Neurocognitive correlates of miRNA expression in the CNS of HIV positive subjects with a history of methamphetamine abuse

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Background

- A growing body of evidence indicates that microRNAs are important regulators of neuronal and brain function[1]
- There may be links between changes in microRNA expression and neuronal function[2]
- Long-term infection with HIV leads to neurocognitive changes and associated cellular and gene expression changes in the central nervous system[3]
- Methamphetamine abuse among HIV-positive individuals represents a "double epidemic" affecting neurobehavioral outcomes[4]

Aims

- To assess differential expression of microRNAs in the Frontal Cortex of HIV-positive individuals with a history of Methamphetamine Abuse.
- Hypothesize that a set of microRNAs are differentially regulated and whose expression correlates to neurocognitive domains and clinical parameters.

Methods

Features of the Study Groups[3]

Table 1. Features of the Study Groups

Group	N	Mean BDI	(SD)	Mean PM hr	(SD)	Mean Age yr	(SD)
Control	5			21.0	(11.9)	38.0	(14)
HIV	6	11.6	(5)	15.2	(16.3)	42.1	(5.7)
METH	5	15.6	(6.7)	19.6	(16.0)	42.1	(11.5)

BDI - Beck's Depression Inventory, PM hr - postmortem interval, SD - standard deviation

Table 2. Neurocognitive Outcomes of the Study Groups

Group	Mean GDS	(SD)	Mean SIP_DS	(SD)	VERBAL_DS	(SD)	LEARN_DS	(SD)	MEMORY_DS	(SD)	EXEC_DS	(SD)	WRKMEM_DS	(SD)	MOTOR_DS	(SD)
Control																
HIV	1.23	0.79	1.78	(1.4)	0.83	(1.0)	0.50	(0.8)	0.58	(0.4)	1.67	(0.9)	1.08	(1.0)	2.00	(1.4)
METH	0.68	0.58	0.73	(0.6)	0.20	(0.4)	0.60	(0.9)	0.70	(1.3)	0.50	(0.7)	0.60	(0.5)	1.60	(1.5)

GDS - Global Deficit Score, SIP - Speed of information processing, DS - Deficit Score, EXEC - Executive functions, WRKMEM - Attention/Working memory, SD - standard deviation

Table 3. HIV Clinical Features of the Study Groups

Group	CD4	(SD)	Mean NCD4	(SD)	Mean Log (PLA_RNA)	(SD)	Mean Log (CSF_RNA)	(SD)
Control								
HIV	53.5	(62.6)	30.67	(48)	3.76	(1.6)	1.94	(0.3)
METH	13.8	(11.5)	13.00	(12)	4.66	(1.3)	3.02	(1.2)

CD4 - CD4+ T-cells per mL, NCD4 - lifetime nadir CD4, PLA_RNA - Plasma viral RNA copies per mL, CSF - cerebrospinal fluid

Procedure

1. Isolate RNA from Frontal Cortex
2. TaqMan - based microRNA Array (380 microRNAs)
3. Quantify expression
4. Compare expression among the three groups (Mann Whitney U)
5. Test for correlation of expression with Neurocognitive and Clinical parameters

Results

Hypothesis Testing - Differential Expression by Group

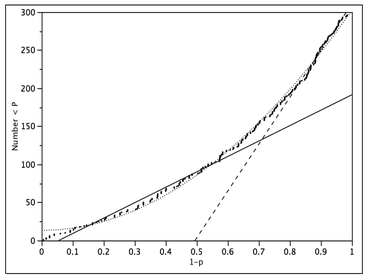

Figure 1. P-plot indicates non-random distribution of p-values from 296 hypothesis tests[5]

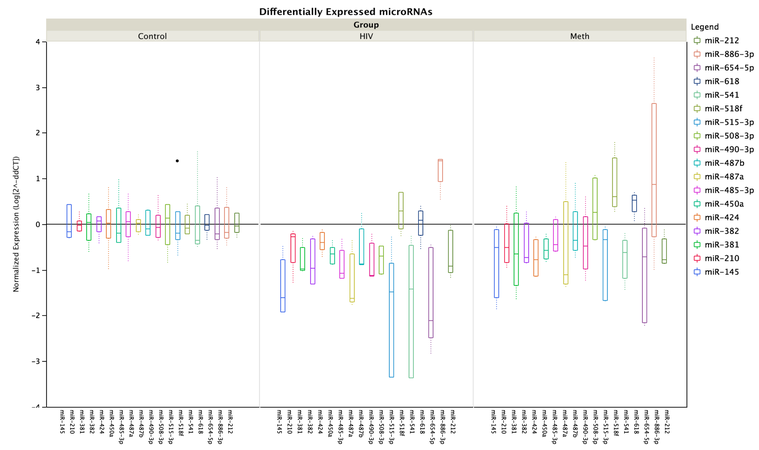

Figure 2. Generally, lower expression in HIV or Meth Groups if significantly different.

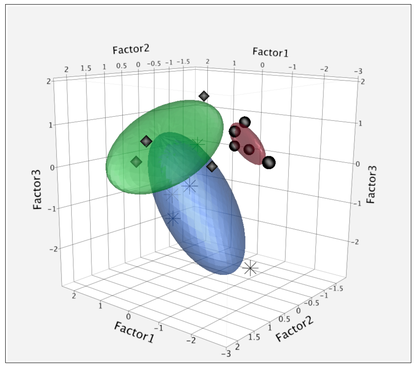

Figure 3. Principal components analysis indicates distinct miR profiles among the three groups.

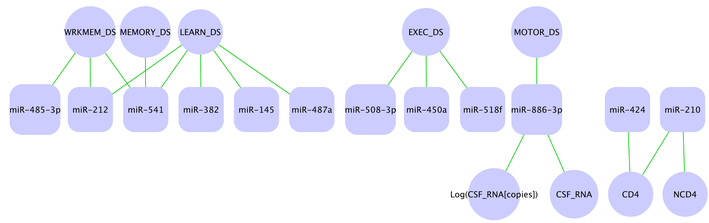

Figure 4. Visualization of micoRNA and clinical correlates.

Correlation Analysis - MicroRNA Expression Compared to Clinical Variables

Table 4. Neurocognitive and Clinical Correlates to miR Expression in the Frontal Cortex

Variable	by Variable	Spearman ρ	Prob>|ρ|
Neurocognitive Variables			
EXEC_DS	**miR-450a**	0.6523	0.0409
EXEC_DS	**miR-508-3p**	0.6461	0.0436
EXEC_DS	**miR-518f**	0.8697	0.0011
LEARN_DS	**miR-145**	-0.6806	0.0303
LEARN_DS	**miR-212**	-0.7838	0.0073
LEARN_DS	**miR-382**	-0.6394	0.0465
LEARN_DS	**miR-487a**	-0.8663	0.0012
LEARN_DS	**miR-541**	-0.8113	0.0044
MEMORY_DS	**miR-541**	-0.7694	0.0093
MOTOR_DS	**miR-886-3p**	0.7245	0.0178
WRKMEM_DS	**miR-212**	-0.702	0.0236
WRKMEM_DS	**miR-485-3p**	-0.6376	0.0473
WRKMEM_DS	**miR-541**	-0.7149	0.0201
Clinical Variables			
CD4	**miR-210**	-0.7927	0.0062
CD4	**miR-424**	-0.7683	0.0094
CSF_RNA	**miR-886-3p**	-0.8795	0.004
Log(CSF_RNA)	**miR-886-3p**	-0.7394	0.036
NCD4	**miR-210**	-0.7693	0.0093

MicroRNA expression was tested for correlation with neurocognitive and clinical variables using Spearman's rho test. Significant correlations are shown.

Conclusions

- Learning, Memory, Working Memory, and Executive Functioning Deficits correlate with micoRNA expression in the CNS of HIV-infected individuals.
- MiR-212 and miR-541 may be potential molecular mediators of neuronal dysfunction in long-term HIV-infection. MiR-210 and miR-424 may be indicators of immune function.

References

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3. Carey, CL et al. "Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection." J Clin Exp Neuropsychology. 26:3:307.
4.Chana, G. et al. "Cognitive deficits and degeneration of interneurons in HIV+ methamphetamine users." 35:3:331.