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Abstract# 499

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Mitochondrial Injury and Cognitive Function in HIV Infection and Methamphetamine Use

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Background

- Mitochondria carry copies of its genome and are critical in providing energy for cellular processes in the central nervous system (CNS).[1]
- Accumulation of damaged mitochondrial DNA (mtDNA) is associated with many neurodegenerative diseases.[2]
- The 4977bp "common deletion" is a significant manifestation of mtDNA damage (**Figure 1**)[3].
- HIV infection and methamphetamine (METH) abuse both may cause damage to mtDNA and possibly lead to neurocognitive morbidity.[4]

Objective

To characterize the relationship between HIV infection, METH use, and mitochondrial injury.

Methods

- We obtained brain tissue from four brain regions from the National NeuroAIDS Tissue Consortium (NNTC): a) frontal lobe, b) frontal BA8, c) middle frontal gyrus, and d) parietal lobe, with associated demographic and neurocognitive data.
- Subjects were divided into 3 groups: a) HIV-infected with evidence of METH use (METH+, n=9), b) HIV-infected with no history of METH use (HIV+, n=11), and c) HIV negative controls (HIV-, n=28). For a subset of individuals, we collected both parietal and frontal lobes.
- We quantified levels of mtDNA and the relative proportion of mtDNA carrying the "common deletion" in brain tissue (white and gray matter) by droplet digital PCR (ddPCR).
- The Global Deficit Score (GDS) was used as a measurement of neurocognitive performance, defining neurocognitive impairment as having a GDS ≥ 0.5.[5]
- Differences between study groups were assessed either by t-test (independent data) or mixed-effects regression analyses (dependent data).
- Associations between continuous variables were assessed by fixed-effects or mixed-effects regression analyses according to independence of the data.
- All statistical analyses were performed in R statistical software.

Acknowledgments

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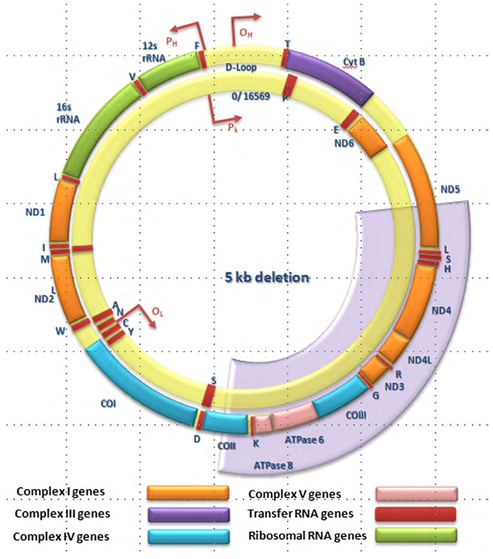
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Table 1. Participant characteristics

	HIV- (n=28)	HIV+ (n=11)	METH+ (n=9)	p-value*
Ethnicity (Hisp:Not Hisp)	7:21	2:9	1:8	0.89
Age	50.5 (44.8-58.5)	45 (39.5-51.5)	46 (44-50)	0.19
CSF HIV RNA Levels (log_{10} copies/mL)	-	2.6 (1.53-3.12)	1.70 (1.28 (2.26)	0.25
Proportion of detectability HIV RNA in CSF (<50 copies)		3/11	5/9	0.36
Plasma HIV RNA Levels (log_{10} copies/mL)	-	2.50 (1.96-5.66)	2.95 (2.65-4.88)	0.59
Proportion of detectability HIV RNA in plasma (<50 copies)		3/11	0/9	0.22
CD4 absolute counts	-	53 (30.5-104)	25 (7-104)	0.37
GDS	-	0.74 (0.47-1.27)	0.54 (0.23-1.84)	0.90

Table 1: Characteristics of our study participants. Median values are shown for each study group. *Represent the p-value of a double-tailed Mann-Whitney or a Fisher test.

Figure 1. Diagram of the mitochondrial "common deletion"



Results

Figure 2. Levels of mtDNA and mitochondrial injury are higher in the white matter of the middle frontal gyrus

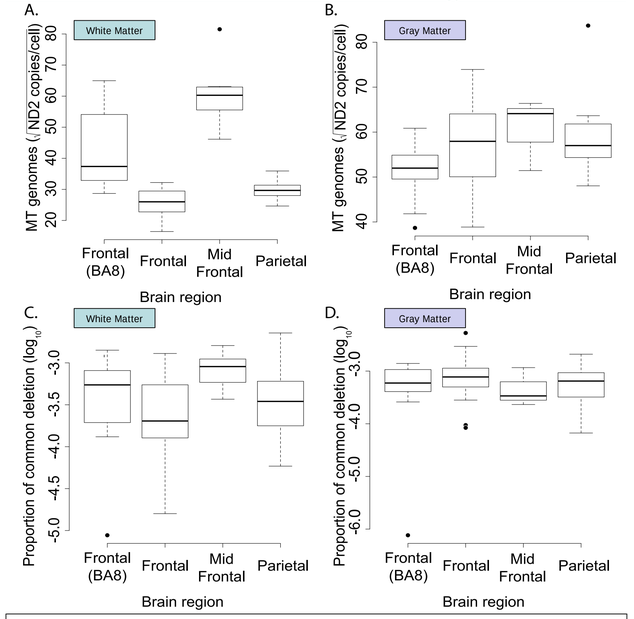


Figure 2: (A, B) Levels of mtDNA per cell and (C, D) the abundance of the "common deletion" in different brain regions in white and gray matter. Significant differences in levels of mtDNA and the abundance of the "common deletion" were seen mostly in white matter. Additionally, the middle frontal gyrus showed the highest levels of mtDNA and mitochondrial injury.

Table 2. MtDNA damage is associated with better neurocognitive function only in METH users

	Association	R^2	p-value
GDS	-	0.88	<0.01
CSF HIV RNA Levels	+	0.99	<0.01
PL HIV RNA Levels	-	0.85	<0.01
CD4 Counts	-	0.99	<0.01

Table 2: Higher abundance of the "common deletion" was associated with lower GDS, higher CSF HIV RNA levels, lower plasma (PL) HIV RNA levels, and lower CD4 counts in a multivariate analysis, while adjusting for age and brain region. These associations were only found in the METH+ group.

Figure 3. Levels of mtDNA and mtDNA damage in white matter are lower in METH users, and mtDNA damage is associated with age

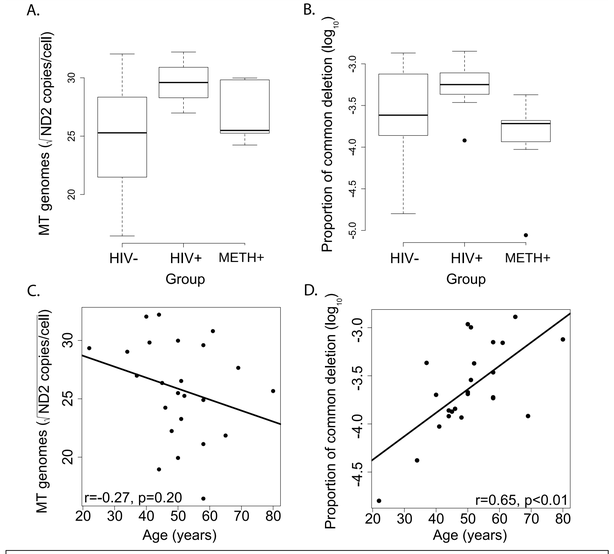


Figure 3: (A) HIV-infected individuals (HIV+) had significantly higher levels of mtDNA per cell compared to HIV negative (HIV-) control, as well as (B) had higher abundance of the "common deletion" compared to METH (METH+) users. (C) While there was no association between the levels of mtDNA per cell and age, (D) higher abundance of the "common deletion" was associated with increasing age.

Conclusions

- When comparing brain samples from four brain regions, levels of mtDNA and mitochondrial injury were highest in the white matter of the middle frontal gyrus (**Figure 2**).
- Higher abundance of the "common deletion" was associated with increasing age (**Figure 3**).
- MtDNA damage was also associated with better neurocognitive function only in METH users (**Table 2**).
- METH use appears to have a protective effect on mitochondrial injury. METH use has been shown to increase autophagy and mediate neuroprotection at low doses.[6]