

Methamphetamine and the Brain: Three Tales

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Conflicts, Real or Potential

1. Consultant, Ridge Diagnostics
(Blood Test for Depression)
2. Consultant, Kyowa Hakko Kirin
(Citicoline Effects)
3. ~ 20 patents, assigned to Harvard
or University of Utah

Overview

- Of Mice and Men
- Rocky Mountain High
- Better Living Through Chemistry

Methamphetamine Abuse in Adolescents: Susceptibility or Resilience?

“The abuse of MA is a serious public health problem because MA can cause persistent dopaminergic deficits in the brains of both animal models and humans. Surprisingly, adolescent PND40 rats are resistant to these MA-induced deficits whereas young adult PND90 rats are not.” Volz et al., Synapse, 2009.

Effects of Exposure of Methamphetamine on the Adolescent Brain (I)

Study Subjects

31 Adolescent methamphetamine users vs. 31 healthy adolescents

40 Adolescent methamphetamine users vs. 40 healthy adults

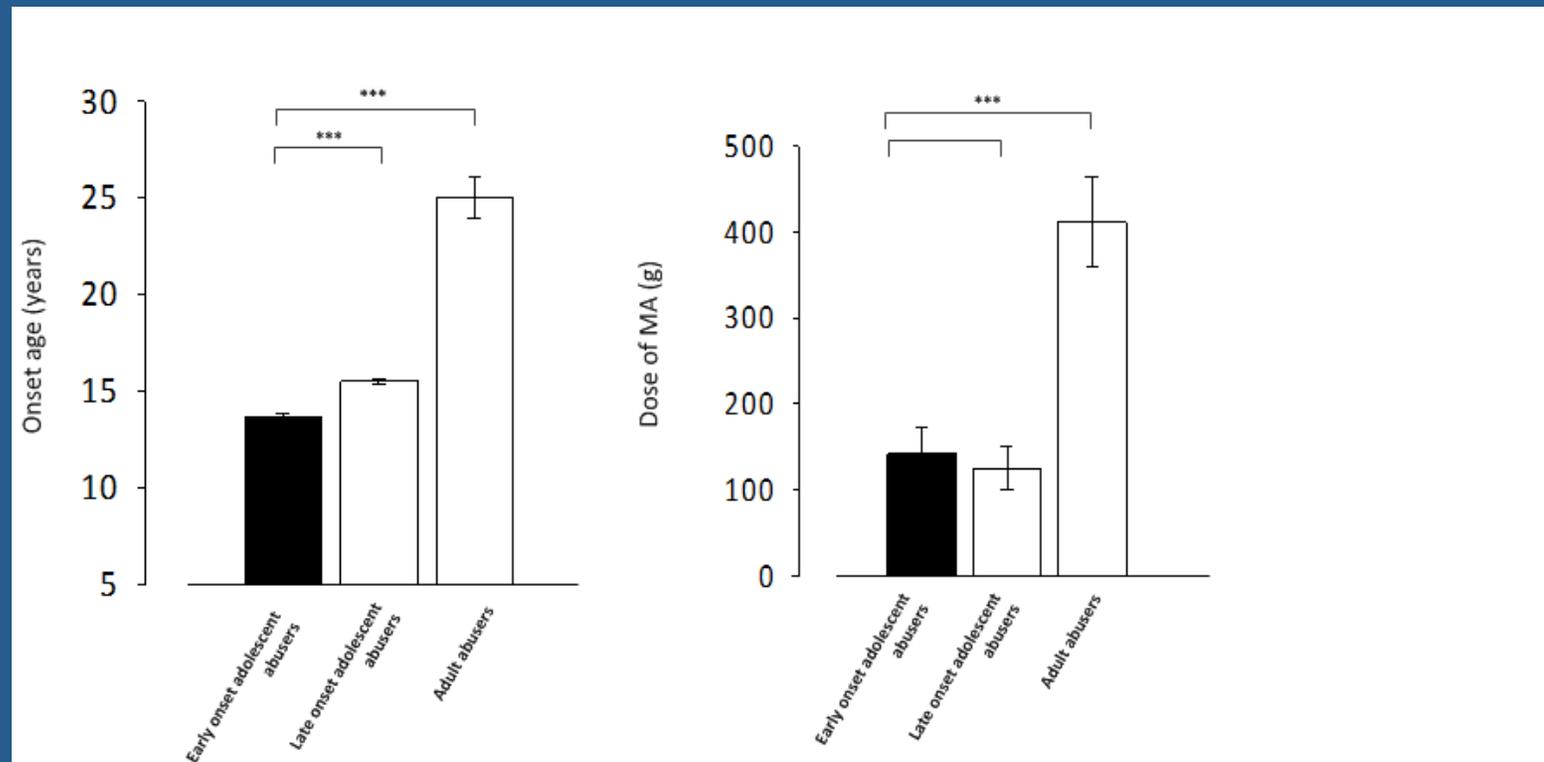
Characteristics	Adolescent group			Adult group		
	Methamphetamine users (n=31)	Control subjects (n=31)	P value†	Methamphetamine users (n=40)	Control subjects (n=40)	P value†
Demographics						
Age — yr						
Mean	18.1±1.5	18.1±1.4	0.97	41.8±6.2	42.1±6.0	0.87
Range	15.4 to 19.9	15.5 to 19.9		34.3 to 57.9	34.4 to 57.1	
Male sex — no. (%)	22 (71.0)	22 (71.0)	NA	34 (85.0)	34 (85.0)	NA
Education — yr	10.6±1.9	11.5±1.2	0.02	11.5±1.9	14.6±2.1	< 0.001
Right handedness — no. (%)	28 (90.3)	25 (80.7)	0.47	39 (97.5)	35 (87.5)	0.20
Smoking — no. (%)						
Current smoker	30 (96.8)	7 (22.6)	< 0.001	37 (92.5)	16 (40.0)	< 0.001
Former smoker	0 (0.0)	0 (0.0)		0 (0.0)	10 (25.0)	
Never smoked	1 (3.2)	24 (77.4)		3 (7.5)	14 (35.0)	

Abbreviations: yr, year; NA, not applicable.
 * Plus-minus values are mean±standard deviation.
 † P values are calculated by Student's t-test for continuous variables and Chi-Square tests or Fisher's exact tests for categorical variables.

Effects of Exposure of Methamphetamine on the Adolescent Brain (II)

Methamphetamine use history of subjects

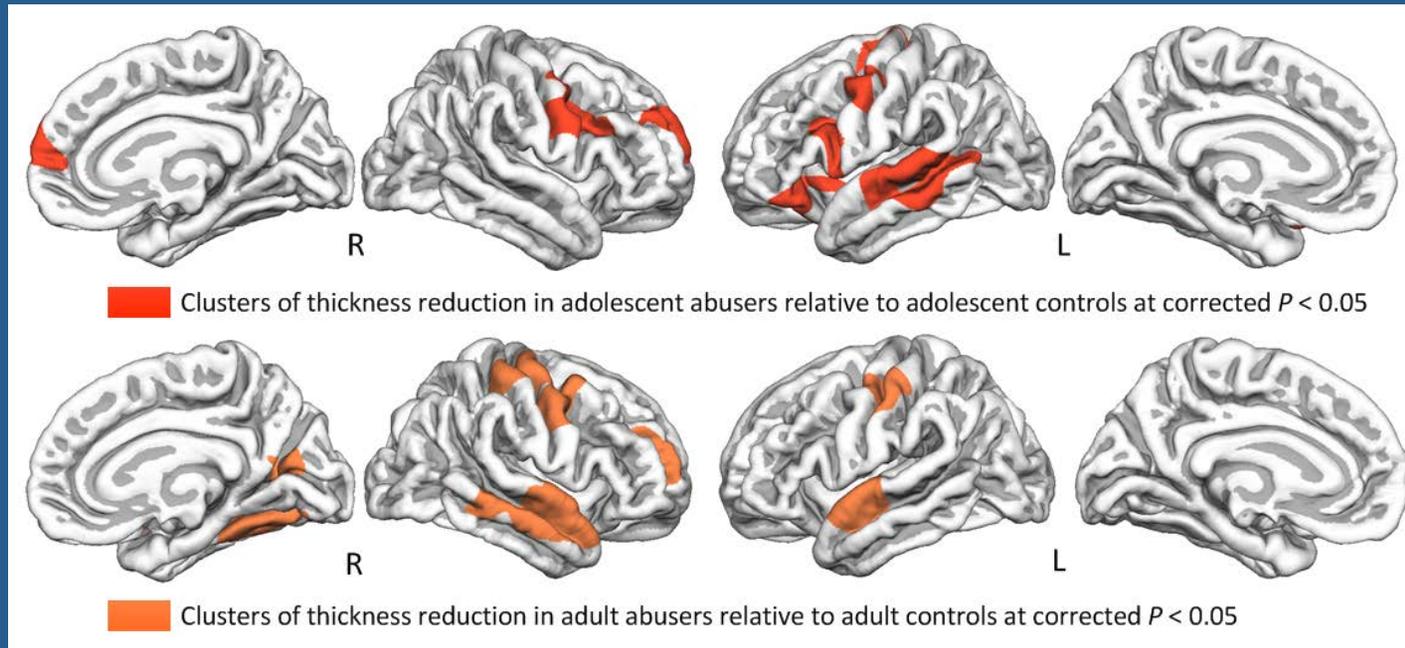
13 early-onset vs. 18 late-onset adolescent users vs. 40 adult users



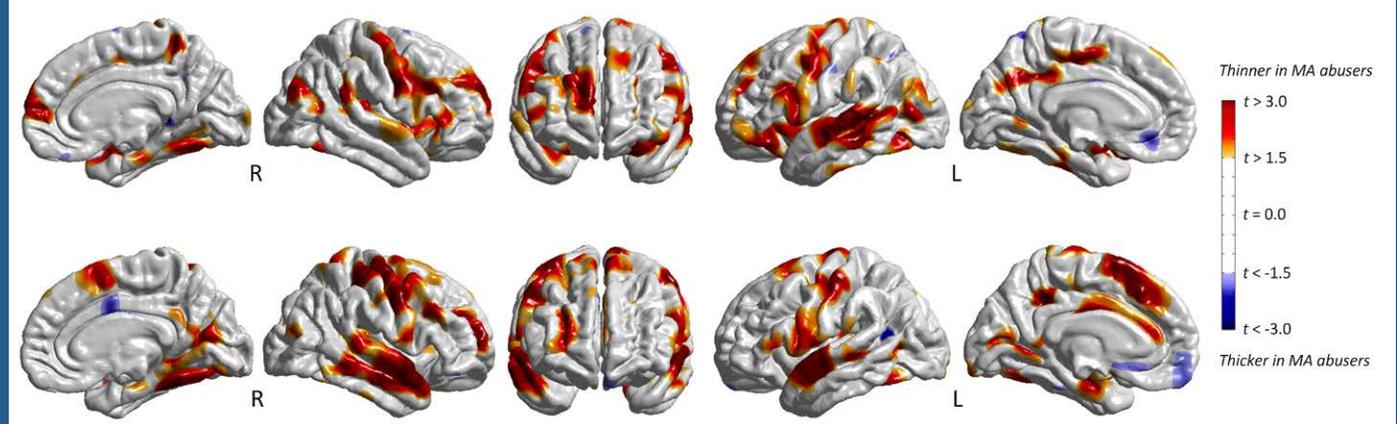
In general, adult users have taken higher lifetime cumulative dose of methamphetamine.

Effects of Exposure of Methamphetamine on the Adolescent Brain (III)

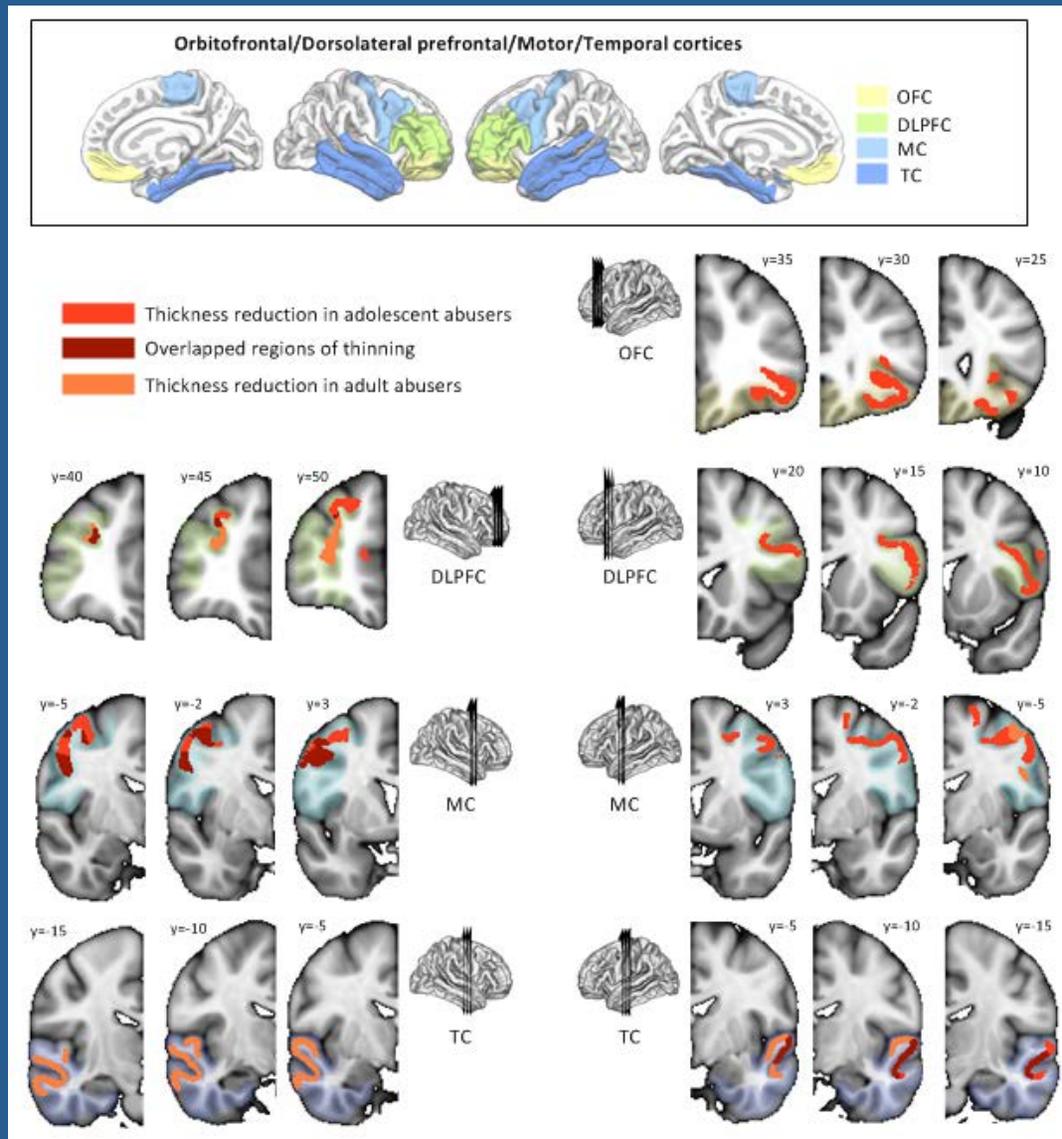
Gray matter alterations in adolescent and adult methamphetamine users



Statistical maps

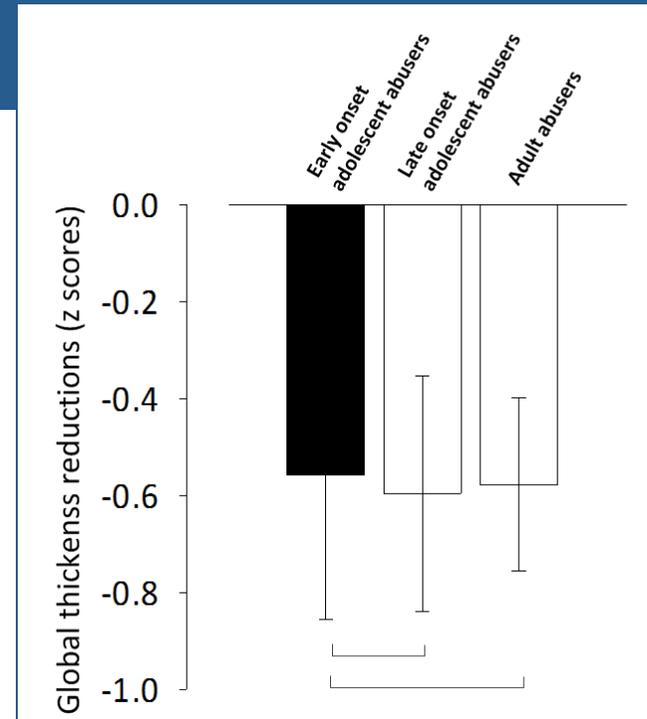
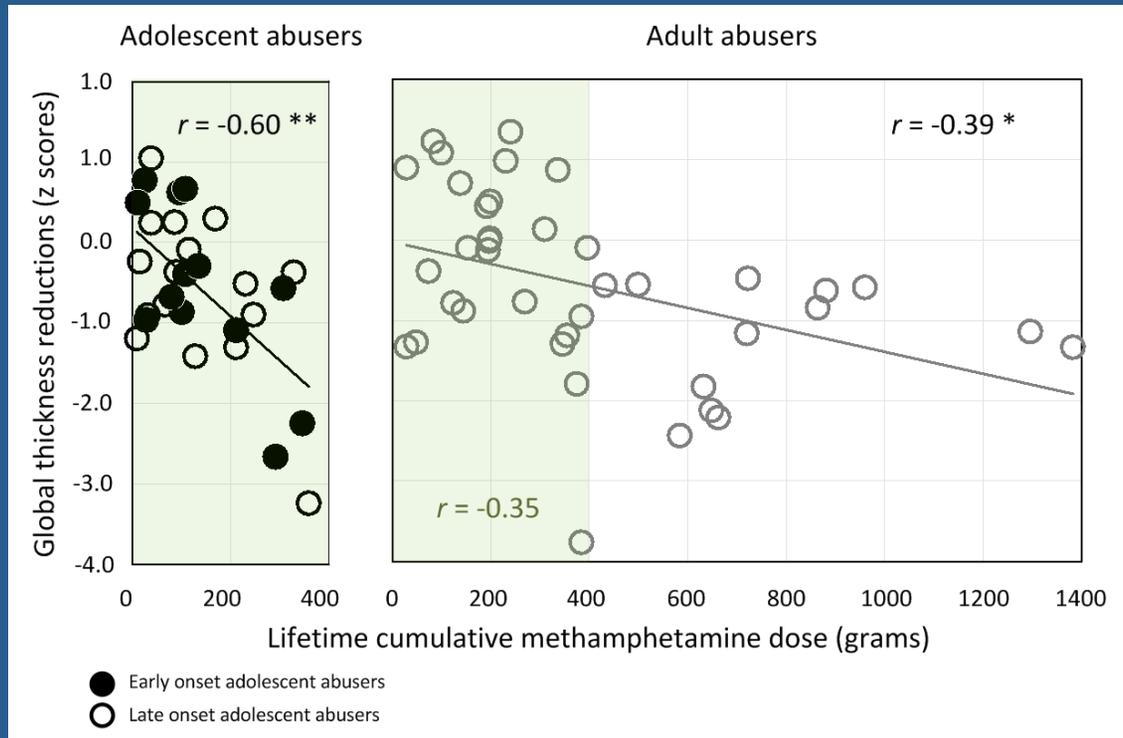


Effects of Exposure of Methamphetamine on the Adolescent Brain (IV)



Similar regional patterns of methamphetamine use-related cortical thickness reductions between adolescent and adult users

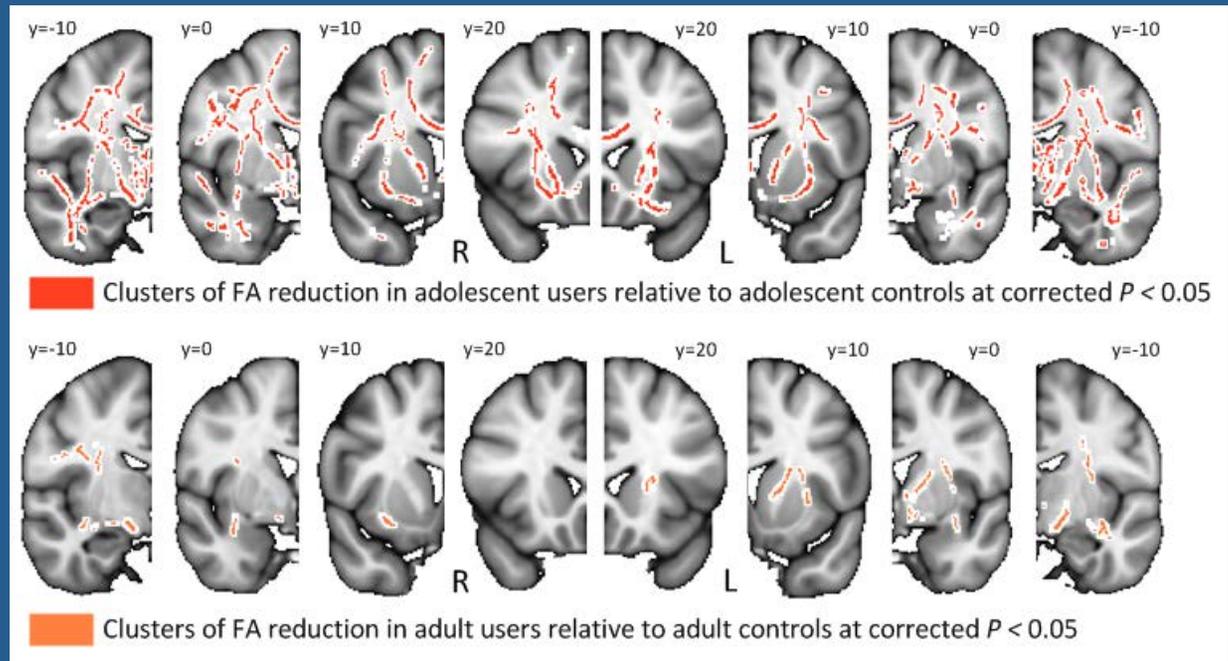
Effects of Exposure of Methamphetamine on the Adolescent Brain (V)



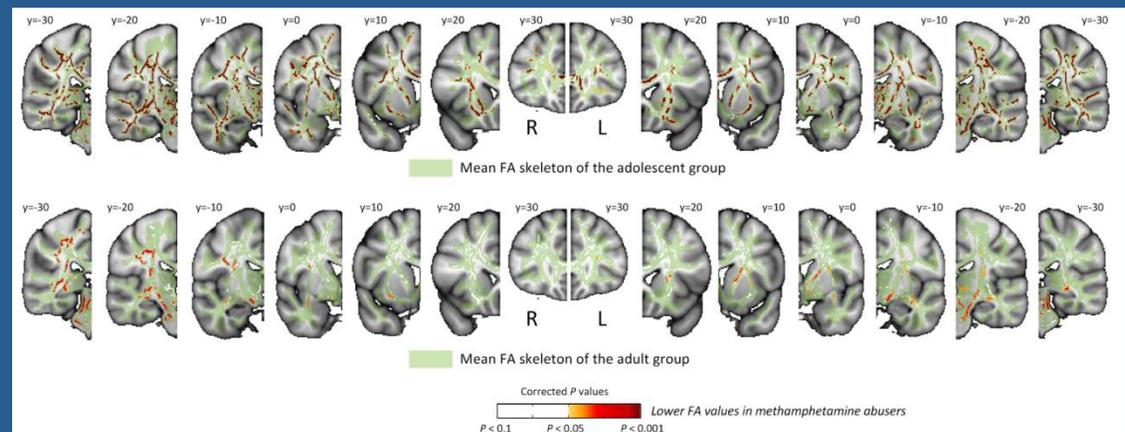
Larger dose-dependent effects of cumulative methamphetamine doses were observed in adolescent users. Gray matter thickness reductions were therefore similar between adult and adolescent user groups, despite a greater amount of methamphetamine use in adult users.

Effects of Exposure of Methamphetamine on the Adolescent Brain (VI)

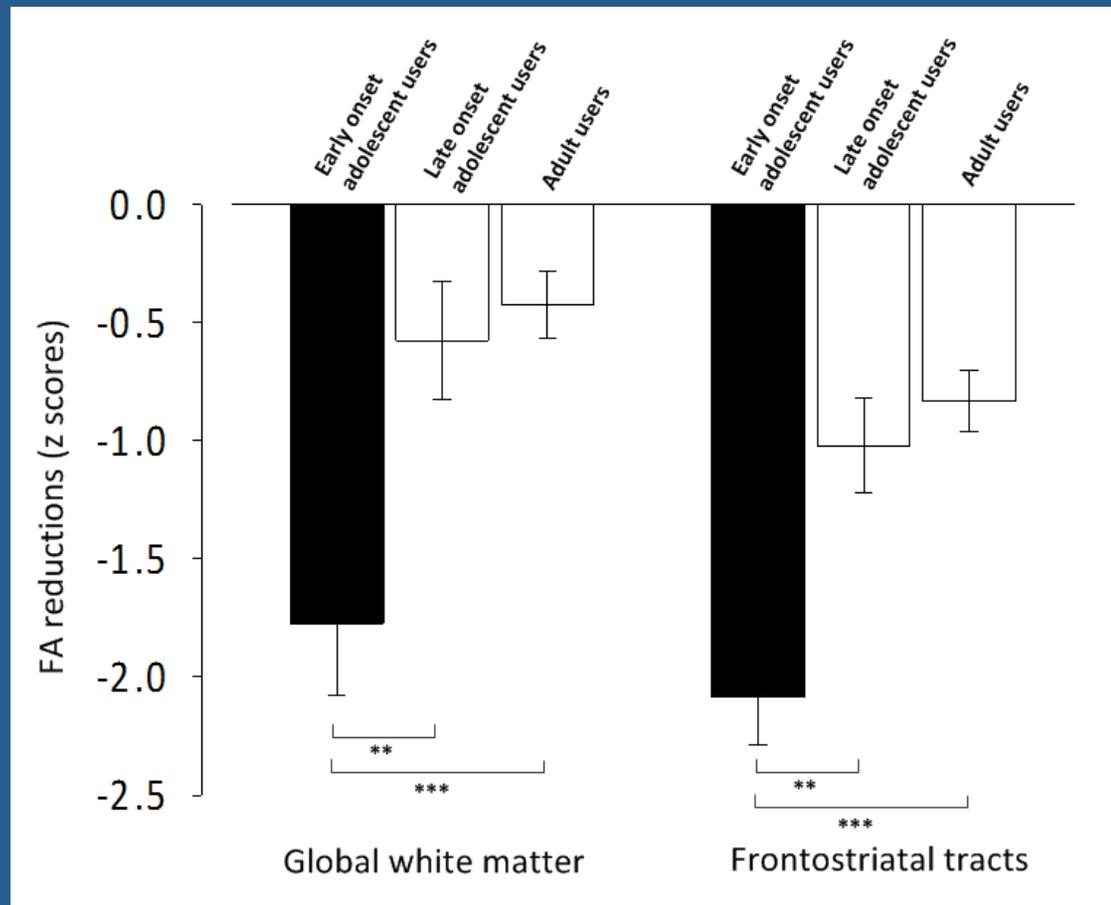
White matter alterations in adolescent and adult methamphetamine users



Statistical maps

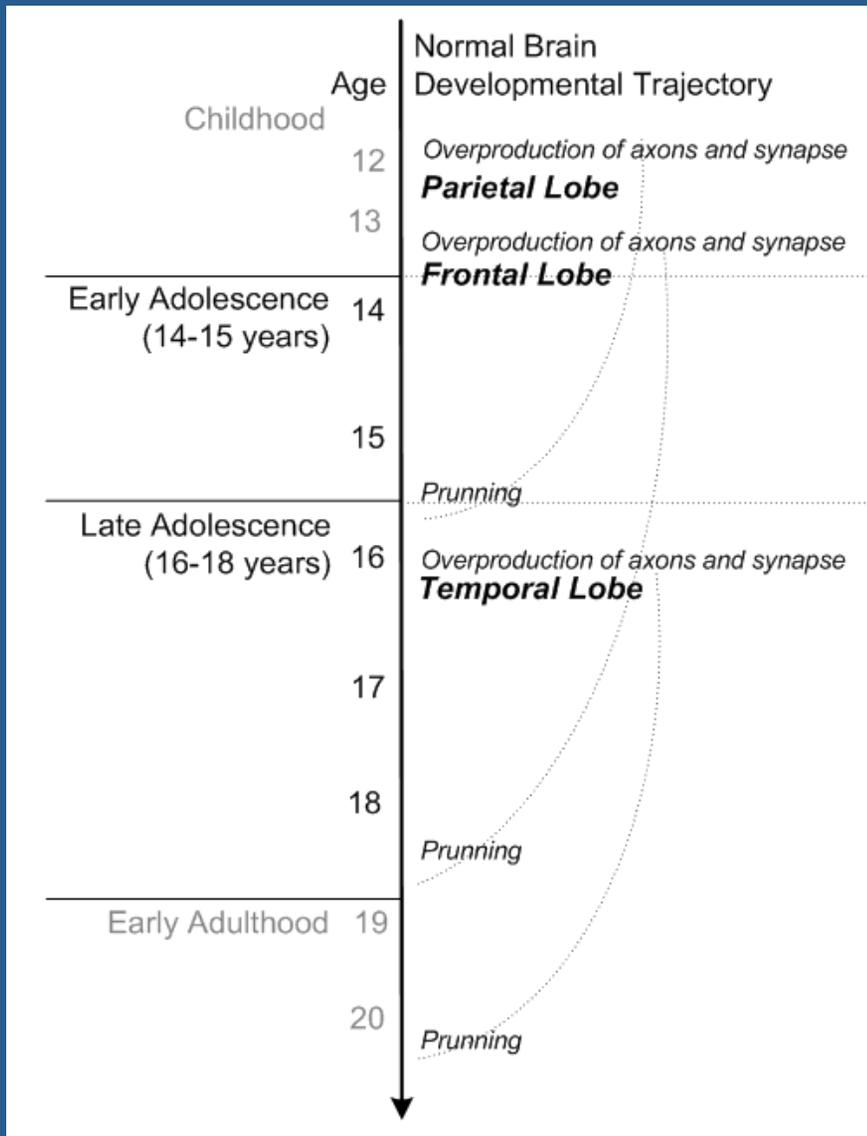
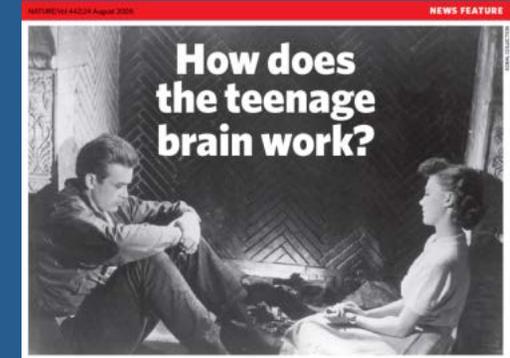


Effects of Exposure of Methamphetamine on the Adolescent Brain (VII)



The extent of FA reduction in white matter in adolescent users was greater than that observed in adult users. The early adolescence-onset group had greater FA reduction in whole-brain white matter and the frontostriatal tract ROI than the late adolescence-onset group although there were no differences in current age or cumulative dosage of methamphetamine between groups

Effects of Exposure of Methamphetamine on the Adolescent Brain (IIX)

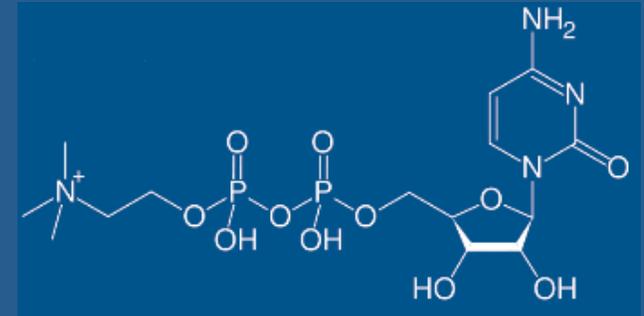


Our findings highlight that the adolescent brain, which undergoes active myelination and maturation, is much more vulnerable to methamphetamine-induced neurotoxicity than the adult brain. This may help explain why adolescent-onset methamphetamine users have a more severe and chronic clinical course than adult-onset users.

Implications and Next Steps

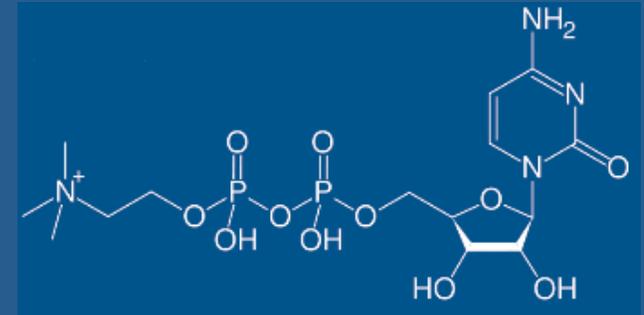
- 1. Preclinical neurotoxicology research needs to be informed by clinical studies, despite their inherent limitations and complexity.
- 2. Prevention and early treatment efforts are likely to be of critical importance.
- 3. Efforts aimed at neuroprotection/resiliency may be important for treatment.

Citicoline



- A natural product and nutritional supplement
- Mechanism
 - Activates the biosynthesis of phospholipids in neuronal membranes (conveys neuroprotection by scavenging toxic lipid breakdown products)
 - Increases norepinephrine and dopamine levels in the central nervous system presumably by increasing the activity of tyrosine hydroxylase (Secades, 2006)
- Already has shown significant efficacy in treating a number of central nervous system disorders including
 - Parkinson's disease, head injury, cerebral infarction and vascular dementia

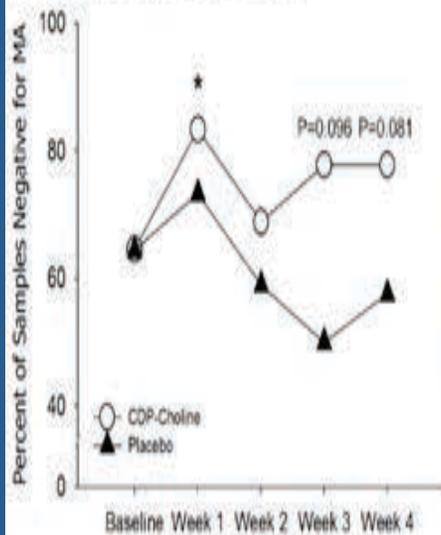
Citicoline



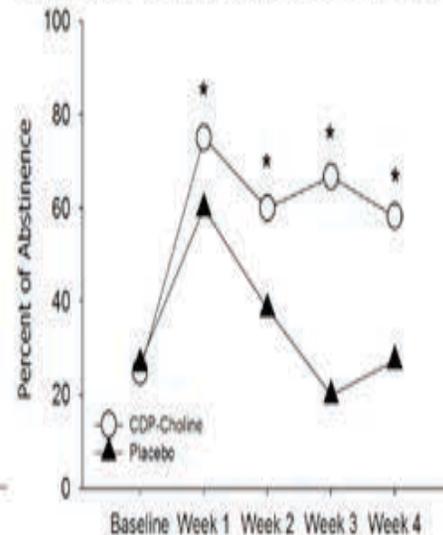
- Significantly decreased urge for cocaine in a group of cocaine dependent subjects following 2 weeks of citicoline relative to placebo. (Renshaw, 1999)
- Cardiovascular safety of combine citicoline and cocaine administration. (Lukas, 2001)
- Established safety in pediatric populations.
- Tends to decrease MA use and, importantly, to increase frontal lobe NAA levels (Yoon, Lyoo, Renshaw, 2010, next slide).

Citicoline Treatment of Methamphetamine Dependence (Study 1 of 2; N = 31)

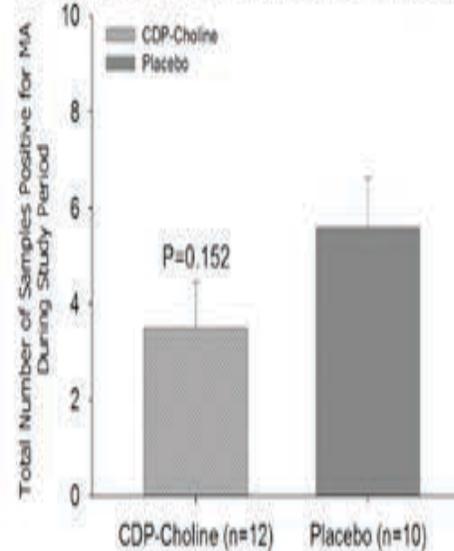
A. Percent of Negative Urine Screen



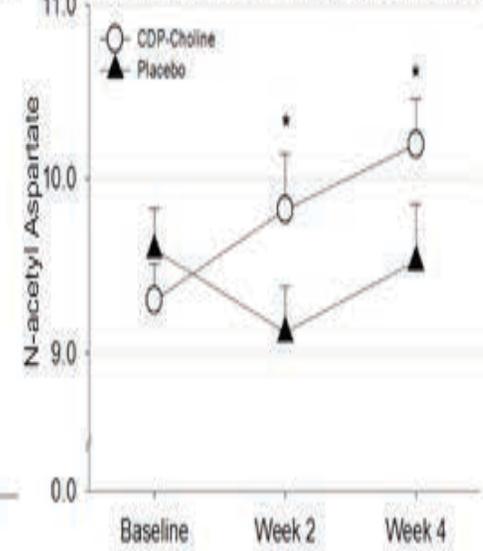
B. Abstinence Rate (Binary test results of urine screen)



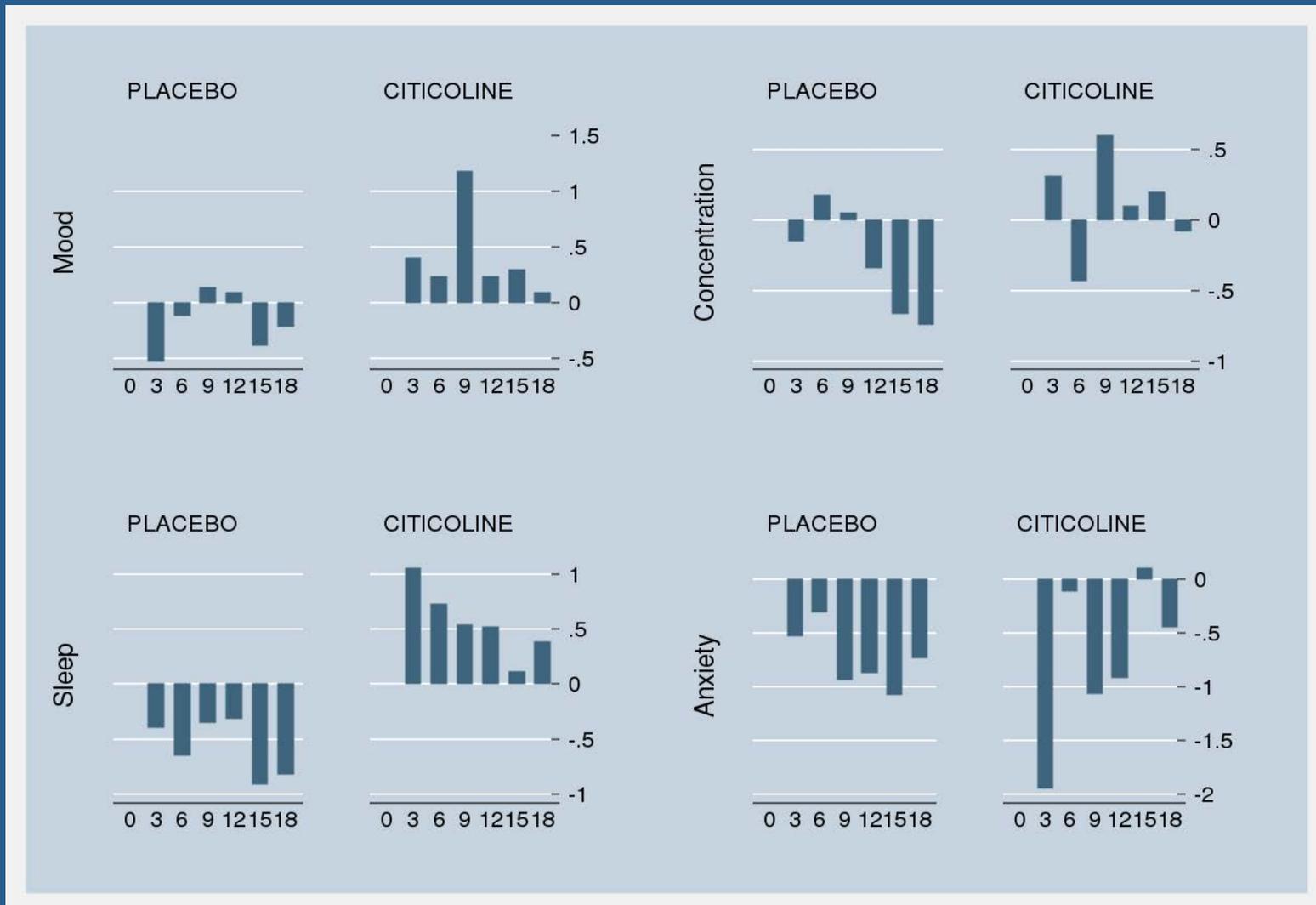
C. Total Number of Positive Urine Screen of Completers



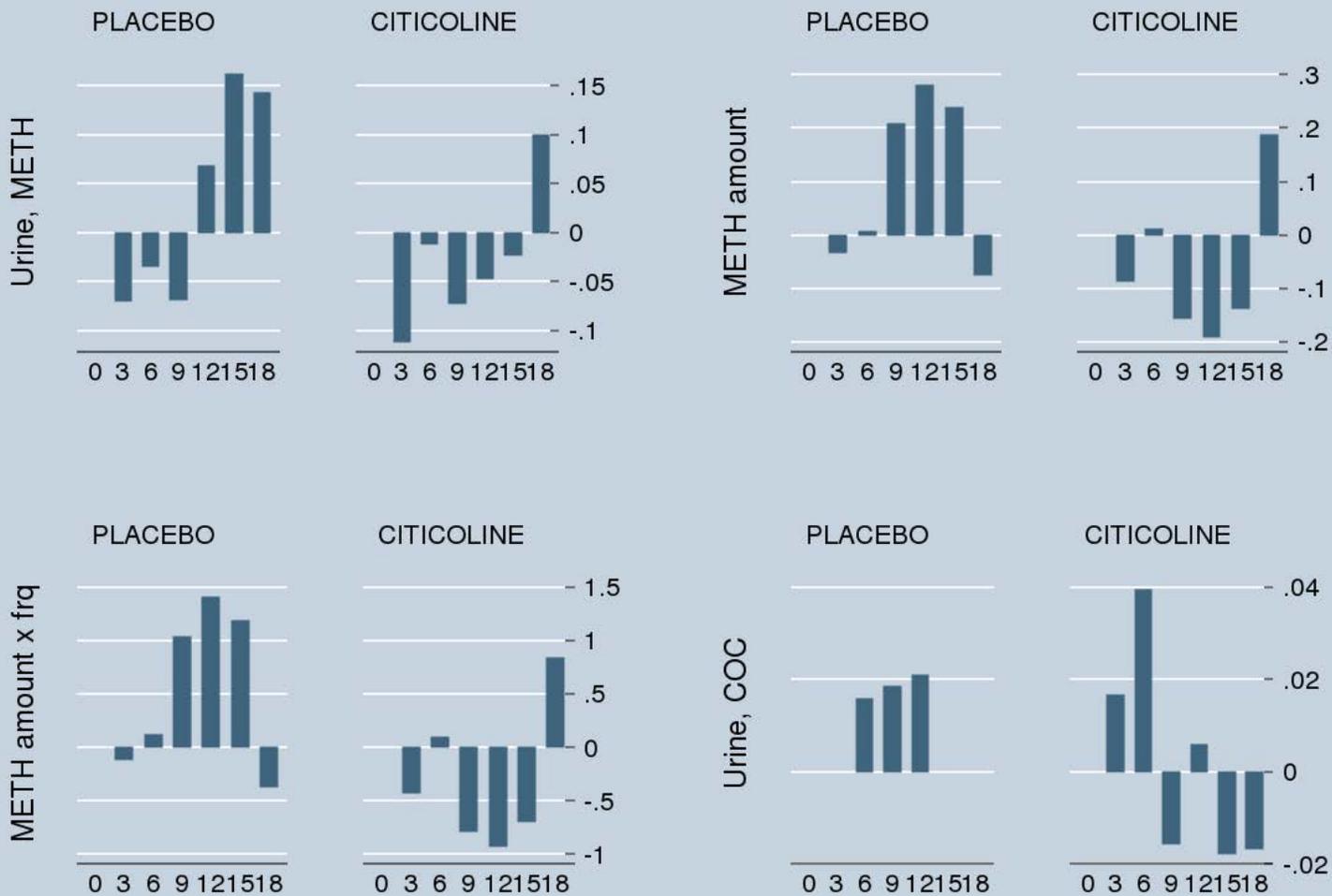
D. Increased NAA in citicoline group relative to placebo



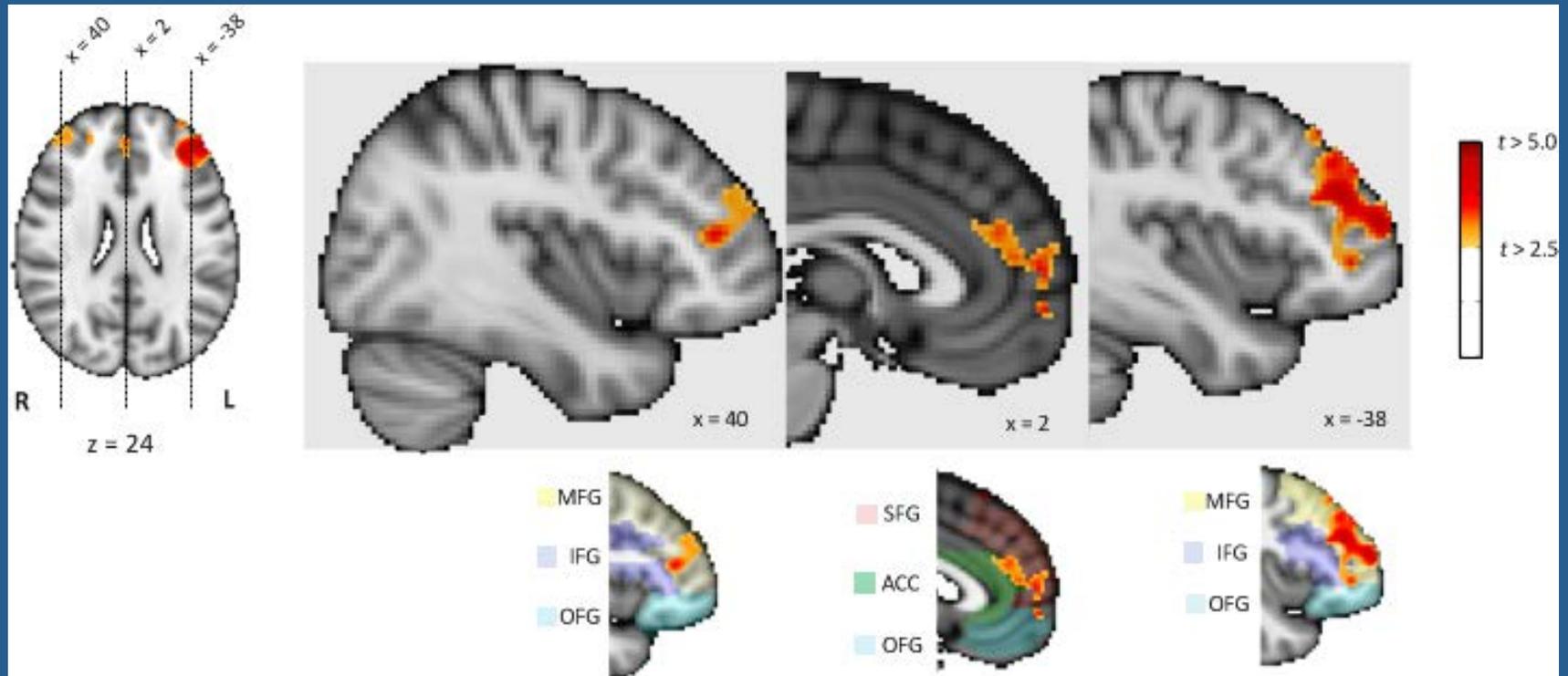
Study 2 of 2: Mood, Concentration, Sleep, and Anxiety (N = 52)



Study 2 of 2: METH (urine, self report) and cocaine (N = 52)



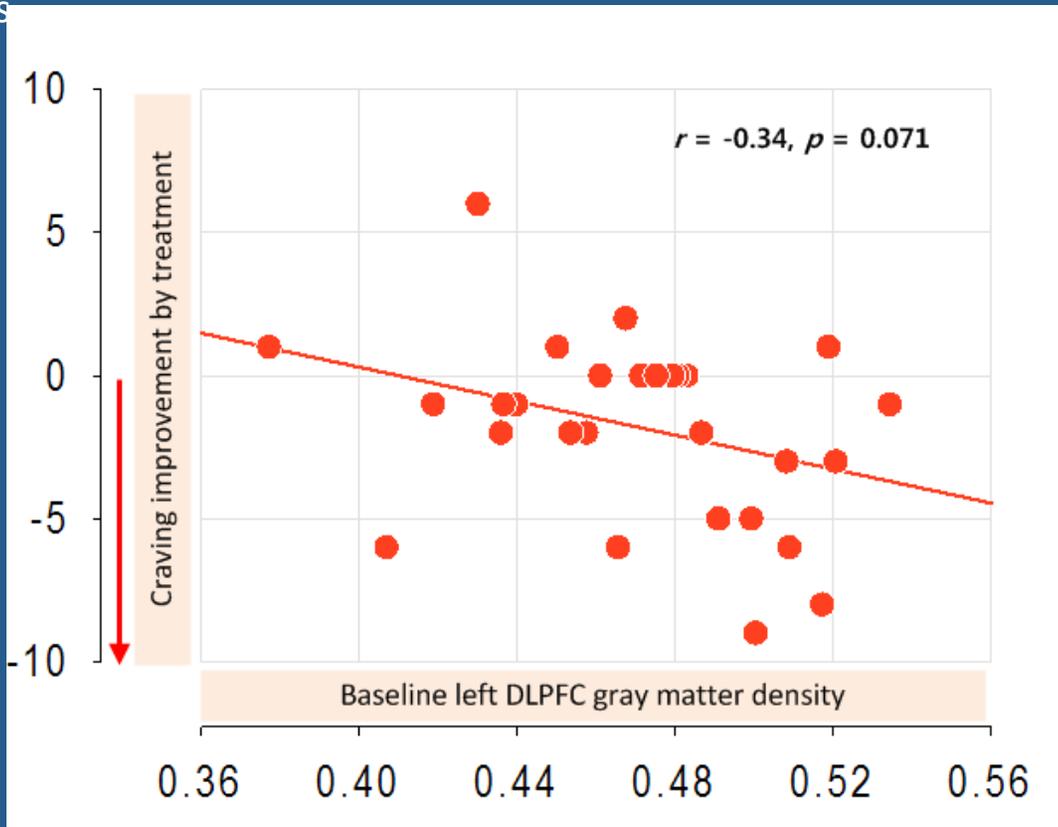
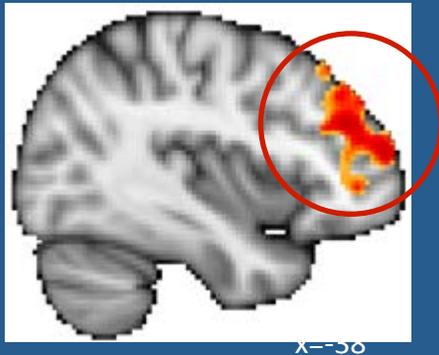
Gray matter volume deficits related METH dependence



44 METH-dependent subjects vs. 27 healthy subjects

Potential treatment targets for craving ♪

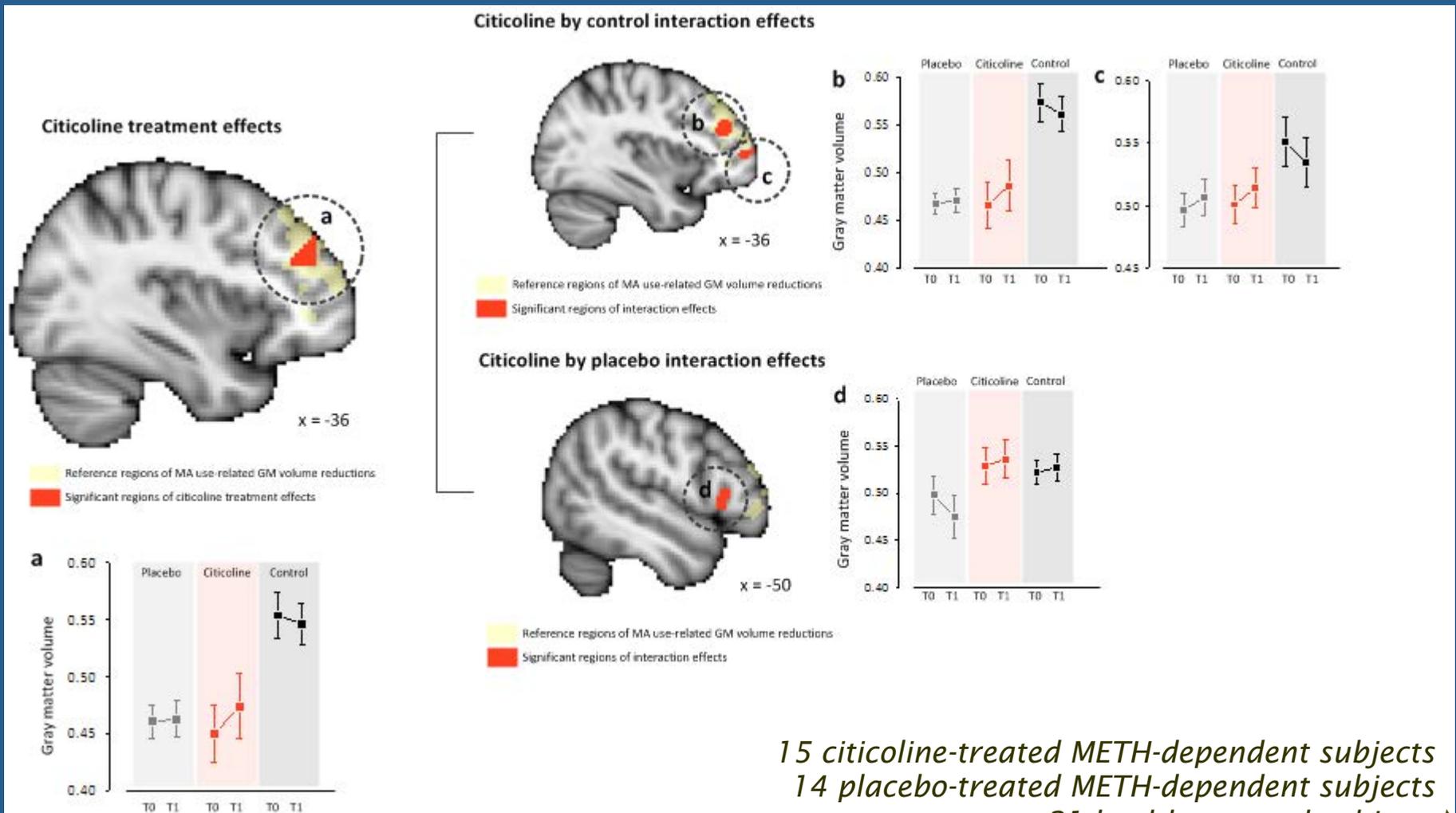
Left DLPFC region of METH effects



29 METH-dependent subjects
with group therapy either with placebo or citicoline treatment ♪

Less METH-related DLPFC volume deficits predict craving improvement ♪

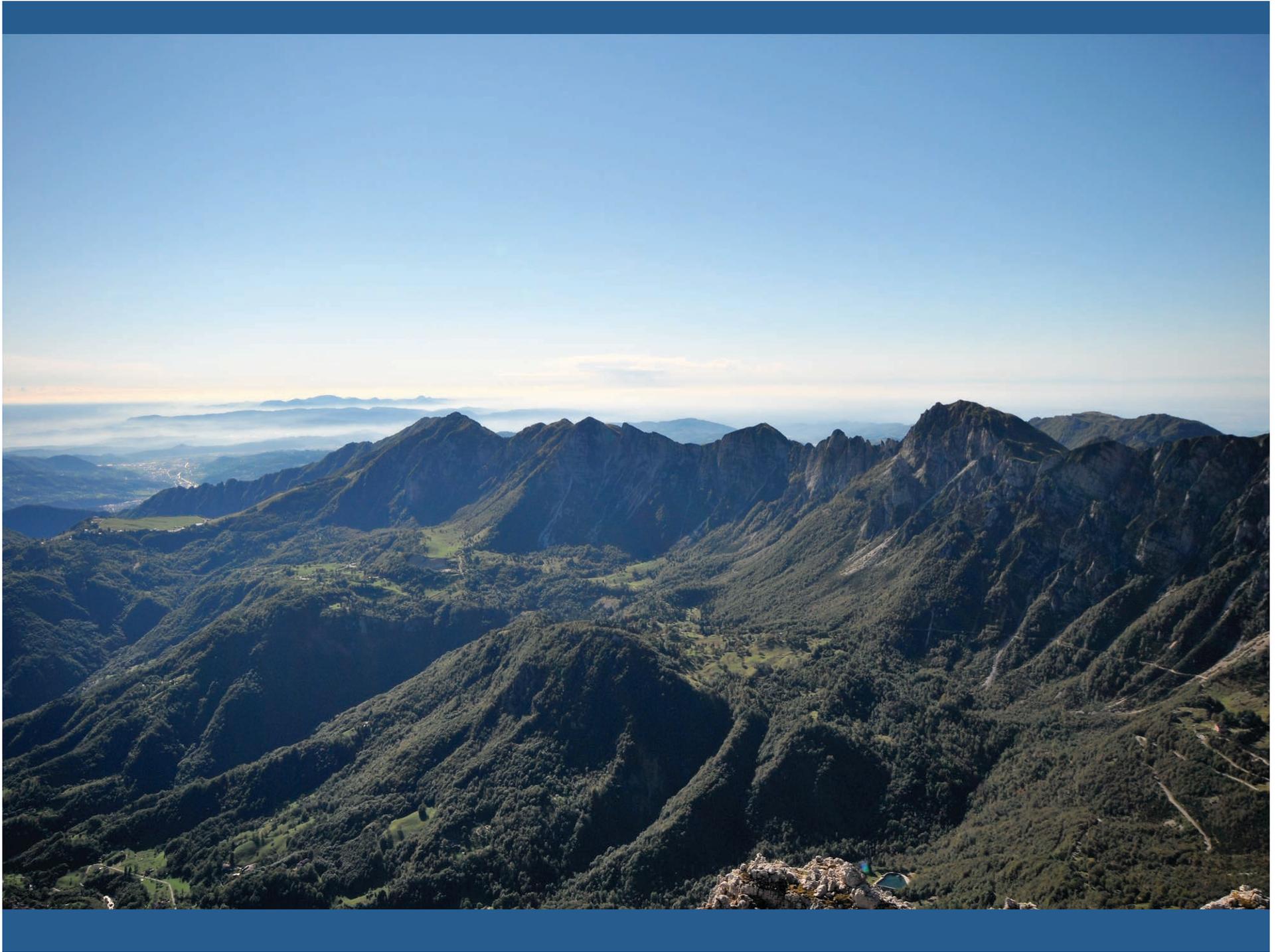
Citicoline treatment effects on left DLPFC gray matter volume ♪



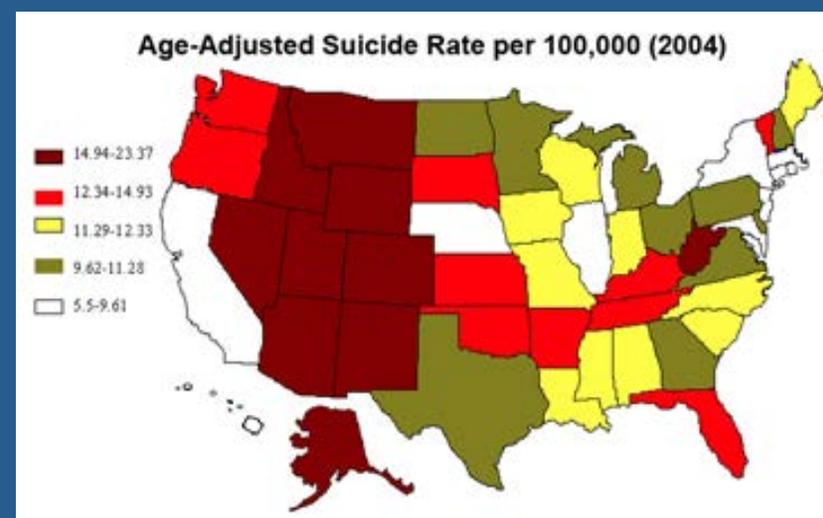
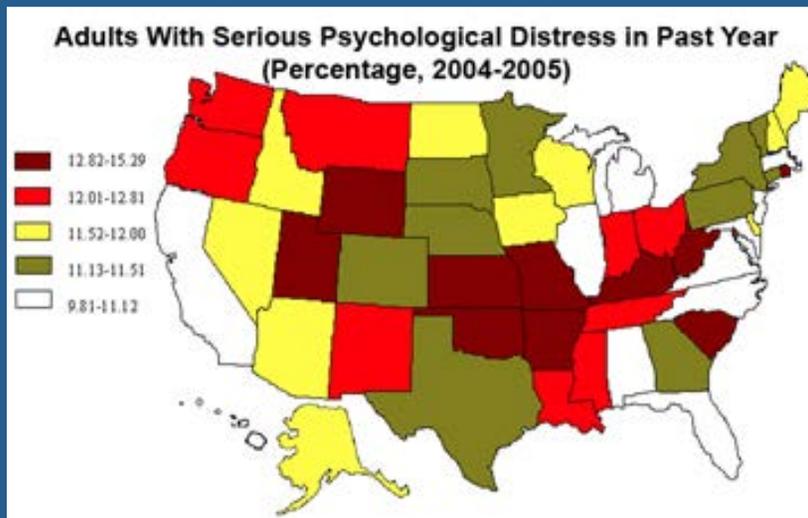
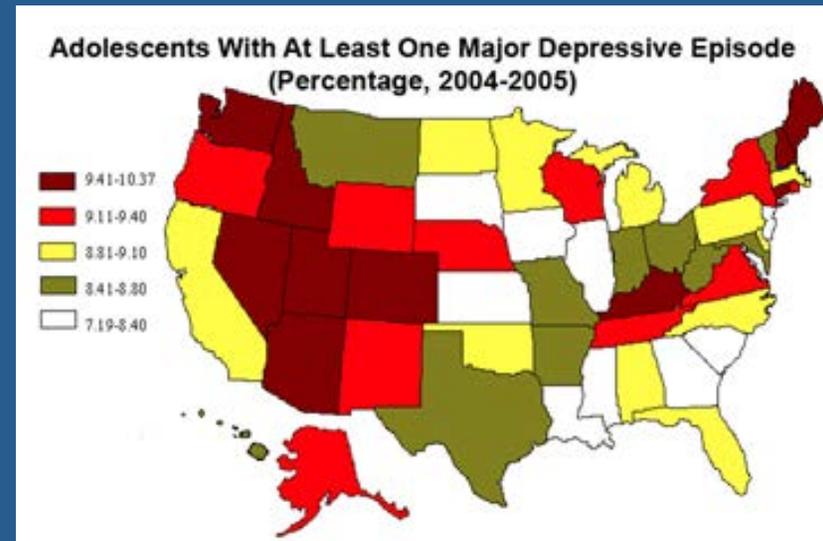
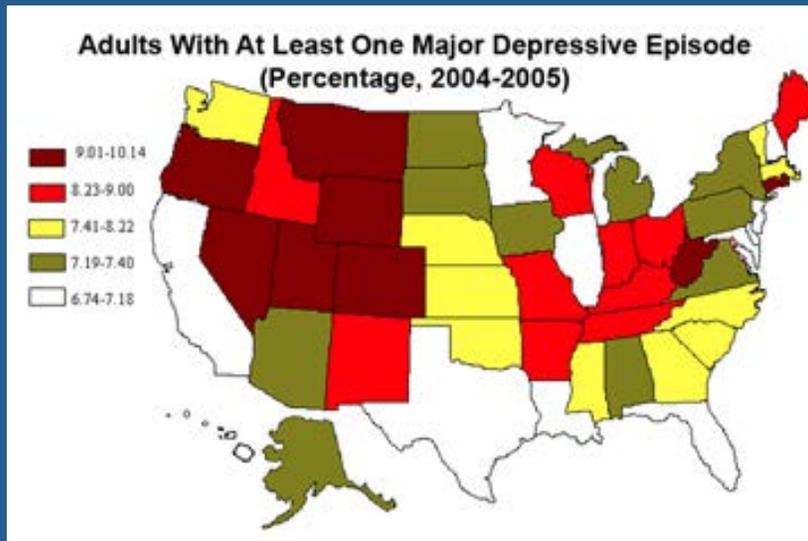
Corrected $p < 0.05$

Rocky Mountain High?





Utah has the highest “Depression Index” of all the U.S. States, based on 4 combined criteria



(Ranking America's Mental Health, 2007)

Established Theory #1

Application for UTAH DRIVER'S LICENSE

Are you a Utah resident?
Prove it with notarized copies of the following:

<input type="checkbox"/> birth certificate	<input type="checkbox"/> passport
<input type="checkbox"/> s.s. card	<input type="checkbox"/> Costco card
<input type="checkbox"/> tax returns since 1999	<input type="checkbox"/> Temple recommend
<input type="checkbox"/> utility bills	<input type="checkbox"/> Mattress tag

for official use only:
Can you believe how annoying the public is? Y N

• Who is your favorite Osmond?
• Do you suffer from...
 blindness? apoplexy? bad taste?
 deafness? fools? hialitosis?
 the plague? delusions of grandeur? psoriasis?

• List family members going back six generations.
PLEASE PRINT

Do you operate a car motorcycle truck ponzi scheme?

Party Affiliation: GOP America-hating Socialist

page 1 of 16

Application for UTAH CONCEALED WEAPON PERMIT

ARE YOU CURRENTLY BREATHING?
Y N

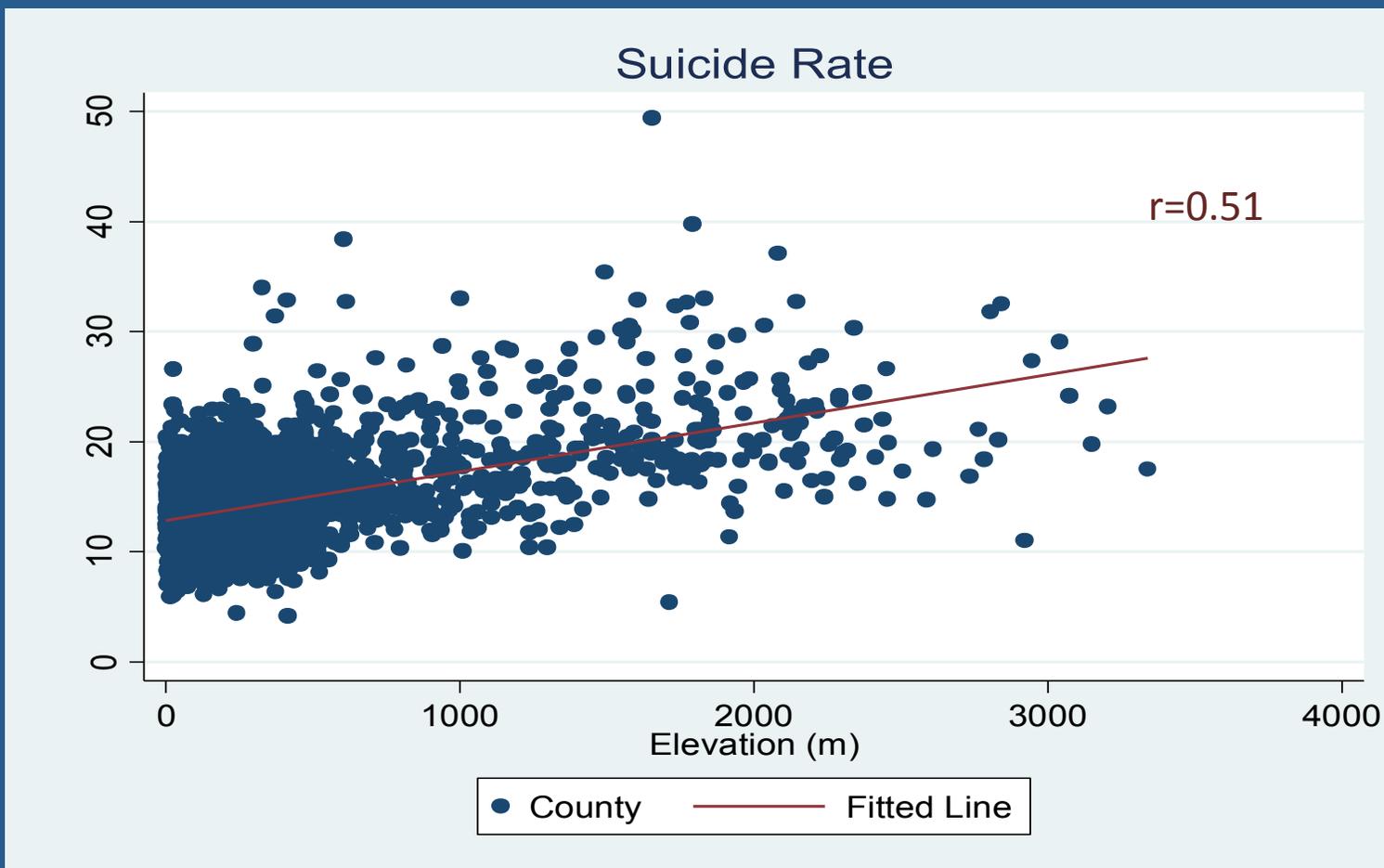
Source: Pat Bagley. The Salt Lake Tribune.
Sunday, July 14, 2010.

Off the Deep End?



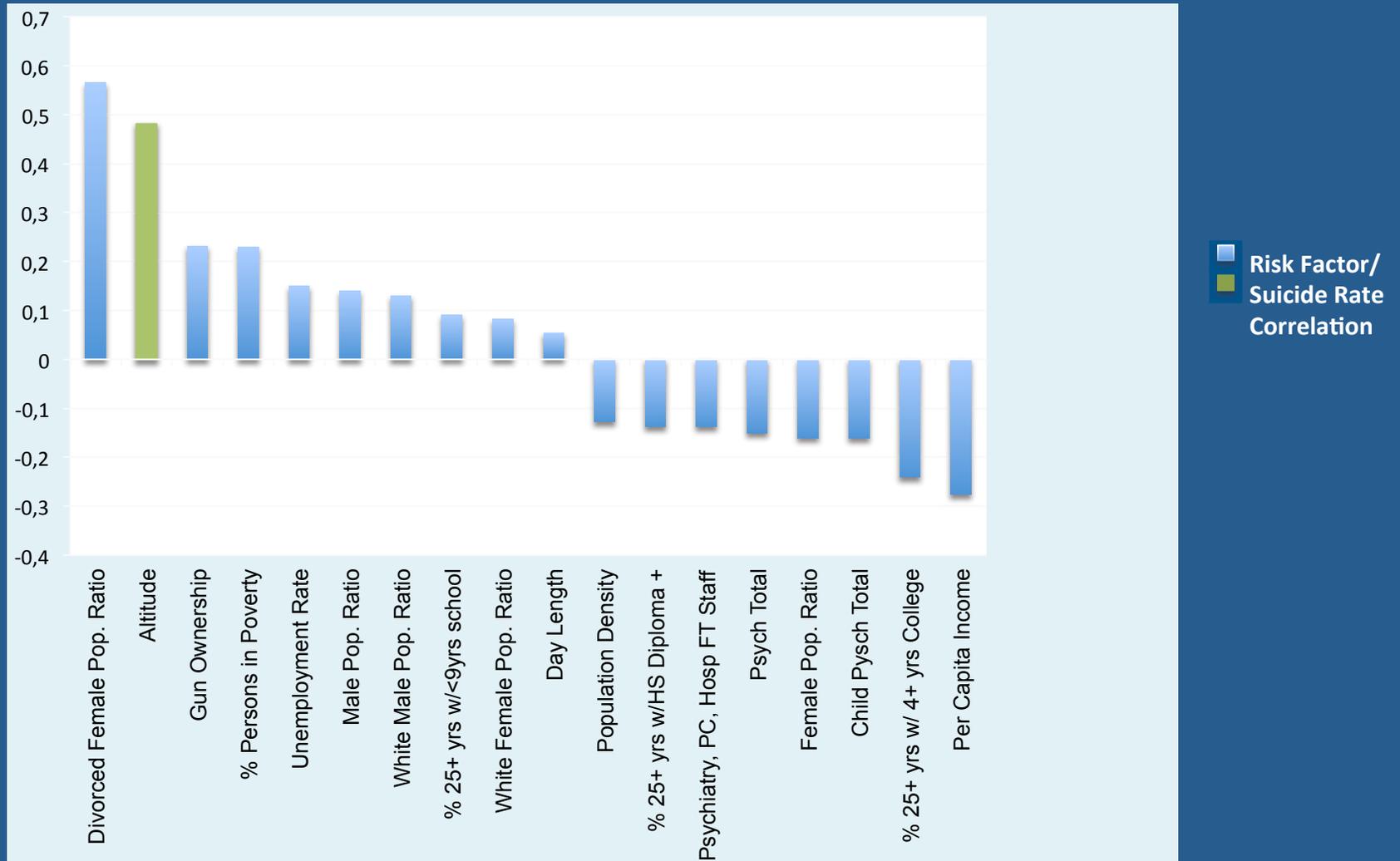
Source: www.images.com

Age-Adjusted Suicide Rate vs. Mean Elevation of Each U.S. County



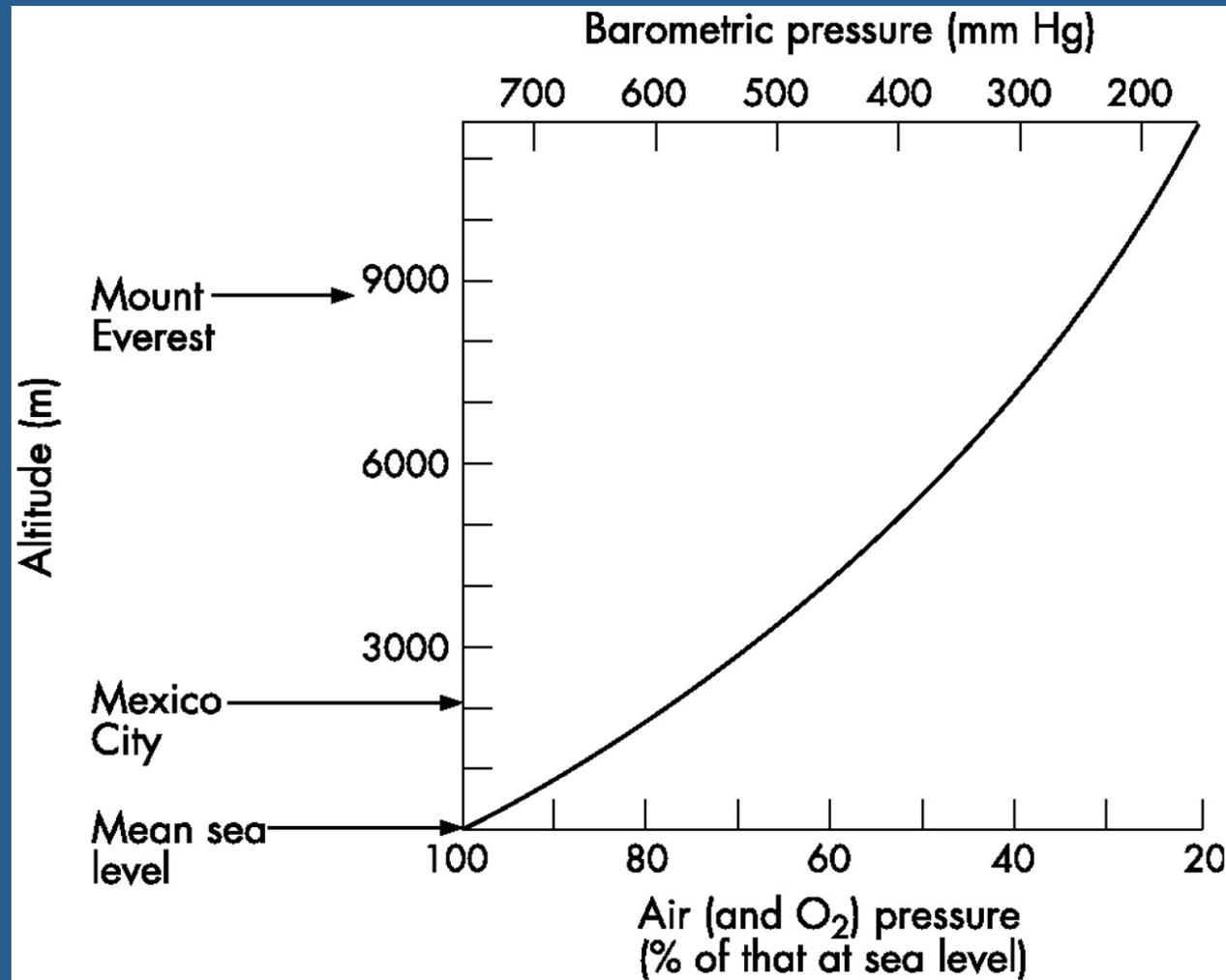
Source: Kim et al., American Journal of Psychiatry (2011) January;168(1):49-54

Correlation Between Suicide Risk Factor and Age-Adjusted Suicide Rates



Source: Kim et al., American Journal of Psychiatry (2011) January;168(1):49-54

Altitude, Barometric Pressure, Air Pressure and Oxygen Tension



Clarke C. *Postgraduate Medical Journal* 2006; 82(973):748-753

Altitude Conversion for Barometric Pressure, Partial Pressure of Oxygen, and the Equivalent Oxygen Concentration at Sea Level



Altitude (Meters)	Altitude (Feet)	Barometric Pressure (P _B)	Partial Pressure of Oxygen (P _i O ₂)	Equivalent O ₂ Concentration at Sea Level (F _i O ₂)	Decrease In F _i O ₂
Sea Level	Sea Level	759.6	149.1	0.209	0%
1,000	3,281	678.7	132.2	0.185	12%
1,219	4,000	661.8	128.7	0.180	14%
1,500	4,921	640.8	124.3	0.174	16%
1,524	5,000	639.0	123.9	0.174	17%
1,829	6,000	616.7	119.2	0.167	20%
2,000	6,562	604.5	116.7	0.164	22%
2,134	7,000	595.1	114.7	0.161	23%
2,438	8,000	574.1	110.3	0.155	26%
8,839	29,000	253.0	43.1	0.060	71%

Auerbach PS, Wilderness Medicine 5th Edition (2007)



Hypobaric hypoxia modulates brain biogenic amines and disturbs sleep architecture.

Ray et al. *Neurochemistry International* (2011)
January; 58(1):112-8

Hypobaric hypoxia modulates brain biogenic amines and disturbs sleep architecture

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Zanfelone and the melatonin
Dietary and the melatonin

ABSTRACT

Subjects to high altitude experience poor quality of sleep due to hypobaric hypoxia (HH). Brain monoamines are the key regulators of sleep architecture. Current literature has limited information on the role of brain monoamines involved in sleep disturbance in HH. The present study aimed to investigate the role of monoamines in sleep architecture changes in low-oxygenated levels and explore the involvement of the biogenic amines in sleep architecture in HH. To hypobaric hypoxia (HH) sleep architecture, body weight of 230–250g, were exposed to simulated altitude – 7000 m, 202 mmHg, partial pressure of O₂ 5.0 mmHg for 7 and 14 days continuously in an animal sleep deprivation chamber. After 7 and 14 days of HH, brain monoamines and dopamine levels were significantly increased in frontal cortex, hippocampus, hypothalamus and cerebellum. In addition, melatonin levels were significantly increased in hypothalamus and hippocampus after 7 days of HH. Tyrosine had very low level in brain monoamines (10–15% significantly increased values). Other Ampt had low and Dopamine Ad. Dopamine (DA) levels were significantly reduced in hypothalamus. Suppression of melatonin synthesis using 5-HT₂ antagonist (Zanfelone) after 7 days of HH, alterations in sleep architecture and monoamine levels were accompanied with reduced total sleep and quantity of sleep. There was a significant increase in sleep latency, total sleep duration (REM sleep), duration of awake period, awake span sleep and a significant decrease in duration of REM sleep and deep sleep on day 7 and 14 of HH. It was concluded that HH causes the suppression of monoamines in sleep architecture and disturbs sleep architecture and the sleep pattern in hypobaric hypoxia.

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1. Introduction

Normal pattern of sleep-wakefulness cycle is modulated by brain monoamines. Gamma amino butyric acid (GABA), dopamine (DA) and acetylcholine (ACh) in locus coeruleus (LC) regulate rapid eye movement (REM) sleep whereas nor-epinephrine (NE) released from monoaminergic cells of LC has a role in wakefulness and arousal (Aston-Jones, 2003; Mallick et al., 1980, 2005). Serotonergic and non-serotonergic cells of the dorsal raphe nucleus which secrete serotonin (5HT), dopamine, GABA and glutamate regulate the wake-sleep cycle and REM sleep intensity (Mason, 2005). Studies exhibiting a wide range of modulation in sleep architecture reveal conflicting effects on sleep-wake pattern, ranging from suppression to increase in REM sleep (Mason, 2005). The delicate interplay of these neurotransmitters in regulation of

sleep-wakefulness is governed by an array of key regulatory enzymes of their biosynthesis and degradation pathway namely tyrosine hydroxylase (TH), glutamate acid decarboxylase (GAD), choline acetyl transferase (CHAT) and acetylcholinesterase (AChE) (Aston-Jones, 2005). These monoamines and enzymes play a vital role in modulating sleep architecture since physical destruction of the monoamines through an chemical inhibition of the enzymatic of their biosynthesis significantly disturbs the sleep-wakefulness pattern (Dawit, 1980).

Sleep architecture is disturbed at high altitude with frequent awakenings associated with pronounced oxygen desaturation and periodic breathing, increase in light REM sleep (stage 1 and 2) and reduction of deep REM sleep (stage 3 and 4) (Panjwani et al., 2007). The most common cause of sleep disturbance at high altitude is hypobaric hypoxia (HH). Continuous hypoxia causes multiple effects on sleep-wakefulness mechanism, and such effects are dependent on severity of hypoxia (Dale et al., 1984). Disturbance in sleep appears at the high altitude, work (Lal, 1984; ISK (Lal and Sarkar), 1995). A recent study at simulated altitude

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Loosely speaking....

- Serotonin goes down and
 - Dopamine goes up....
-
- But results depend on species, strain, sex, altitude, length of exposure, etc...

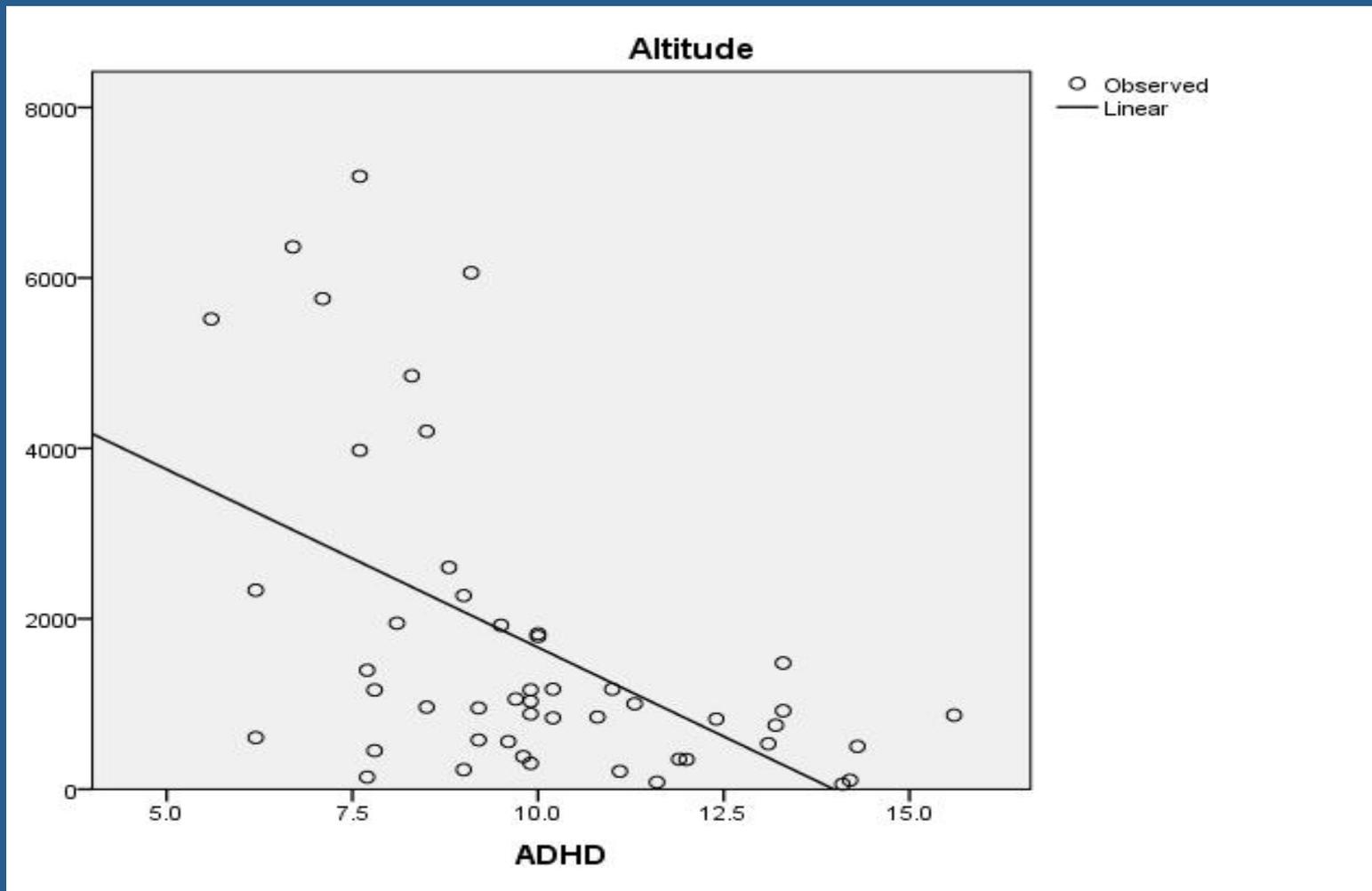
Monoamine content in striatum of female rats after hypoxia exposure (Mass Spec Analysis)

	Serotonin (ng/mg)	Dopamine (ng/mg)
<i>1 week exposure</i>		
4.5K (local conditions)	0.066±0.020	0.970±0.195
10K	0.088±0.017	1.519±0.197 [#]
20K	0.047±0.006 [*]	0.882±0.237 [*]
<i>2 week exposure</i>		
4.5K (local conditions)	0.075±0.018	1.152±0.323
10K	0.087±0.023	2.010±0.247 [#]
[#] - p≤0.1 comparatively to 4.5K group [*] - p≤0.1 comparatively to 10K group		

Animal Studies Show that Hypobaric Hypoxia or Anoxia Increase Dopamine Efflux & Extracellular DA in Brain

- Ray et al. *Neurochem Int* 2011; (58)1:112–8.
 - Simulated 7,620 meters for **7 days** ($p < 0.01$) or **14 days** ($p < 0.05$) both reduced frontal cortex DA *in vivo*.
- Gursoy et al. *Neurochem Res* 2008; 33(9):1838-44.
 - DA release in striatal slices increased from 4 ± 2 pmol/mg protein (in normoxia) to 162 ± 14 (in anoxia).
- Orset et al. *Neurochem Int* 2005; 46(8):623-33.
 - Exposure to **10% O₂** induced a **+80%** increase in striatal DA *in vivo*, which returned to baseline with normoxia (~21% O₂).

Sometimes More Dopamine is Helpful: ADHD



Why We Take Risks – It's the Dopamine



Ken Fisher / Stone / Getty

Salt Lake City is 6th most dangerous place to drive in U.S.

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» **Jordan School District superintendent ushers in 'new dawn'**

Posted 3 hours ago

The Salt Lake Tribune



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First published Aug 03 2011 10:05AM

Updated Aug 6, 2011 09:59PM

Salt Lake City is the nation's sixth most dangerous place to drive, according to statistics gathered by the National Highway Traffic Safety Administration.

Utah's capital city recorded a traffic fatality rate of 16.51 per 100,000 population, based on 2009 accident reports.

The most dangerous place to drive, according to a Wednesday data-mining report by CNBC.com, was Fort Lauderdale, Fla., with a 22.39 fatality rate, followed in order by Orlando, Fla., 19.95; Augusta-Rich County, Ga., 19.57; Little Rock, Ark., 17.94; and San Bernardino, Calif., 17.12.

On the other end of the spectrum, CNBC.com reported that Arlington, Va., was the safest place to drive, based on a 0.48 traffic fatality per 100,000 population rate. In second place was Vancouver, Wash., 1.23; third was Moreno Valley, Calif., 1.57; fourth Rochester, N.Y., 1.93; and in fifth place, Spokane, Wash., 1.98.



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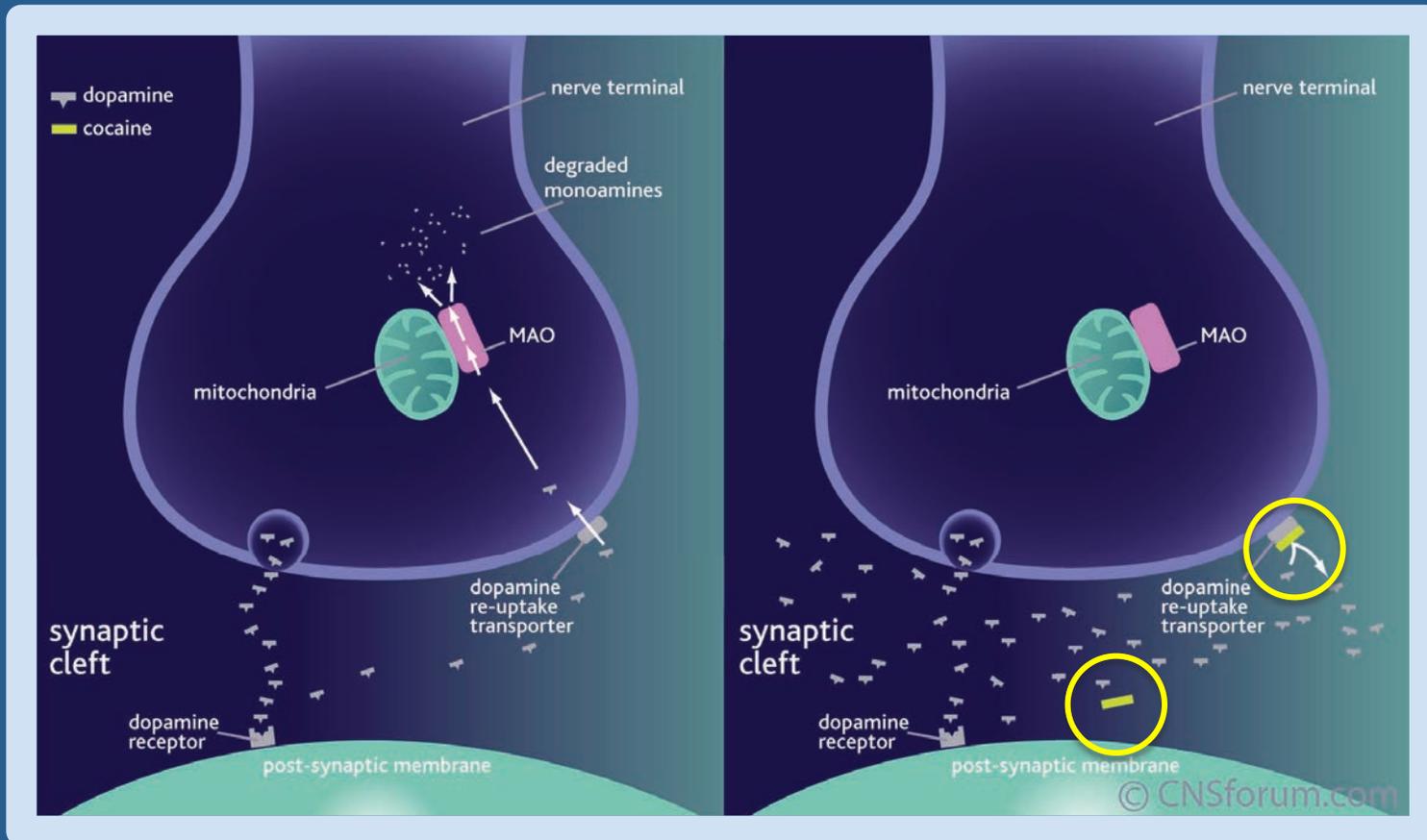
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Image from: cocagrowers.org

Cocaine: Mechanism of Action



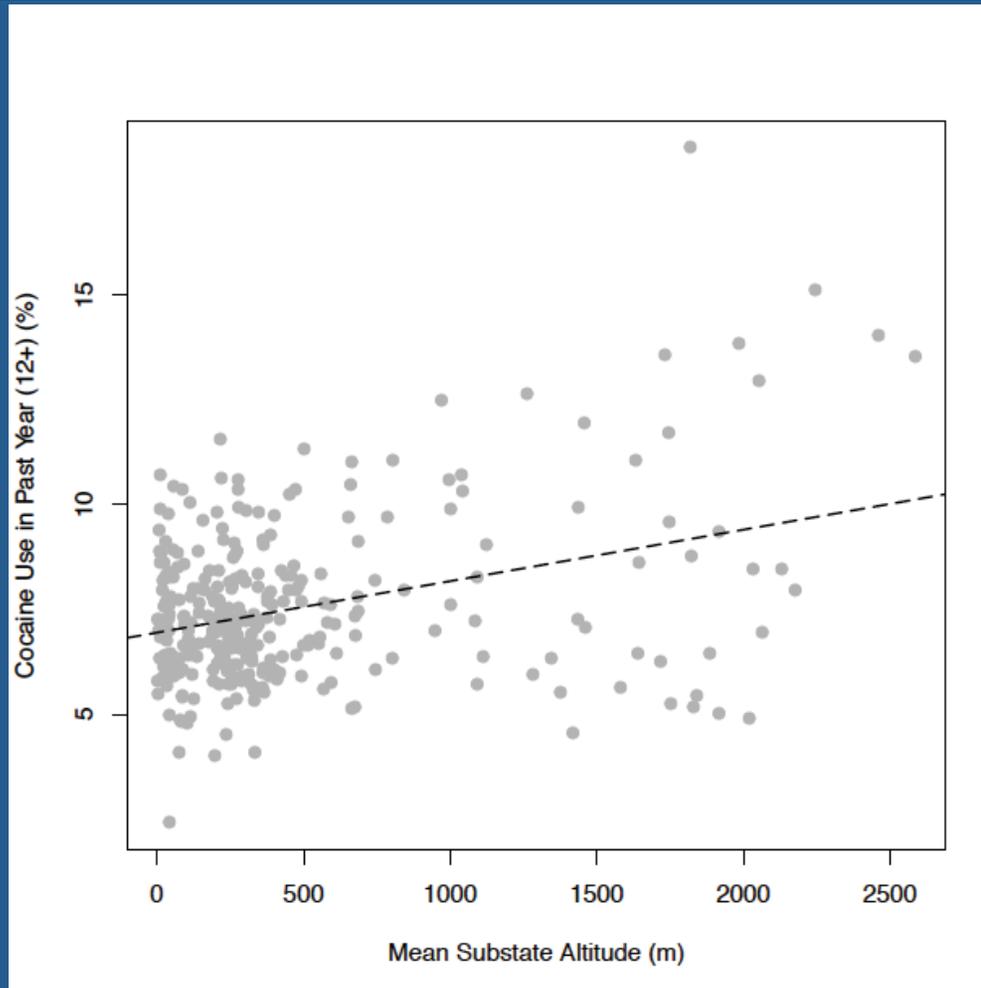
Cocaine binds to dopamine re-uptake transporters on the pre-synaptic membranes of dopamine neurons. This binding inhibits the removal of dopamine from the synaptic cleft

Source: Lundbeck Institute

Cocaine, Altitude & Suicide

- Longstanding history of coca leaf use by high mountain dwellers. Coca leaf use is proportional to altitude in Peru.
- Coca is thought to reduce the symptoms of **Altitude Sickness** (nausea, dizziness, headache, fatigue).
- Cocaine use is **highly** associated with suicide, more than alcohol or other drugs of abuse.

Cocaine Use in Past Year vs. Altitude of Residence



$t = 6.5725, df = 323$

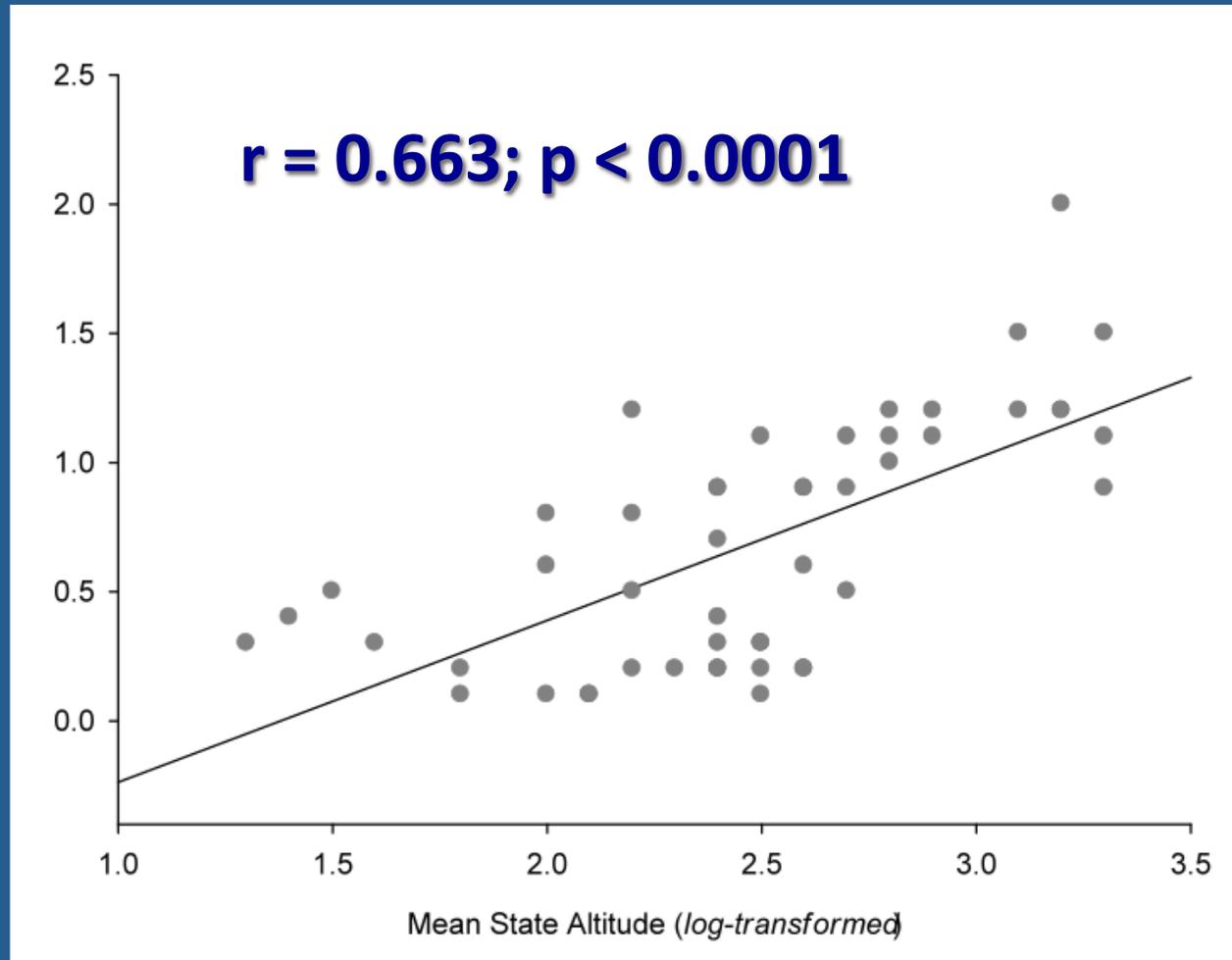
$p = 1.985 e^{-10}$

$R = 0.343574$

Analysis by Namkug Kim, Ph.D.

References: 1) Substance Abuse and Mental Health Services Administration, Office of Applied Statistics, 2008b. Substate substance abuse estimates from the 1991-2001 National Surveys on Drug Use and Health. Rockville, MD. <http://oas.samhsa.gov/substate2k5/SecD.htm>. 2) National Geospatial-Intelligence Agency and National Aeronautics and Space Administration, 2000. Shuttle Radar Topography Mission (STRM) Dataset. United States Geological Survey, Sioux Falls, SD.

Altitude and Methamphetamine Use in the NSDUH 2002-05 (n ~ 70,000)



Correlation between mean state altitude and 12-month self-reported methamphetamine use in the 48 contiguous states and the District of Columbia (excludes Alaska and Hawaii).

This remains true....

Only for MA abuse/dependence.

Even after correcting for: age, ethnicity,
education, socioeconomic status,
employment, MA laboratory seizures,
subpopulations, and other substance
abuse.

Methamphetamine in Suicide Decedents

- Utah, 1996-2002, N = 442, 9%
- New South Wales, 1997-2006, N = 1415, 4%
(M > F)
- NVDRS, 2006, N=15,396, 4.7%
- Kentucky, 1993-2002, N = 2,864, 1.2%
- Mobile, AL, 1990-1998, N = 333, 1%
- San Diego, CA, 1981-82, N = 179, 2%

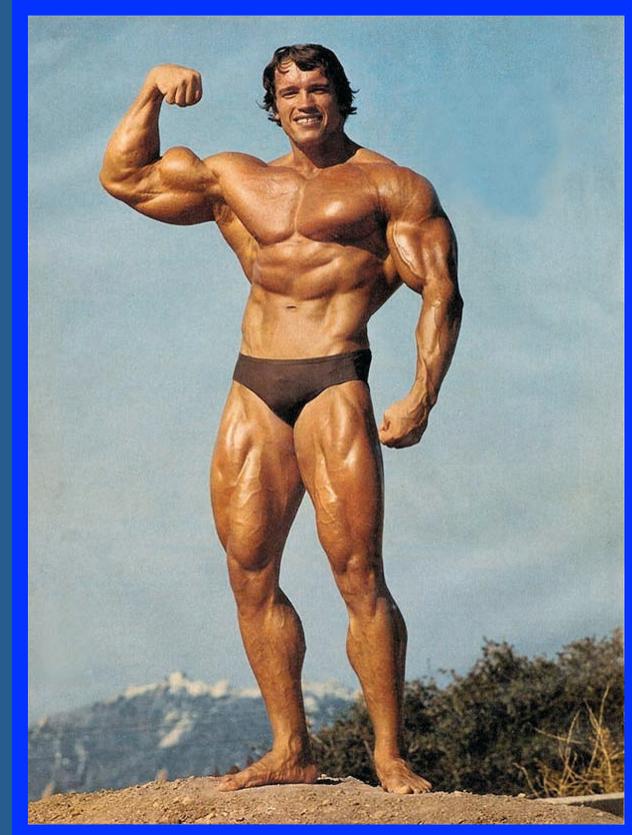
Implications?

1. Stimulant abuse is more prevalent at higher altitudes.
2. This is likely related, at least in part, to hypoxia related changes in dopamine release.
3. Treatment strategies in mountainous areas may need to take this into account.

Depression and Methamphetamine

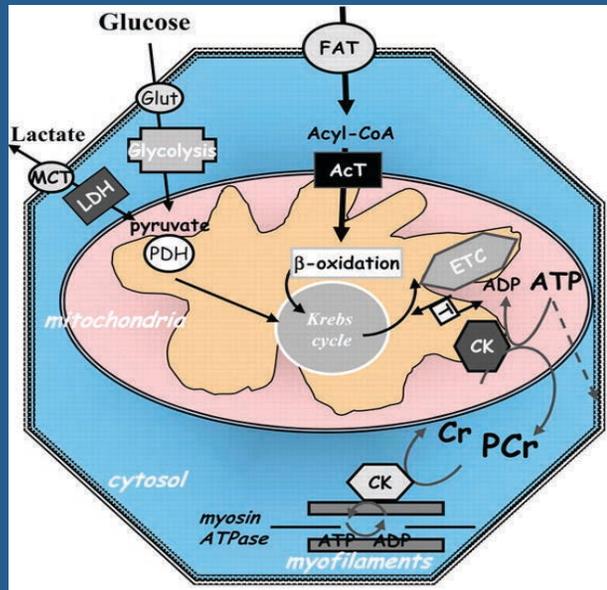
- Commonly co-morbid
- Difficult to treat; antidepressant rx linked to relapse and manic switch
- May be associated with craving and relapse
- May be differentiated from methamphetamine withdrawal symptoms
- More common in women

Nutritional Supplement: Creatine?



Creapure®

Phosphocreatine (PCr) and the Creatine Kinase (CK) Reaction

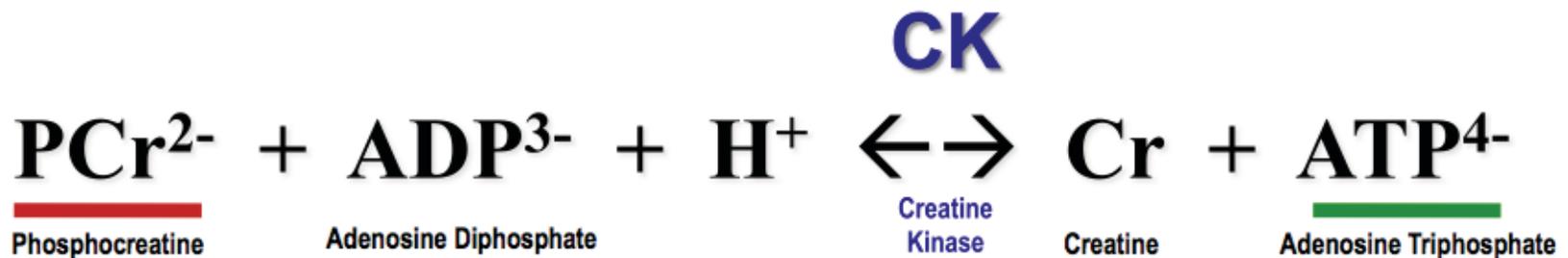


Ventura-Clapier et al. *Cardiovascular Research* 2008;79(2):208-217.

5 Nutrients that Enhance ATP and Improve Cognition

- Glucose
- Oxygen ←
- Pyruvate
- Creatine ←
- L-Carnitine

Owen et al. *Nutrients* 2011;3(8):735-55.

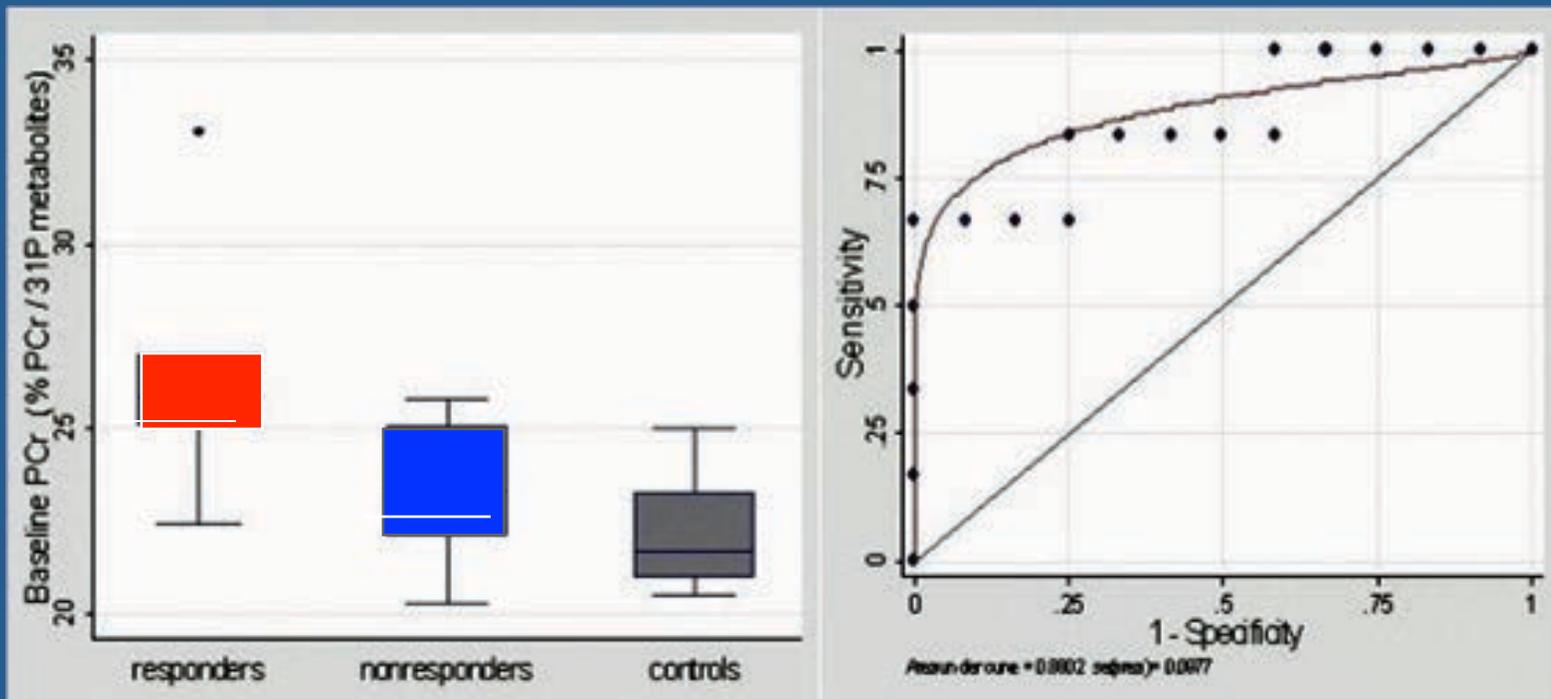


Creatine and the brain...?

Currently being evaluated for potential neuroprotective efficacy (many positive preclinical studies).

NIH-sponsored clinical trials in Huntington's Disease, Parkinson's Disease, and Alzheimer's Disease.

Does creatine have anything to do
with depression?



Baseline PCr Levels in:

■ MDD Treatment Responders

■ MDD Non-Responders

■ Controls

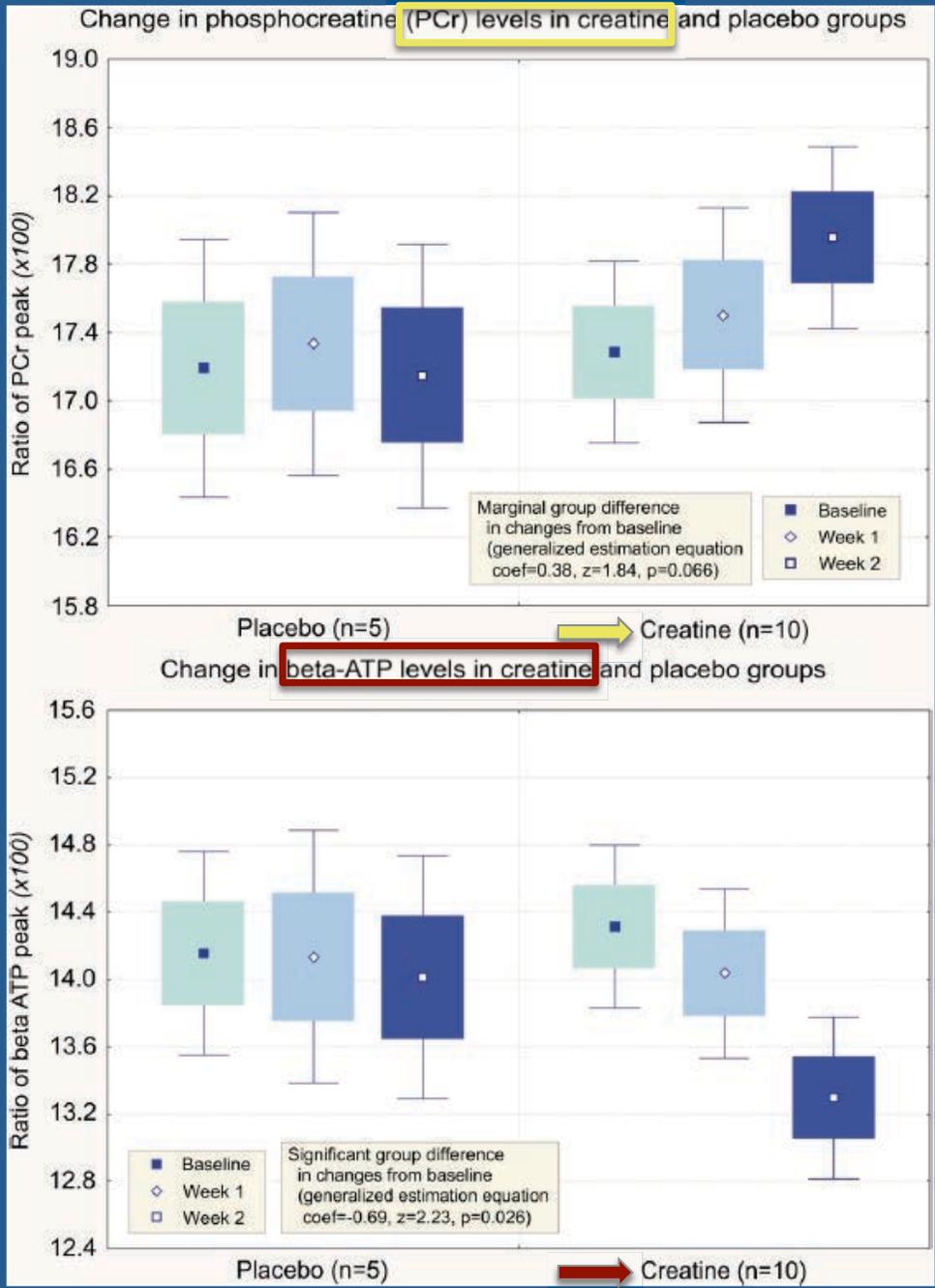
“Baseline PCr” Predicts Treatment Response

- Sensitivity = 83%

- Specificity = 75%

Area under the ROC curve = 0.88

(Iosifescu et al., Biological Psychiatry 2008; 63:12)



Lyoo et al. (2003)

MRS of high-energy phosphate metabolites in human brain following oral supplementation of creatine-monohydrate.

Psychiatry Research 123: 87–100

Δ PCr

Δ β-NTP (ATP)

(Lyoo et al. Psychiatry Research: Neuroimaging 2003; 123)

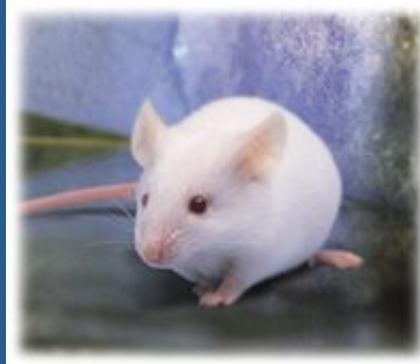
Rats are not humans with affective illness



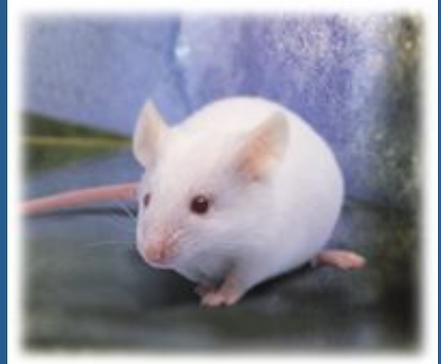
Happy



Sad



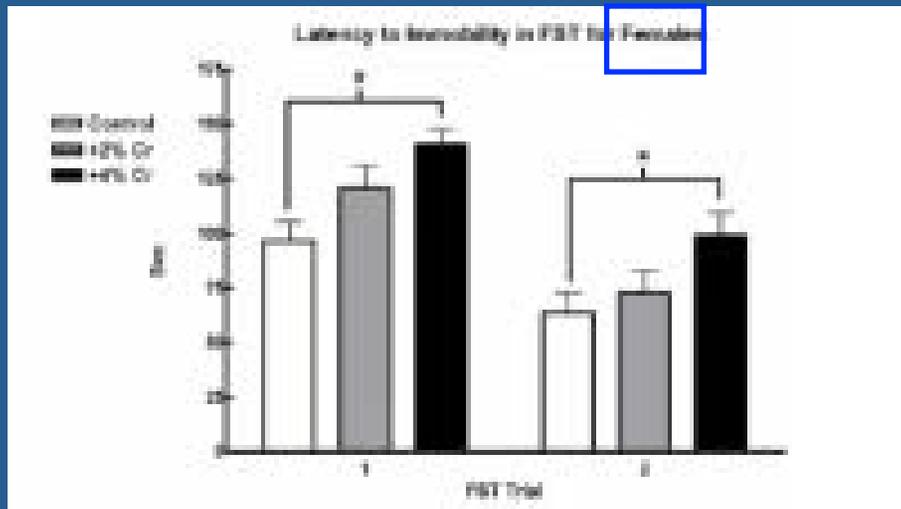
Grumpy



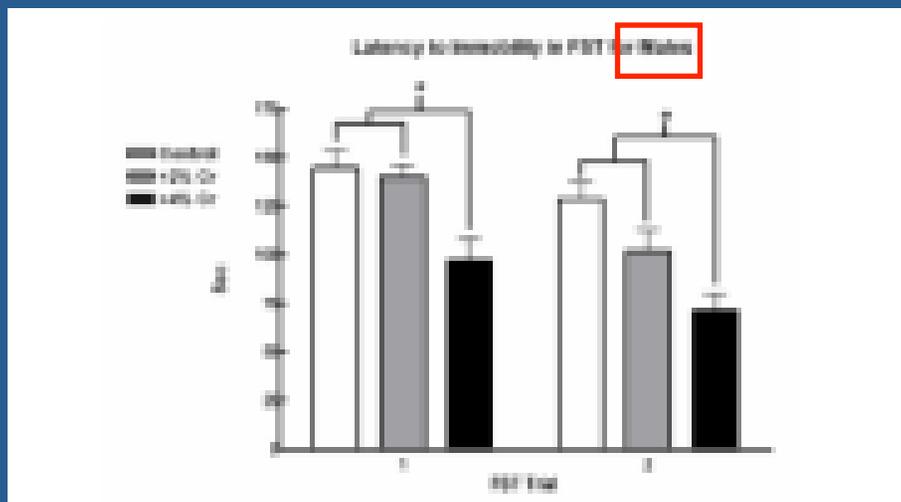
Hopeless

Carlezon et al

Chronic Creatine Supplementation Alters Depression-Like Behavior in Rodents in a Sex-Dependent Manner



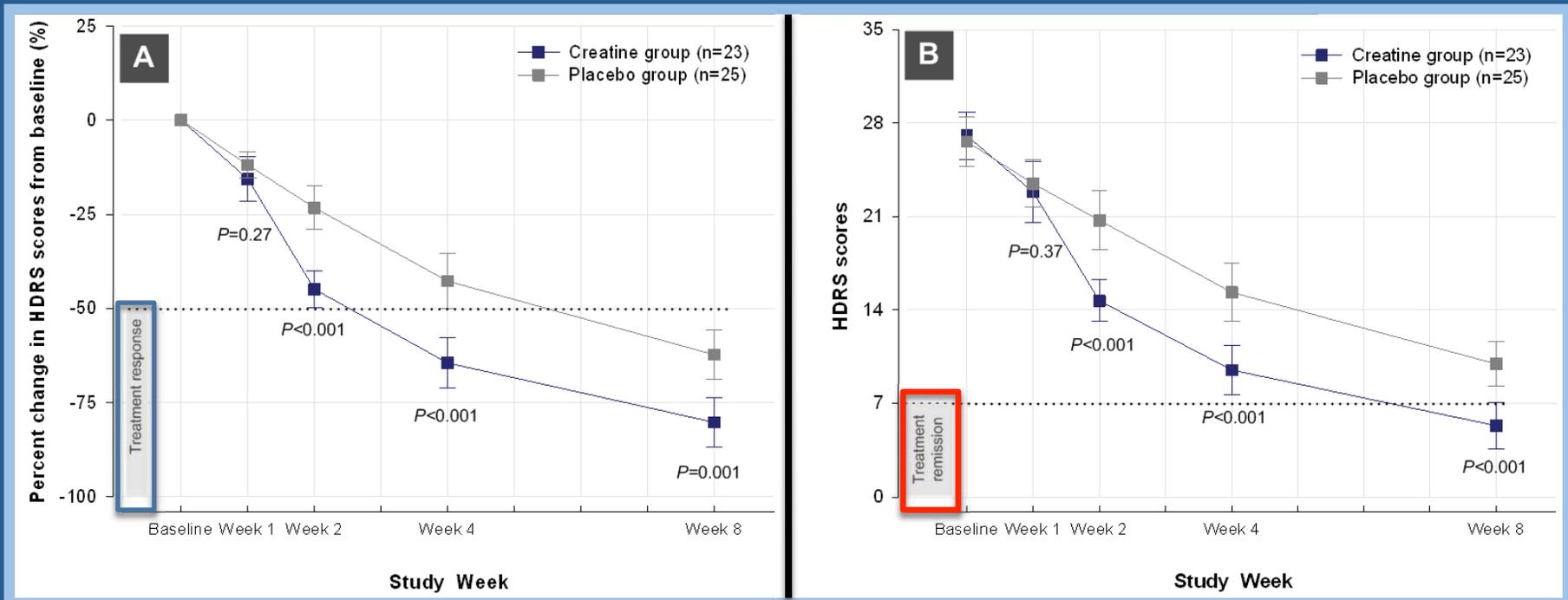
FEMALES



MALES

(Allen et al., 2010)

SSRI Augmentation in Adult Female Major Depression: RCT of Creatine vs. Placebo added to Lexapro®



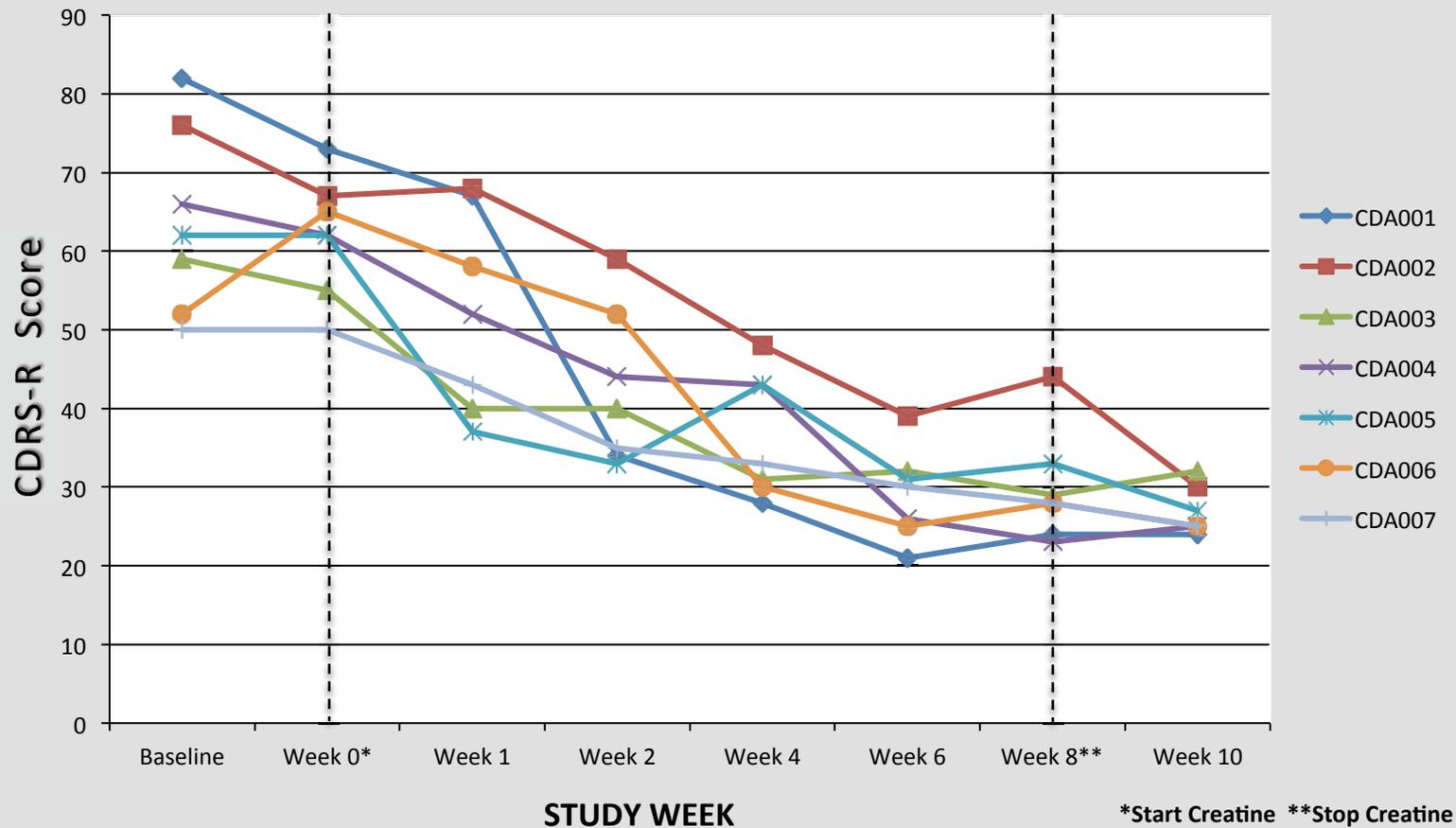
[A] CLINICAL RESPONSE: Percent decrease in Hamilton Depression Rating Scale scores (RESPONSE = ↓50%)

[B] CLINICAL REMISSION: Change in HDRS scores from baseline to 8 weeks (REMISSION ≤ 7)

Source: Lyoo, Yoon, Kim and Renshaw, *AJP*, 2012.

Creatine for Female Adolescents with SSRI-Resistant Major Depression[‡]

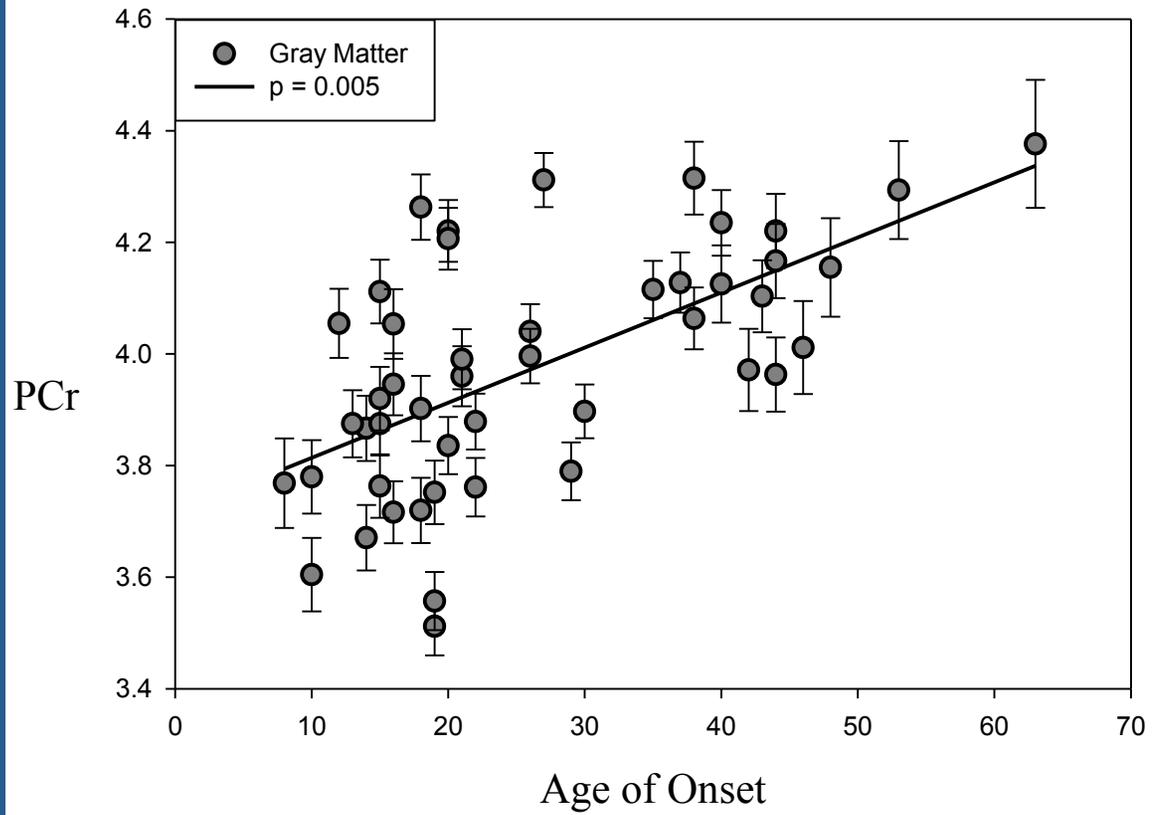
CHILDREN'S DEPRESSION RATING SCALE-REVISED (CDRS-R) SCORES: BASELINE TO 8 WEEKS



Source: Kondo, Sung, Hellem, Fiedler, Shi, Jeong and Renshaw. *J Affect Disord* 2011; 135(1-3):354-61.

[‡] Follow-on Creatine Adolescent Dose-Finding Study – Funded by NIMH 04/01/2012; Renshaw & Kondo [MH096858]

Gray Matter

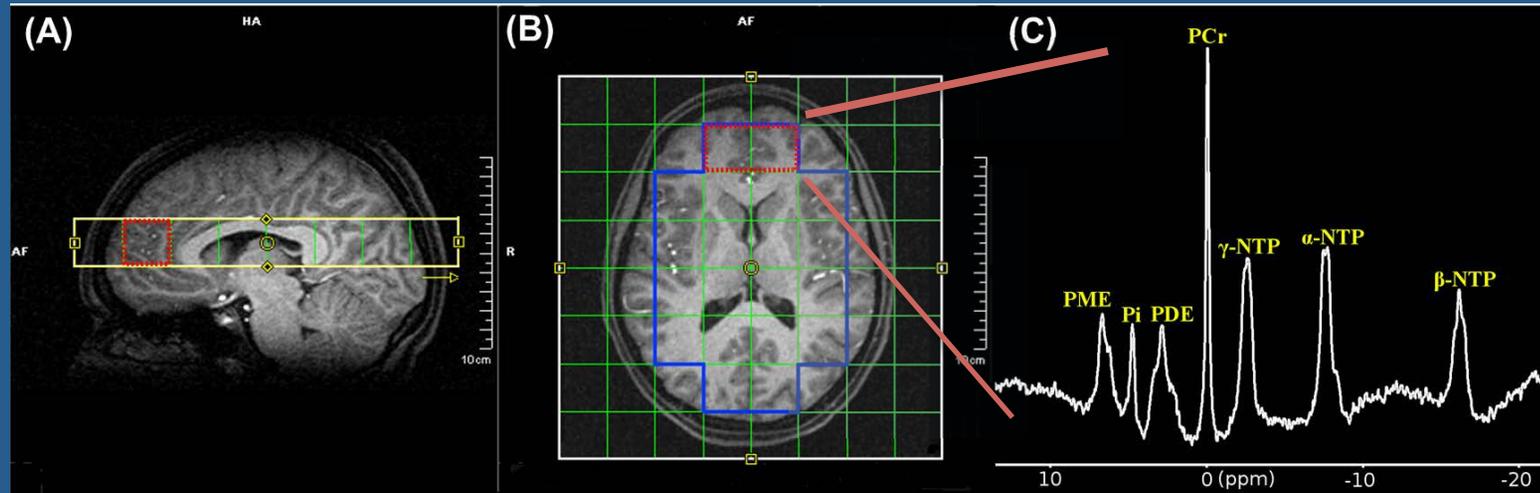


Age Effects on Depression with Altitude

Age Range	Beta	p-value
12-17	.466	.001
17-25	.409	.004
25+	.338	.018

How does this relate to
methamphetamine?

^{31}P -MRS



2D MRSI voxel placement and region of interest (frontal lobe)

- Two dimensional MRSI grid placement:
 - (A) Sagittal view
 - (B) Axial views. Dotted red line in the figure shows frontal lobe region of interest.
 - (C) A representative ^{31}P spectrum is displayed in frequency domain with 10 Hz exponential filtering.

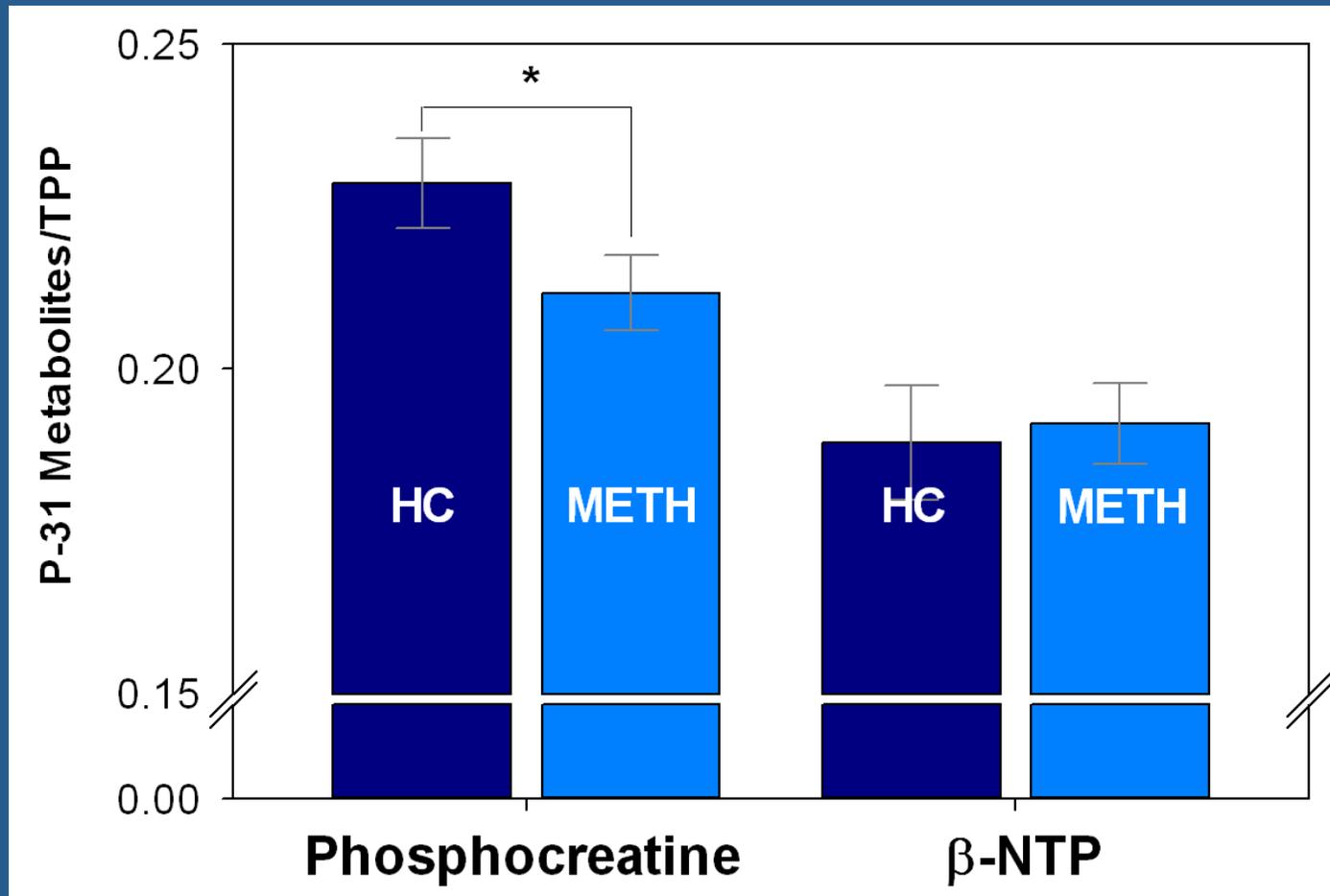
γ -ATP: -2.76 ppm
 α -ATP: -7.8 ppm
 β -ATP: -16.5 ppm

PCr : 0 ppm

PME : +6 ppm (2 ~ 8)

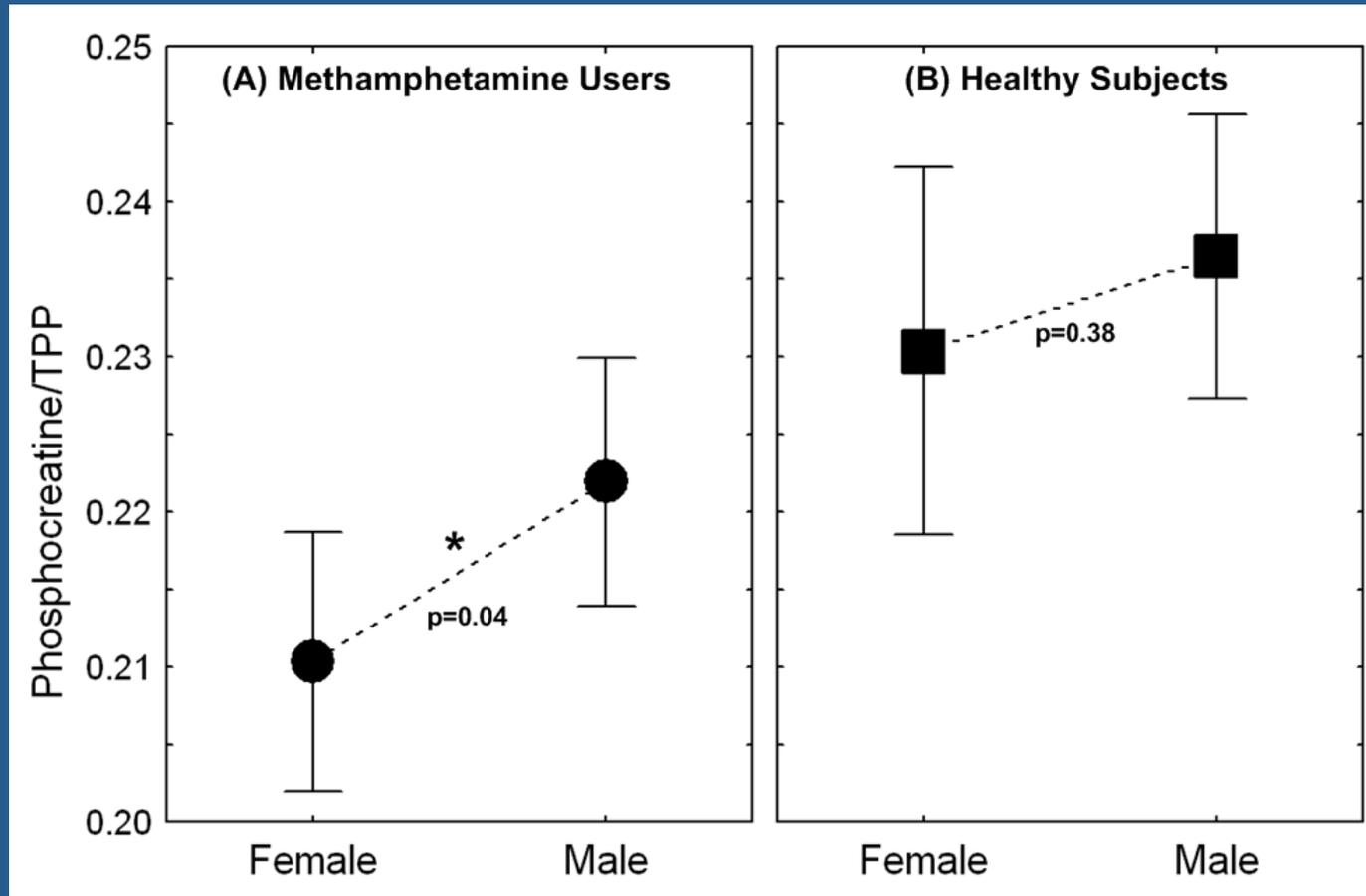
Pi : +5 ppm

PDE : +2 ppm (1.9 ~ 3.8)



Comparison of frontal lobe phosphorus metabolites levels in methamphetamine (METH, n=51) dependent subjects compared to healthy controls (HC, n=23). **Phosphocreatine levels were significantly reduced in METH users compared to HC ($p < 0.001$)**. There were no significant differences in β -NTP levels between the HC and METH groups. Error bars represent 95% confidence intervals. TPP, total exchangeable phosphate pool ($\text{pi} + \text{PCr} + \alpha, \beta, \gamma\text{-ATP}$).

Comparison of gender difference in PCr levels.



- (A) In METH-dependent subjects, female METH users (n=23) had significantly lower PCr levels compared to male METH users (n=28).
- (B) Healthy subjects did not show significant gender difference.

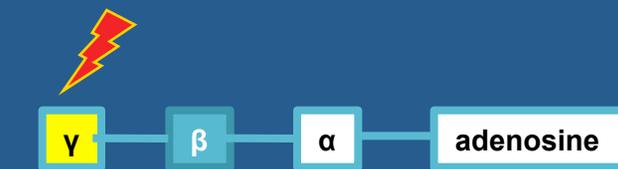
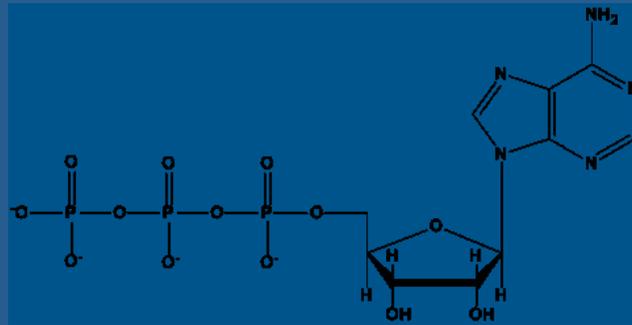
Magnetization Transfer: Beyond Static Measurements

Creatine Kinase

- Creatine kinase (CK)
 - $\text{PCr}^{2+} + \text{ADP}^- \leftrightarrow \text{Cr} + \text{ATP}^{2-}$
 - Enzyme that replenishes adenosine triphosphate (ATP) levels in phosphocreatine-creatine (PCr-Cr) circuit for temporal and spatial energy buffering.
- Two cytosolic CK subunits including "B" (brain type) and "M" (muscle type)
 - Brain type-CK (CK-BB) is the major isoenzyme in brain.
- Creatine
 - Involved in bioenergetic homeostasis in human brain
 - Creatine supplementation may activate CK to augment the energy state of neurons and to increase mitochondrial energy production (Saks, 2000).
 - Should abnormal CK activity or flux is observed in METH users, creatine supplementation may recover compromised CK system.

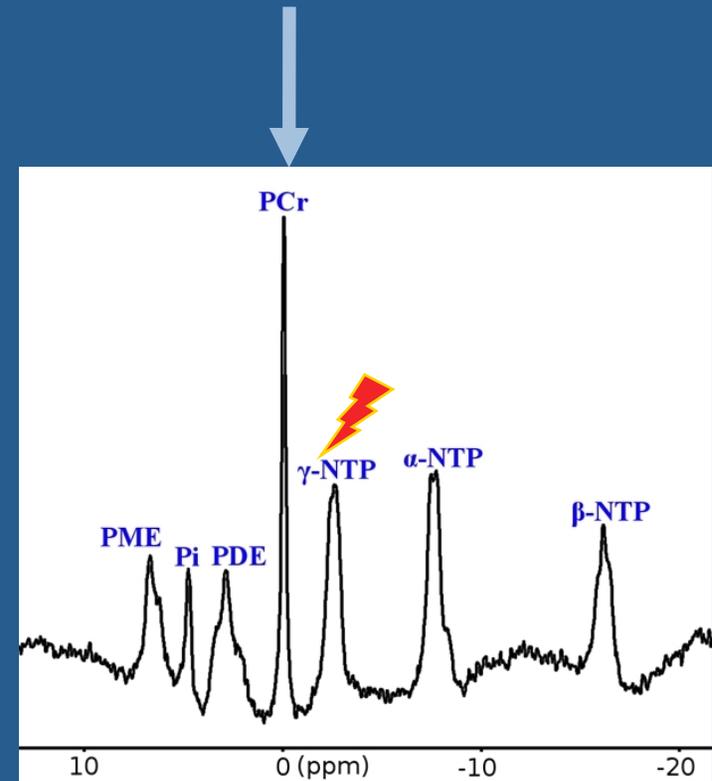
Chemical exchanges: γ -ATP and PCr

ATP (Adenosine triphosphate)

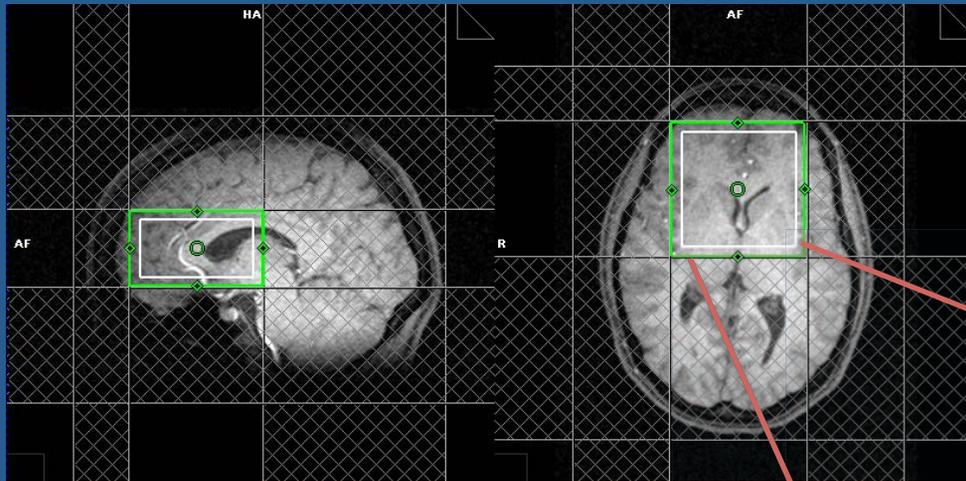


Creatine kinase (CK)

PCr



^{31}P -MT Spectroscopy



Frontal-striatal voxel placement

γ -ATP saturated spectra at -2.7 ppm (left) and control spectra to compensate 'RF bleedover' at +2.7 ppm (right)

