Methamphetamine and the Brain: Three Tales

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THE BRAIN INSTITUTE

THE UNIVERSITY OF UTAH

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

Table. Demographic and Clinical Characteristics of Study Participants *

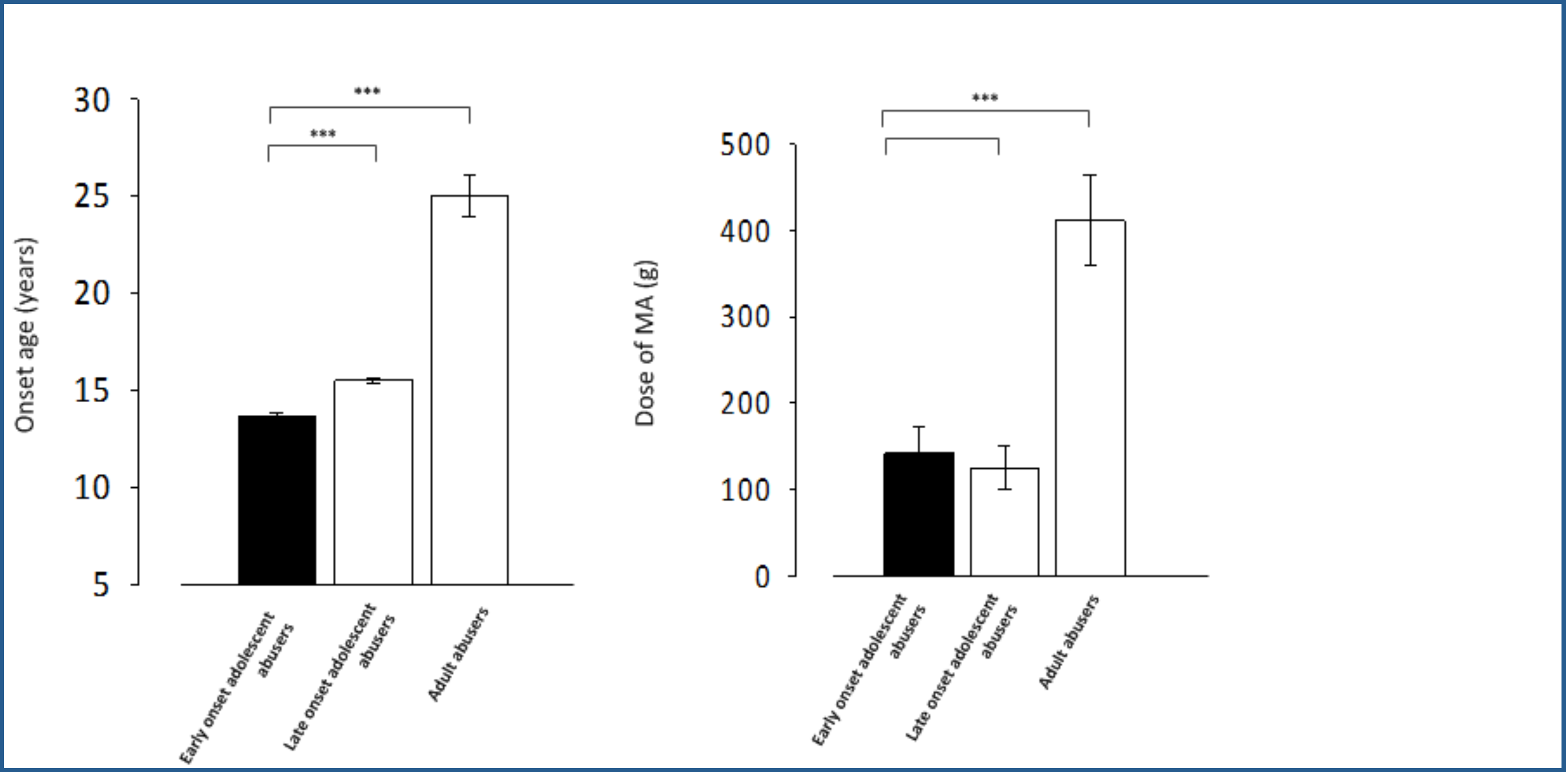
Characteristics	Adolescent group			Adult group		
	Methamphetamine users (n=31)	Control subjects (n=31)	P value†	Methamphetamine users (n=40)	Control subjects (n=40)	P value†
Demographics						
Age — yr						
Mean	18.1±1.5	18.1±1.4	0.97	41.8±6.2	42.1±6.0	0.87
Range	15.4 to 19.9	15.5 to 19.9		34.3 to 57.9	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

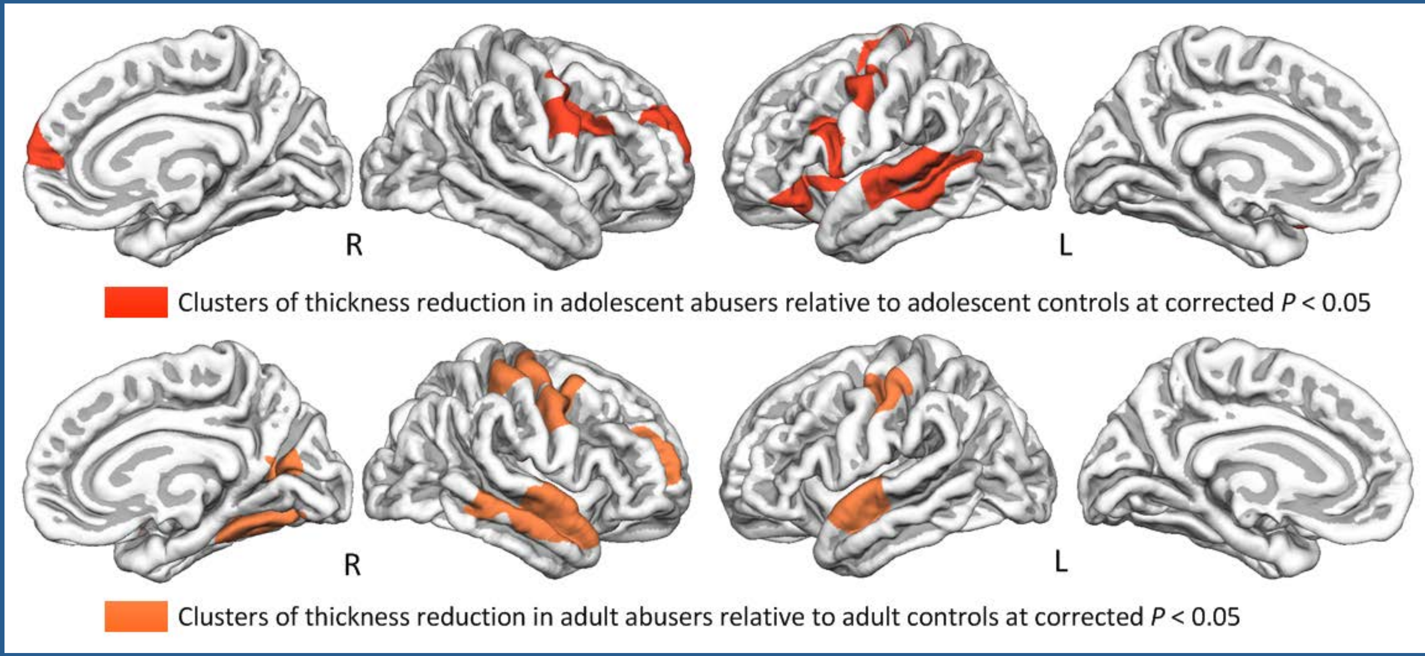
13 early-onset vs. 18 late-onset adolescent users vs. 40 adult users



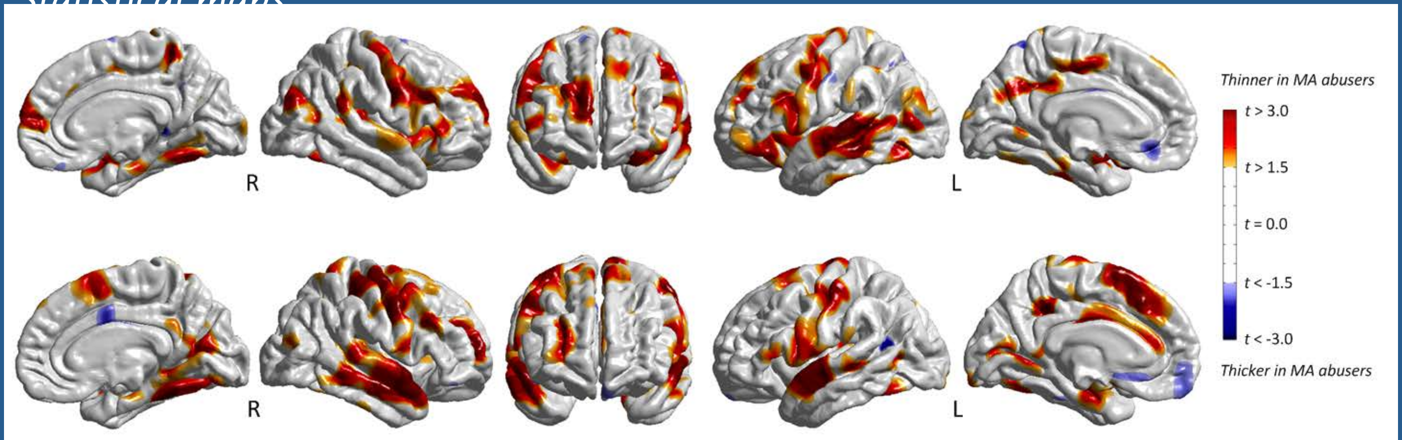
In general, adult users have taken higher lifetime cumulative dose of methamphetamine.

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

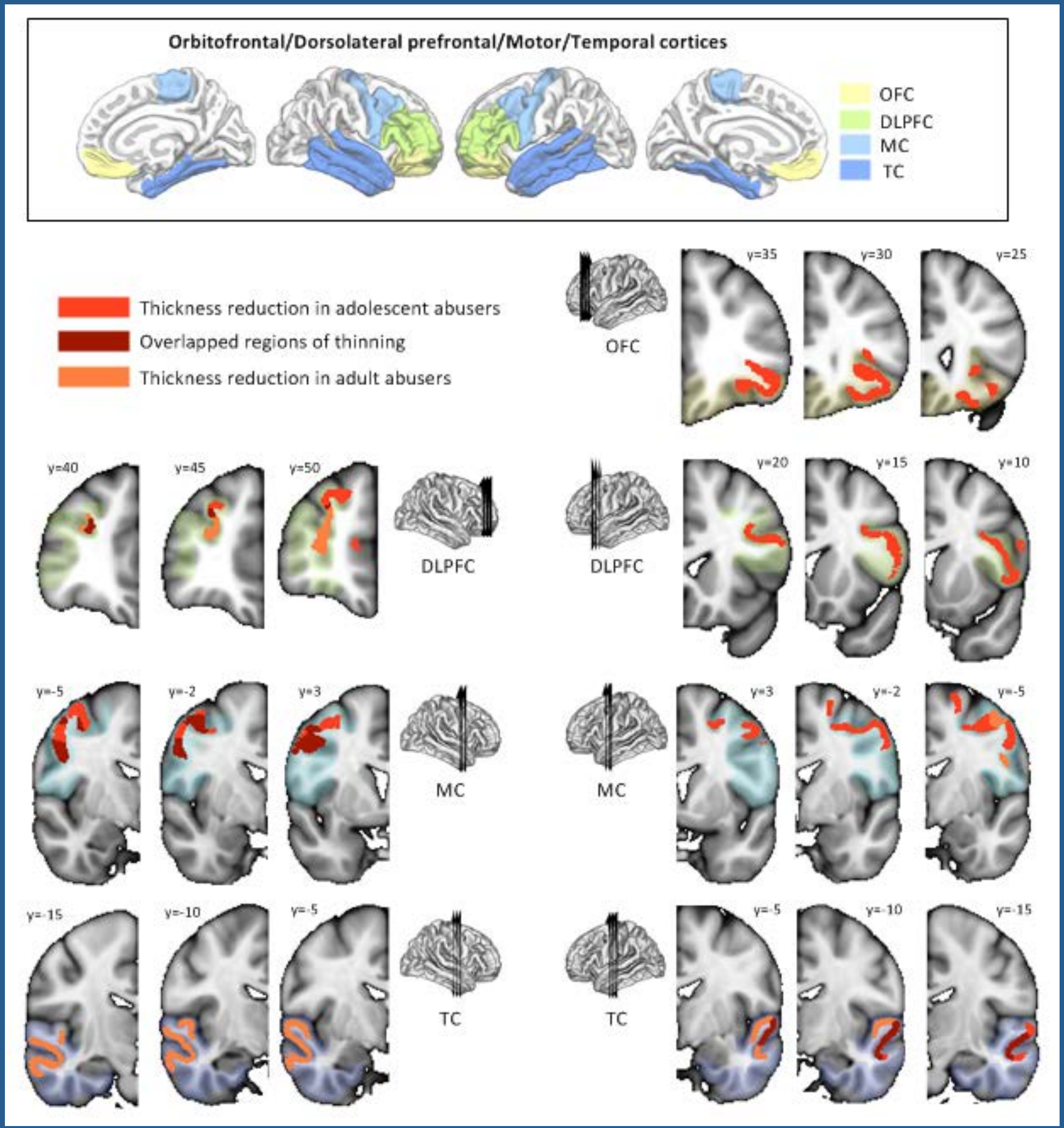
Gray matter alterations in adolescent and adult methamphetamine users



Statistical maps

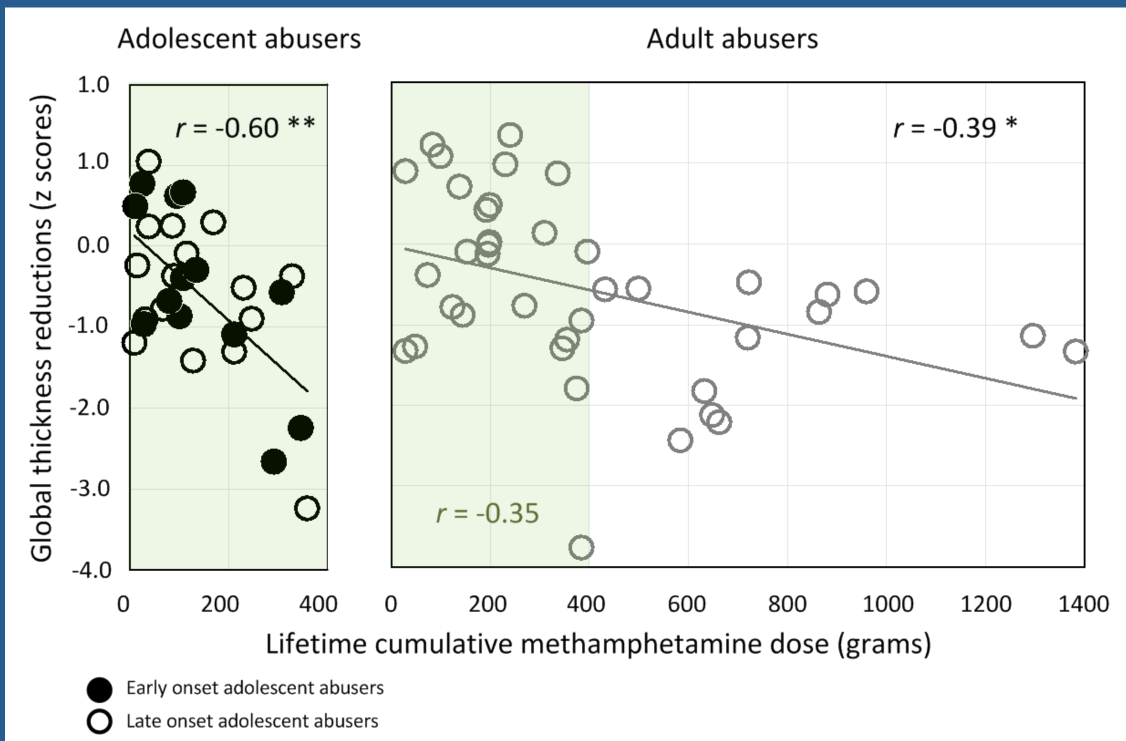


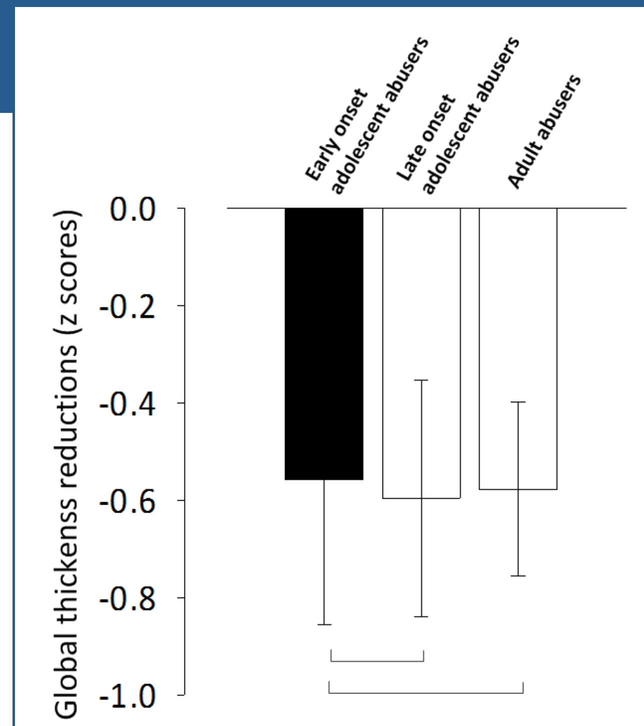
Effects of Exposure of Methamphetamine on the Adolescent Brain (IV)



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)

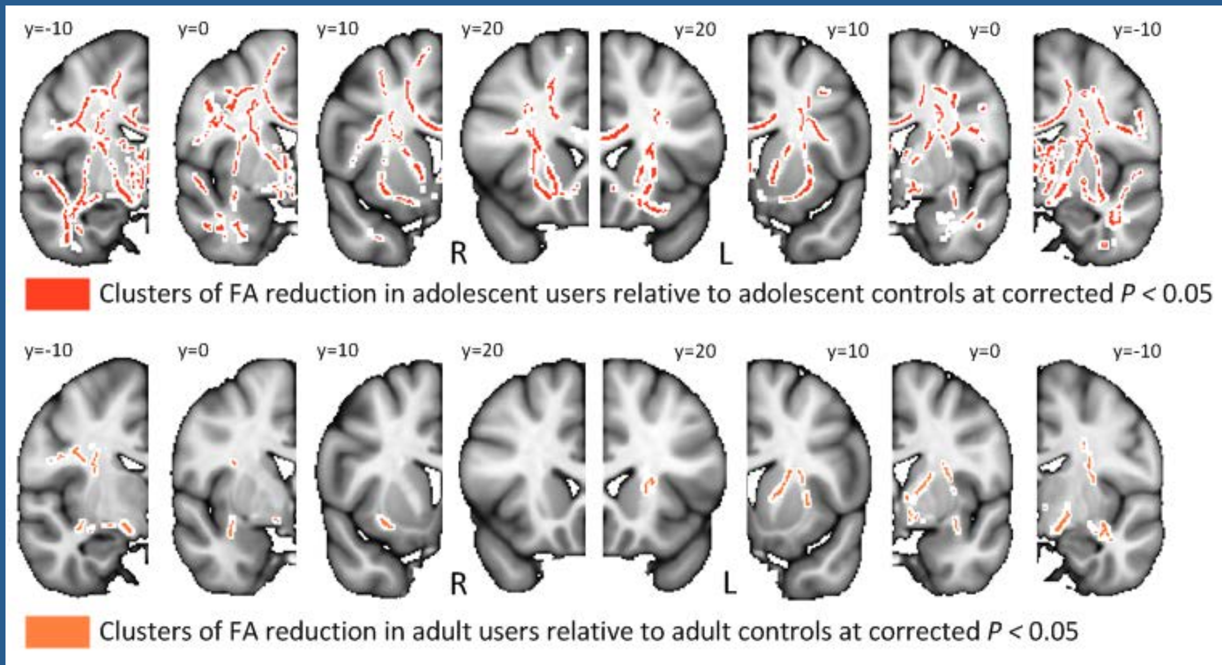




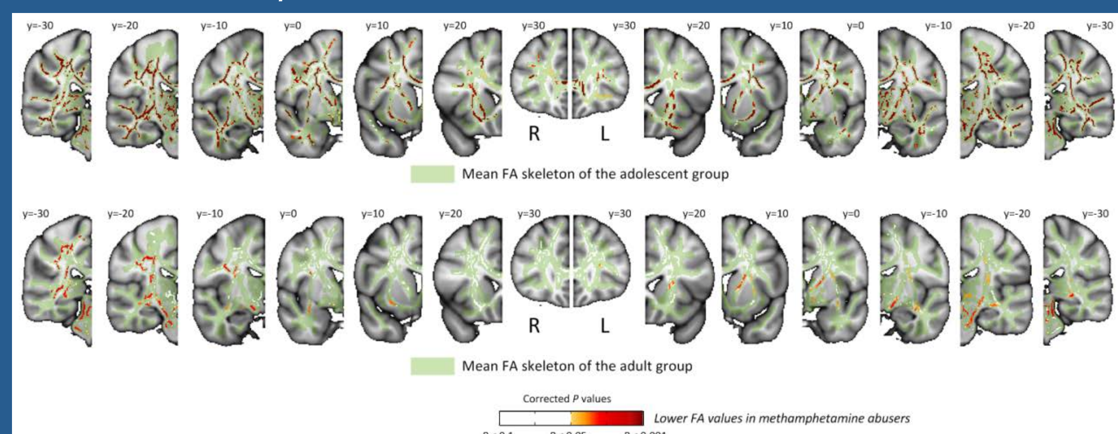
Larger dose-dependent effects of cumulative methamphetamine doses were observed in adolescent users. Gray matter thickness reductions were therefore similar between adult and adolescent user groups, despite a greater amount of methamphetamine use in adult users.

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

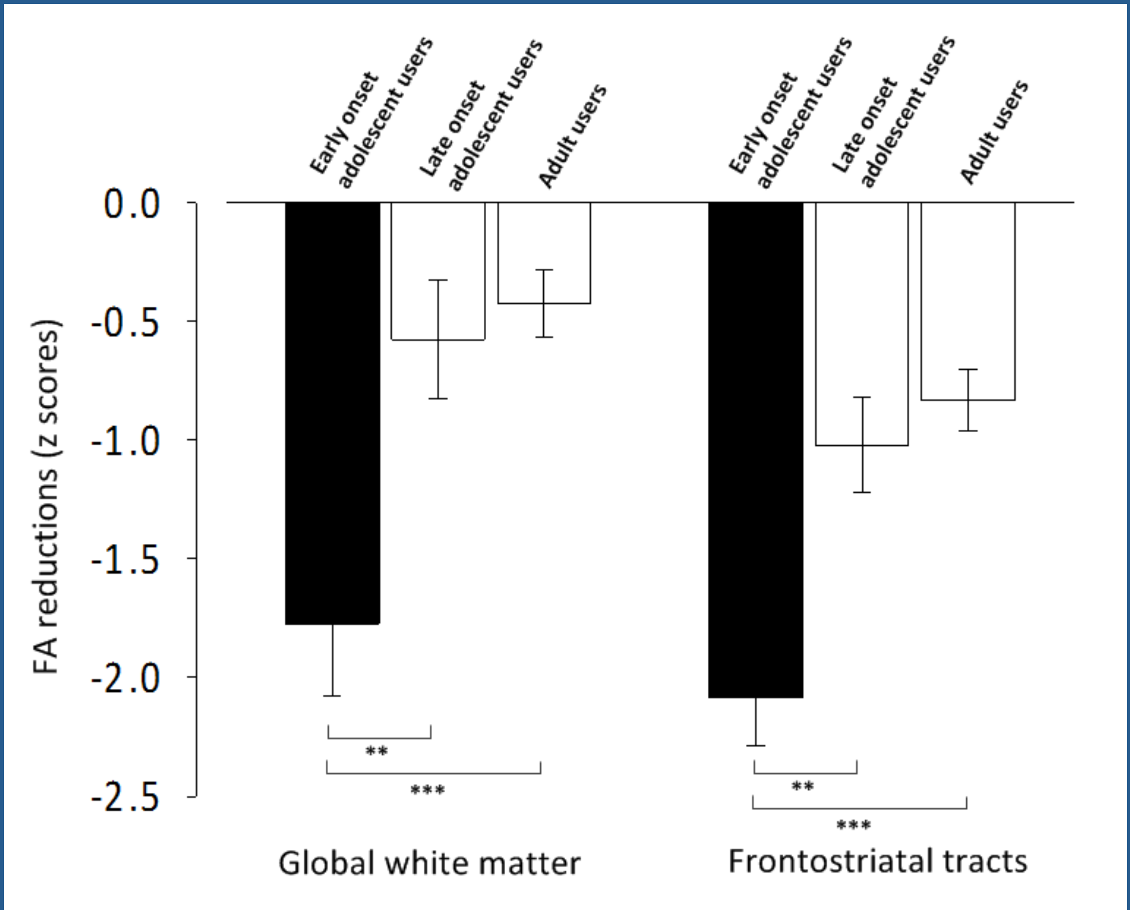
White matter alterations in adolescent and adult methamphetamine users



Statistical maps

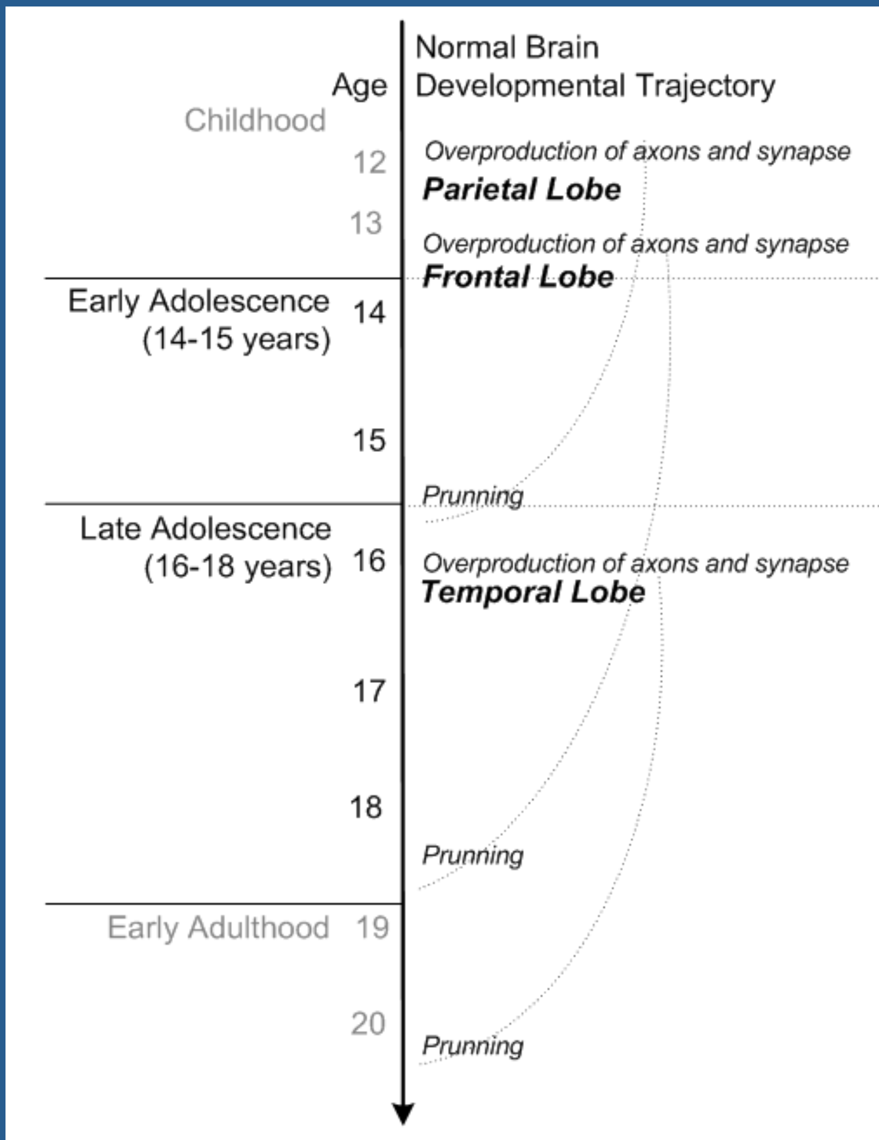


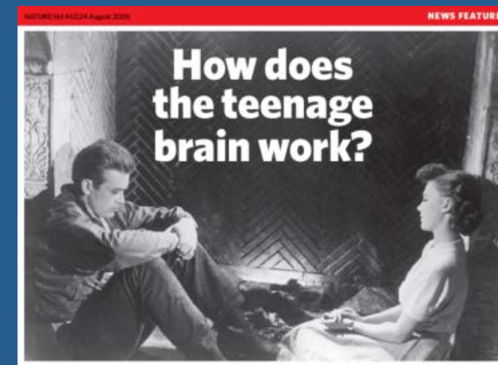
Effects of Exposure of Methamphetamine on the Adolescent Brain (VII)



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.

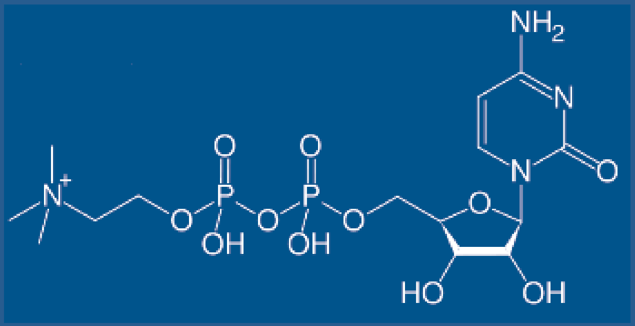
Implications and Next Steps

•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.

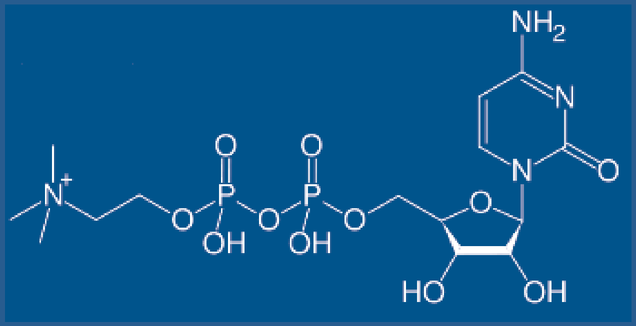
•3. Efforts aimed at neuroprotection/ resiliency may be important for treatment.

Citicoline



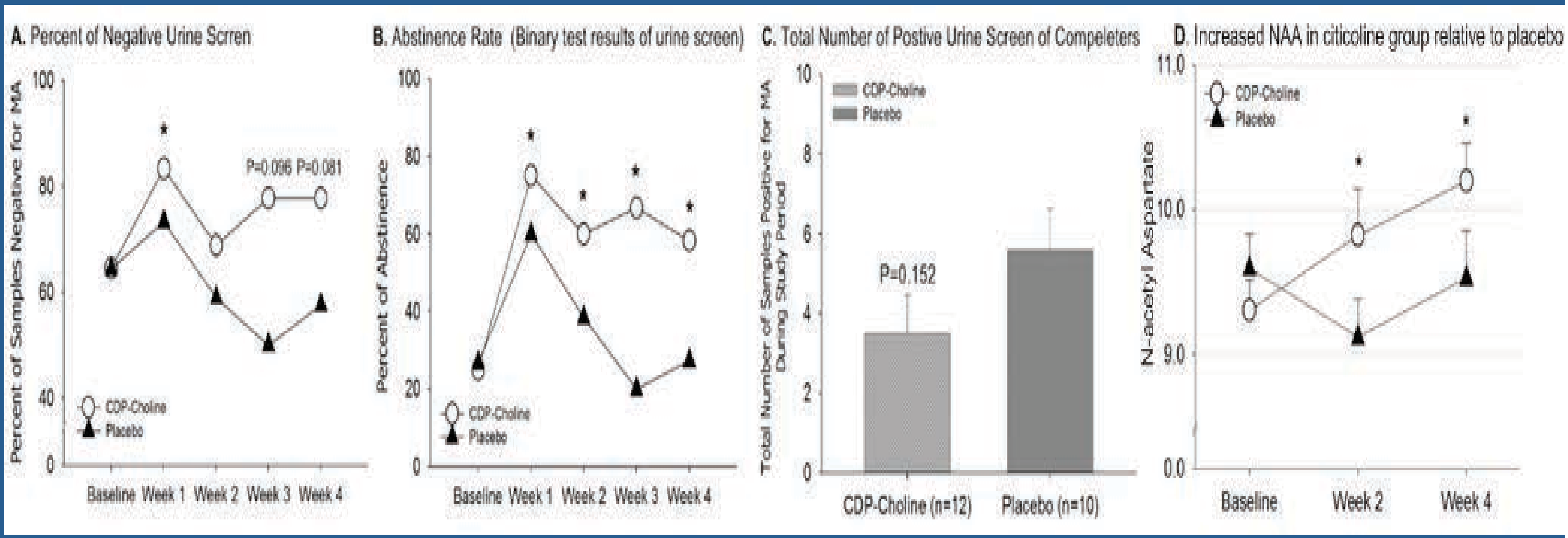
- A natural product and nutritional supplement
- Mechanism
  - Activates the biosynthesis of phospholipids in neuronal membranes (conveys neuroprotection by scavenging toxic lipid breakdown products)
  - Increases norepinephrine and dopamine levels in the central nervous system presumably by increasing 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

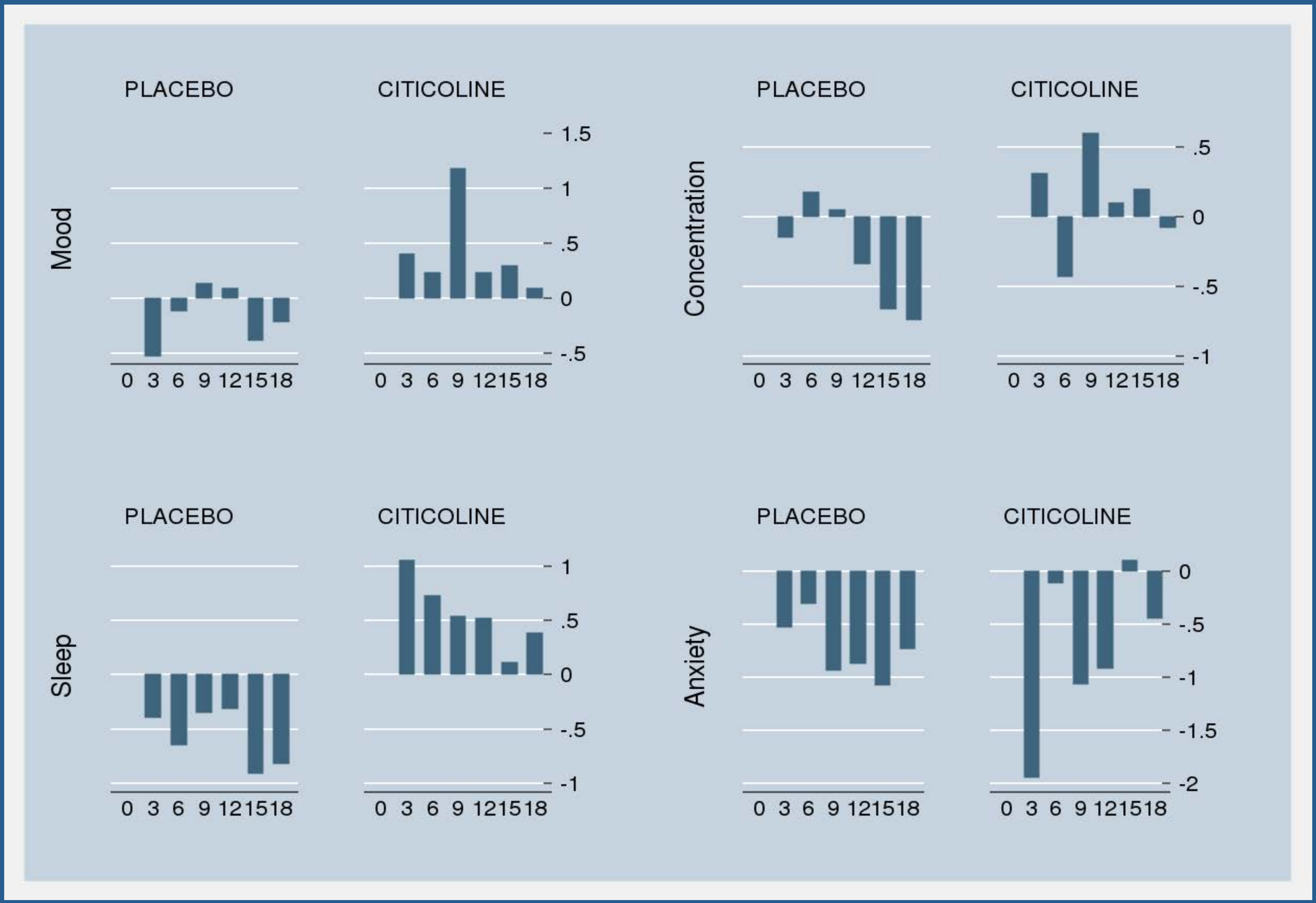


- Significantly decreased urge for cocaine in a group of cocaine dependent subjects following 2 weeks of citicoline relative to placebo. (Renshaw, 1999)
- Cardiovascular safety of combine citicoline and cocaine administration. (Lukas, 2001)
- Established safety in pediatric populations.
- Tends to decrease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

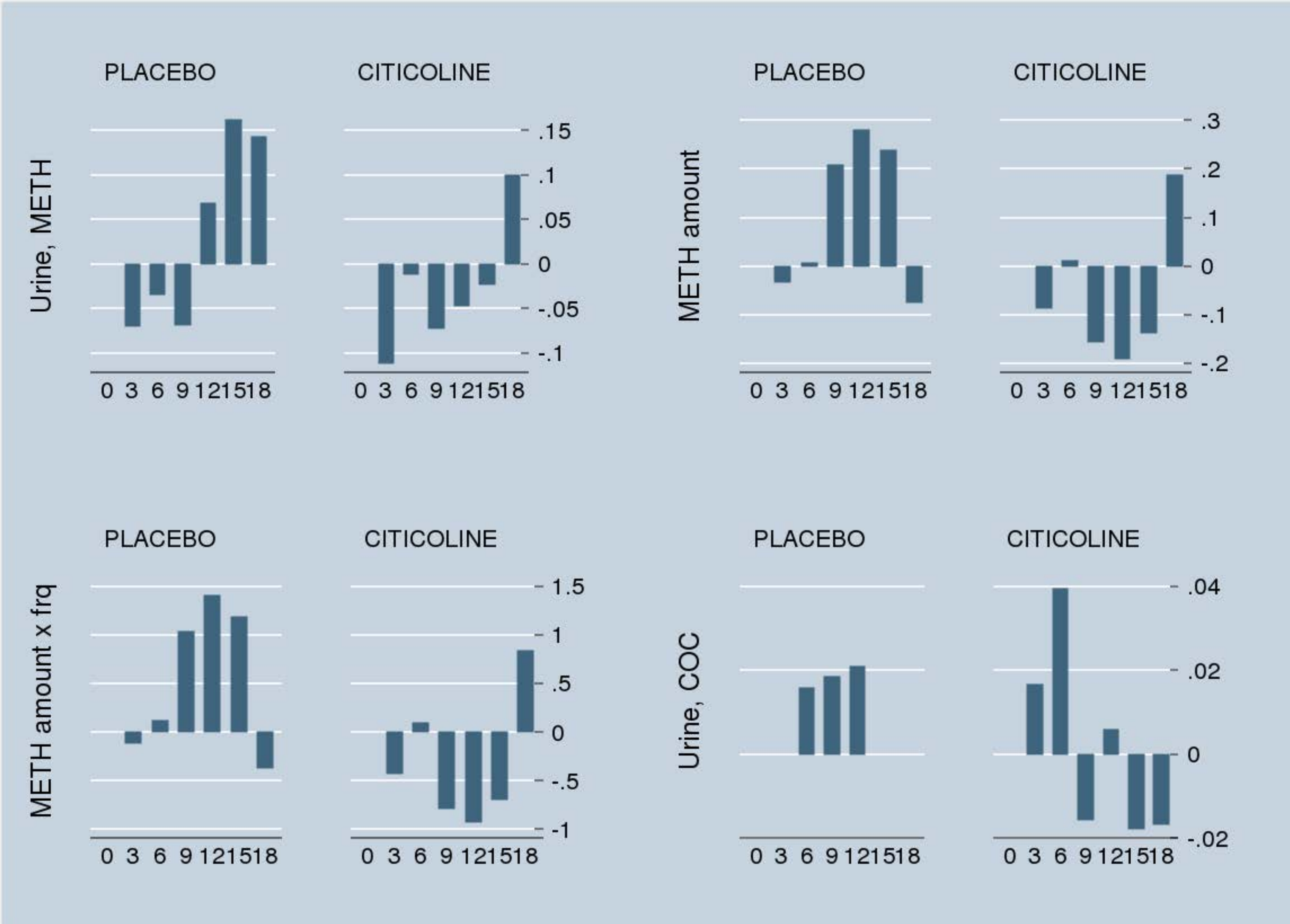
Citicoline Treatment of Methamphetamine Dependence (Study 1 of 2; N = 31)



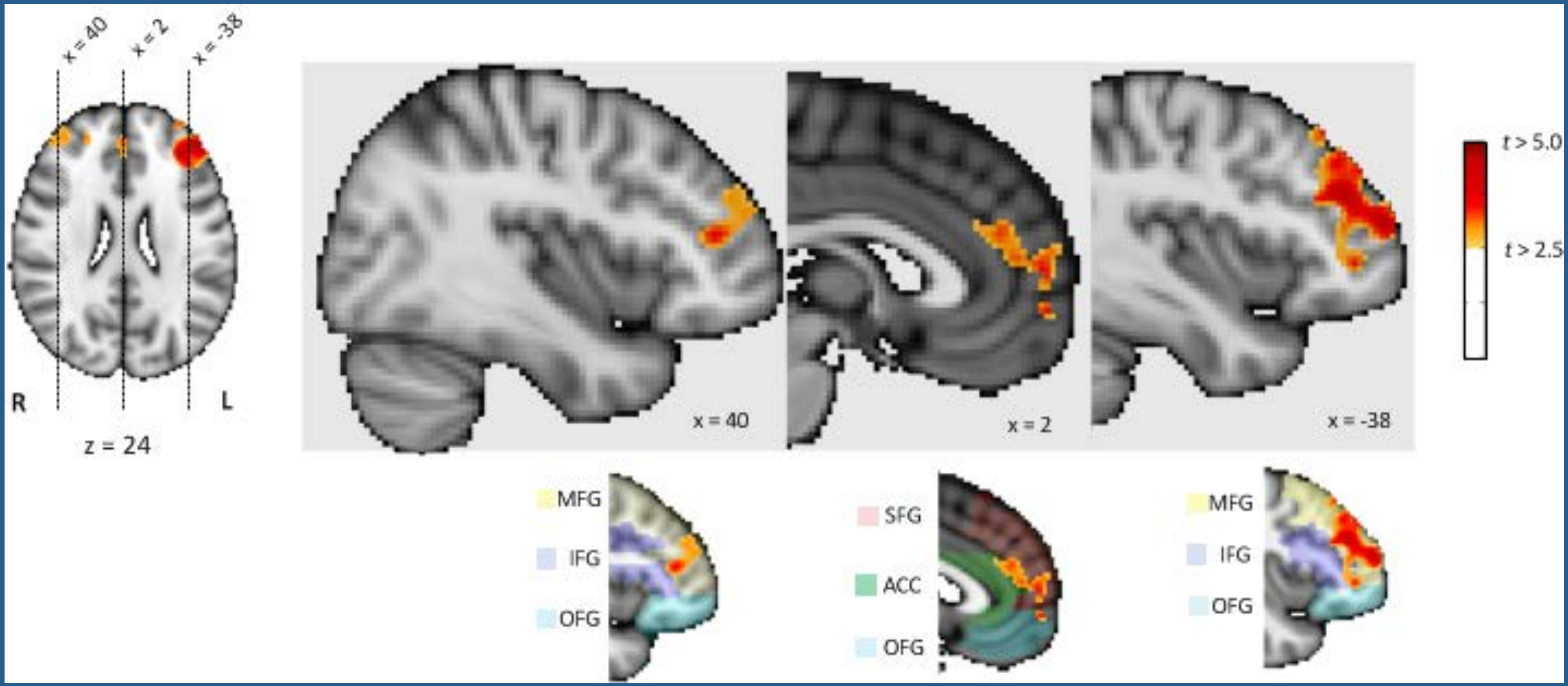
Study 2 of 2: Mood, Concentration, Sleep, and Anxiety (N = 52)



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



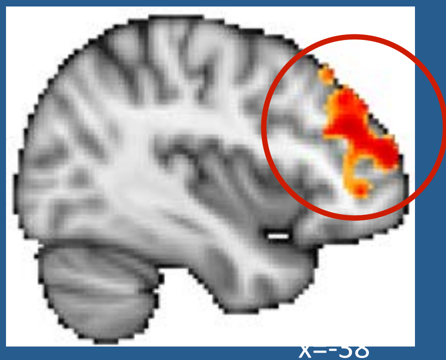
Gray matter volume deficits related METH dependence

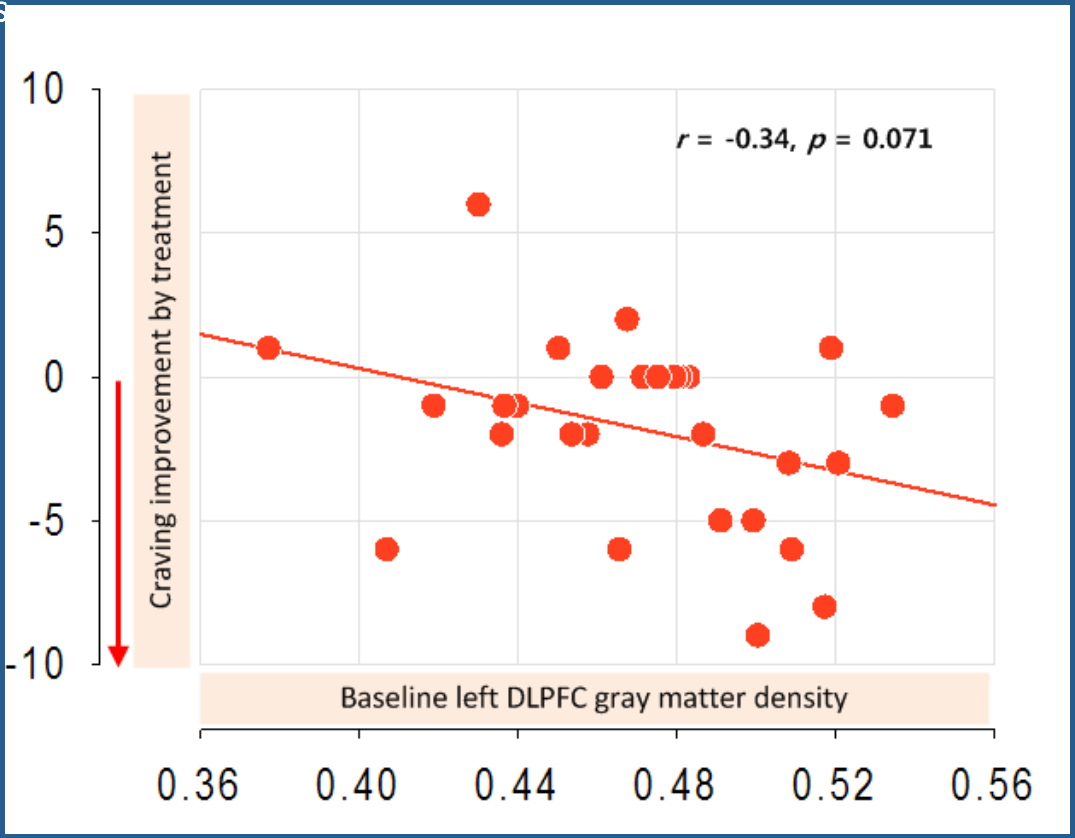


44 METH-dependent subjects vs. 27 healthy subjects

Potential treatment targets for craving

Left DLPFC region of METH effects

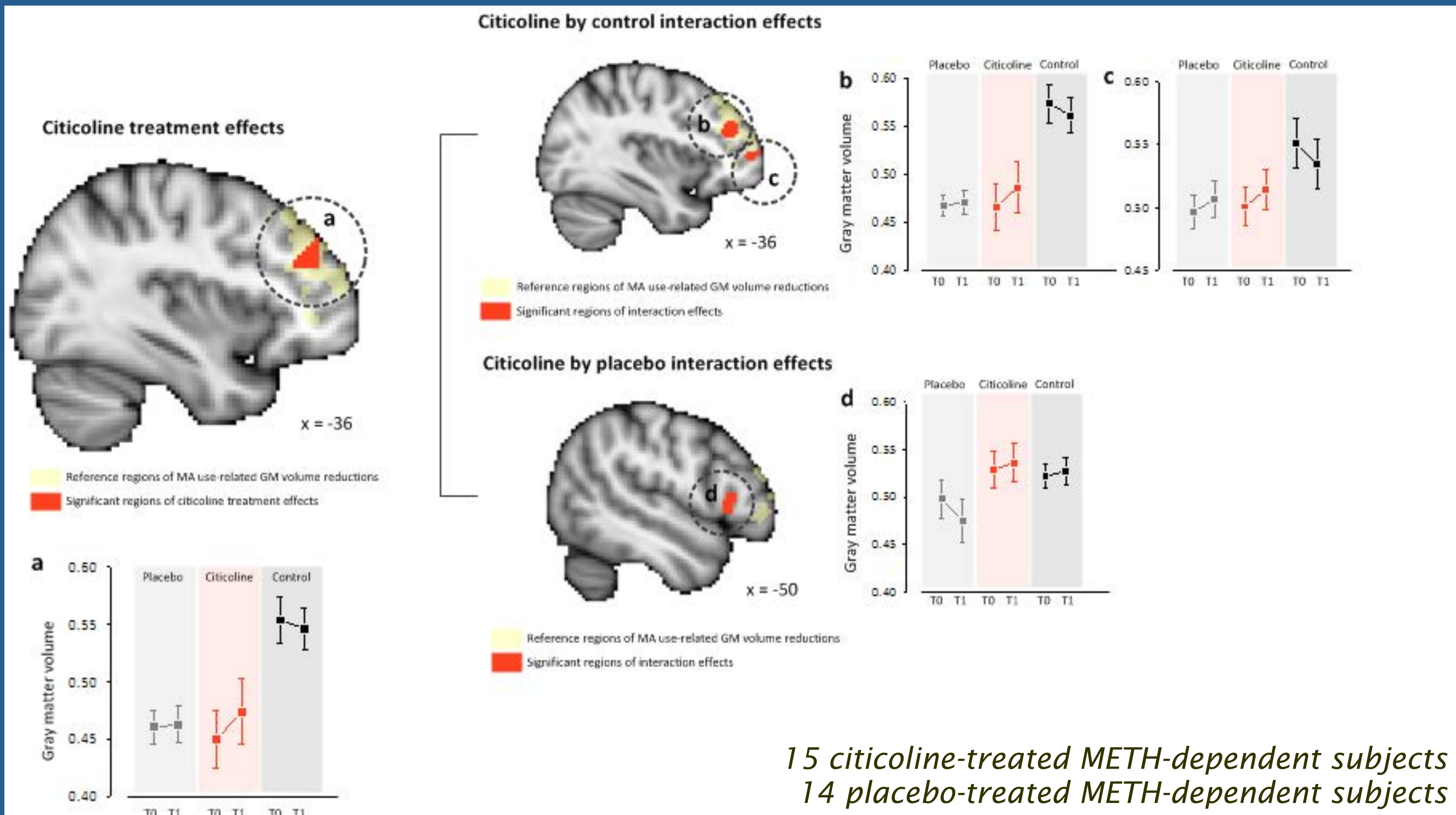




29 METH –dependent subjects
with group therapy either with placebo or citicoline treatment

Less METH-related DLPFC volume deficits predict craving improvement

Citicoline treatment effects on left DLPFC gray matter volume

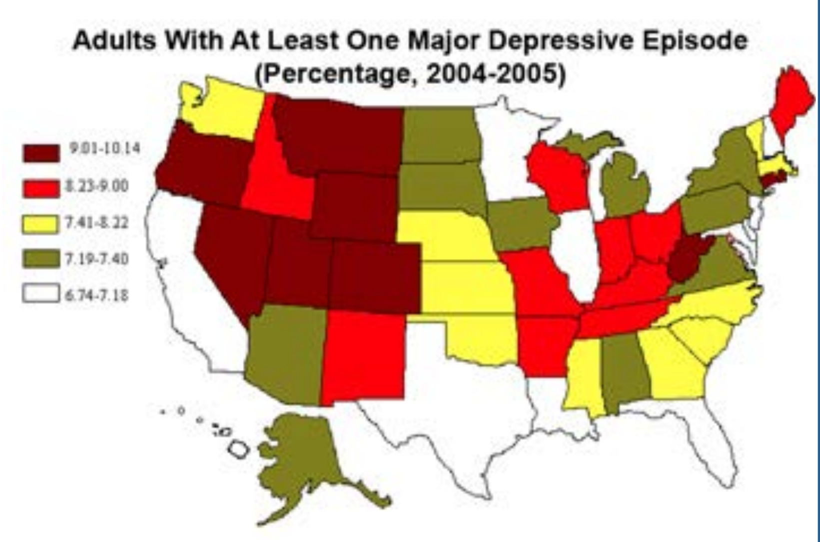


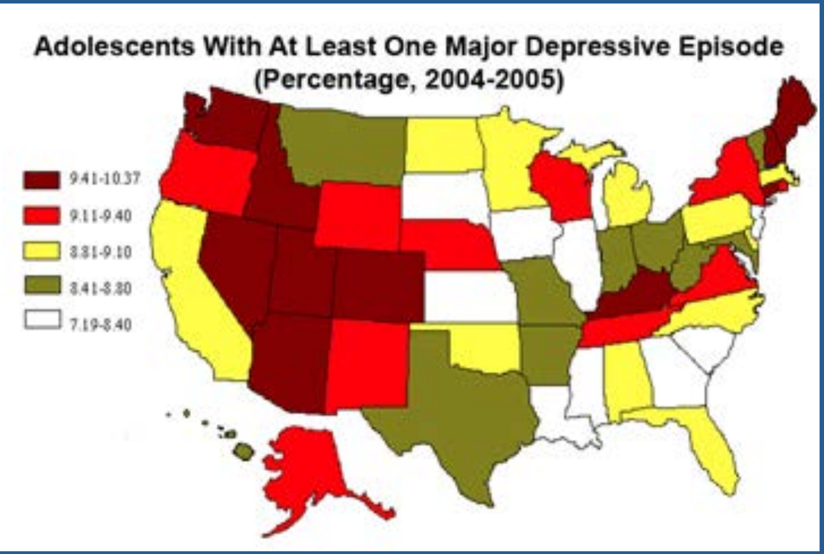
15 citicoline-treated METH-dependent subjects
14 placebo-treated METH-dependent subjects
21 healthy control subjects

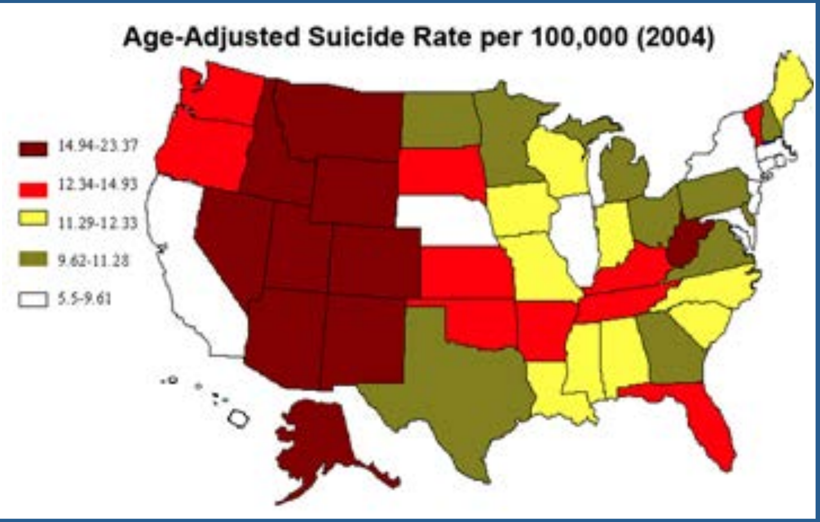
Corrected *p* < 0.05

Rocky Mountain High?

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

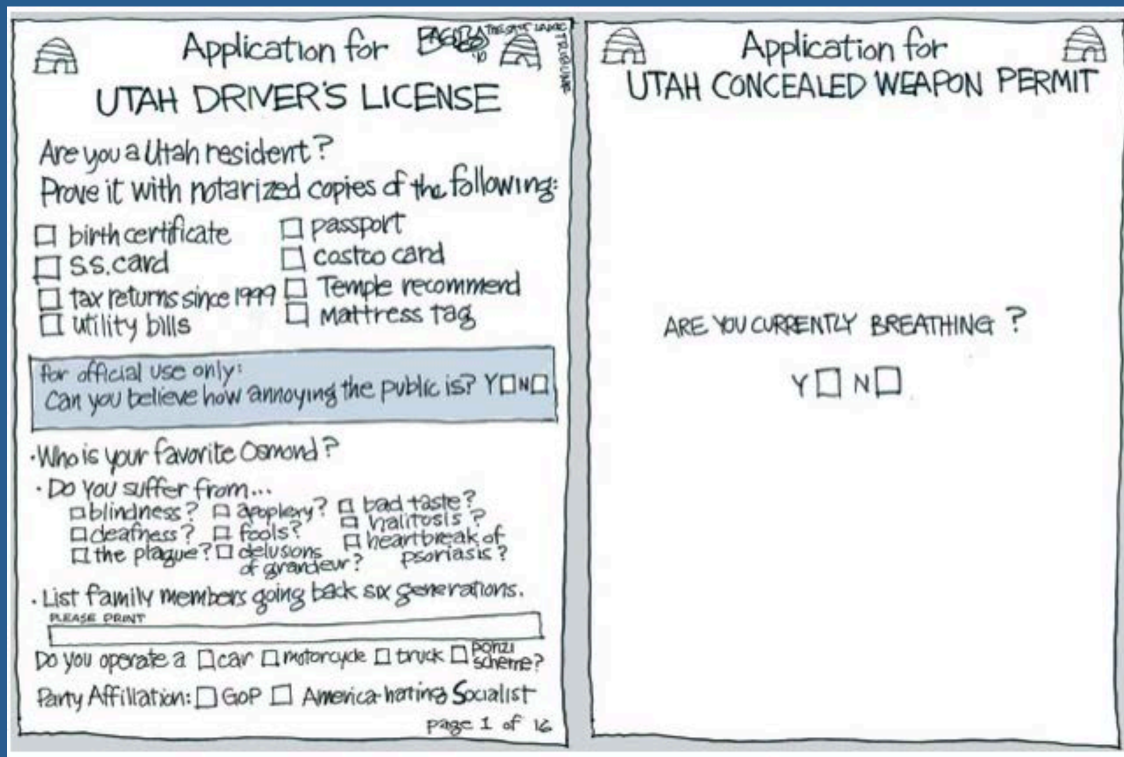






(Ranking America's Mental Health, 2007)

Established Theory #1

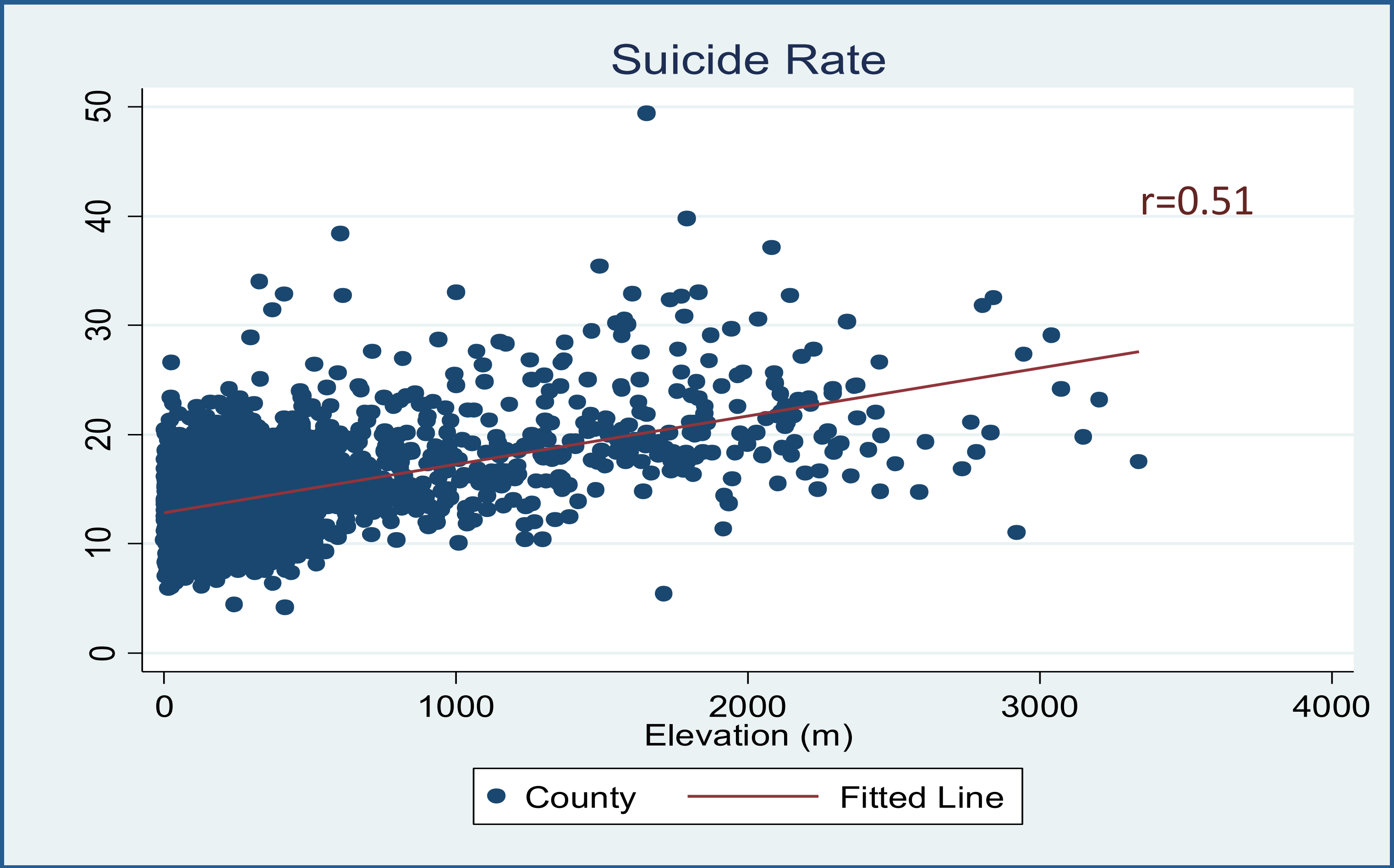


Source: Pat Bagley. The Salt Lake Tribune.
Sunday, July 14, 2010.

Off the Deep End?

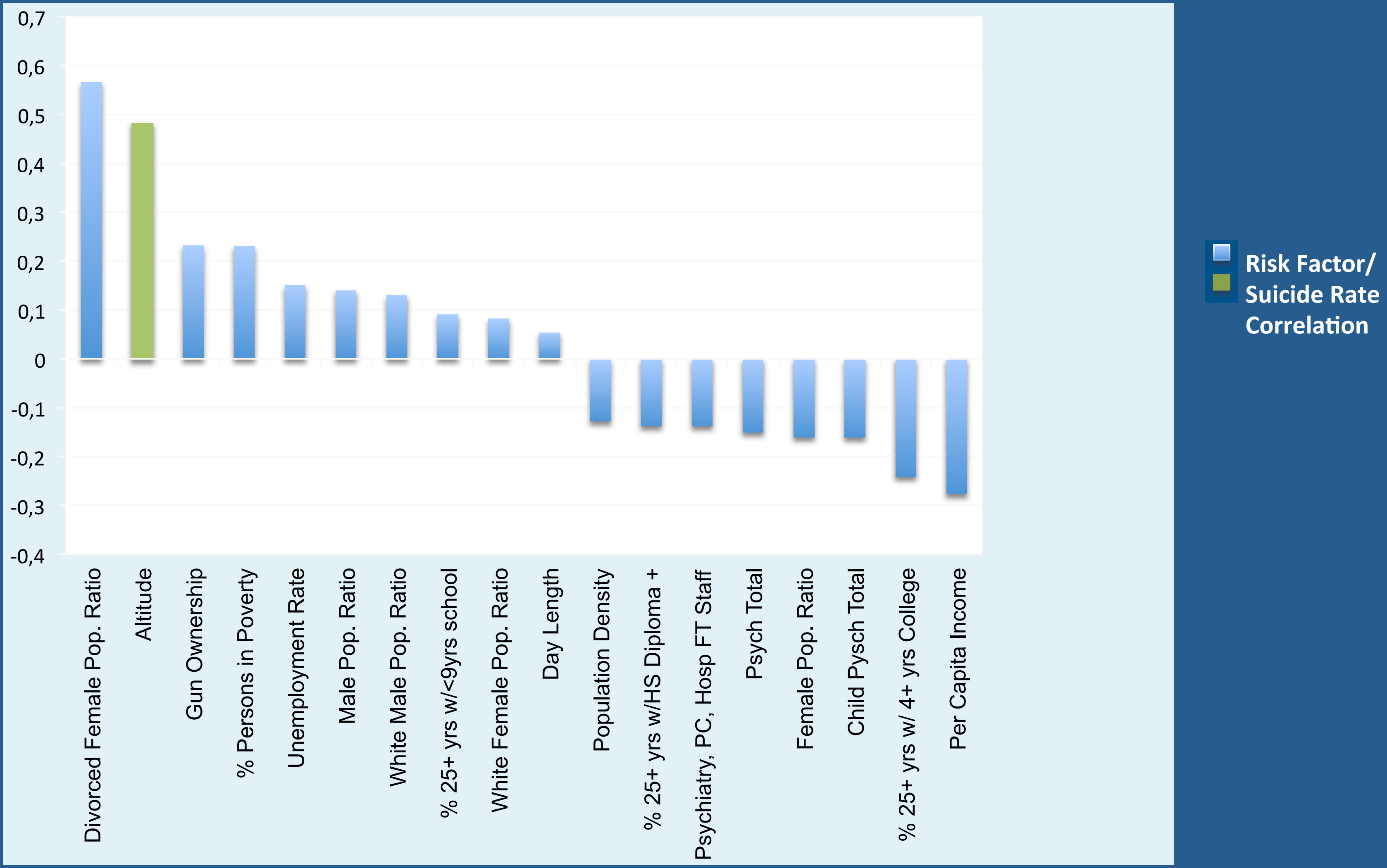
Source: www.images.com

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



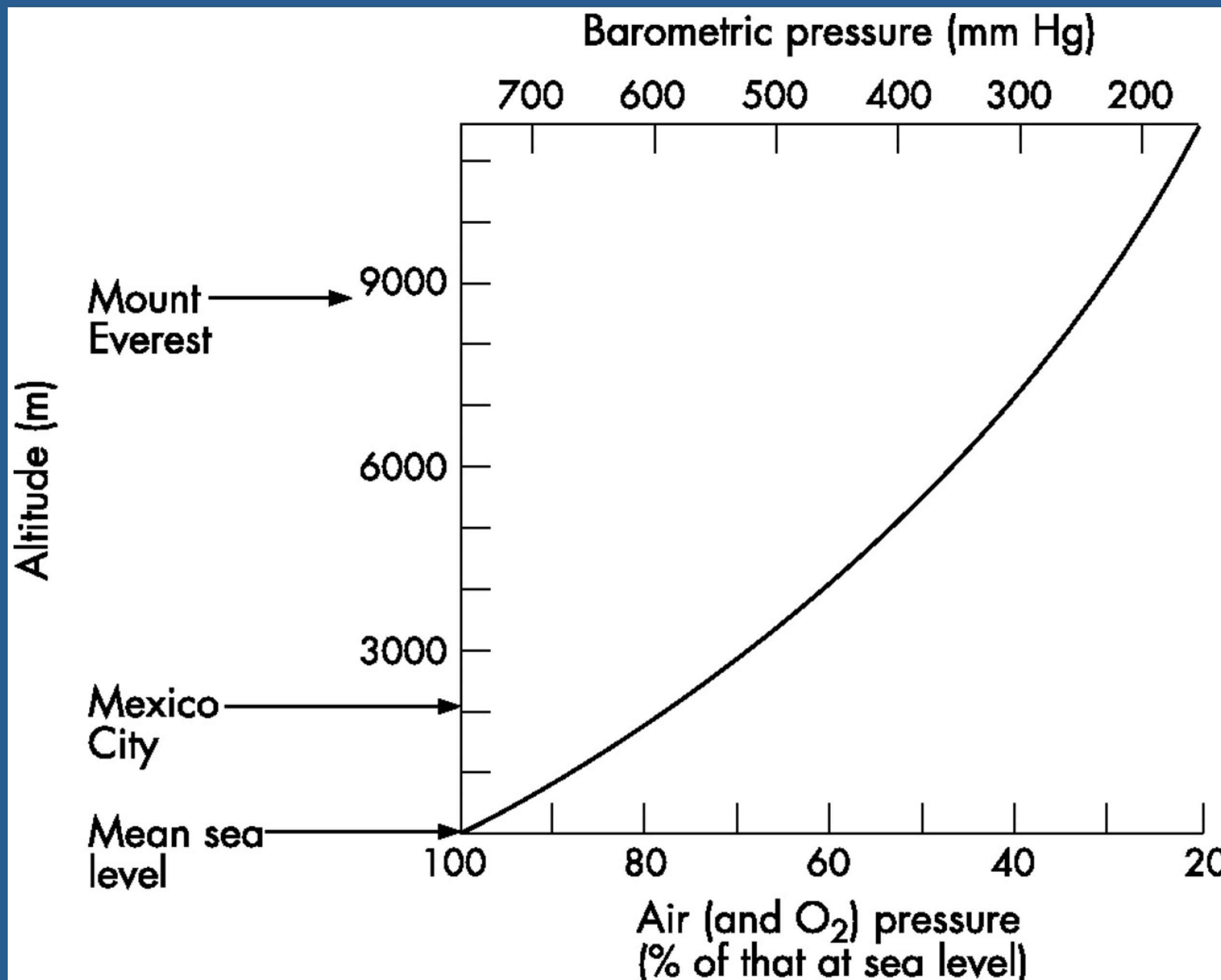
Source: Kim et al., American Journal of Psychiatry (2011) January;168(1):49-54

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 (PiO_2)	Equivalent O_2 Concentration at Sea Level (FiO_2)	Decrease In FiO_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

Neurochemistry International 58 (2011) 112–118

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/neuint

Hypobaric hypoxia modulates brain biogenic amines and disturbs sleep architecture

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ABSTRACT

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)
1 week exposure		
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*
2 week exposure		
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

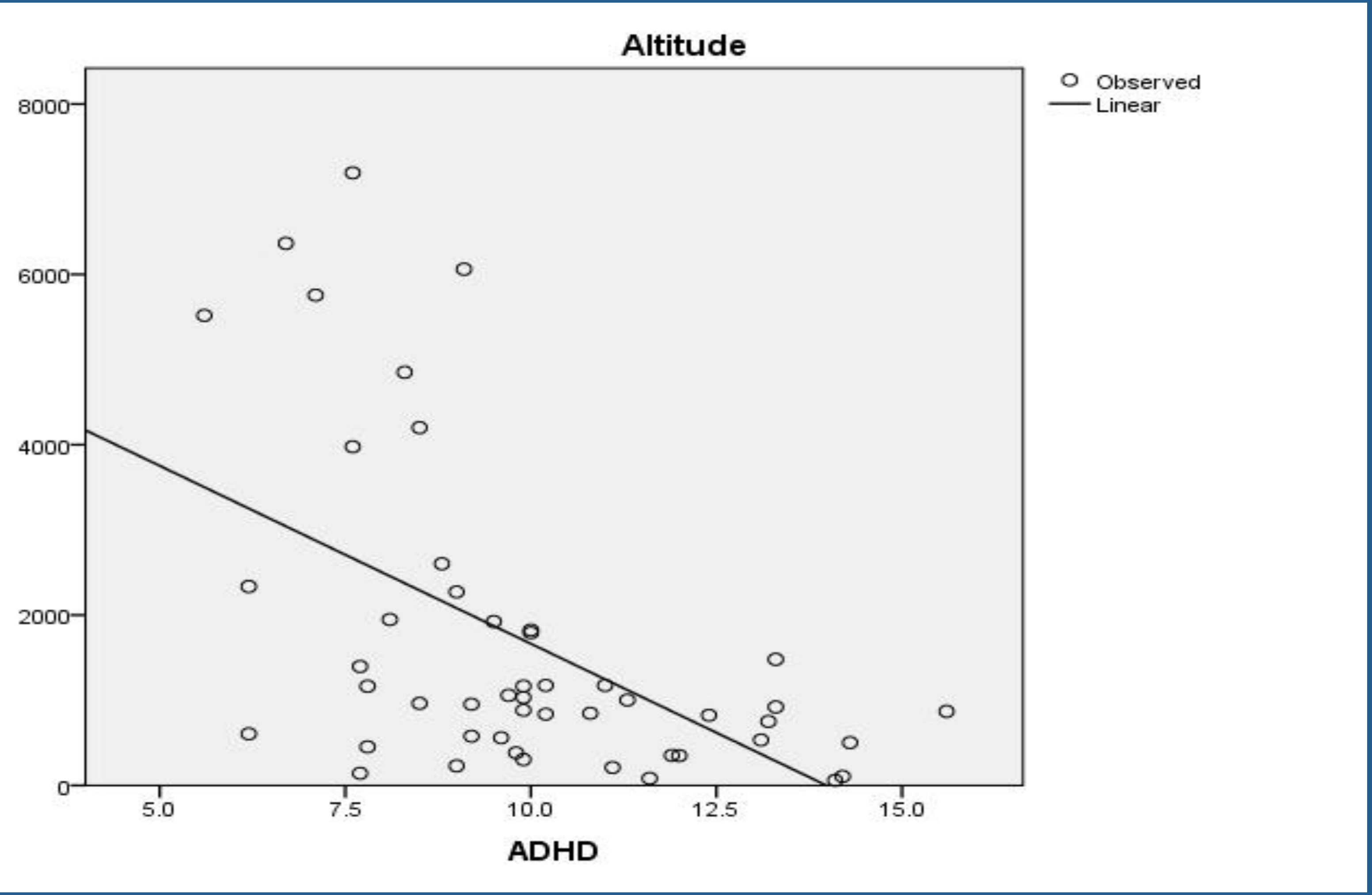
Animal Studies Show that Hypobaric Hypoxia or Anoxia Increase Dopamine Efflux & Extracellular DA in Brain

- 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 $\pm$ 2** pmol/mg protein (in normoxia) to **162 $\pm$ 14** (in anoxia).

- Orset et al. *Neurochem Int* 2005; 46(8):623-33.
  – Exposure to **10% O_2** induced a **+80%** increase in striatal DA *in vivo*, which returned to baseline with normoxia (~21% O_2).

Sometimes More Dopamine is Helpful: ADHD



Why We Take Risks – It's the Dopamine


Ken Fisher / Stone / Getty

TIME Health Tuesday, 12/30/08

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

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Posted 3 hours ago

The Salt Lake Tribune

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.

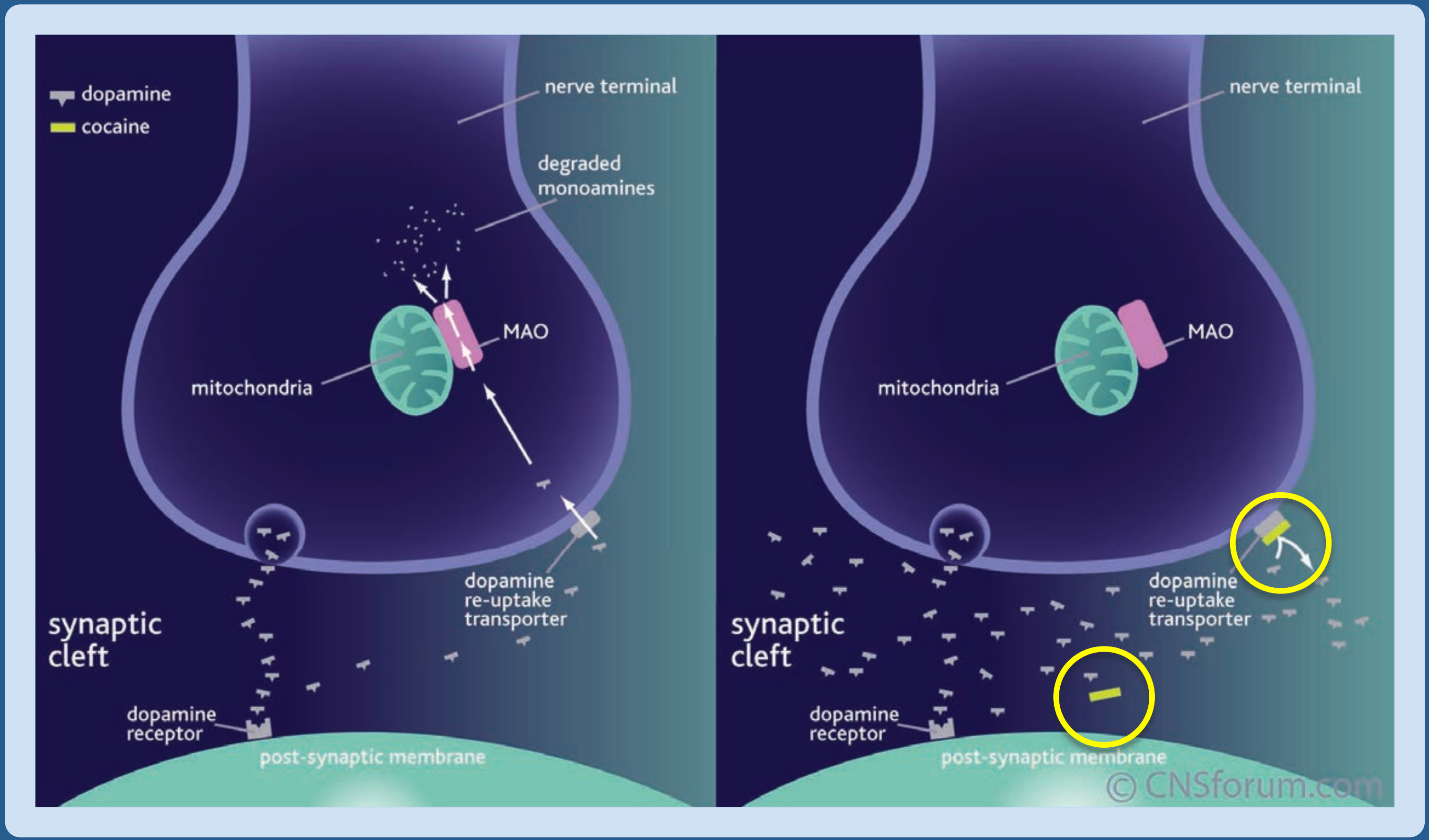
The most dangerous place to drive, according to a Wednesday data-mining report by CNBC.com, was Fort Lauderdale, Fla., with a 22.39 fatality rate, followed in order by Orlando, Fla., 19.95; Augusta-Rich County, Ga., 19.57; Little Rock, Ark., 17.94; and San Bernardino, Calif., 17.12.

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.

Tweet 4 +1 0 Like 507

Image from: cocagrowers.org

Cocaine: Mechanism of Action



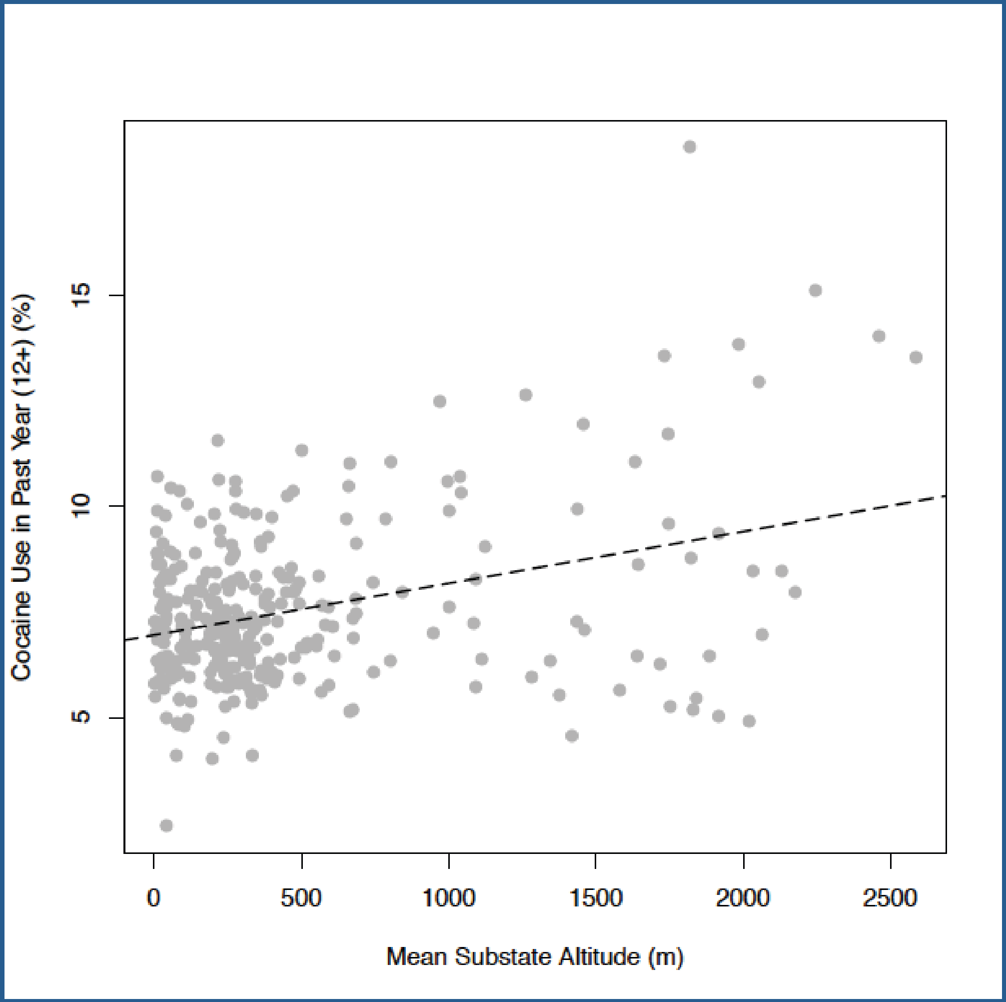
Cocaine binds to dopamine re-uptake transporters on the pre-synaptic membranes of dopamine neurons. This binding inhibits the removal of dopamine from the synaptic cleft

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

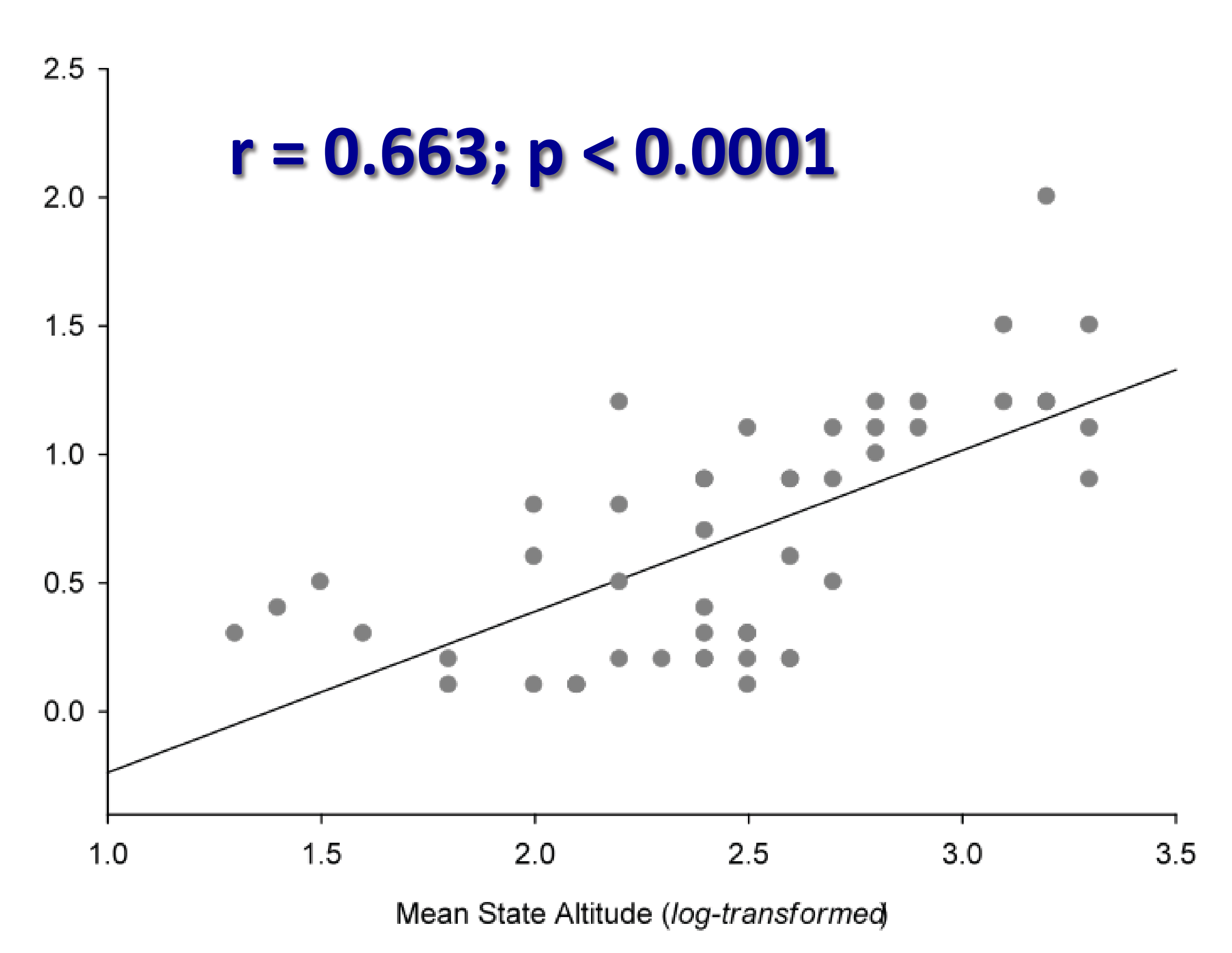
$p = 1.985\ e^{-10}$

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, Souix 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?

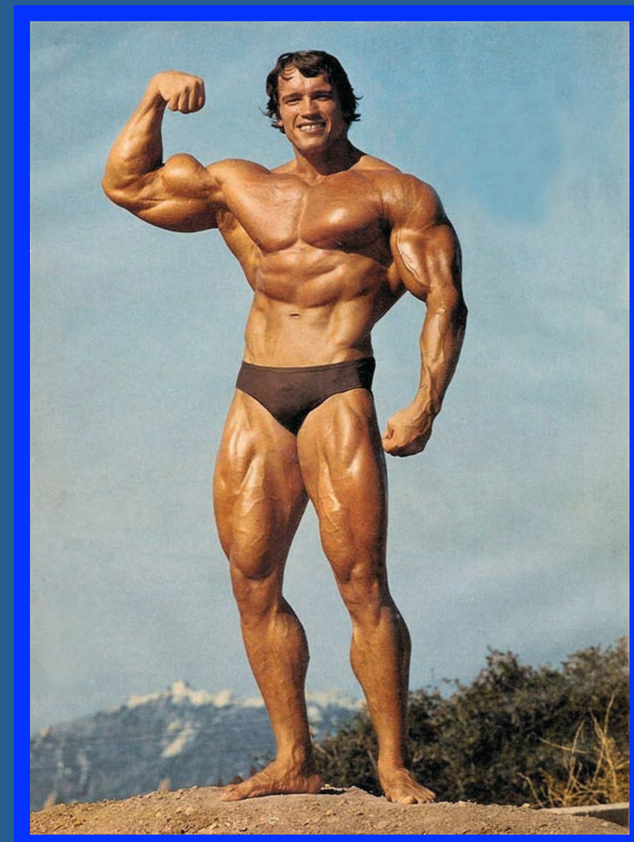
1. Stimulant abuse is more prevalent at higher altitudes.
2. This is likely related, at least in part, to hypoxia related changes in dopamine release.
3. Treatment strategies in mountainous areas may need to take this into account.

Depression and Methamphetamine

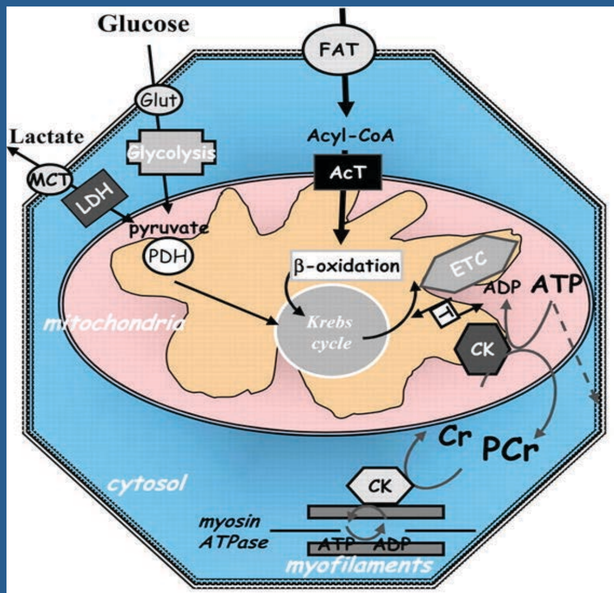
- Commonly co-morbid
- Difficult to treat; antidepressant rx linked to relapse and manic switch
- May be associated with craving and relapse
- May be differentiated from methamphetamine withdrawal symptoms
- More common in women

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.

CK

$$PCr^{2-} + ADP^{3-} + H^{+} \leftrightarrow Cr + ATP^{4-}$$

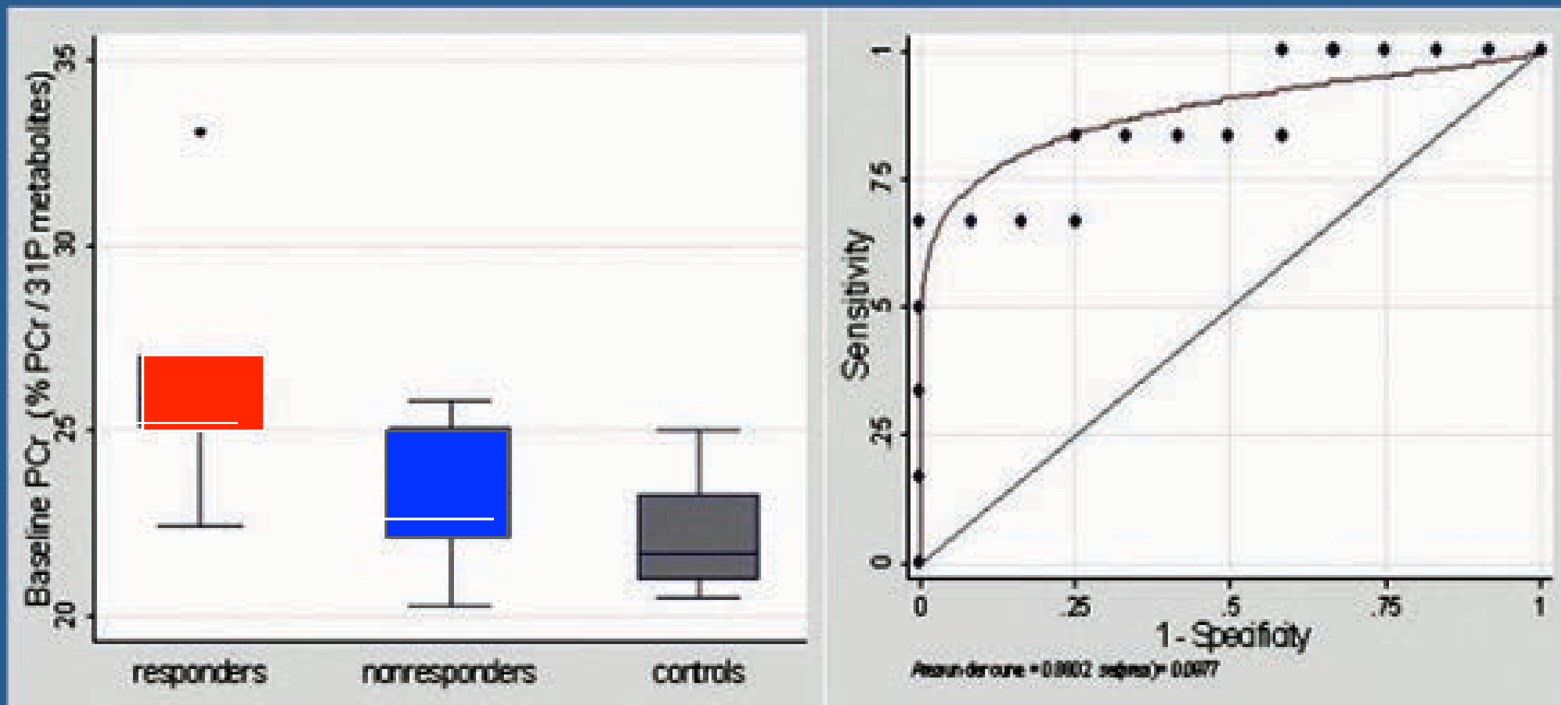
Phosphocreatine — Adenosine Diphosphate — Creatine Kinase — Creatine — Adenosine Triphosphate

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?



<u>Baseline PCr Levels in</u>:

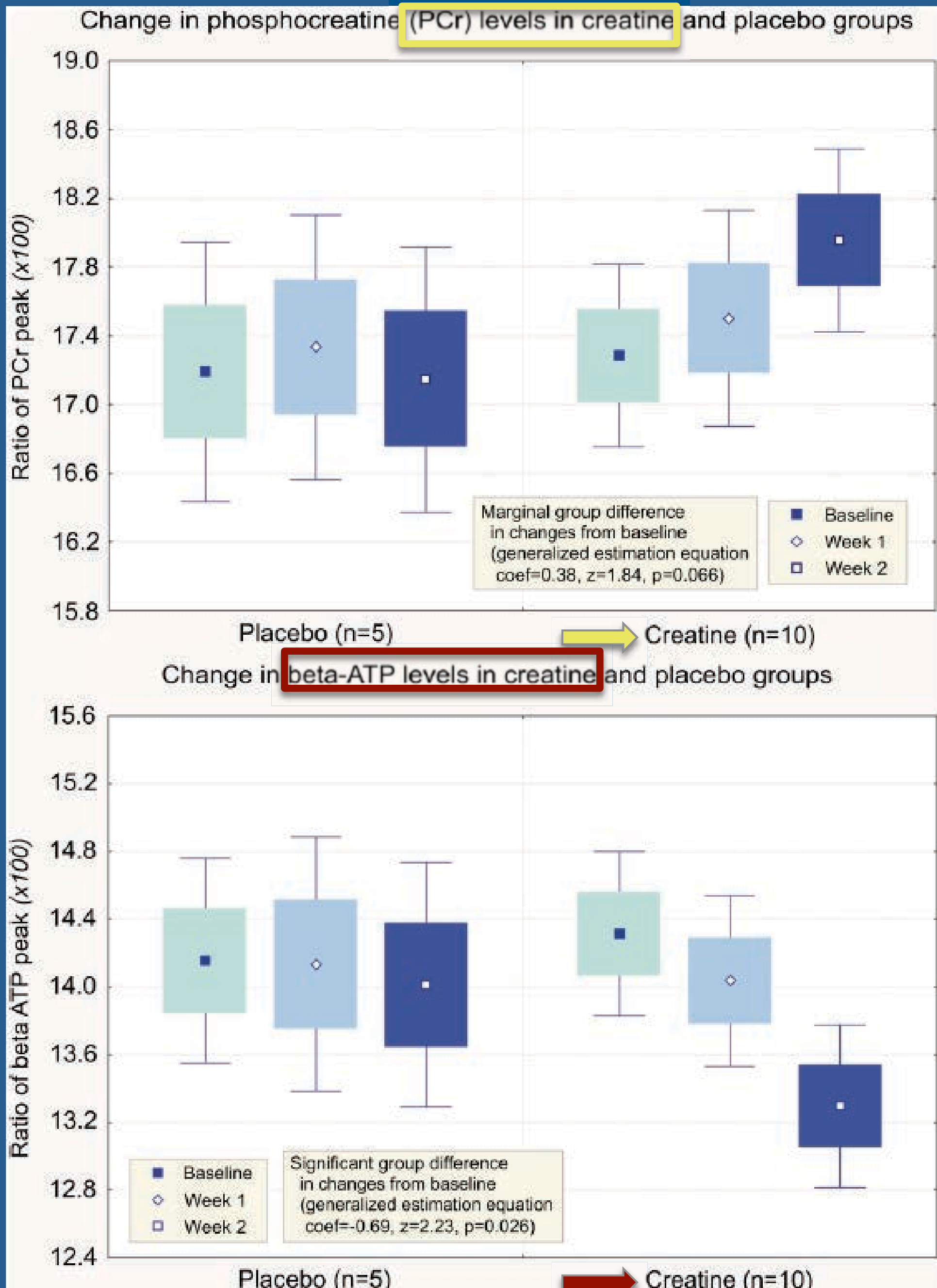
- MDD Treatment Responders
- MDD Non-Responders
- Controls

"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

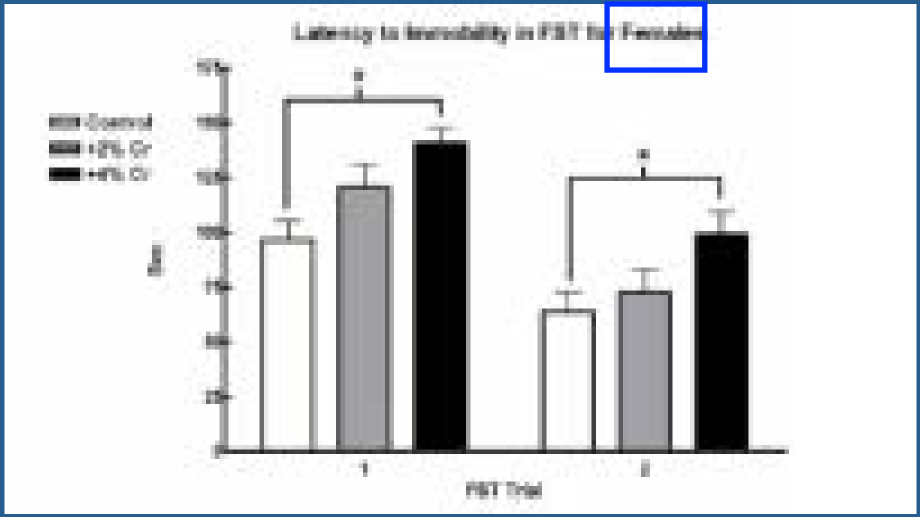
Sad

Grumpy

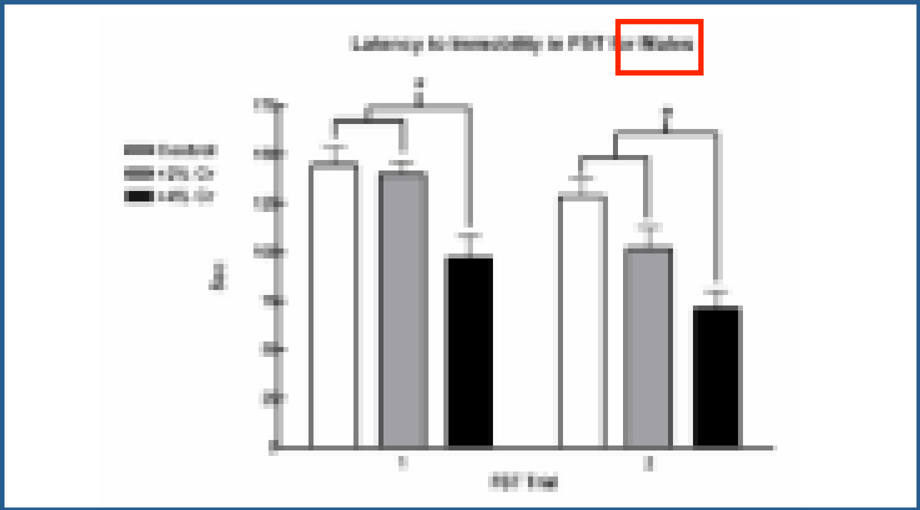
Hopeless

Carlezon et al

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



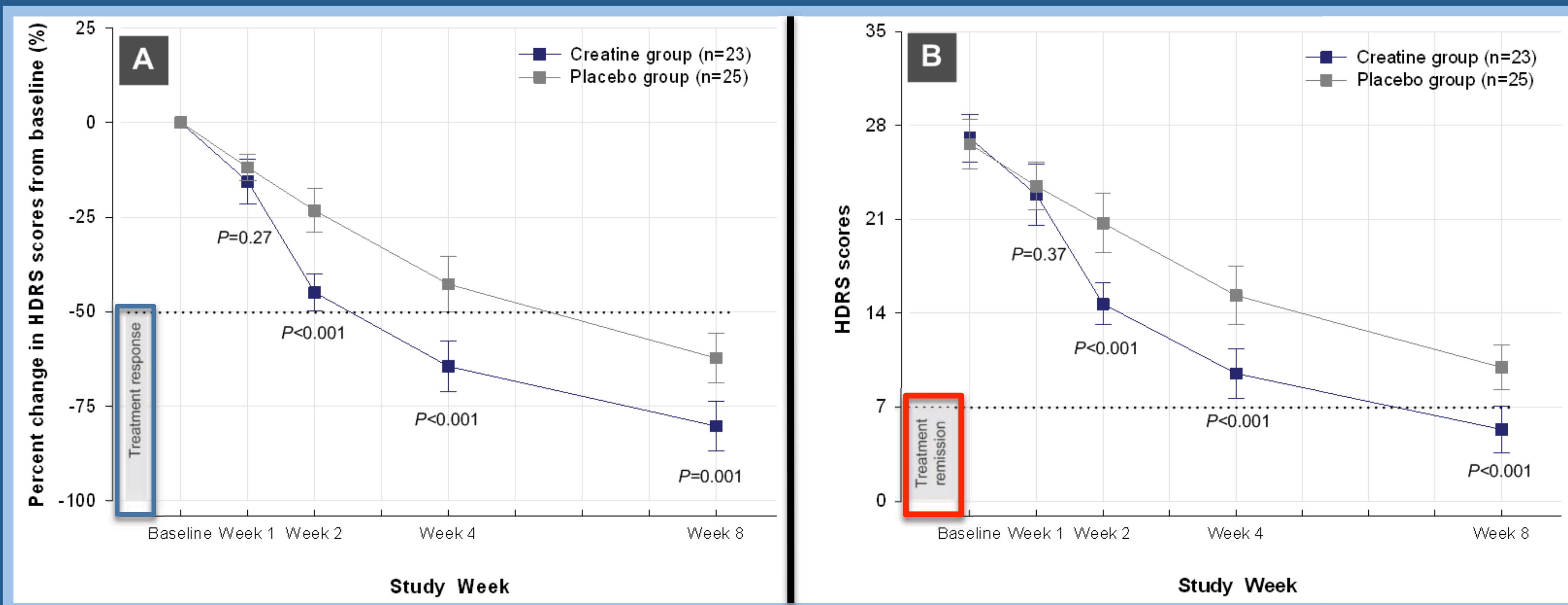
FEMALES



MALES

(Allen et al., 2010)

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

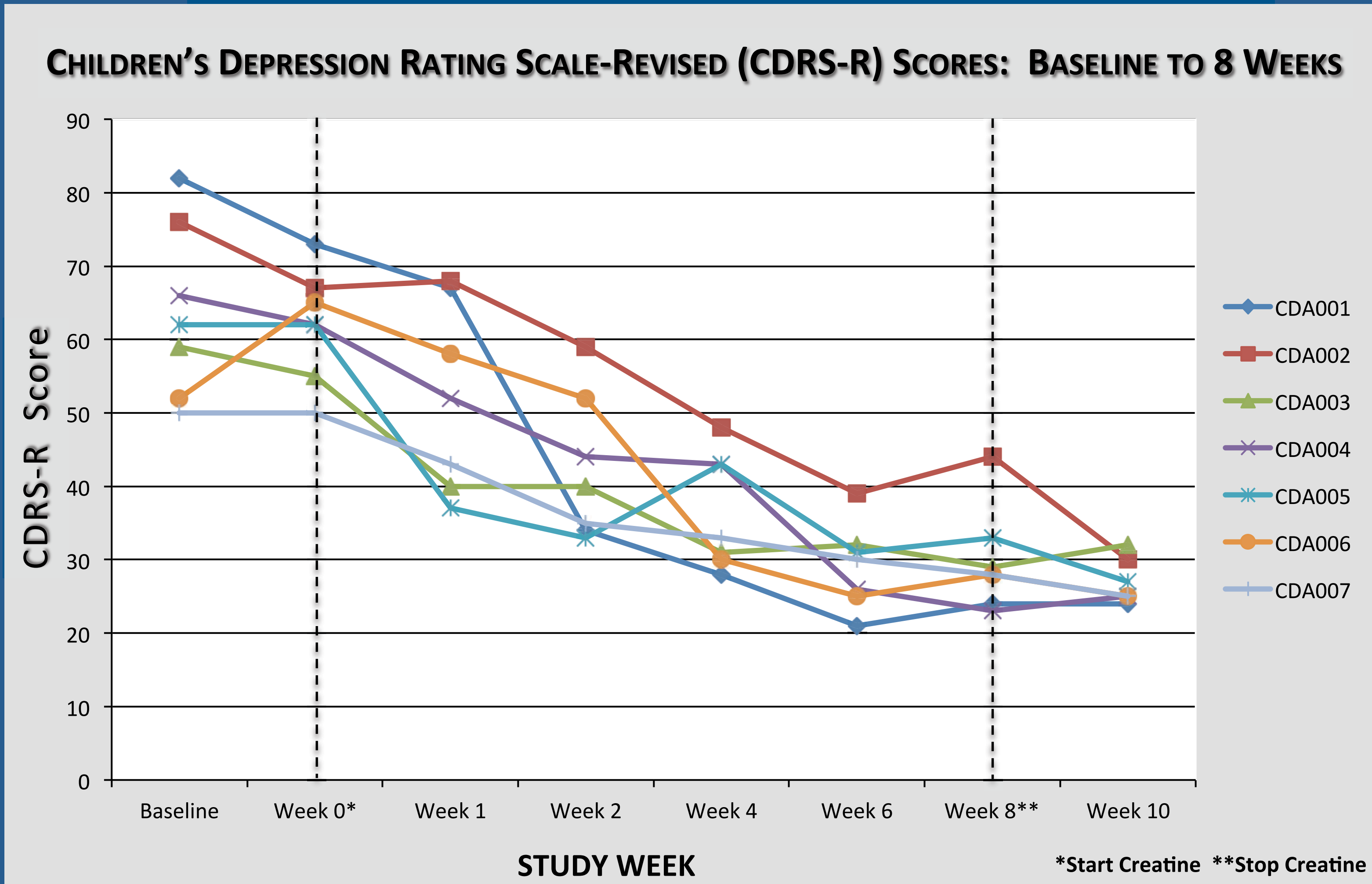


[A] CLINICAL RESPONSE: Percent decrease in Hamilton Depression Rating Scale scores (RESPONSE = ⇓50%)

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

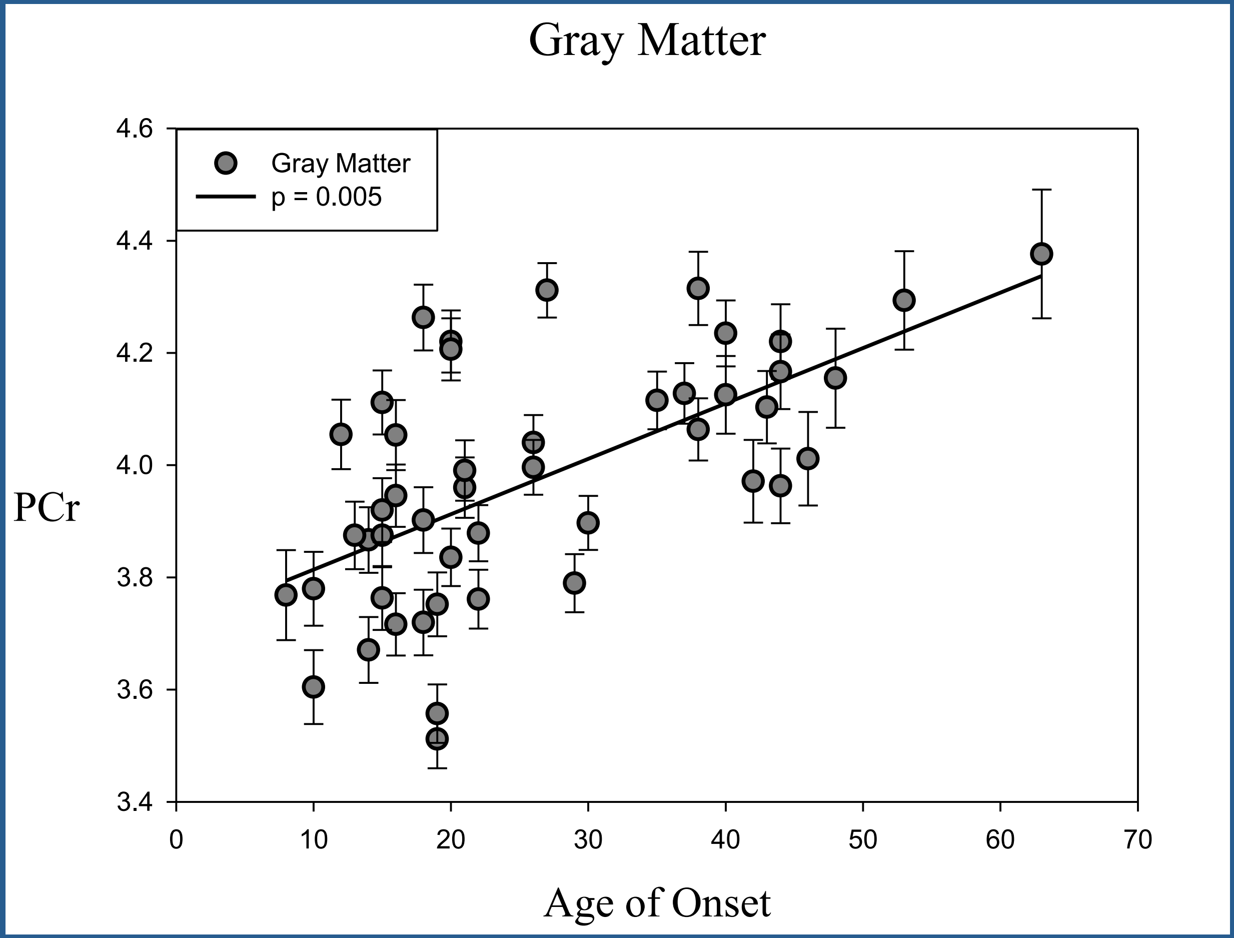
Source: Lyoo, Yoon, Kim and Renshaw, *AJP, 2012.*

Creatine for Female Adolescents with SSRI-Resistant Major Depression‡



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]

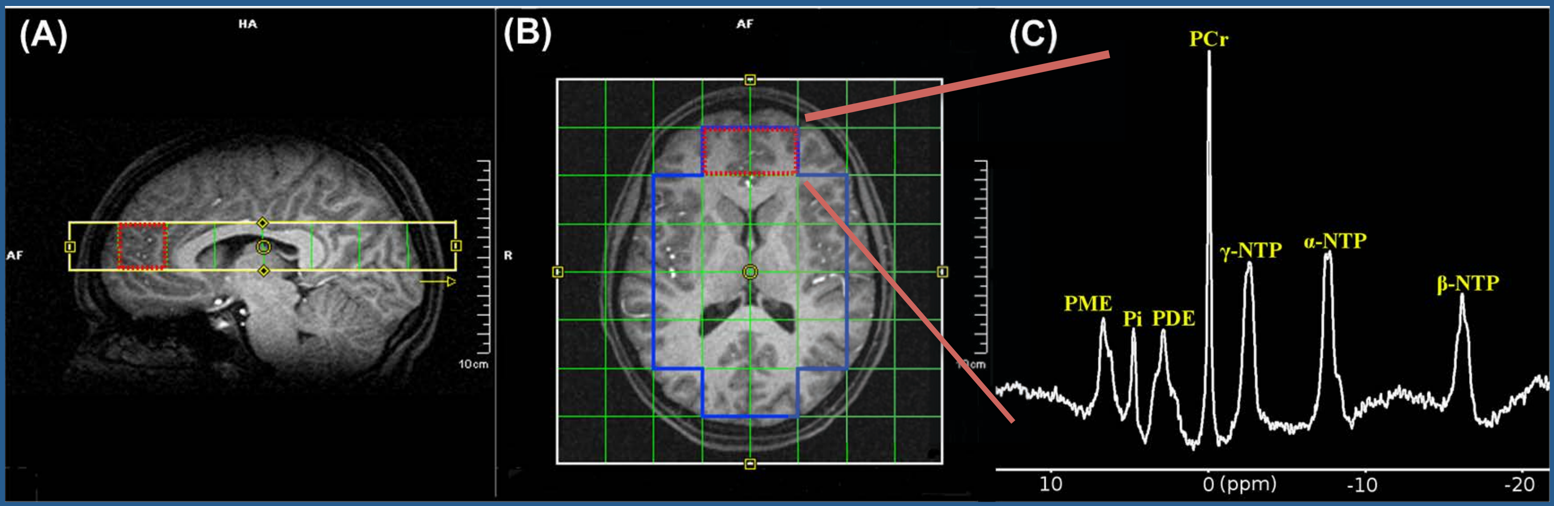

Gray Matter
Gray Matter
p = 0.005
PCr
4.6
4.4
4.2
4.0
3.8
3.6
3.4
0
10
20
30
40
50
60
70
Age of Onset

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



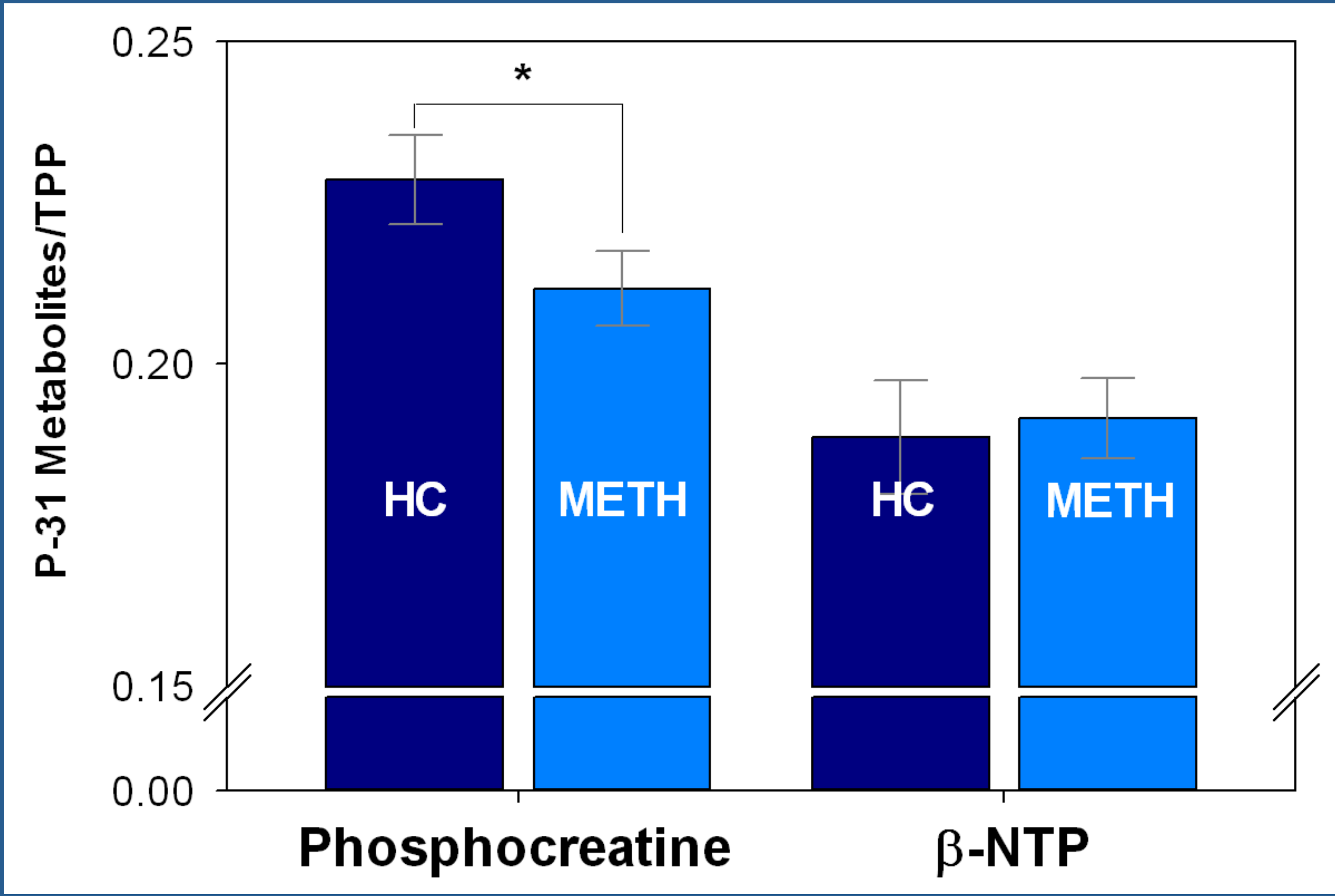
2D MRSI voxel placement and region of interest (frontal lobe)

- 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

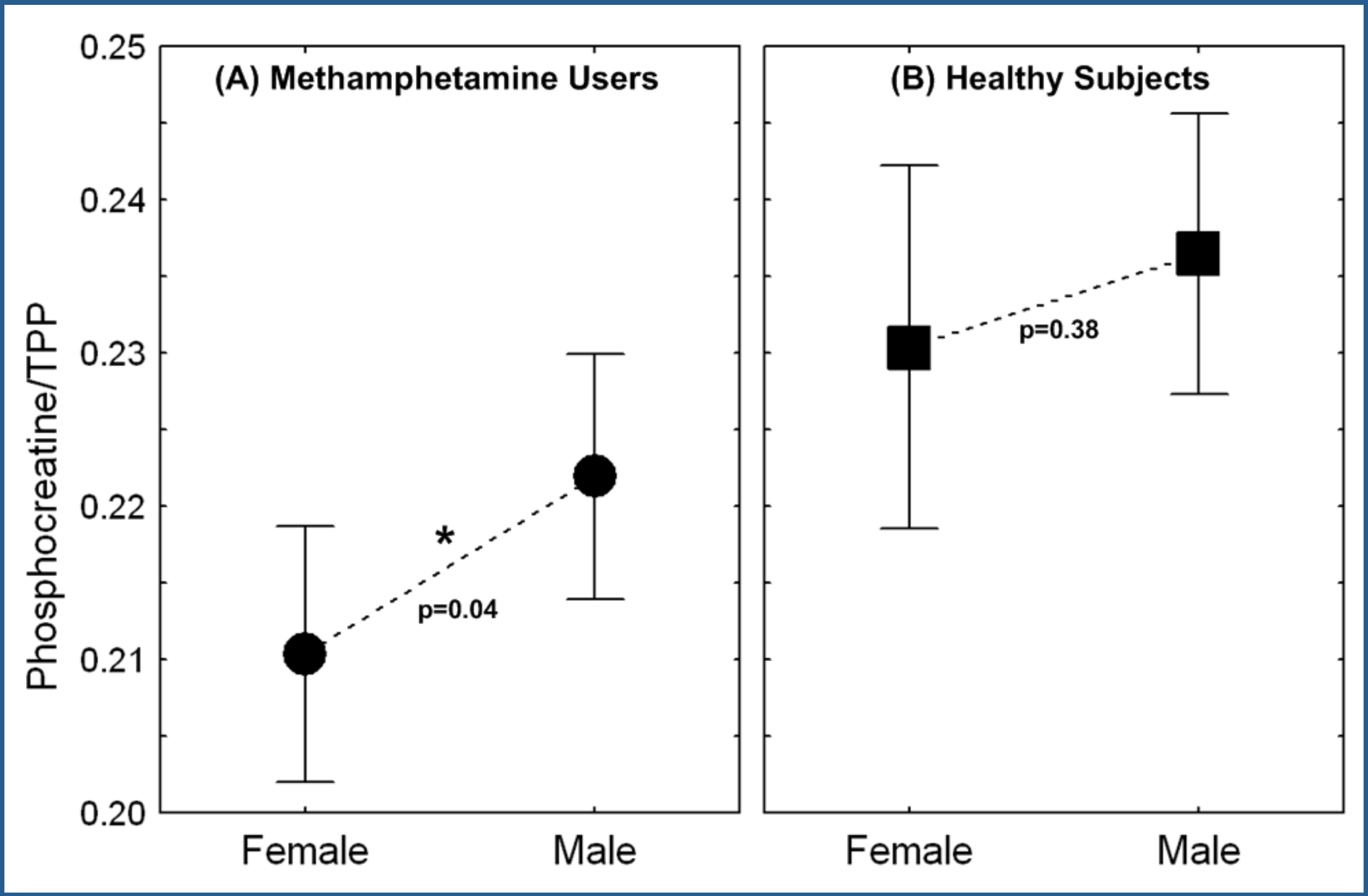
PCr : 0 ppm

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 (pi+PCr+α, β, γ-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.

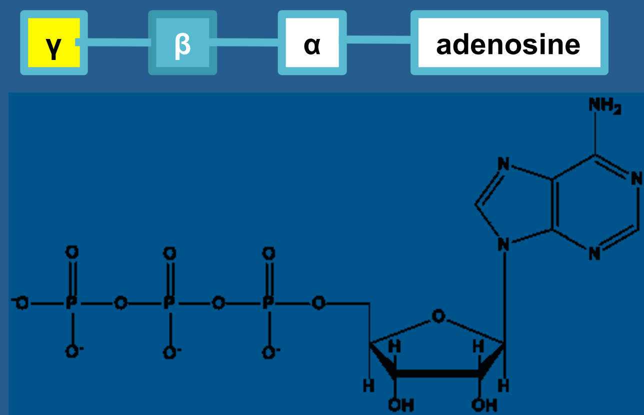
Magnetization Transfer: Beyond Static Measurements

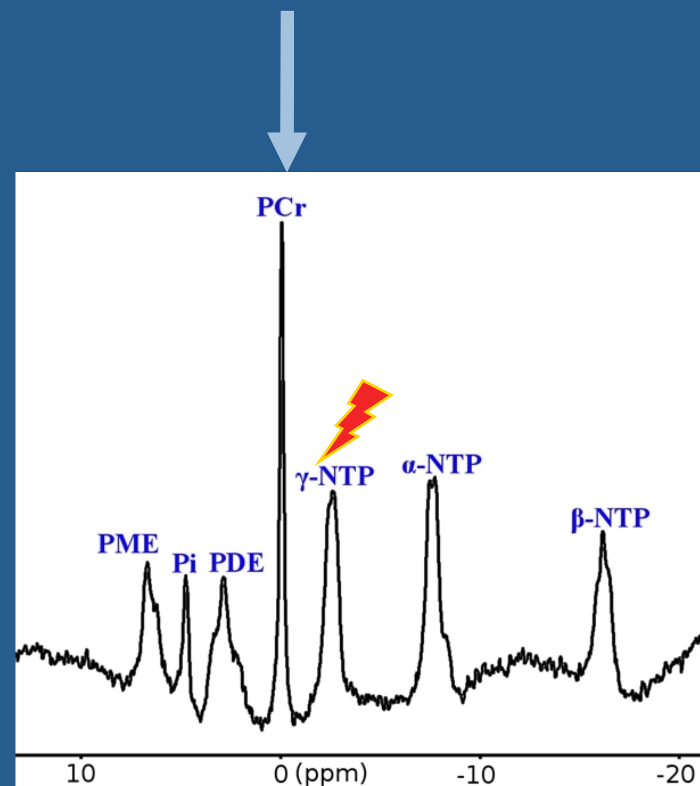
Creatine Kinase

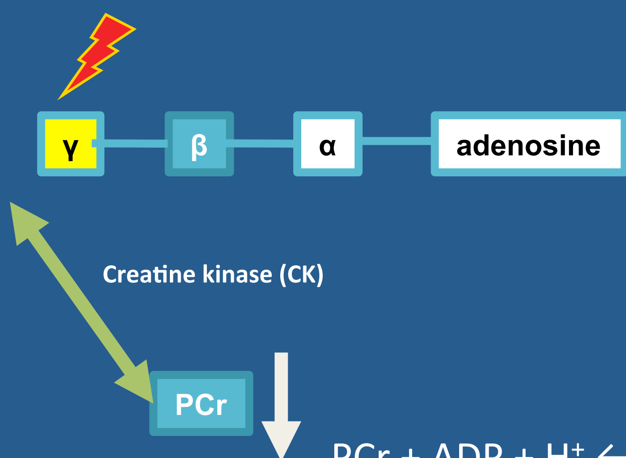
- Creatine kinase (CK)
  - $PCr^{2+} + ADP^{-} \leftrightarrow Cr + ATP^{2-}$
  - Enzyme that replenishes adenosine triphosphate (ATP) levels in phosphocreatine-creatine (PCr-Cr) circuit for temporal and spatial energy buffering.
- Two cytosolic CK subunits including "B" (brain type) and "M" (muscle 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)

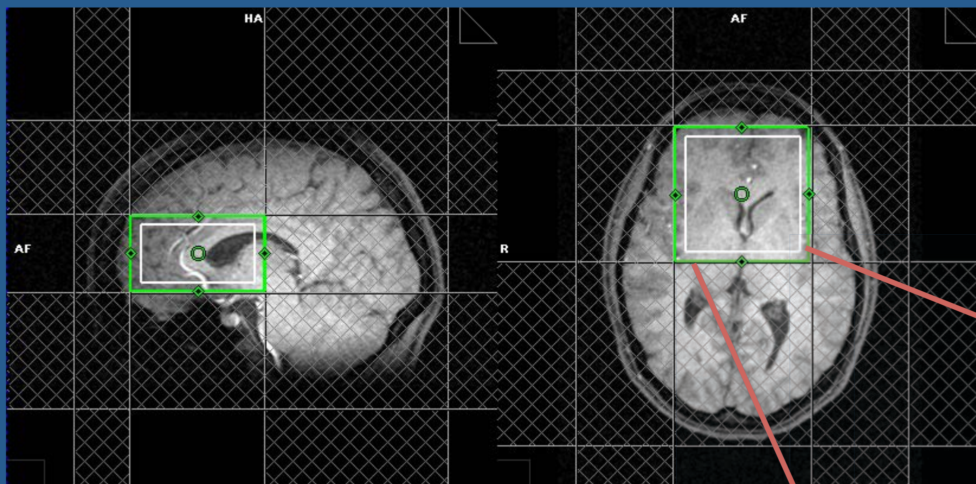






$PCr + ADP + H^+ \leftrightarrow ATP + Cr$

^{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)