Center for fMRI. Both structural and functional data were transformed to Talairach/Tournoux space. The functional volumes were then co-registered to the structural T1 volume. Gaussian blurring using a 5 mm full width half maximum (FWHM) kernel was applied to the BOLD data. Skull stripping was achieved with in-house software and remaining image values were normalized by the median across time. Deconvolution analysis of the contrast of interest (complexity) was performed with AFNI and included the motion parameters from the motion registration described above. The main contrast of interest was the effect of increasing levels of task complexity, progressing from tapping to sequencing to alternating, modeled as a linear effect.

2.3.4. Group BOLD data processing—Structural T1s were merged together for localization. One sample t-tests were performed for each group comparing the complexity effect to zero, using the fit coefficients from the deconvolution analysis. This preliminary analysis revealed the distribution of large complexity effects common to all groups. To address the principal hypotheses, voxel-wise, multiple linear regression analysis was performed using HIV, METH, and the interaction term (HIVxMETH) as independent predictors of the BOLD complexity response. Clusters were considered significant if each uncorrected voxel was significant at p<.025 and had a volume of at least 25 contiguous voxels (1526 mm^3). This cluster size was obtained using a Monte Carlo simulation (performed in AFNI) to control for a family -wise at .015. Contiguity was defined as voxels sharing a corner. These thresholded and clustered volumes were produced for each of the predictors: HIV, METH, and HIVxMETH.

In post hoc analyses, the significant clusters in the HIV by METH interaction volume were used as regions of interest, and the mean fit coefficients for the complexity effects were extracted for each individual so that these could be plotted by group to illustrate the form of the observed interaction effects.

3. Results

3.1. Behavioral Results

An analysis of variance revealed that rate of responses varied by task ($p<.001$) as expected, i.e., number of responses decreased with increasing task difficulty (see Figure 1). However, there was no significant effect of group, or group by task interaction. An analysis of individual group differences by task showed that the HIV+ only group was slower than the control group during the TAP condition ($p<.05$). Left handed subjects did not differ in response rates to right handed subjects.

3.2. fMRI Results

Within-group t-tests of the complexity effect revealed large areas of positive activation which included clusters in the striatum, sensorimotor and parietal cortex, cingulate, and cerebellum in all four groups (Figure 2), representing increased activation with increasing sequence complexity while response rate decreased with task complexity. Multiple regression of the two risk factors (HIV, METH) and the interaction (HIVxMETH) produced distinct patterns of complexity-related activation for each of the three predictors. All significant areas of activation are summarized in Table 3.

As predicted, HIV was associated with less complexity-related activation in bilateral striatal structures (Figure 3 HIV C). There were also significant, HIV-related reductions of activation in the cerebellum and in the right precentral gyrus (Figure 3 D and A respectively). In contrast, there was evidence for greater complexity-related activation in one cluster in right superior frontal cortex.

Also as predicted, METH was associated with less complexity-related activation in sensorimotor and parietal cortex (Figure 3 A and B), and similar decreases were also observed in cerebellar vermis regions (Figure 3D). In contrast, the METH group showed more task-related activation in two clusters in the right hemisphere: in the cerebellum and in the temporal lobe.

Significant HIVxMETH interaction effects occurred in 6 clusters: caudate nucleus, frontal cortex, sensorimotor/parietal cortex, insular/temporal cortex, superior parietal cortex and cerebellum (Figure 3 right panel). In contrast to expectations, however, these interactions reflected a blunting of the main effects of HIV and METH; i.e., the dually-affected participants exhibited smaller effects in these regions than predicted from the main effects (Figure 3). To better illustrate the nature of these effects, the six clusters exhibiting significant HIVxMETH interactions were extracted and applied to individual activation maps. The mean fit coefficient (i.e., complexity-contrast coefficient) for each of these clusters was computed for each individual. Example scatterplots of the individual subjects' cluster means for the three largest HIVxMETH regions are shown by group in Figure 4. Notably, the dually-affected participants differ less from controls relative to the HIV and METH groups. In general, the HIV- and METH-related decreases in complexity-related activation were significantly less pronounced in the dually affected participants. Additionally, there were two significant clusters in which activation patterns indicated opposing effects compared to the predominant pattern. That is, the single risk factors produced increased complexity-related activation relative to controls and the interactions

reflected significantly smaller increases in the dually affected participants in the right frontal and left parietal cortices.

3.2.1. Post hoc analysis of drug exposure—Although the reported methamphetamine use was not significantly different between groups, the drug use reported by the METH-only group was somewhat higher than that in the HIV+METH group. Consequently, we performed additional analyses to determine whether the blunting of METH effects observed in dually-affected participants might be associated with higher METH exposure in the METH-only group. Accordingly, we repeated the voxel-wise regression analyses using either the (log transformed) estimated total quantity of methamphetamine use or the (log transformed) estimated total days of use to model the main effect of METH (instead of the binary variable coding for METH.) As in the earlier analysis, HIV status and an HIVxUse interaction term were also included in these models. The clusters exhibiting HIVxUse interactions were essentially identical to those obtained using the METH group term for both. Mean fit coefficients from the original parietal HIVxMETH interaction cluster (ROI) also showed no correlation with the use variables (p> 0.72) suggesting that degree of complexity-related activation within METH users was not related to severity of METH exposure.

4. Discussion

In this study, we compared participant groups with and without METH exposure and HIV infection on a cued motor programming task to identify differences in the degree of BOLD activation elicited by increasing task complexity. As expected, there was comparatively less complexity-related activation in basal ganglia in the HIV group, and in parietal regions in the METH group. Surprisingly, the significant interaction effects we observed suggested that these HIV and METH effects were blunted in the dually affected participants. This occurred despite comparable response rates on the task and comparable performances on neuropsychological assessments. Thus, the observed effects of combined HIV and METH on BOLD responses to motor task complexity suggest opposing effects of these factors at a neural level.

In general, the main effects of HIV observed here are consistent with earlier studies. Reports of prominent HIV-related damage in striatum (Becker et al., 2011; Jernigan et al., 1993; Jernigan et al., 2005), as well as HIV-related impairment on motor and psychomotor tasks (Berger and Arendt, 2000; Bogdanova et al., 2008; Chao et al., 2003; Gonzalez et al., 2008), are consistent with the observation here that HIV-infection is associated with a diminished striatal response to the demands of complex motor tasks. Effects in cortex and cerebellum are also consistent with earlier reports of HIV-related damage in these areas (Becker et al., 2012; Jernigan et al., 2005; Sullivan et al., 2011).

As predicted, we observed the largest main effects of METH in somatosensory and superior parietal areas, consistent with our previous study of parietal lobe volume increases in METH participants (Jernigan et al., 2005). These alterations may be mediated by effects of METH on striatal dopamine and glutamate receptors; i.e., dopamine release from nigrostriatal terminals may modulate activity in efferent striato-cortical pathways by disinhibiting thalamocortical circuits (Gross and Marshall, 2009). Alterations in these circuits associated with chronic METH use may lead to the reduced functional response in somatosensory and superior parietal cortices observed in the present study.

The most surprising findings in the present study were the unexpected interaction effects associated with comorbid HIV infection and METH dependence. Contrary to our predictions, main effects appeared to be blunted in the dually-affected participants. This

appeared to be the case both in regions exhibiting significant main effects of HIV (i.e., striatum) and in regions exhibiting significant main effects of METH (i.e., parietal cortex). One possibility for the reduced effects in the dually affected participants could occur because the participants in this group either suffered from less severe HIV-related disease than the other HIV+ participants. However, we found that HIV-disease markers in the dually affected participants were not significantly different from those in the HIV+ group, which included present and nadir CD4 T-4 cell counts, estimated duration of infection, CSF and plasma levels of HIV-RNA, and antiretroviral (ARV) treatment. In post-hoc analyses it was also confirmed that the ARV treatment regimens taken by the two HIV+ groups were similar in CNS penetration index. Thus it is unlikely that the smaller effects in the dually affected individuals were due to less severe HIV-related disease.

Another possibility for the interaction effects could be that this group had experienced less METH exposure relative to the METH-only participants. Estimates of severity of prior use exhibited a large degree of variability in both METH-only and dually affected groups. Although the two groups did not differ significantly on these indices, the METH-only group appeared to have higher reported levels of use, both as indexed by total estimated exposure and by estimates of frequency of use. We therefore tested for interaction effects by modeling METH, not as a binary variable, but rather as a continuous estimate of lifetime exposure in grams of METH, or using the estimate of total days used. We reasoned that any differences attributable to intensity of METH exposure would contribute to the main effect of METH in these analyses and would not spuriously inflate the HIVxMETH effects. Surprisingly, modeling the effects of METH with these continuous variables of use instead, resulted in almost no change in the interaction effects. Thus, although the participants varied widely in their METH use, this did not account for the more normal levels of complexity-related activation observed in dually-affected participants of the current study.

These findings thus raise the possibility that opposing effects of HIV and METH occur at the neural level in some circuits. Strong evidence links release of high levels of vesicular dopamine to METH induced neurotoxicity in striatal neurons, and there is also evidence that microglial activation plays a mediating role (Thomas et al., 2009). If, consistent with evidence cited above, striatal dopamine levels are downregulated in HIV-infection, then HIV could, in some respects, act like agents such as tyrosine hydroxylase inhibitors, which are protective against METH-induced neurotoxicity in striatum (Thomas et al., 2009) as well as effects in cortex linked to this toxicity (Gross and Marshall, 2009). Conversely, in the relatively DA depleted striatum of HIV-infected individuals, METH exposure may in some cases have the effect of partially restoring DA levels. Thus, comorbid HIV and METH may to some degree mitigate specific HIV- and METH-related alterations in striatum, as well as METH-related alterations in parietal cortex.

These results differ from an additive model suggested by other studies such as the spectroscopy study which found an additive effect of HIV and METH on metabolite abnormalities (Chang et al., 2005b). These differences could be attributed to methodological or cohort differences in the studies. Further studies using multi-modal imaging techniques in the same subjects may help disentangle these complexities but this study adds to the evidence that HIV and METH may affect these systems differently in combination.

This study has a number of limitations. The sample sizes are fairly small which limited the number of covariates that could be modeled to those of greatest interest for the current study, although other potentially important factors need further inquiry. Although we examined the effects of methamphetamine exposure (duration and quantity) these measures are all self report and the two methamphetamine groups were not matched on these variables. The effects of acute and chronic methamphetamine exposure, and the recency of

use could be quite different between groups although this could not be fully examined in this study. It may also be important for these interaction effects whether HIV precedes methamphetamine use (or the reverse) and the timing of their comorbidity. Nicotine use was more prevalent in the both METH groups but was considerably higher in the METH only group. Finally, possible morphometric changes in the group were not used as covariates and could affect activation patterns.

Further studies are needed to confirm these unexpected results in human HIV-infected and METH dependent groups, and to pursue the mechanisms that may mediate functional interactions in striato-thalamo-cortical circuits of these frequently co-occurring human risk factors.

Acknowledgments

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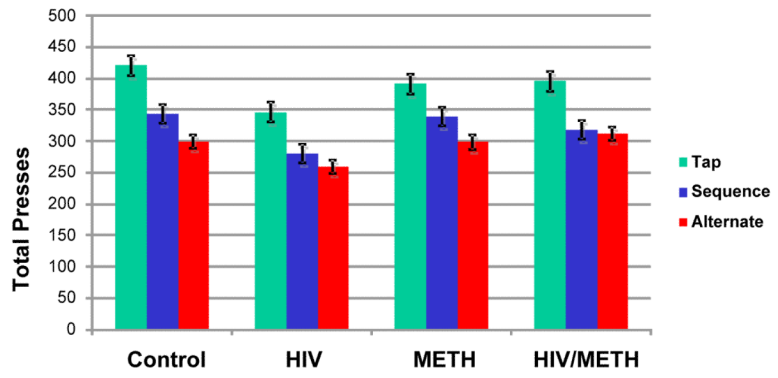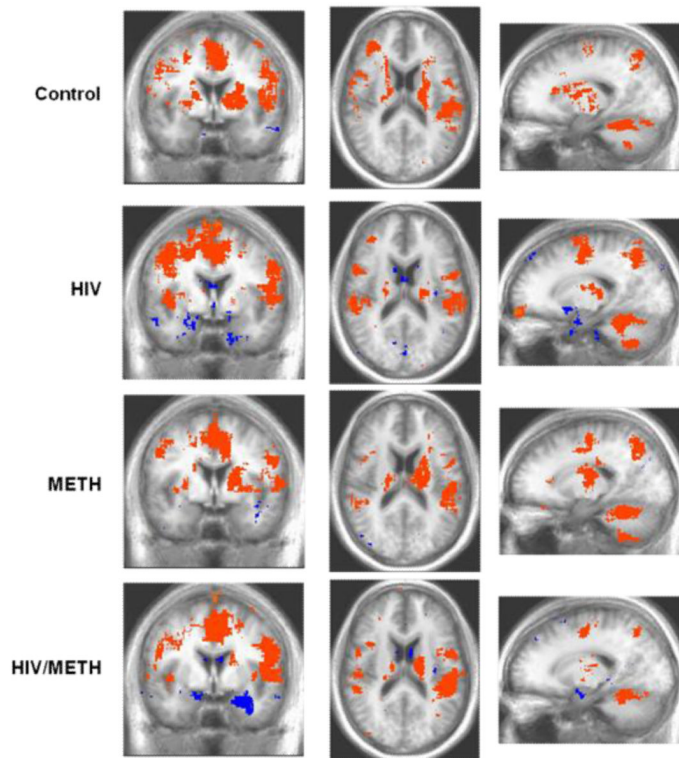
Figure 1.
Behavioral Results

Figure 2.
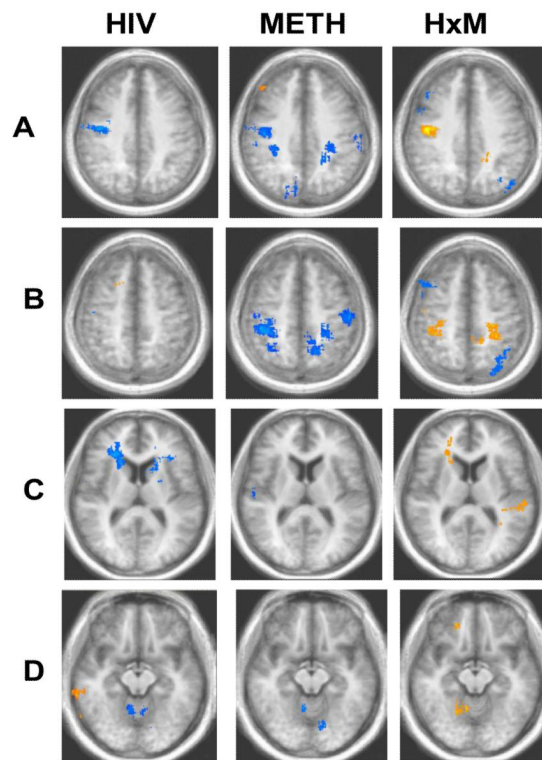Single group t-test of complexity related activation
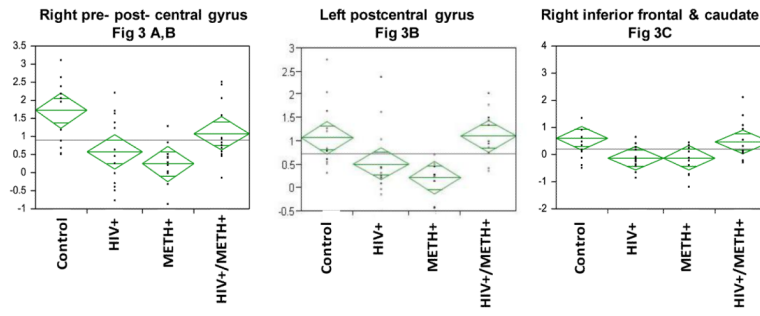
Figure 3.
Significant clusters by risk factor

Figure 4.
Mean individual fit coefficients for 3 interaction clusters by group

Table 1

Demographics

	Control	HIV	METH	HIV/METH
N	12	13	12	13
Age	40.3 (11.6)	38.0 (8.5)	38.2 (10.4)	35.6 (6.9)
Education	13.5 (2.1)	13.0 (1.1)	12.8 (1.8)	12.9 (2.4)
Handedness R/L	10/2	12/1	11/1	10/3
Ethnicity (% Caucasian)	33	77	92	62
Average T	53.8 (4.3)	47.1 (7.2)	48.7 (4.2)	49.5 (5.2)
Impaired (%)	0.0	23.1	25.0	15.4
Nicotine current (%)	17	15	83	54
Hx Alcohol (%)	42	54	83	77
Hx Cannabis (%)	0	15	67	46
Hx Cocaine (%)	0	15	17	23
Hx Opiates (%)	0	0	17	8
Hx Other Drugs (%)	0	0	0	8
Hx Major Depression (%)	8	70	25	46
Hx ADHD (%)	8	15	8	15

Average T is the mean across neurobehavioral tests

Table 2

HIV and METH related characteristics

HIV Variables	n	Nadir CD4	Current CD4	Log Plasma HIV Viral load	Log CSF HIV Viral load	Years HIV+	ARV use Current/ Never/Past
HIV	13	308.3 (197.8)	508.6 (211.5)	2.6 (1.1) n=11	2.0 (0.5) n=10	6.9 (7.7) n=11	8/5/0
HIV/METH	13	329.8 (242.3)	470.7 (214.7)	2.8 (1.4)	2.3 (1.1) n=12	8.7 (5.3) n=12	7/5/1

METH Variables		Total Meth use (grams)	Total Meth use (days)	Age at first Meth use	Last Meth Use (days)
METH	12	4658.8 (6966.4)	3154.3 (3283.4)	20.7 (7.6)	261.3 (185.9)
HIV/METH	13	1940.1 (2544.6)	1916.8 (1556.2)	24.8 (7.6)	153.9 (185.2)

Table 3

Brain Regions showing complexity associated activation related to the three predictors in a simultaneous multiple regression. Cluster size 25 voxels , p<.015

Brain region	Volume mm³	Mean T	Talairach (x,y,z)	Panel in Figure 3
Reduced contrast related to HIV				
Left caudate, putamen and accumbens	5698	−2.306	35, −27, −14	C
L amp; R cerebellum (declive)	2569	−2.494	15, 65, −18	D
Right caudate, right medial frontal gyrus	2445	−2.45	−26, −29, 11	C
Right pre-central gyrus	2423	−2.517	−47,13,42	A
Increased contrast related to HIV				
Right superior frontal gyrus	1940	2.427	7, −7, 66	B
Reduced contrast related to METH				
Right pre and post central gyrus, IPL	10814	−2.569	−34, 36, 49	A,B
R amp; L cerebellum superior (dentate)	5889	−2.571	−4, 47, −4	A, D
Left precuneus, cingulate	4937	−2.506	19, 57, 45	A,B
Left post-central and IPL	4232	−2.429	50, 24, 51	A,B
Increased contrast related to METH				
Right cerebellum (VIII)	2636	2.307	50, 24, 51	Not shown
Right superior and middle temporal gyrus	1850	2.386	−64, 28, −1	B
Increased contrast related to HIVxMETH interaction				
Right pre and postcentral gyrus	3832	2.574	−43, 13, 41	A, B
Left postcentral gyrus	3426	2.525	21, 28, 48	B
Right inferior frontal gyrus and caudate nucleus	1690	2.345	−28, −38, −1	C
Left superior temporal gyrus and insula	1600	2.349	36, 32, 16	D
Decreased contrast related to HIVxMETH interaction				
Right mid and superior frontal gyrus	3335	−2.442	−46, −13, 43	B
Left superior parietal gyrus, precuneus	2039	−2.284	26, 76 ,49	A, B

Talairach coordinates indicate the location of the maximum intensity voxel within the cluster