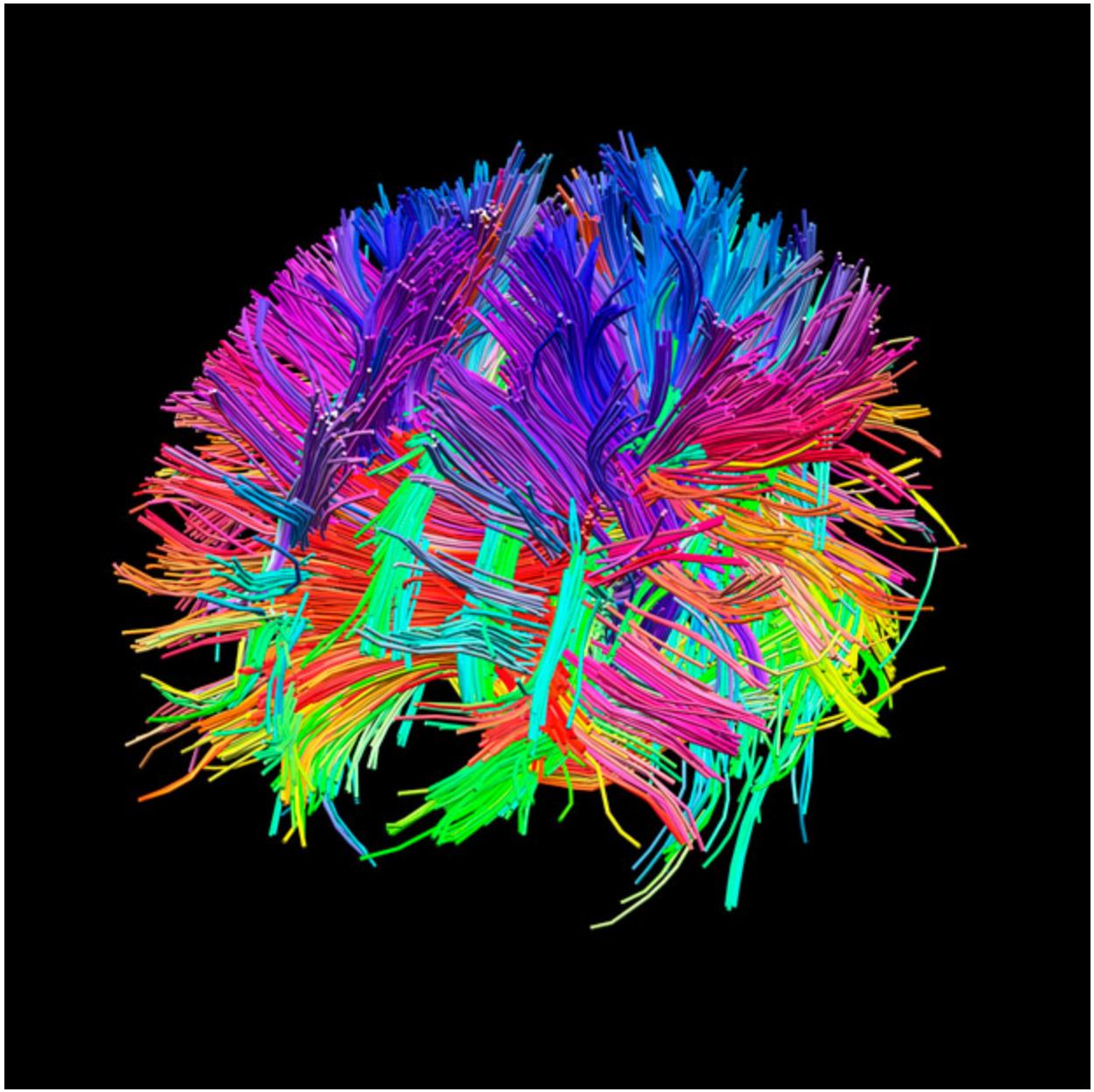
Psychiatric Disorders in Mitochondrial Diseases; Mitochondrial Dysregulation in Psychiatric Disorders

Andrew A. Nierenberg, MD
Director, Bipolar Clinic and Research Program, Massachusetts General Hospital
Professor of Psychiatry,
Harvard Medical School

Outline

- Mitochondria and the brain
- Psychiatric Disorders in Mitochondrial Diseases
- Mitochondrial Dysregulation in Psychiatric Disorders

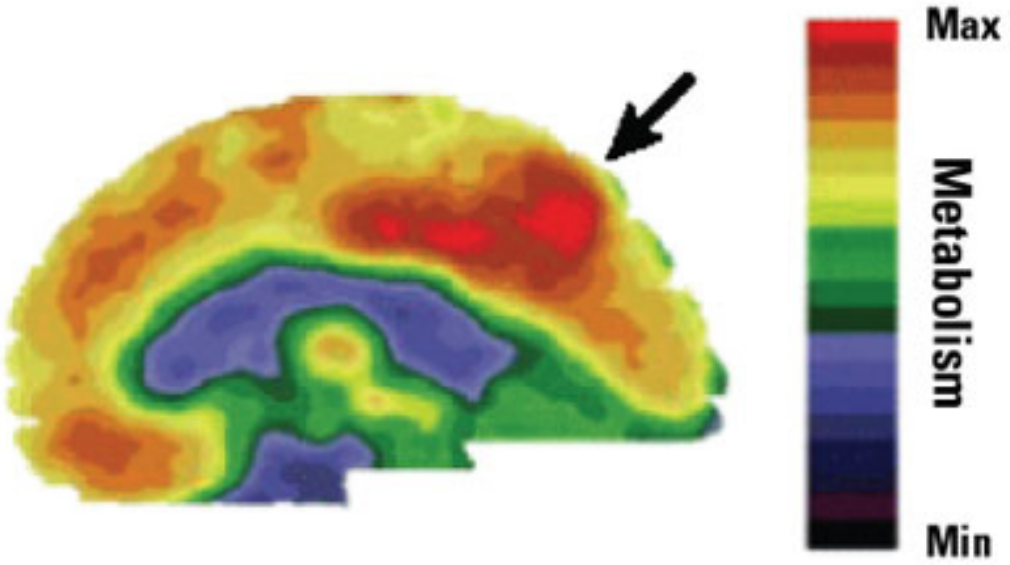
http://phenomena.nationalgeographic.com/2013/04/02/a-new-push-to-explore-the-brain/



http://protomag.com/assets/unveiling-the-brains-architecture?page=4

FIGURE 2.

The cortical areas associated with the highest resting metabolic rates in the conscious resting state are located in the posteromedial parietal cortex (posterior cingulate cortex and precuneus, arrow)[16]

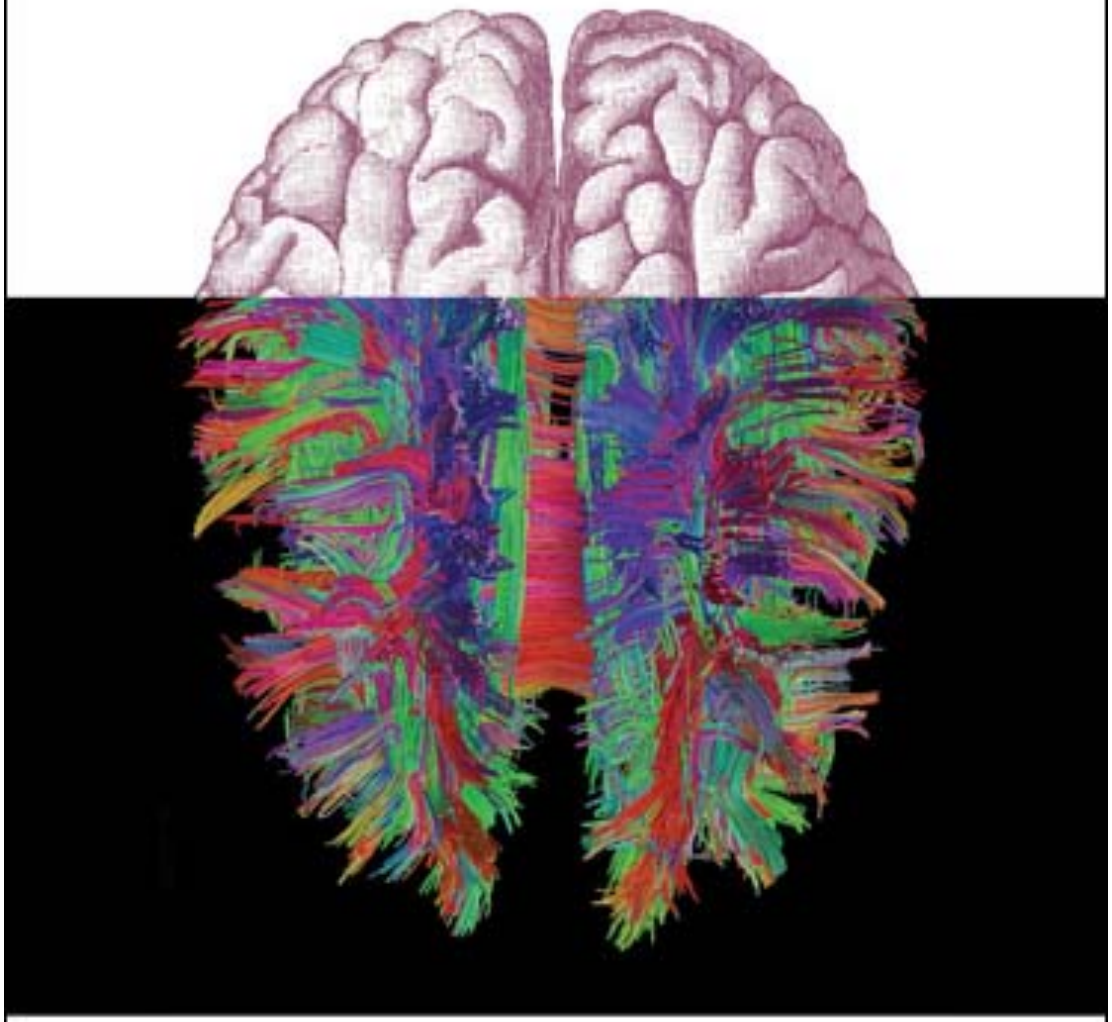


Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci.* 2001;2:685-694. Reprinted with permission.

Max=maximun; Min=minimum.

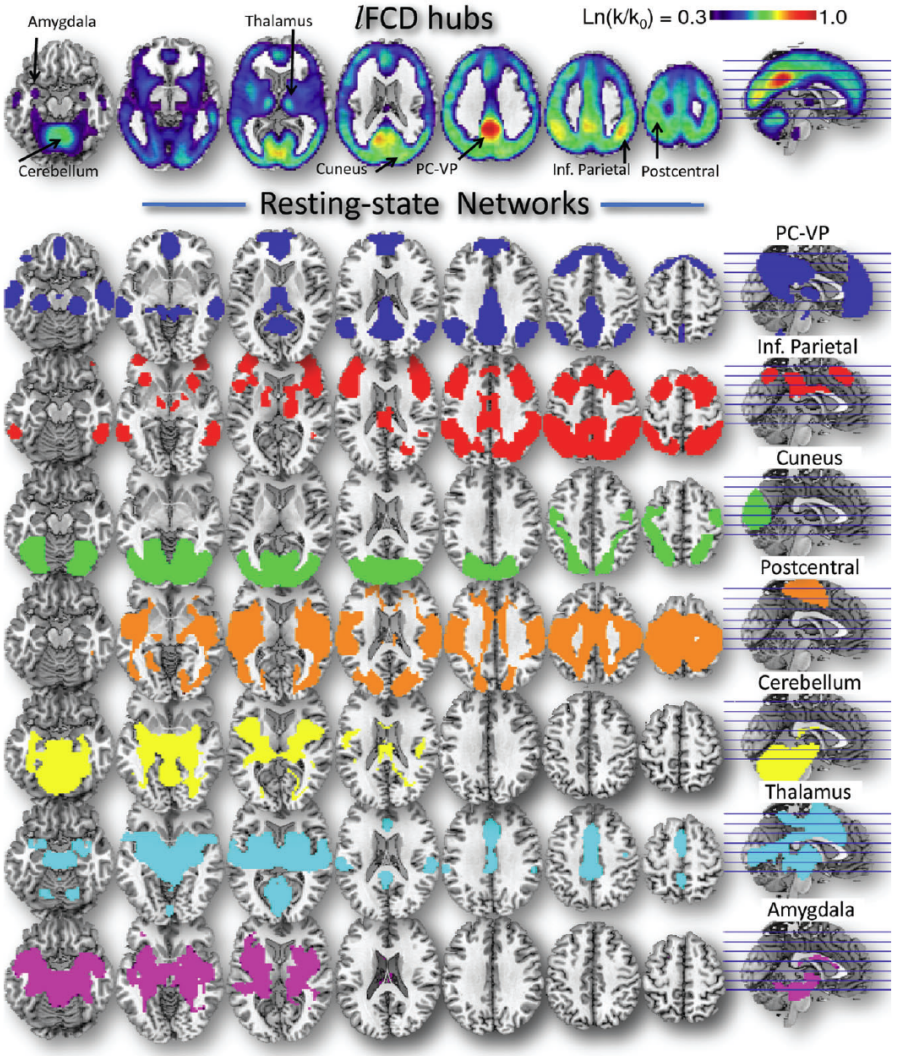
Cavanna AE. *CNS Spectr.* Vol 12, No 7. 2007.

Networks of the Brain



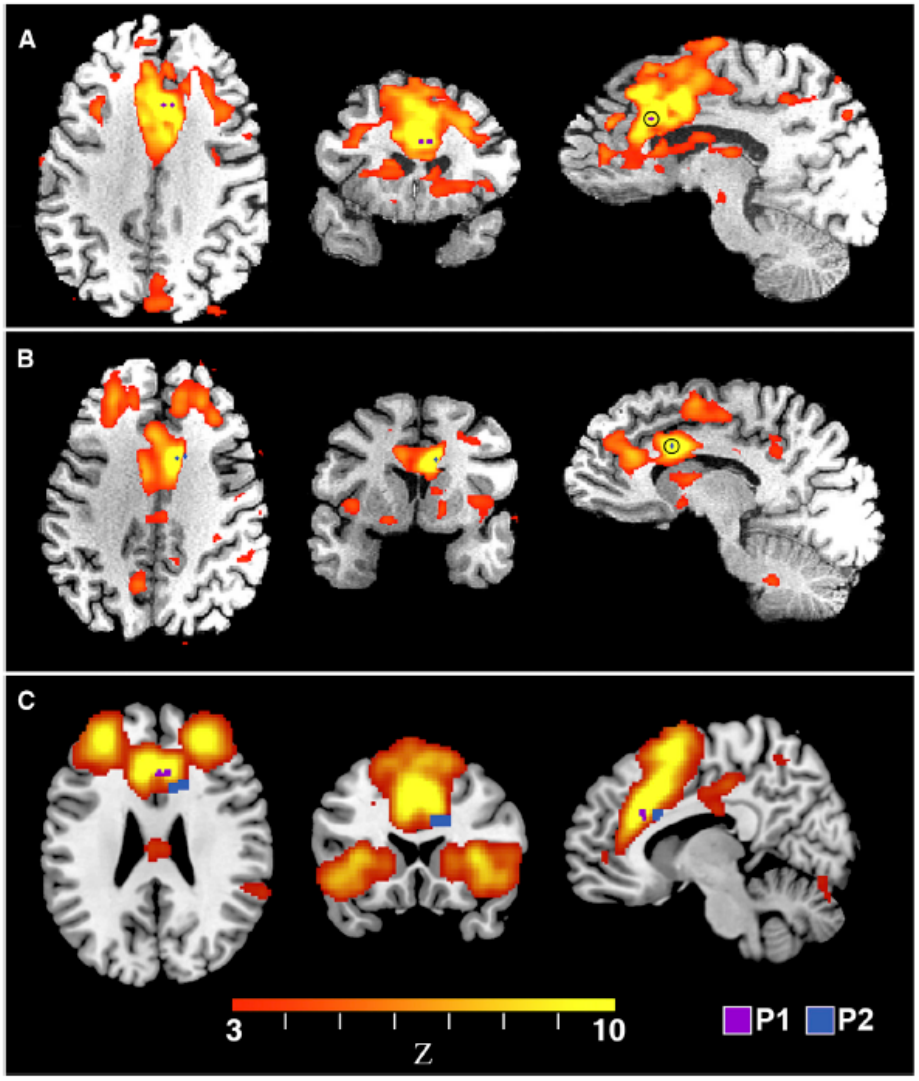
Olaf Sporns

Default Mode Network

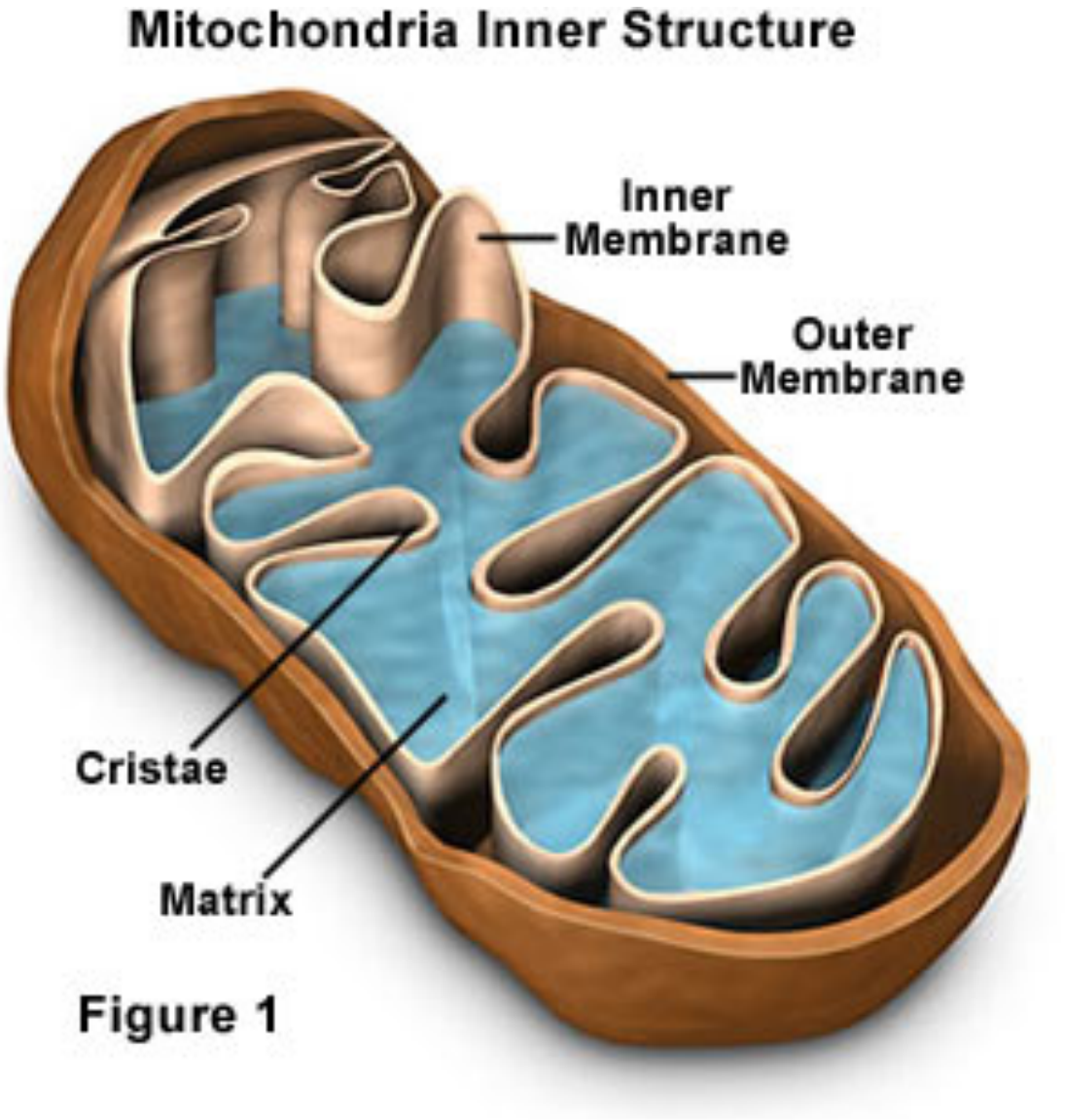


Tomasi and Volkow Cerebral Cortex September 2011;21:2003--2013

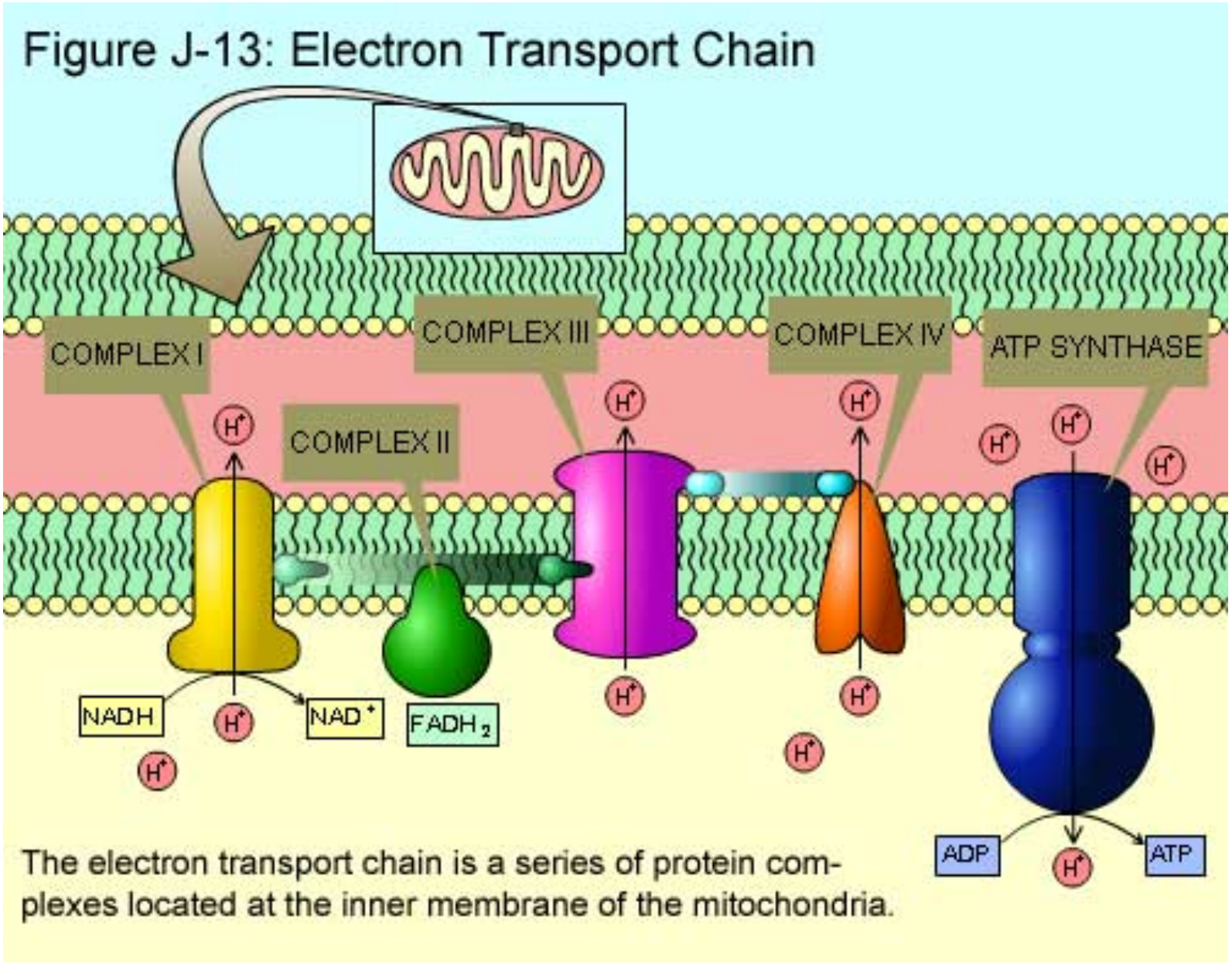
Will to Persevere



Parvizi et al. Neuron 80, 1359–1367, December 18, 2013

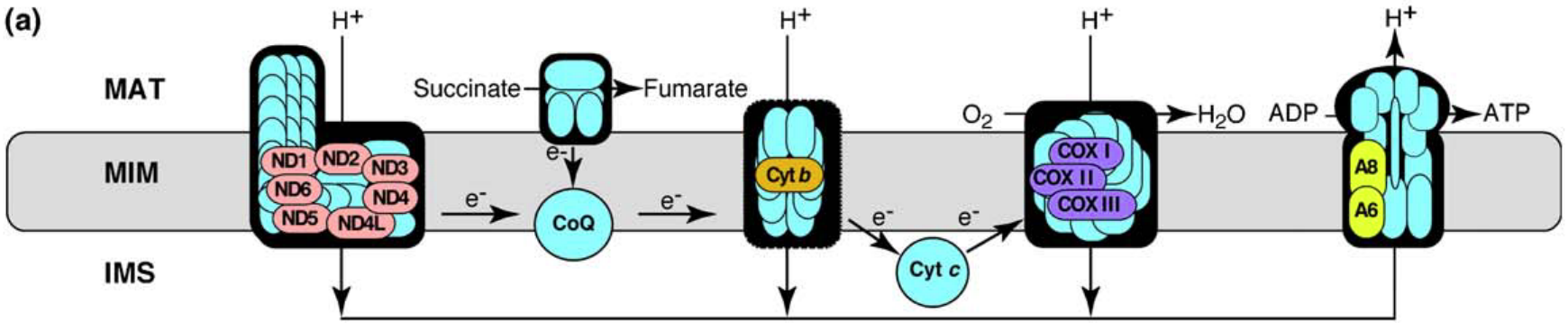


http://www.cartage.org.lb/en/themes/sciences/zoology/AnimalPhysiology/Anatomy/AnimalCellStructure/Mitochondria/mitochondria.jpg



hopes.stanford.edu/treatmts/ebuffer/j1.html

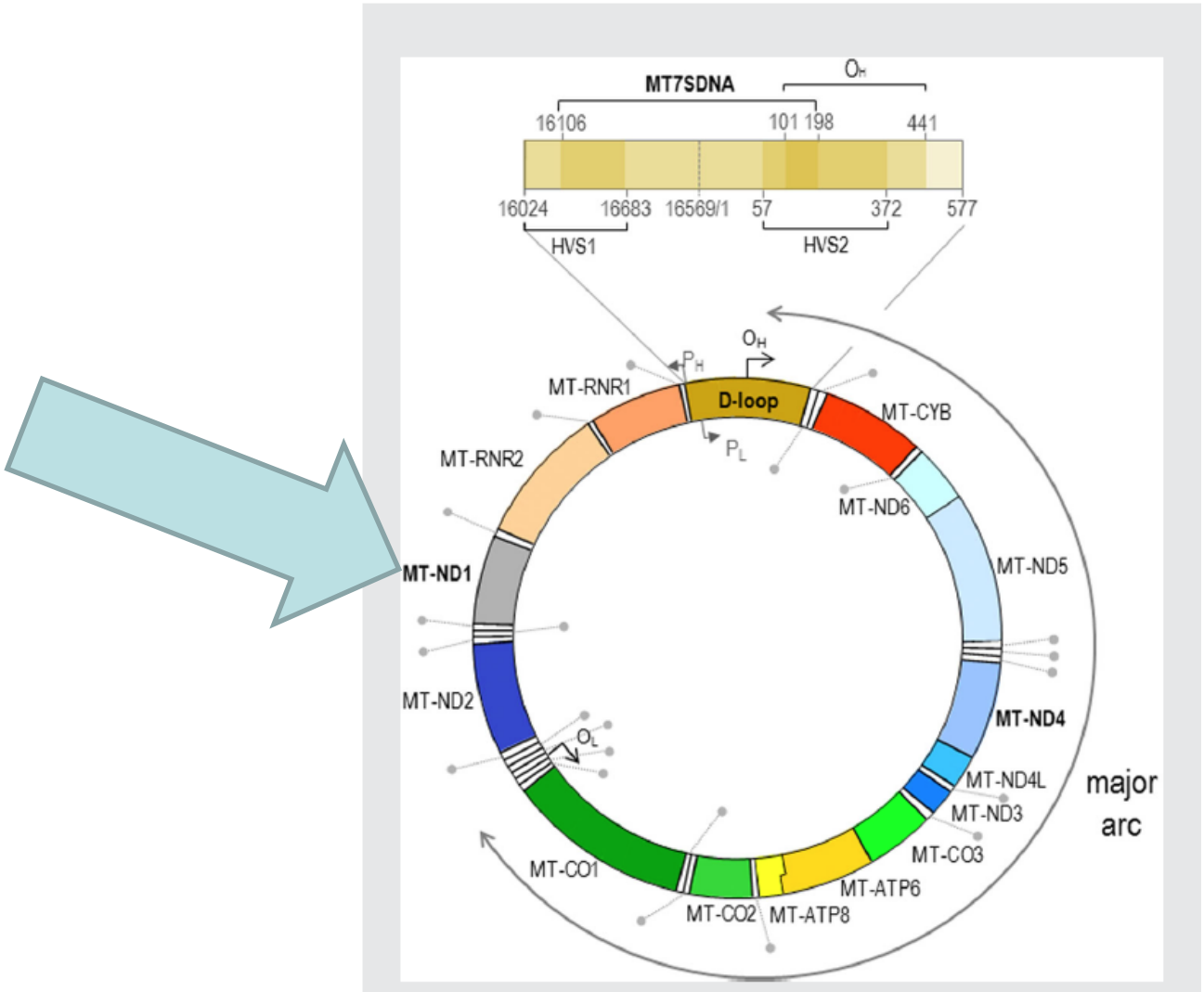
Mito Architecture



Subunits	Complex I	Complex II	Complex III	Complex IV	Complex V
mtDNA-encoded:	7	0	1	3	2
nDNA-encoded:	~39	4	10	10	~14
"Assembly" factors:	~13	2	4	~20	2

Schon et al. Trends in Molecular Medicine 16 (2010) 268–276

Mito Genome



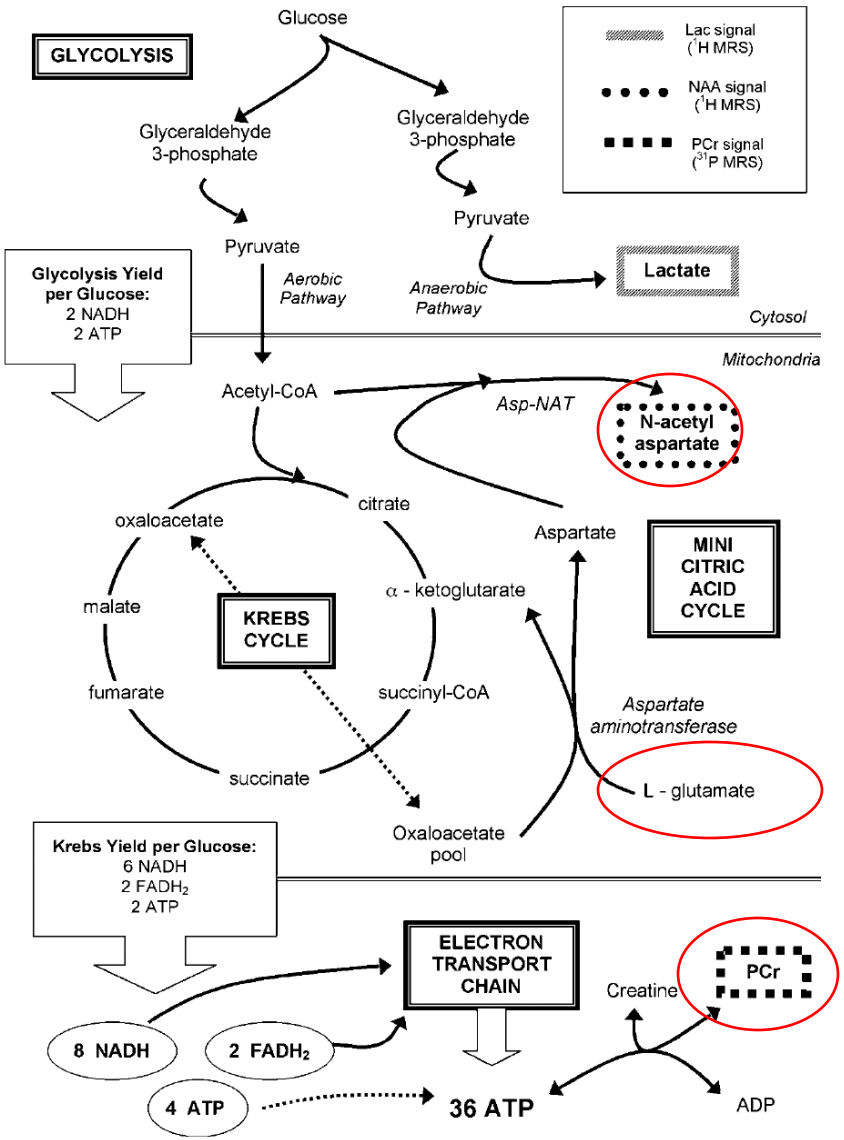
Torell et al. Am J Med Genet Part B 162B:213–223.

Mitochondria Energy Pathway

- Convert redox energy
  - from food into high energy phosphate bonds of ATP
- Reducing equivalents
  - donated to NADH
- Electron energy from NADH
  - donated to mitochondrial electron transport chain
- Generates proton gradient
  - transfer of energy to ATP

Mitochondria

- Provide energy
  - ATP
  - Reactive oxygen species (ROS)
  - Needed for proteins and membranes synthesis
- Neuronal plasticity
  - Neurogenesis, dendritogenesis, synaptogenesis
  - Regulates cell survival
  - Regulates apoptosis



Molecular Psychiatry (2005) 10, 900–919

Oxidative Stress

- Natural Reactive Oxygen Species (ROS) from mitochondrial respiration
  - Superoxide anion
  - Nitric oxide
  - Hydrogen peroxide
- ROS can exceed metabolic capacity
  - Peroxynitrite
  - Hydroxy radical

Oxidative Stress

- Cellular dysfunction or death
- Non-physiologic ROS reactivity
  - Proteins
  - Nucleic acids
  - Carbohydrates
  - Lipids
- Due to dysfunctional electron flow in mitochondrial inner membrane

Oxidative Stress

- ROS damage mitochondria
- Decreased ATP
- Damaged membrane
- Abnormal calcium sequestration
- Apoptosis
- Neurons especially susceptible

Psychiatric Disorders in Mitochondrial Diseases

Lifetime Prevalence Psychiatric Disorders in Mito Disease

- 50% of children with depression
- 70% of adults with major psychiatric disorders
- Onset of psychiatric disorders averaged 13 years before diagnosis of mito disease
- Psychiatric disorders resistant to psychiatric medications

Fattal O, et al. CNS Spectr 2007;12:429–438 Morava E, et al. Mitochondrion 2010; 10:528–533

Psychiatric Presentations

- Major depressive disorder
- Bipolar disorder
- OCD
- Anorexia
- Bizarre hallucinations
- Anxiety disorders
- Substance abuse
- Borderline personality disorder, and catatonia.

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Psychiatric Symptoms

Measured items	MT group		HN group	
	mean	SD	mean	SD
GSI	1.44	0.91	0.46	0.53
Somatization	1.77	1.10	0.98	0.83
Obsessive-compulsive	1.65	1.04	0.47	0.68
Interpersonal sensitivity	1.55	0.97	0.40	0.51
Depression	1.90	1.21	0.75	1.03
Anxiety	1.32	1.14	0.42	0.63
Hostility	1.26	1.00	0.48	0.50
Phobia	1.14	1.11	0.29	0.56
Paranoia	1.42	1.05	0.28	0.39
Psychoticism	0.92	0.60	0.13	0.24
Additional items	1.48	0.96	0.43	0.66
BDI-SF	12.85	8.33	4.40	5.36
HDRS	15.62	8.62	7.30	5.52
HAQ-DI	0.82	0.59	0.71	0.59

Inczedy-Farkas et al. Behavioral and Brain Functions 2012, 8:9

47 Reported Cases

- Depression with psychotic features
- Psychosis
- Cognitive deterioration
- Anxiety disorders
- Bipolar disorder
- Frontal lobe syndrome

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Physical Manifestations

- Muscle weakness or atrophy
- seizure disorder
- migraine or headache
- hearing loss
- short stature
- Type 2 diabetes mellitus, severe constipation often with ileus, ataxia (N=6), dysarthria, strokes

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

fMRI

- White-matter lesions
- Cerebral or cerebellar atrophy
- Ischemia or an old infarct
- Basal ganglia calcifications or hyperintensities

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Mito Neurologic Findings

- White matter deterioration.
- Underlying defect in the respiratory chain or concomitant oxidative stress
- Neuronal death
- Replacement of neurons by glial cells

Finsterer J, Mahjoub SZ. 2012. Primary mitochondrial arteriopathy. Nutr Metab Cardiovasc Dis 22:393–399.

Mito Mutations

- MELAS 3243 and 3271mutations.
- MERRF (myoclonus epilepsy with ragged-red fibers) 8363 and 8344,
- CPEO with a 7.5 kb deletion and a 3.3 kb deletion
- MNGIE and two novel mutations.
- No clear genotype/psychiatric phenotype relationship

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Physical Manifestations

- Wolf-Parkinson-White syndrome
- Ophthalmoplegia
- Ptosis
- Cardiomyopathy
- Cardiac conduction defect
- Abnormal movements

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Deterioration on psychotropic medications

- Typical and atypical antipsychotics impair complex I
- SSRIs and tricyclic antidepressants inhibit the mitochondrial respiratory chain and oxidative phosphorylation
- Valproic acid induces carnitine deficiency

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Treatment

- Coenzyme Q10,
- Creatine monohydrate
- Alpha lipoic acid
- Vitamin E, vitamin C, and riboflavin
- Antioxidant idebenone
- Reduction or discontinuation of psychotropic drugs

Anglin et al. The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:394–409)

Mitochondrial Dysregulation in Psychiatric Disorders

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Genomics 84 (2004) 1041–1050

GENOMICS

www.elsevier.com/locate/ygeno

Mitochondrial DNA 3644T→C mutation associated with bipolar disorder

Kae Munakata[a], Masashi Tanaka[b], Kanako Mori[a], Shinsuke Washizuka[a], Makoto Yoneda[c], Osamu Tajima[d], Tsuyoshi Akiyama[e], Shinichiro Nanko[f], Hiroshi Kunugi[g], Kazuyuki Tadokoro[g], Norio Ozaki[h], Toshiya Inada[h], Kaoru Sakamoto[i], Takako Fukunaga[i], Yoshimi Iijima[j], Nakao Iwata[k], Masahiko Tatsumi[l], Kazuo Yamada[m], Takeo Yoshikawa[m], Tadafumi Kato[a,*]

Downregulation in components of the mitochondrial electron transport chain in the postmortem frontal cortex of subjects with bipolar disorder

Xiujun Sun, MB, MSc; Jun-Feng Wang, MB, PhD; Michael Tseng, MD; L. Trevor Young, MD, PhD

J Psychiatry Neurosci 2006;31(3):189-96.

Mitochondrial Genes

Table 2: Summary of mitochondria-related gene candidates differentially expressed in the postmortem frontal cortex between control (CTL) subjects and subjects with bipolar disorder (BD)*

UniGene ID	Gene symbol	Ratio (BD/CTL)	*p* value	Gene name
Hs.115467	LOC90624	1.13	0.028	Hypothetical protein LOC90624
Hs.117747	MMAA	1.11	0.011	Methylmalonic aciduria type A
Hs.59889	HMGCS2	1.11	0.026	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2
Hs.94949	MCEE	1.10	0.006	Methylmalonyl CoA epimerase
Hs.113823	CLPX	1.09	0.009	Caseinolytic protease X homologue
Hs.180408	SLC25A16	0.90	0.018	Solute carrier family 25
Hs.351875	**COX6C**	**0.90**	**0.012**	**Cytochrome c oxidase polypeptide Vic (complex IV)**
Hs.433951	GPX4	0.90	0.010	Glutathione peroxidase 4
Hs.90443	**NDUFS8**	**0.90**	**0.013**	**NADH-ubiquinone oxidoreductase 23-kd subunit (complex I)**
Hs.115721	PRSS25	0.89	0.026	Protease, serine, 25
Hs.169611	DIABLO	0.89	0.025	Diablo homologue
Hs.248267	MPST	0.89	0.001	Mercaptopyruvate sulfurtransferase
Hs.211914	**NDUFS7**	**0.89**	**0.012**	**NADH-ubiquinone oxidoreductase 20-kd subunit (complex I)**
Hs.401903	**COX5A**	**0.89**	**0.015**	**Cytochrome c oxidase polypeptide Va (complex IV)**
Hs.155433	**ATP5C1**	**0.89**	**0.034**	**ATP synthase gamma chain (complex V)**
Hs.246310	**ATP5J**	**0.89**	**0.017**	**ATP synthase coupling factor 6 (complex V)**
Hs.461420	MSRB2	0.89	0.021	Methionine sulfoxide reductase B2
Hs.310542	TOMM40	0.88	0.014	Translocase of outer mitochondrial membrane 40 homologue
Hs.411125	MRPS12	0.86	0.040	Mitochondrial ribosomal protein S12
Hs.429	**ATP5G3**	**0.83**	**0.007**	**ATP synthase lipid-binding protein (complex V)**
Hs.47649	MCCC1	0.80	0.009	Methylcrotonoyl-Coenzyme A carboxylase 1 (α)
Hs.17355	**UQCRC2**	**0.78**	**0.019**	**Ubiquinol-cytochrome C reductase complex core protein (complex III)**
Hs.157113	COQ7	0.75	0.038	Coenzyme Q7 homologue, ubiquinone

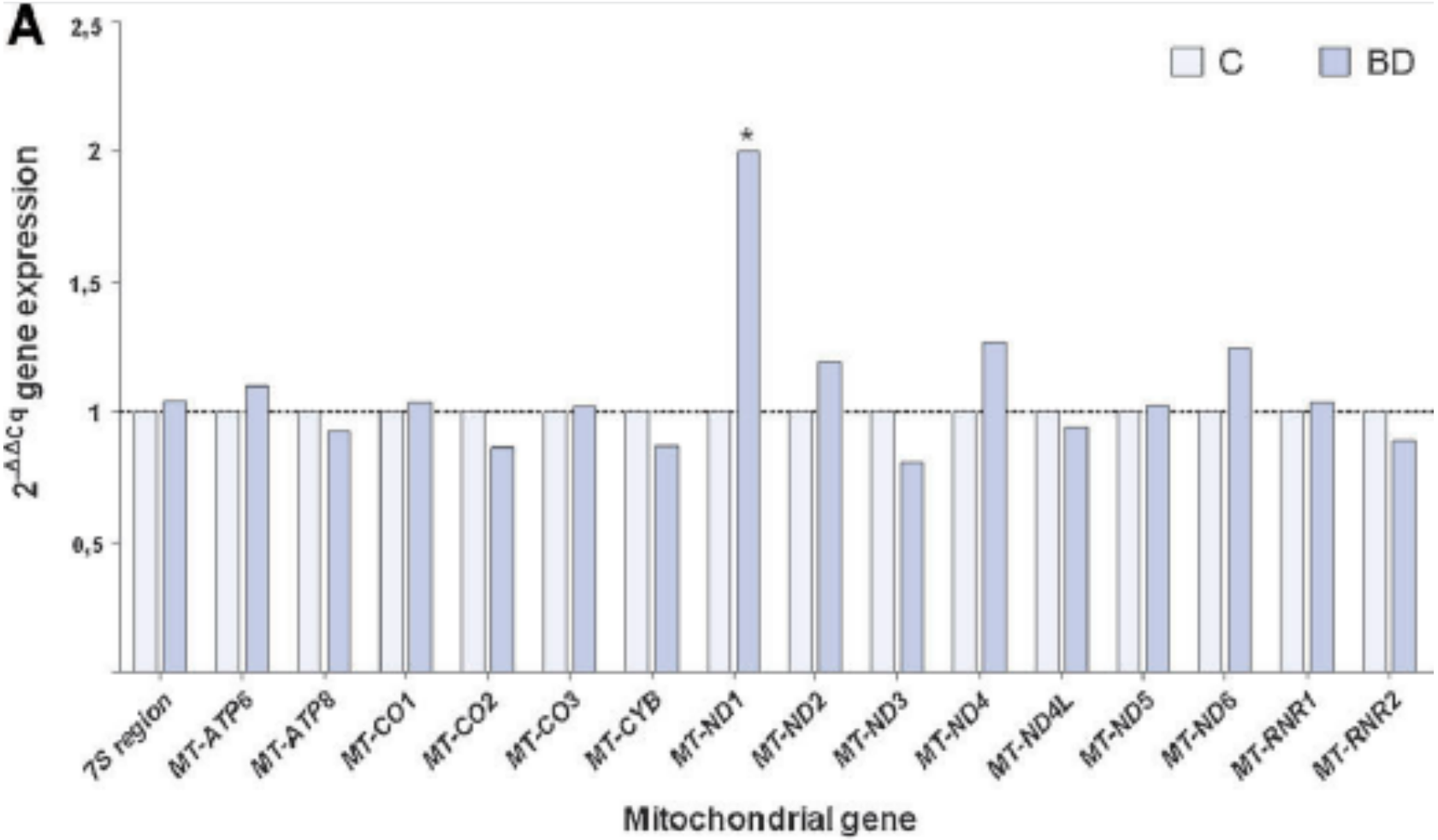
*Results were not corrected for multiple testing and are reported if they achieved a nominal $p < 0.05$.
Genes highlighted in bold are components of complexes I, III, IV or V of the mitochondrial electron transport chain.

Downregulated Genes

- NADH ubiquinone oxidoreductase
  - Complex I
- Ubiquinol-cytochrome c reductase
  - Complex III
- Cytochrome c oxidase polypeptide
  - Complex IV
- ATP synthase
  - Complex V

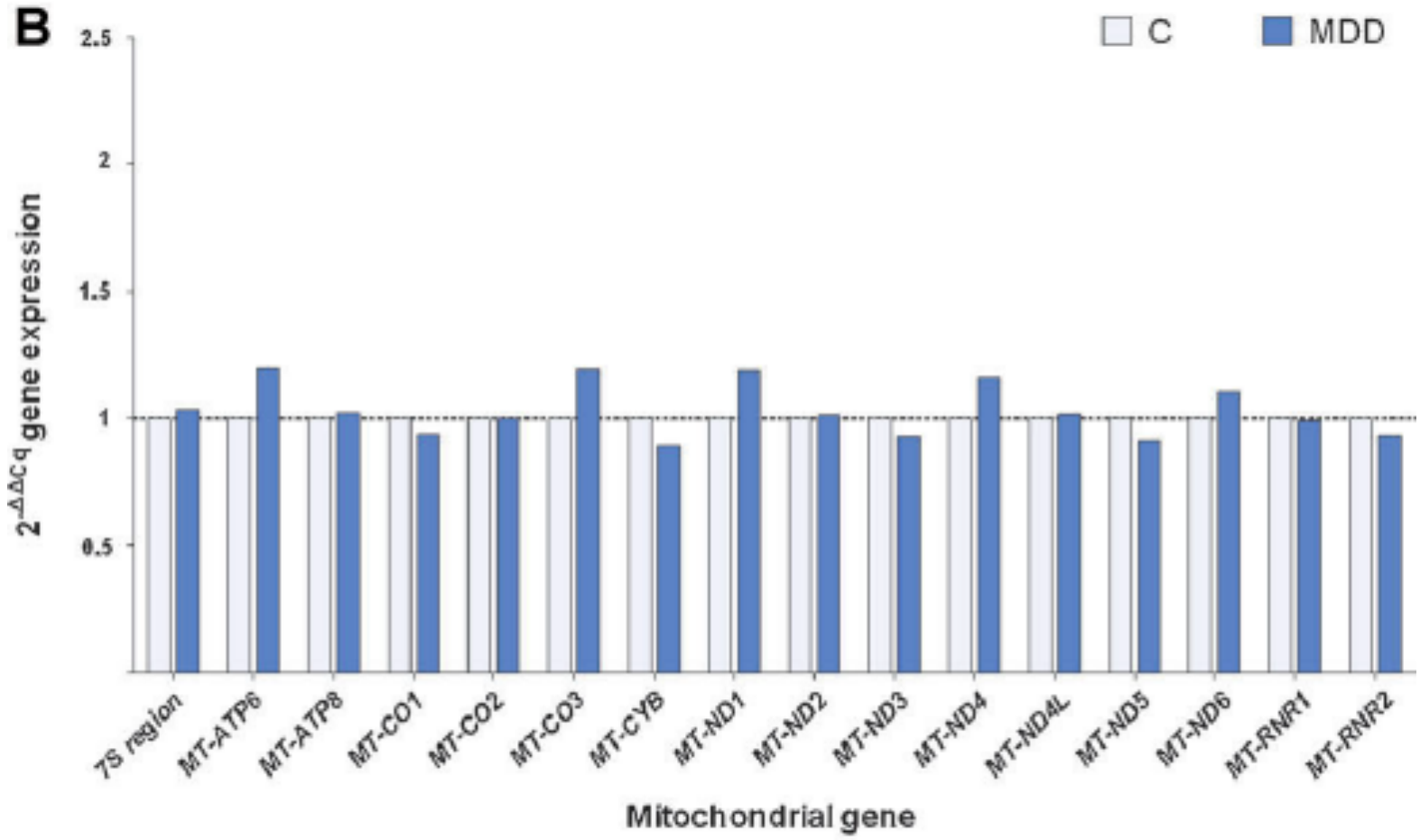
Sun et al. J Psychiatry Neurosci 2006;31:189

Bipolar Disorder



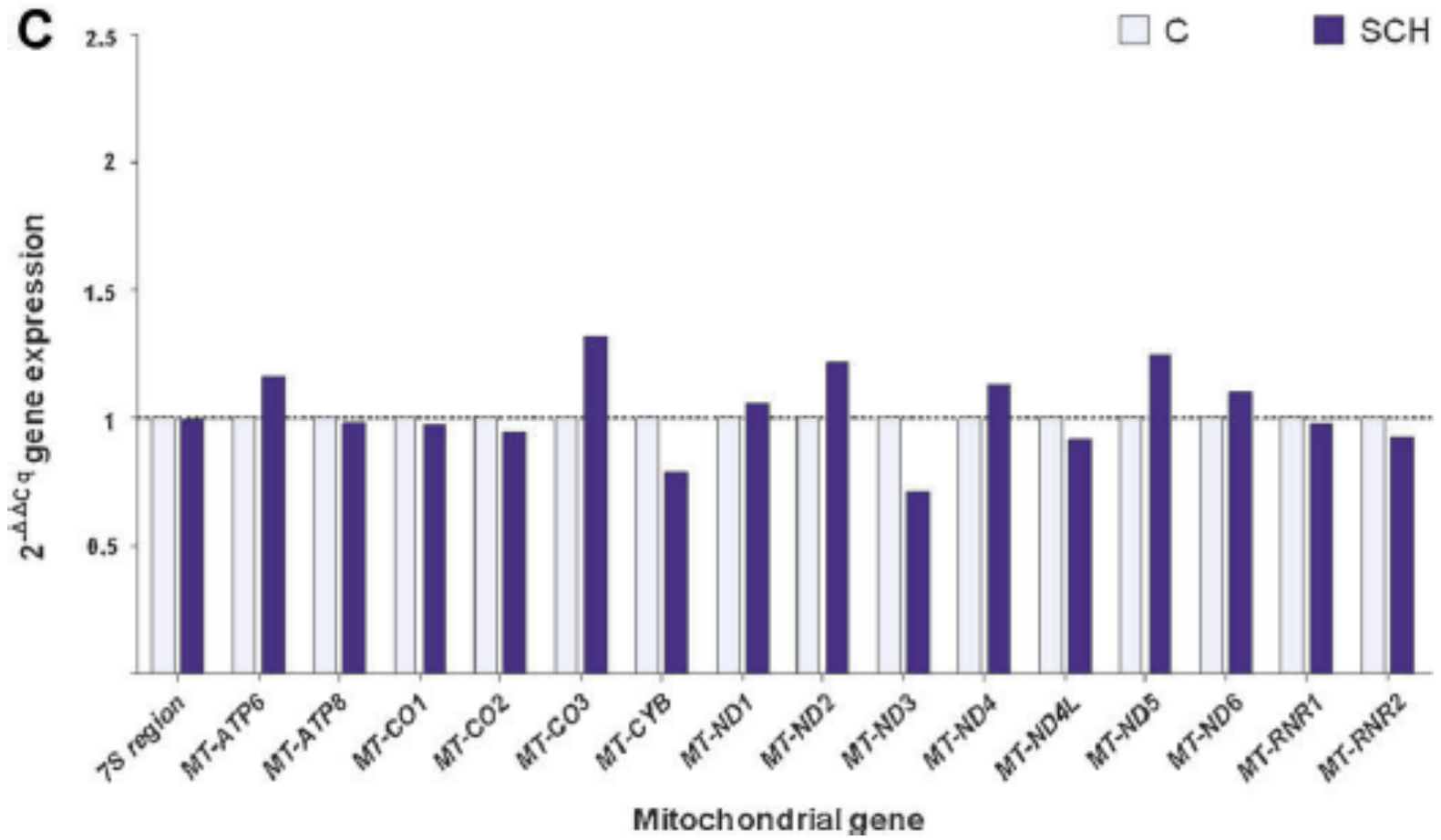
Torell et al. Am J Med Genet Part B 162B:213–223.

Major Depressive Disorder

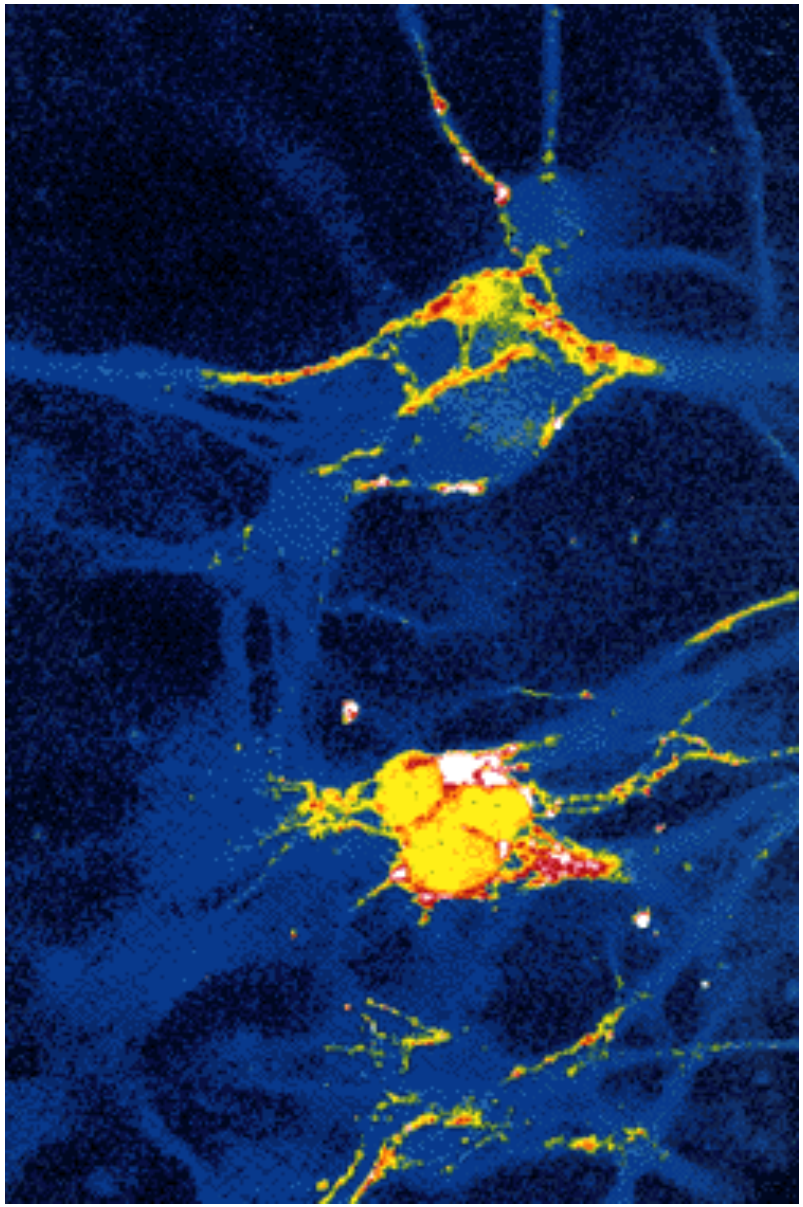


Torell et al. Am J Med Genet Part B 162B:213–223.

Schizophrenia



Torell et al. Am J Med Genet Part B 162B:213–223.



Free radical activity increased in neurons after decrease in BDNF

Eugene M. Johnson, PH.D, Washington University, and *Neuron*

Mitochondrial Abnormalities in Bipolar Disorder

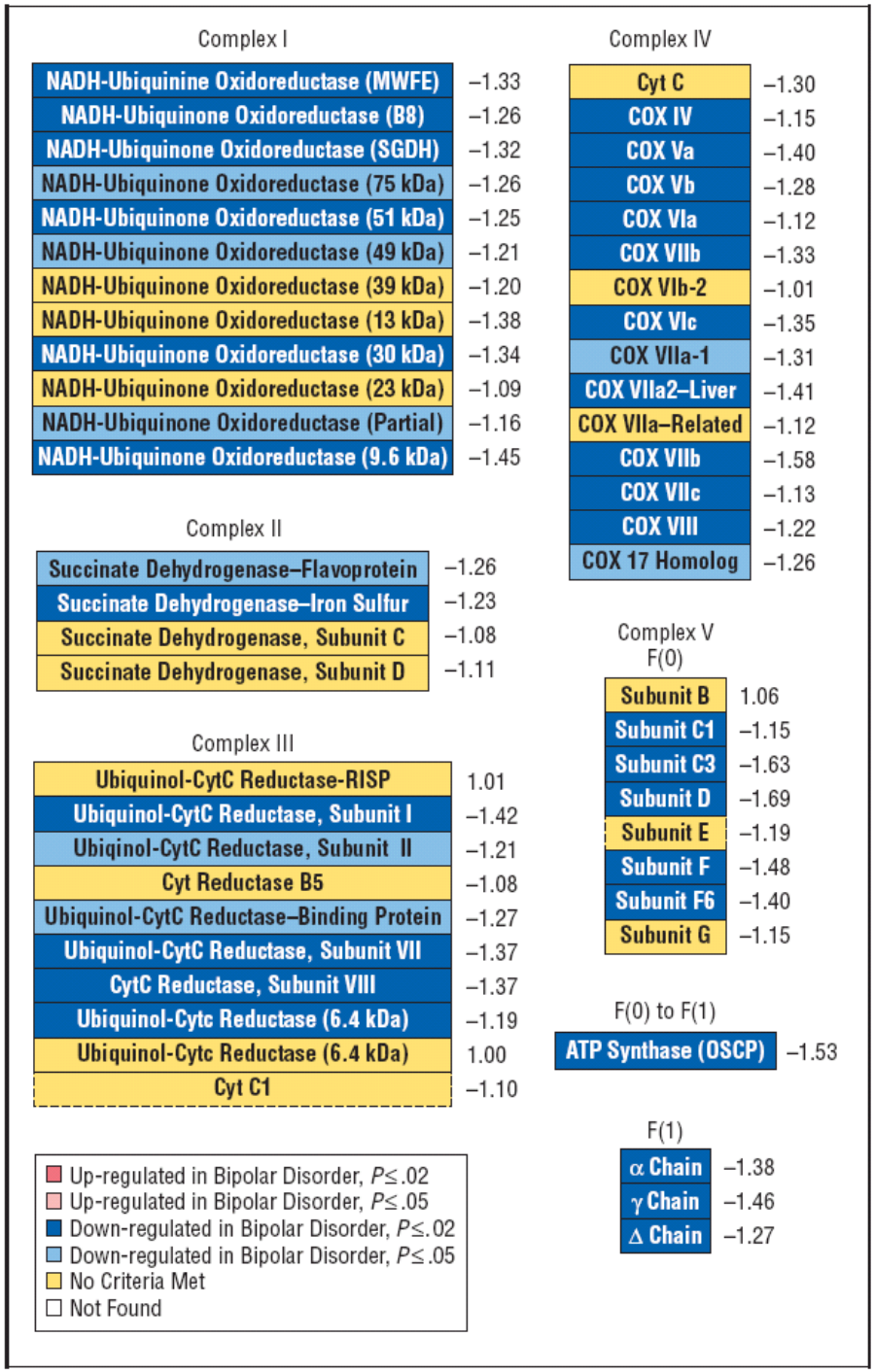
- Altered mitochondrial gene expression
- Decreased brain energy metabolism
- Altered calcium metabolism
- Dysregulated calcium channel genes
- Decreased oxidative stress with lithium and valproate

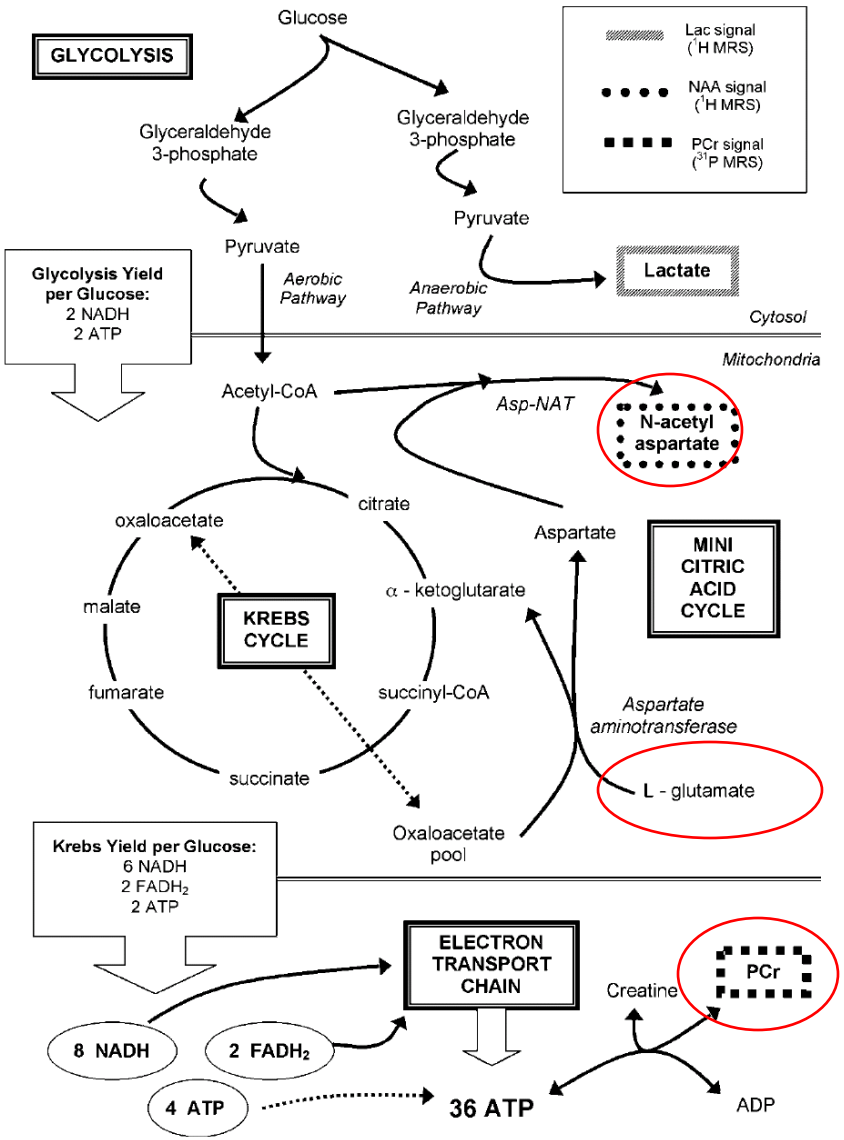
ORIGINAL ARTICLE

Molecular Evidence for Mitochondrial Dysfunction in Bipolar Disorder

Christine Konradi, PhD; Molly Eaton, BA; Matthew L. MacDonald, BS; John Walsh, MS; Francine M. Benes, MD, PhD; Stephan Heckers, MD

Arch Gen Psychiatry. 2004;61:300-308


Complex I
NADH-Ubiquinine Oxidoreductase (MWFE) –1.33
NADH-Ubiquinone Oxidoreductase (B8) –1.26
NADH-Ubiquinone Oxidoreductase (SGDH) –1.32
NADH-Ubiquinone Oxidoreductase (75 kDa) –1.26
NADH-Ubiquinone Oxidoreductase (51 kDa) –1.25
NADH-Ubiquinone Oxidoreductase (49 kDa) –1.21
NADH-Ubiquinone Oxidoreductase (39 kDa) –1.20
NADH-Ubiquinone Oxidoreductase (13 kDa) –1.38
NADH-Ubiquinone Oxidoreductase (30 kDa) –1.34
NADH-Ubiquinone Oxidoreductase (23 kDa) –1.09
NADH-Ubiquinone Oxidoreductase (Partial) –1.16
NADH-Ubiquinone Oxidoreductase (9.6 kDa) –1.45
Complex II
Succinate Dehydrogenase–Flavoprotein –1.26
Succinate Dehydrogenase–Iron Sulfur –1.23
Succinate Dehydrogenase, Subunit C –1.08
Succinate Dehydrogenase, Subunit D –1.11
Complex III
Ubiquinol-CytC Reductase-RISP 1.01
Ubiquinol-CytC Reductase, Subunit I –1.42
Ubiqinol-CytC Reductase, Subunit II –1.21
Cyt Reductase B5 –1.08
Ubiquinol-CytC Reductase–Binding Protein –1.27
Ubiquinol-CytC Reductase, Subunit VII –1.37
CytC Reductase, Subunit VIII –1.37
Ubiquinol-Cytc Reductase (6.4 kDa) –1.19
Ubiquinol-Cytc Reductase (6.4 kDa) 1.00
Cyt C1 –1.10
Up-regulated in Bipolar Disorder, P≤.02
Up-regulated in Bipolar Disorder, P≤.05
Down-regulated in Bipolar Disorder, P≤.02
Down-regulated in Bipolar Disorder, P≤.05
No Criteria Met
Not Found
Complex IV
Cyt C –1.30
COX IV –1.15
COX Va –1.40
COX Vb –1.28
COX VIa –1.12
COX VIIb –1.33
COX VIb-2 –1.01
COX VIc –1.35
COX VIIa-1 –1.31
COX VIIa2–Liver –1.41
COX VIIa–Related –1.12
COX VIIb –1.58
COX VIIc –1.13
COX VIII –1.22
COX 17 Homolog –1.26
Complex V
F(0)
Subunit B 1.06
Subunit C1 –1.15
Subunit C3 –1.63
Subunit D –1.69
Subunit E –1.19
Subunit F –1.48
Subunit F6 –1.40
Subunit G –1.15
F(0) to F(1)
ATP Synthase (OSCP) –1.53
F(1)
α Chain –1.38
γ Chain –1.46
Δ Chain –1.27



Molecular Psychiatry (2005) 10, 900–919

ORIGINAL ARTICLE

Differences in Lymphocyte Electron Transport Gene Expression Levels Between Subjects With Bipolar Disorder and Normal Controls in Response to Glucose Deprivation Stress

Alipi V. Naydenov, BS; Matthew L. MacDonald, BS; Dost Ongur, MD, PhD; Christine Konradi, PhD

Arch Gen Psychiatry. 2007;64:555-564

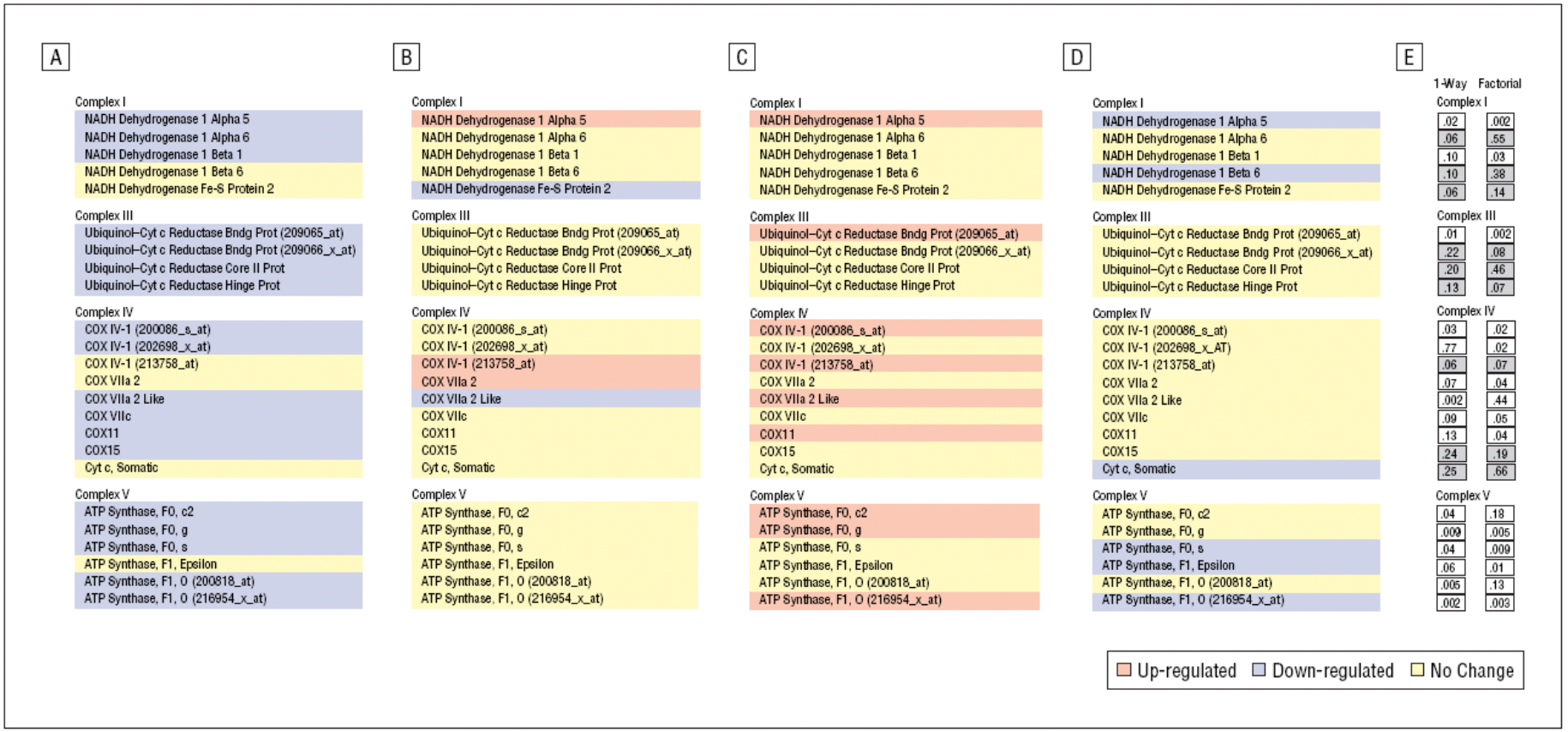


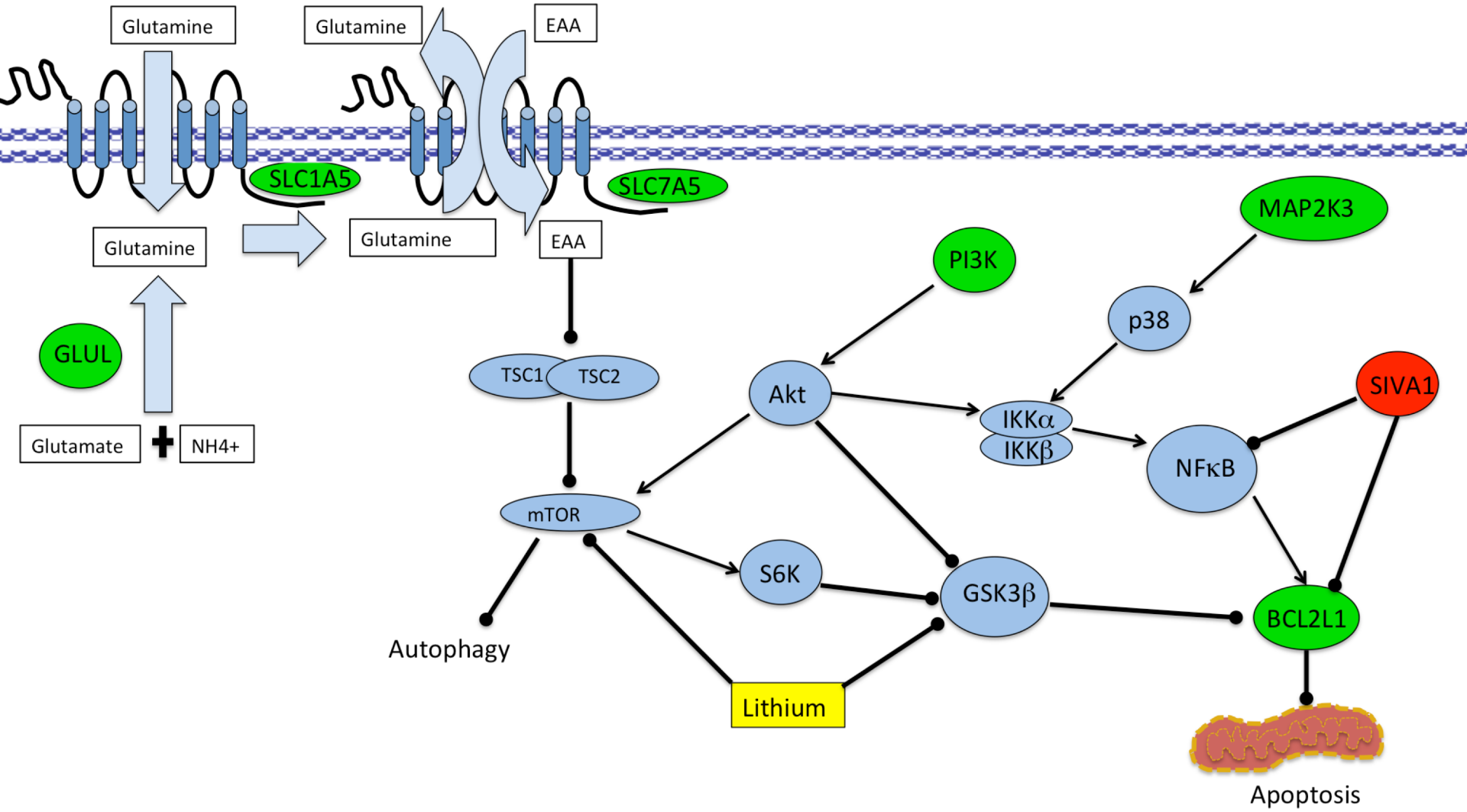
Figure 1. Probe sets of the electron transfer chain with $P<.05$ (*t* test) in low glucose for bipolar disorder lymphocytes over normal control lymphocytes (A), normal glucose for bipolar disorder lymphocytes over normal control lymphocytes (B), low over normal glucose for normal control lymphocytes (C), and low over normal glucose for bipolar disorder lymphocytes (D). NADH indicates reduced nicotinamide adenine dinucleotide; Fe-S, iron-sulfur; cyt c, cytochrome c; bndg, binding; prot, protein; COX, cytochrome c oxidase; and ATP, adenosine triphosphate. E, *P* values of 1-way and factorial analyses of variance (glucose level × treatment); shading indicates that the analysis of variance did not reach significance in both the 1-way and factorial analyses.

Naydenov et al. Arch Gen Psychiatry. 2007;64:555-564

Gene-expression differences in peripheral blood between lithium responders and non-responders in the "Lithium Treatment -Moderate dose Use Study" (LiTMUS).

Robert D. Beech[1*], Janine J. Leffert[1], Aiping Lin[2], Louisa G. Sylvia[3], Sheila Umlauf[4], Shrikant Mane[4], Hongyu Zhao[5], Charles Bowden[6], Joseph R. Calabrese[7], Edward S. Friedman[8], Terence Ketter[9], Dan V Iosifescu[10], Michael Thase[11], and Andrew Nierenberg[3].

		Current Study: Li+OPT_R vs NR		**Lowthert et al., 2012: Bipolar Depression_R vs NR**	
REFSEQ_ID	SYMBOL	Fold-Difference	p-value	Fold-Difference	p-value
NM_138578.1	BCL2L1	1.63	0.01	1.35	0.37
NM_033480.2	FBXO9	1.47	0.02	1.42	0.07
NM_014632.2	MICAL2	1.45	0.01	1.56	0.03
NM_002756.3	MAP2K3	1.43	0.07	1.66	0.06
NR_002206.1	GTF2IP1	1.42	0.01	1.47	0.01
NM_002343.2	LTF	1.42	0.02	1.46	0.05
NM_001033056.1	GLUL	1.32	0.02	1.36	0.22
NM_002756.3	MAP2K3	1.32	0.04	1.66	0.06
NR_002139.1	HCG4	1.31	0.01	1.43	0.13
NM_001031617.2	COX19	-1.30	0.03	-1.41	0.01
NM_198795.1	TDRD1	-1.31	0.05	-1.37	0.08
NM_178231.1	ALS2CR14	-1.31	0.04	-1.56	0.05
XM_939697.1	C9orf130	-1.31	0.01	-1.66	0.03
NM_005317.2	GZMM	-1.32	0.05	-1.59	0.03
XM_936461.1	LOC647389	-1.32	0.02	-1.43	0.08
XM_930344.2	LOC644934	-1.33	0.02	-1.31	0.37
NM_198271.2	LMOD3	-1.36	0.02	-1.41	0.05
XM_940430.1	LOC648852	-1.43	0.01	-1.63	0.04
NM_018973.3	DPM3	-1.45	0.00	-1.73	0.00
NM_001004322.1	FLJ38717	-1.45	0.02	-1.49	0.02


Glutamine
Glutamine
EAA
SLC1A5
SLC7A5
Glutamine
Glutamine
EAA
GLUL
Glutamate
NH4+
PI3K
MAP2K3
p38
TSC1
TSC2
Akt
IKKα
IKKβ
SIVA1
NFκB
mTOR
S6K
GSK3β
BCL2L1
Autophagy
Lithium
Apoptosis

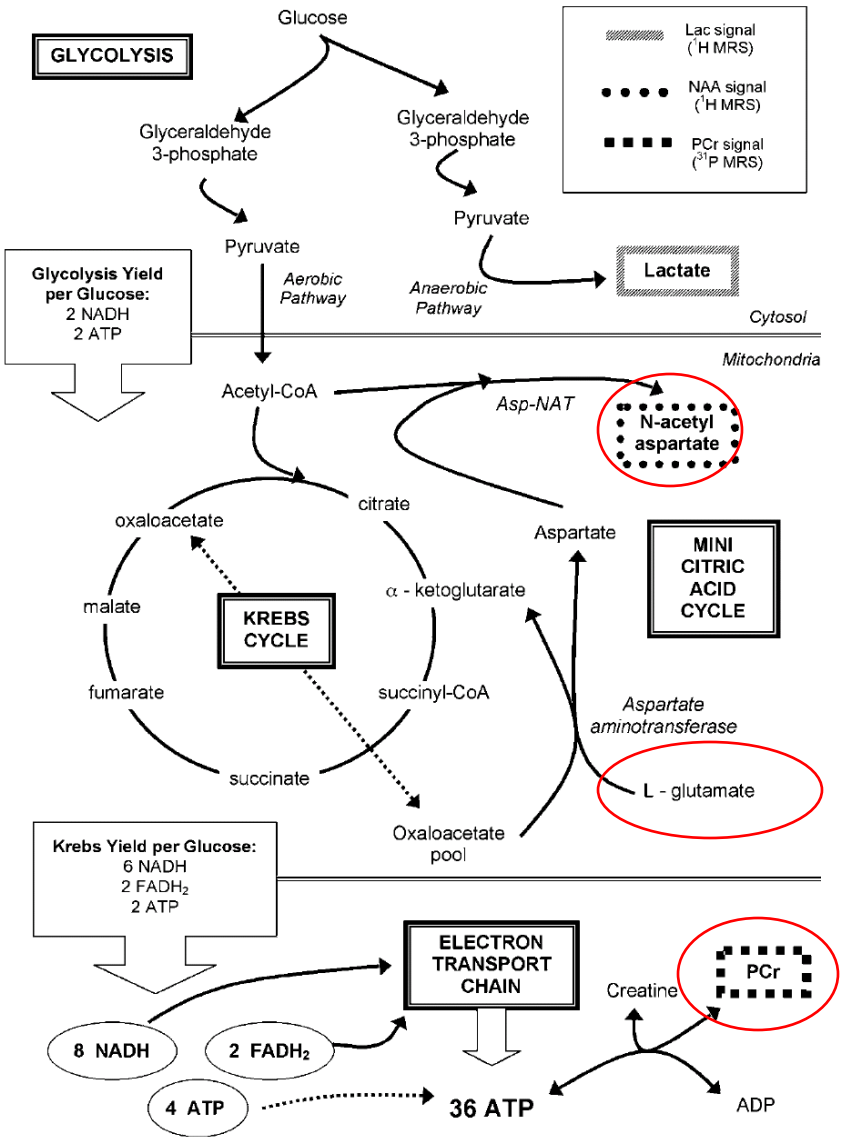
Bipolar Disorders 2007: 9 (Suppl. 1): 119–127

BIPOLAR DISORDERS

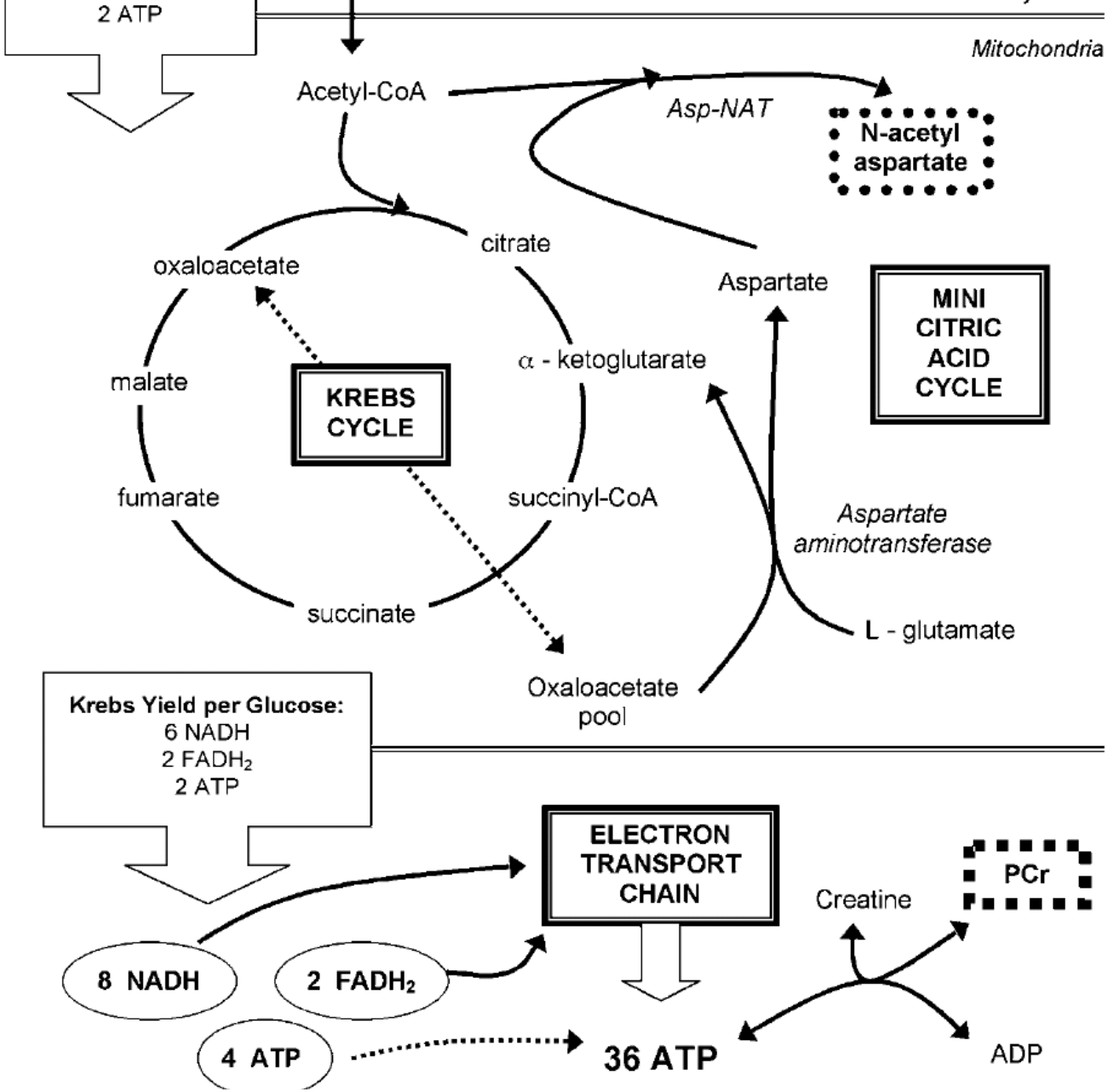
Original Article

Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an *in vivo* ^{1}H MRS study

Benício N Frey[a,b,c], Jeffrey A Stanley[d], Fabiano G Nery[a,e], E Serap Monkul[a,f], Mark A Nicoletti[a,g], Hua-Hsuan Chen[h], John P Hatch[a], Sheila C Caetano[a,d], Oswaldo Ortiz[g], Flávio Kapczinski[b,c] and Jair C Soares[a,g,h]

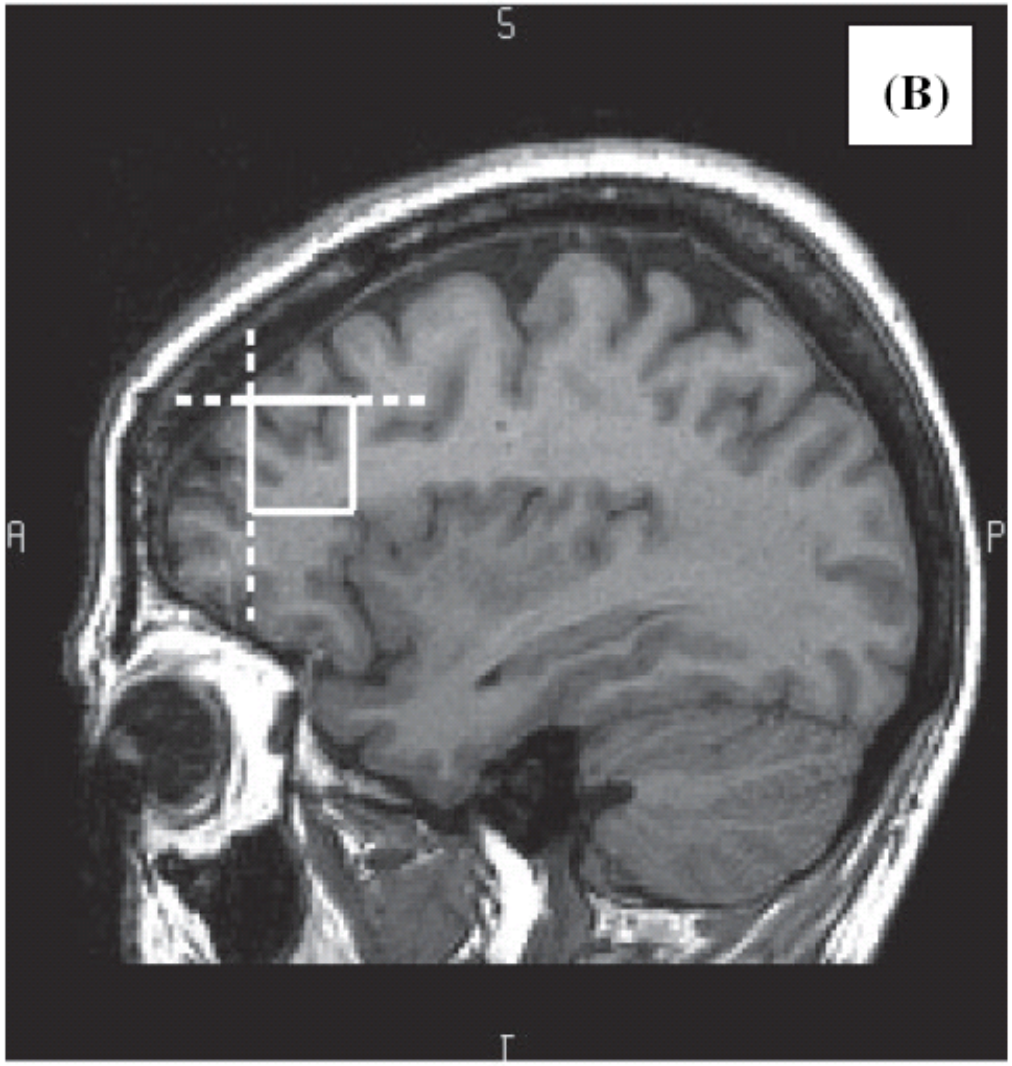


Molecular Psychiatry (2005) 10, 900–919

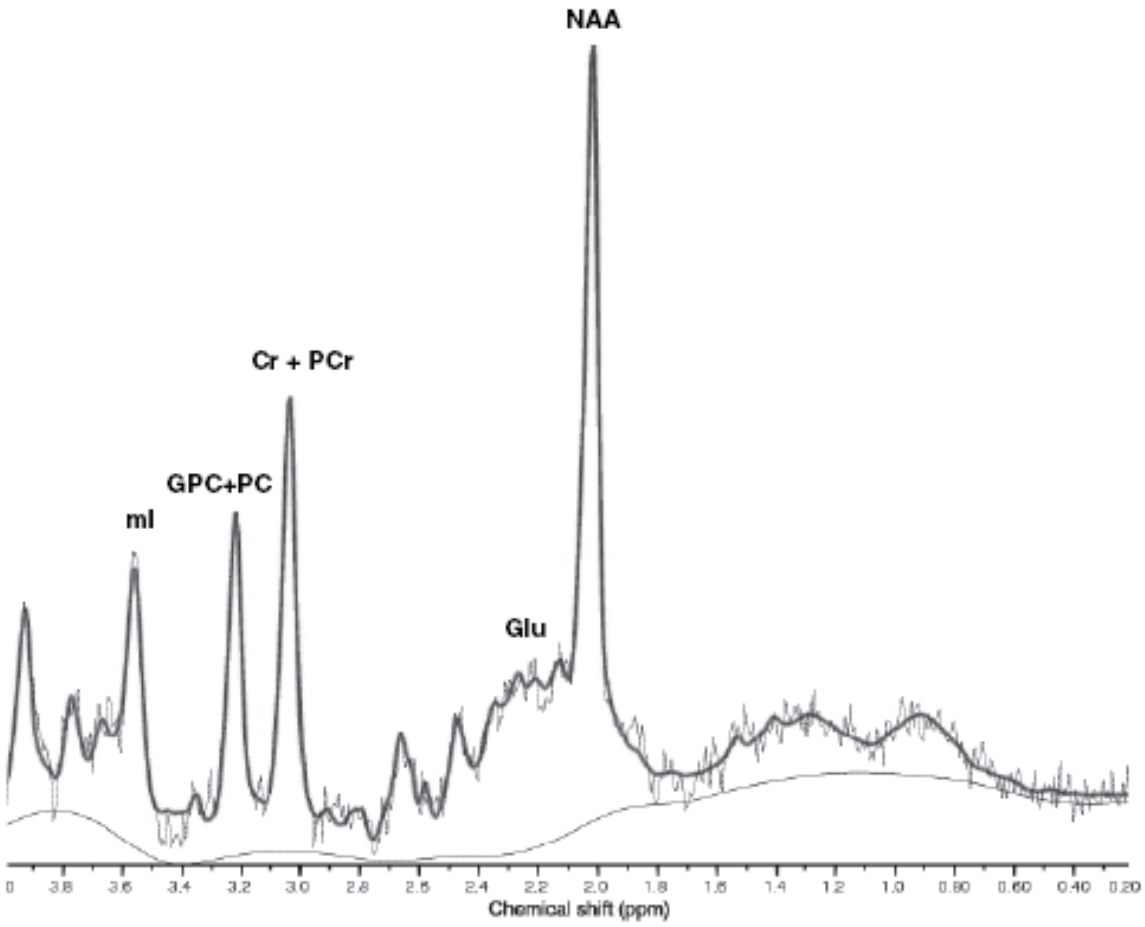


Molecular Psychiatry (2005) 10, 900–919

Prefrontal Cortex



MRS: Metabolic Metabolites



Lower Levels of Creatine and Phosphocreatine in Bipolar Disorder

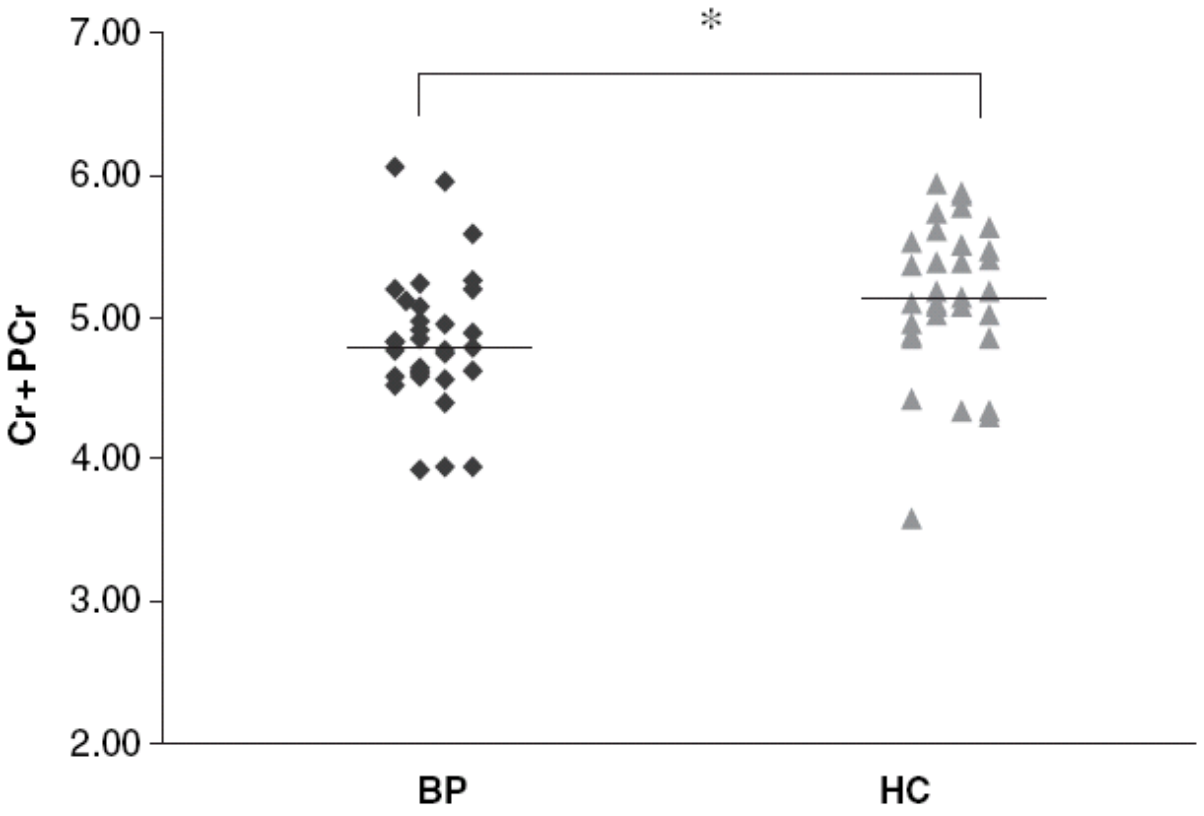


Fig. 3. Cr + PCr levels in bipolar subjects and healthy controls. Cr + PCr = creatine plus phosphocreatine; BP = bipolar subjects; HC = healthy controls. *p = 0.018.

Lower Levels Choline containing compounds in Bipolar Disorder

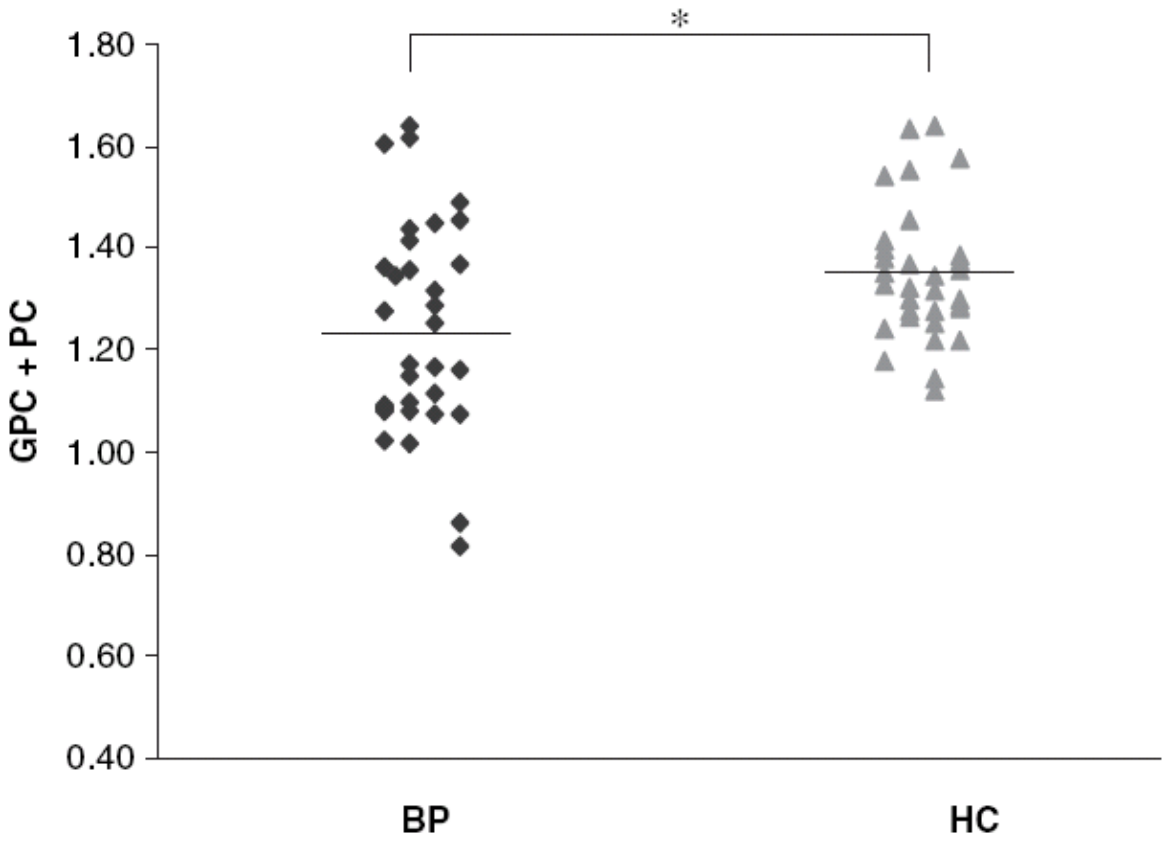
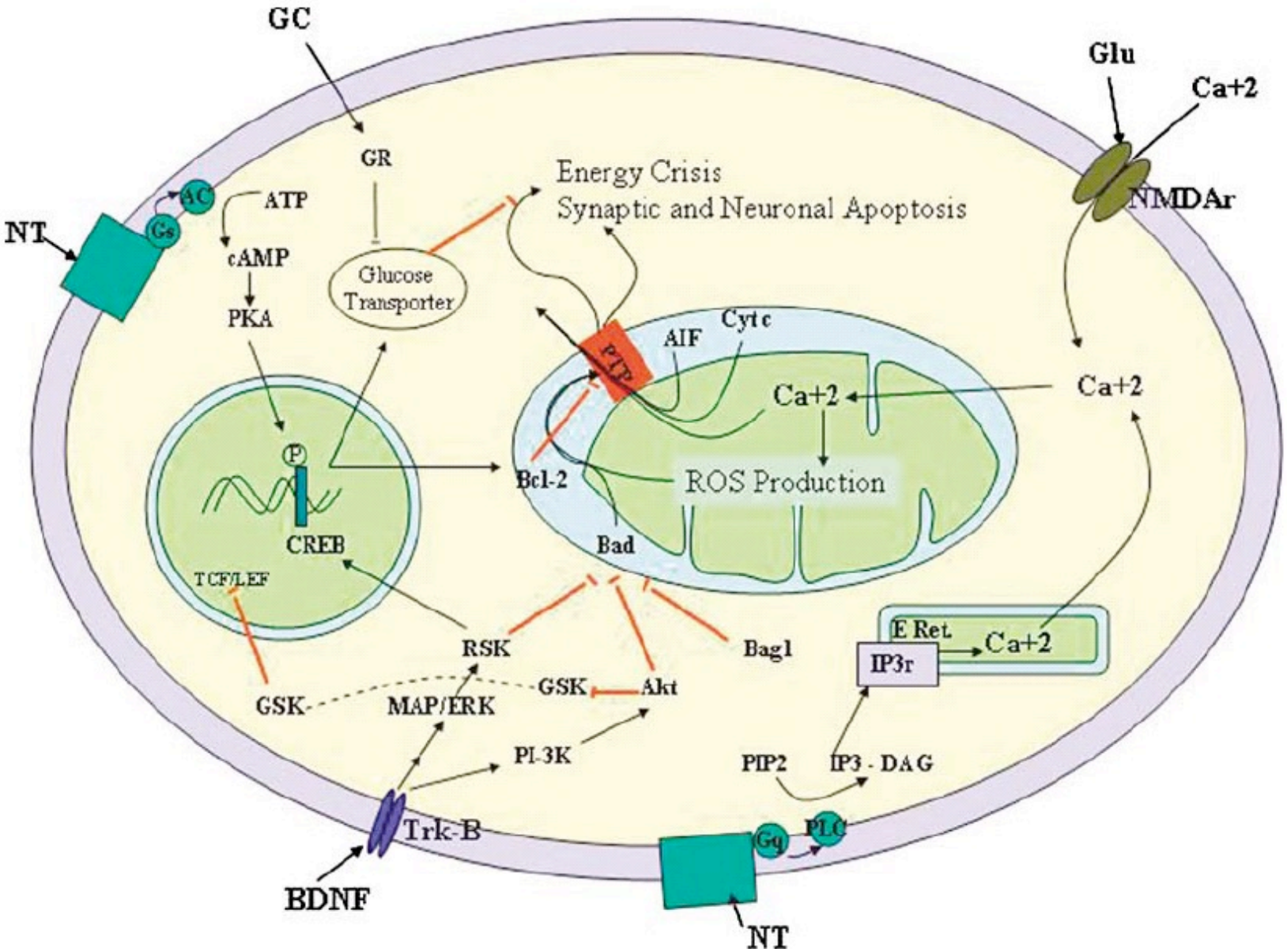


Fig. 4. GPC + PC levels in bipolar subjects and healthy controls. GPC + PC = choline-containing compounds; BP = bipolar subjects; HC = healthy controls. *p = 0.019.

Neuropsychopharmacology (2008), 1–15

www.neuropsychopharmacology.org



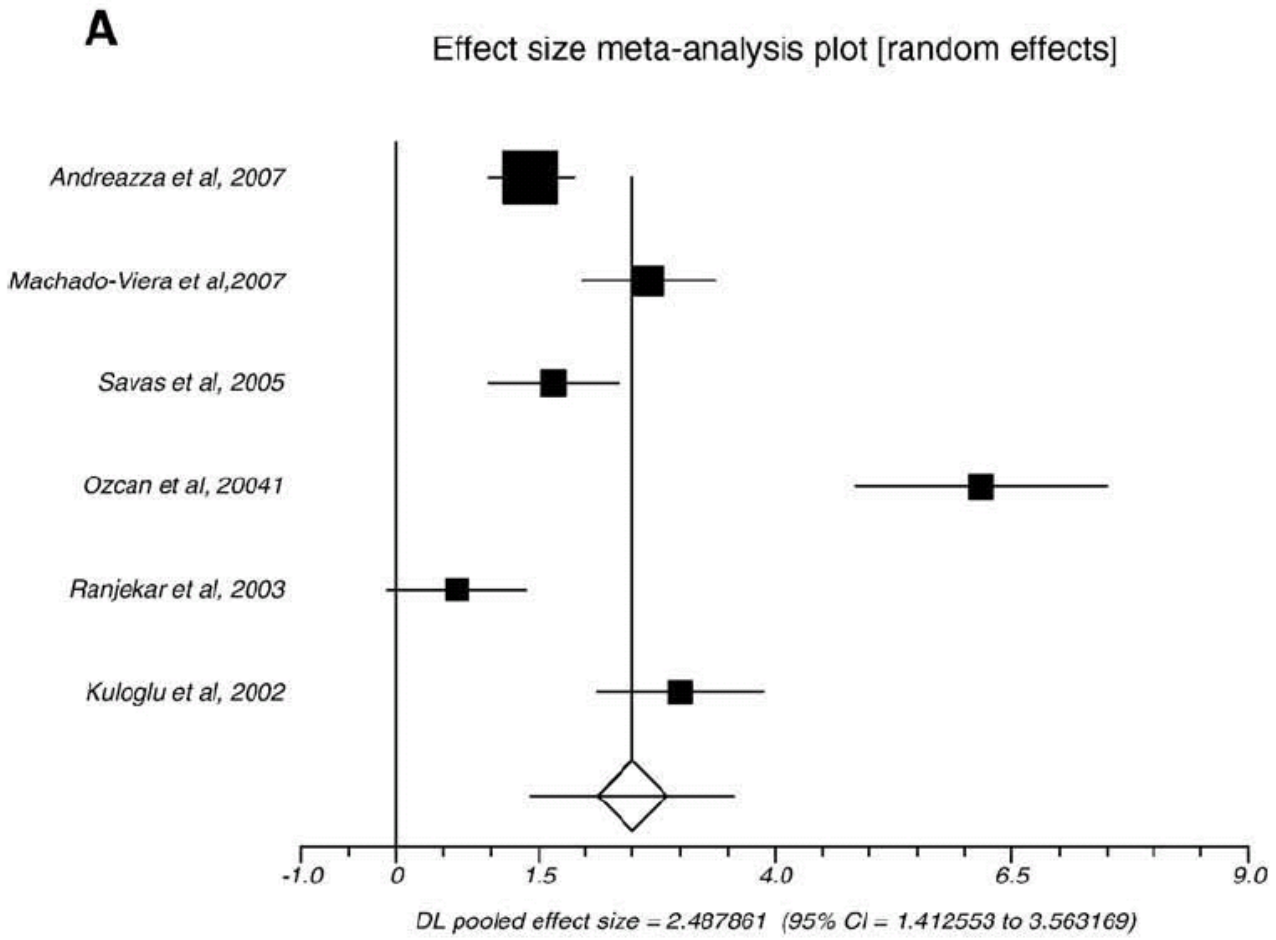
Peripheral Markers of Oxidative Stress

Peripheral Markers of Oxidative Stress

- Thiobarbituric acidic reactive substances (TBARS)
- Superoxide dismutase (SOD)
- Catalase
- Glutathione
- Nitric oxide

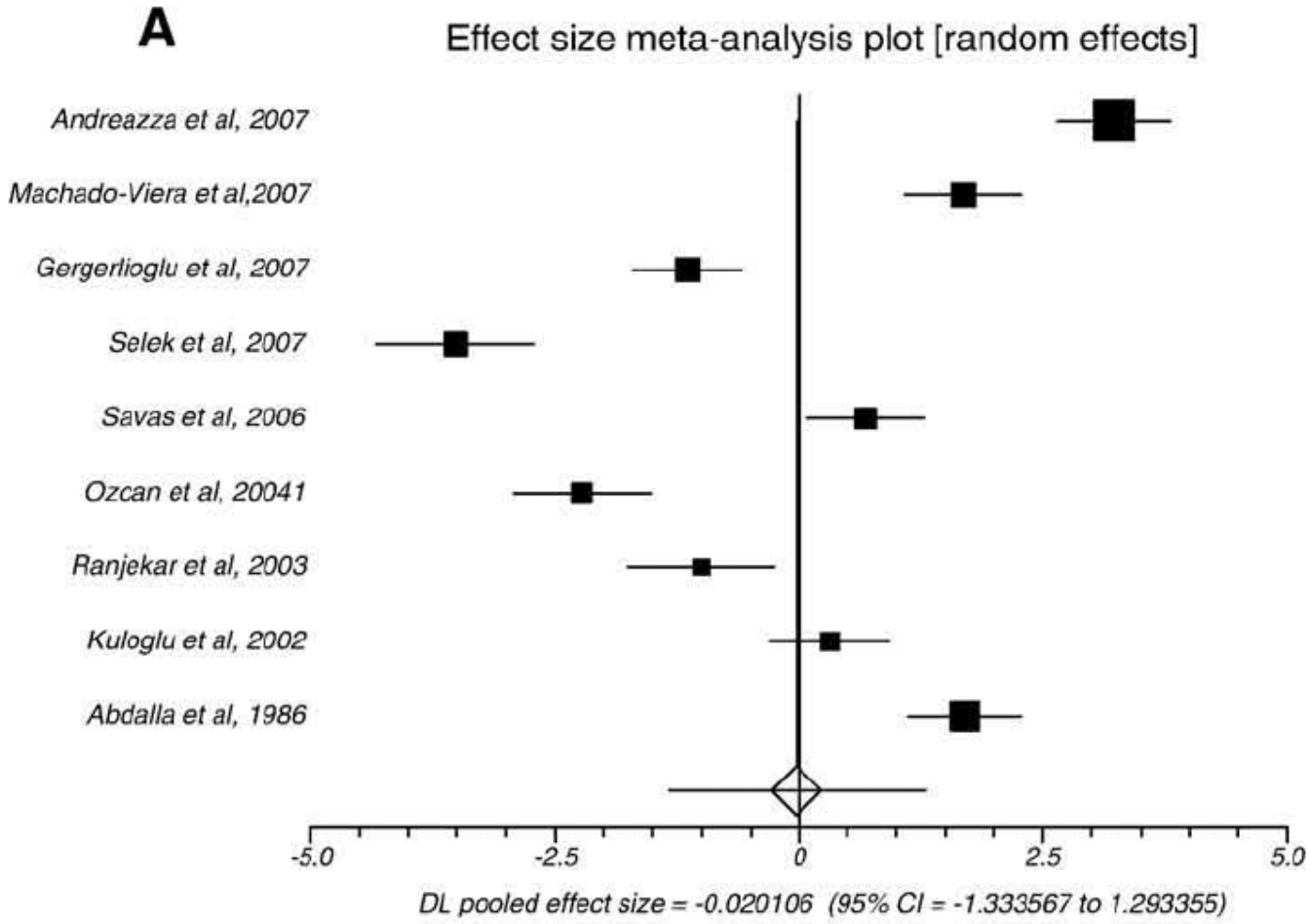
Andreazza, A.C., et al., Oxidative stress markers in bipolar disorder: A meta-analysis, J. Affect. Disord. (2008), doi:10.1016/j.jad.2008.04.013

TBARS Meta-analysis



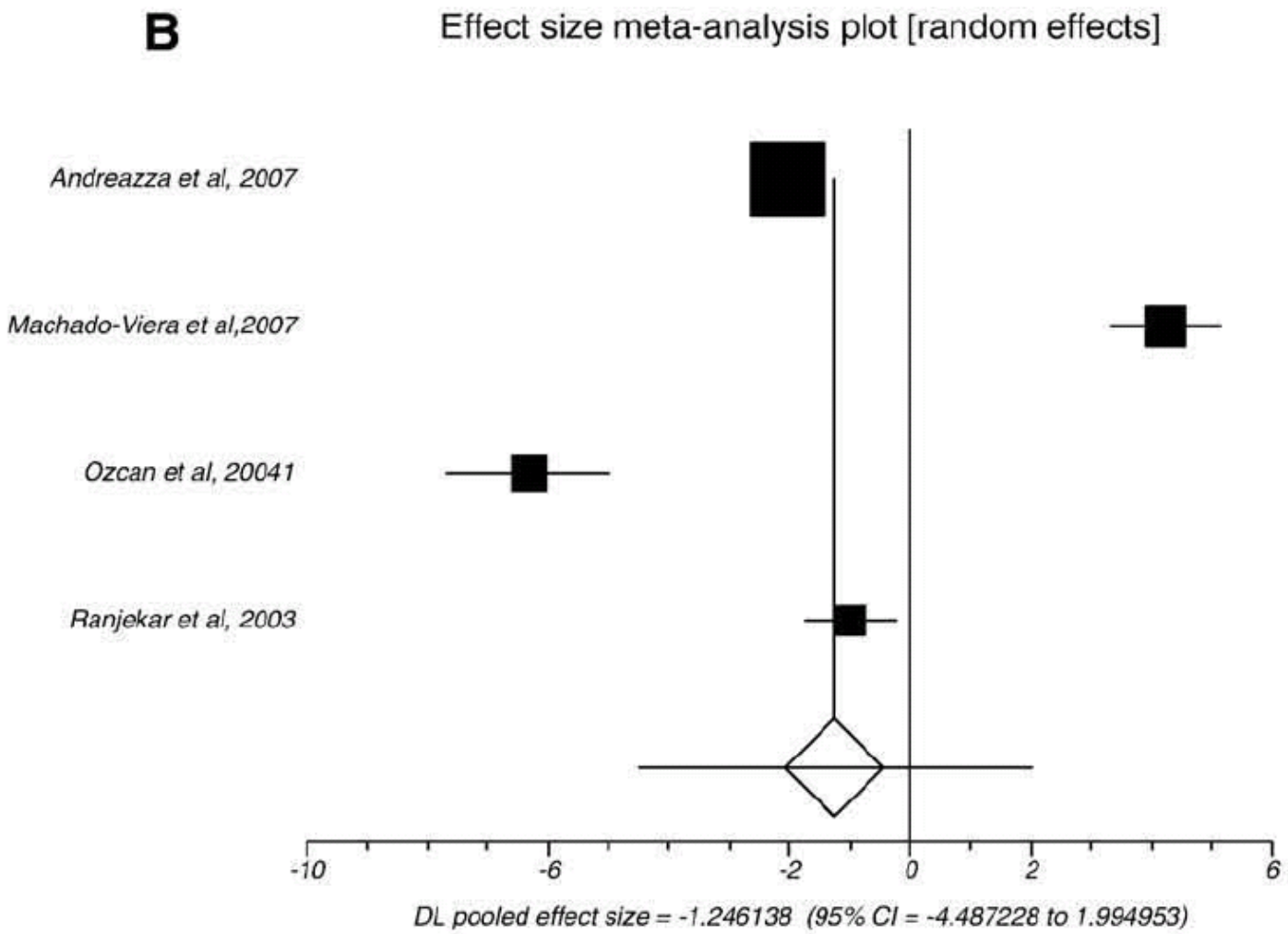
Andreazza, A.C., et al., Oxidative stress markers in bipolar disorder: A meta-analysis, J. Affect. Disord. (2008), doi:10.1016/j.jad.2008.04.013

Cu Zn Super Oxide Dismutase Meta-analysis



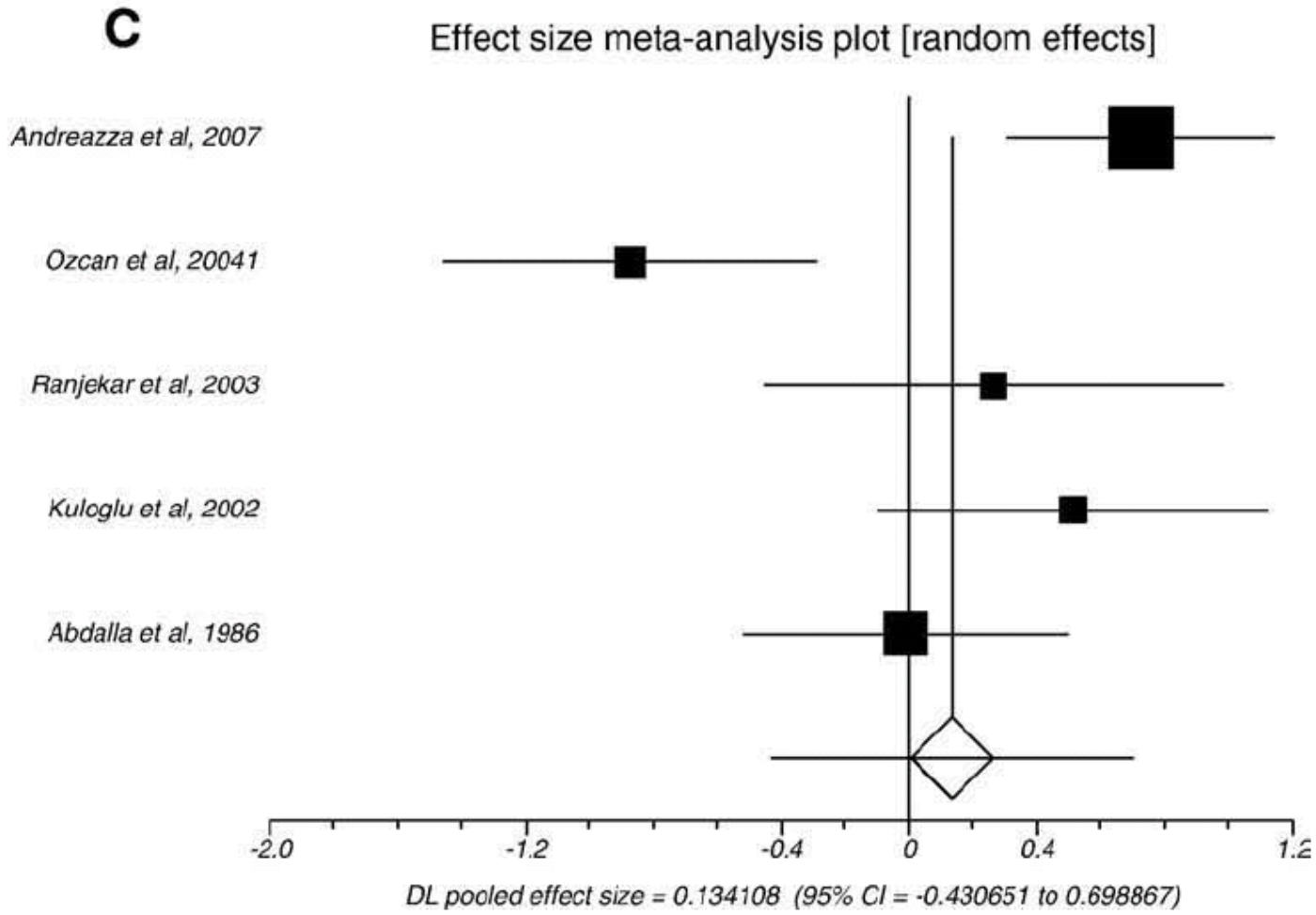
Andreazza, A.C., et al., Oxidative stress markers in bipolar disorder: A meta-analysis, J. Affect. Disord. (2008), doi:10.1016/j.jad.2008.04.013

Catalase Meta-analysis



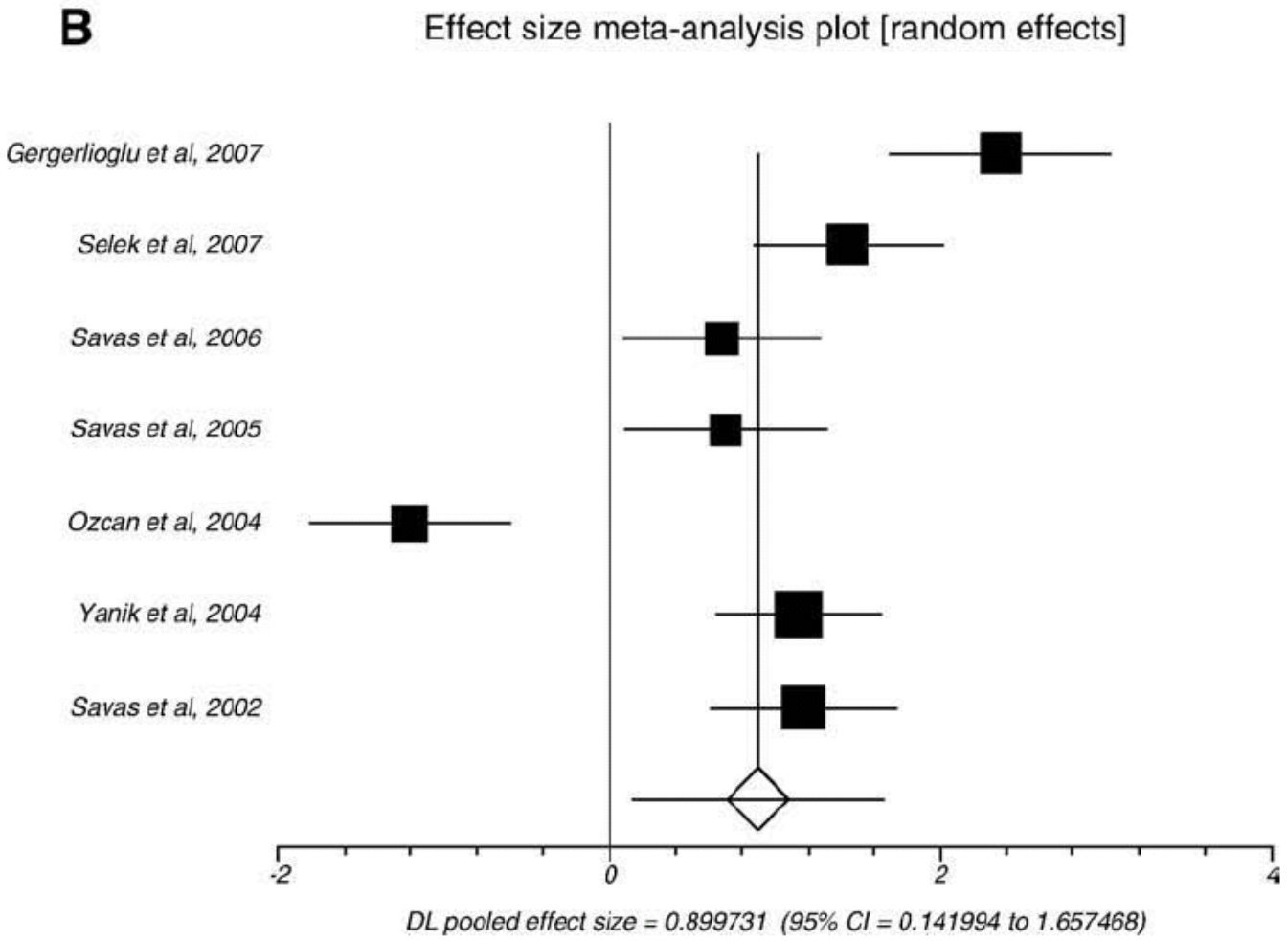
Andreazza, A.C., et al., Oxidative stress markers in bipolar disorder: A meta-analysis, J. Affect. Disord. (2008), doi:10.1016/j.jad.2008.04.013

Glutathione Peroxidase Activity Meta-analysis



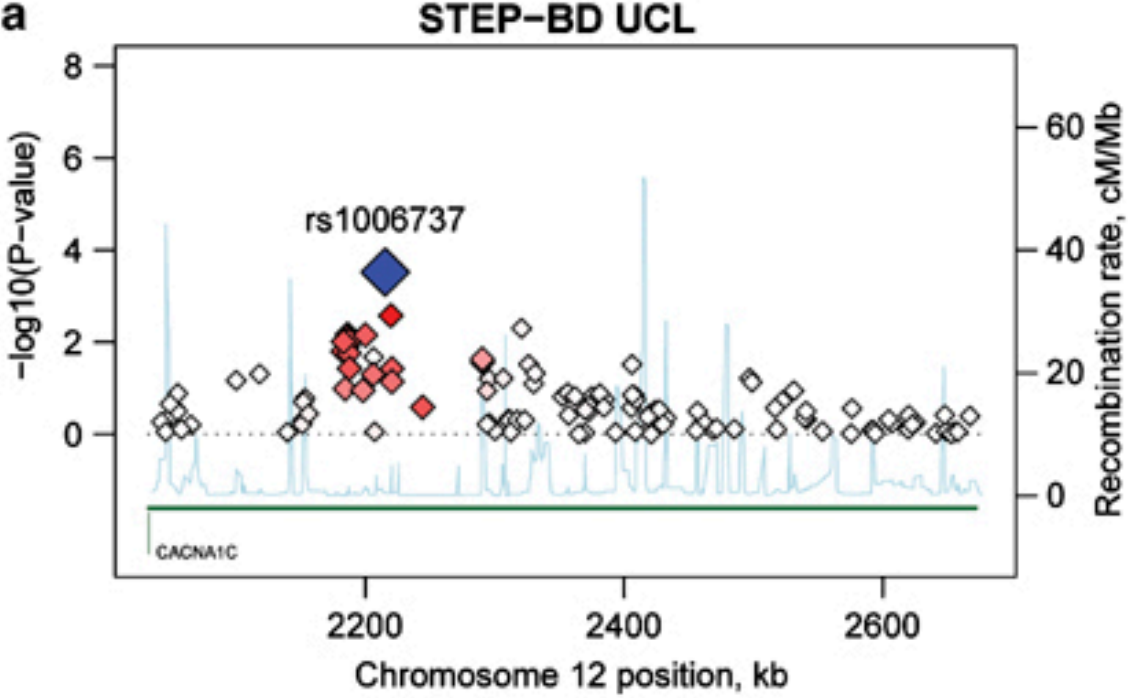
Andreazza, A.C., et al., Oxidative stress markers in bipolar disorder: A meta-analysis, J. Affect. Disord. (2008), doi:10.1016/j.jad.2008.04.013

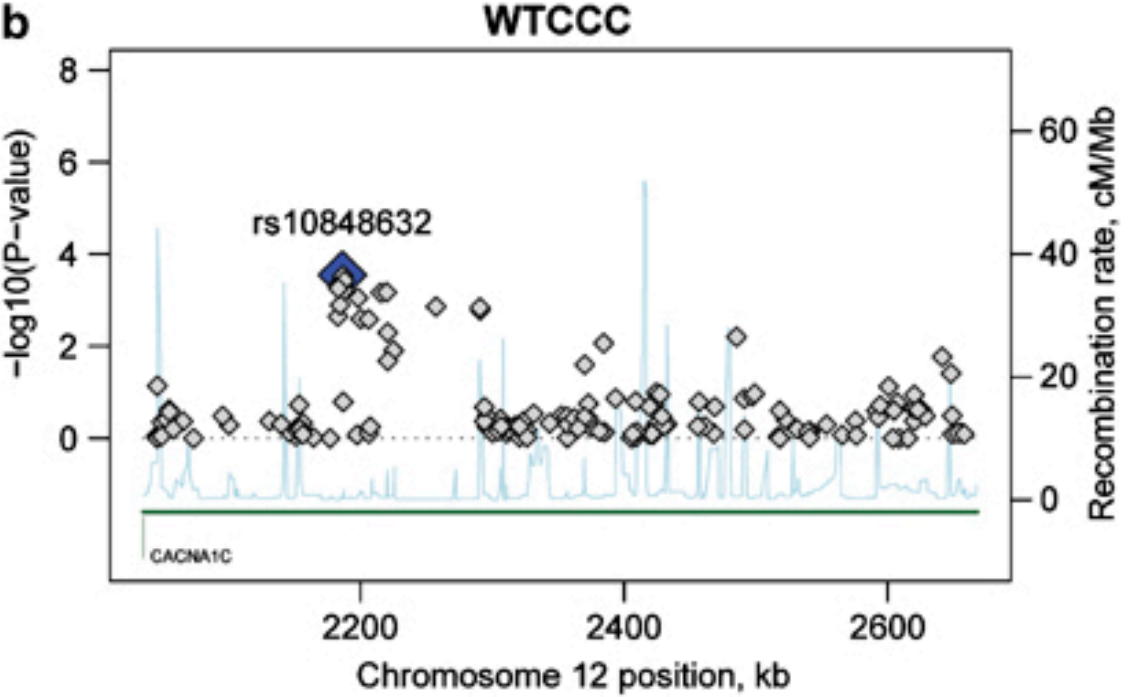
Nitric Oxide Meta-analysis



Andreazza, A.C., et al., Oxidative stress markers in bipolar disorder: A meta-analysis, J. Affect. Disord. (2008), doi:10.1016/j.jad.2008.04.013

Calcium Channel Genes



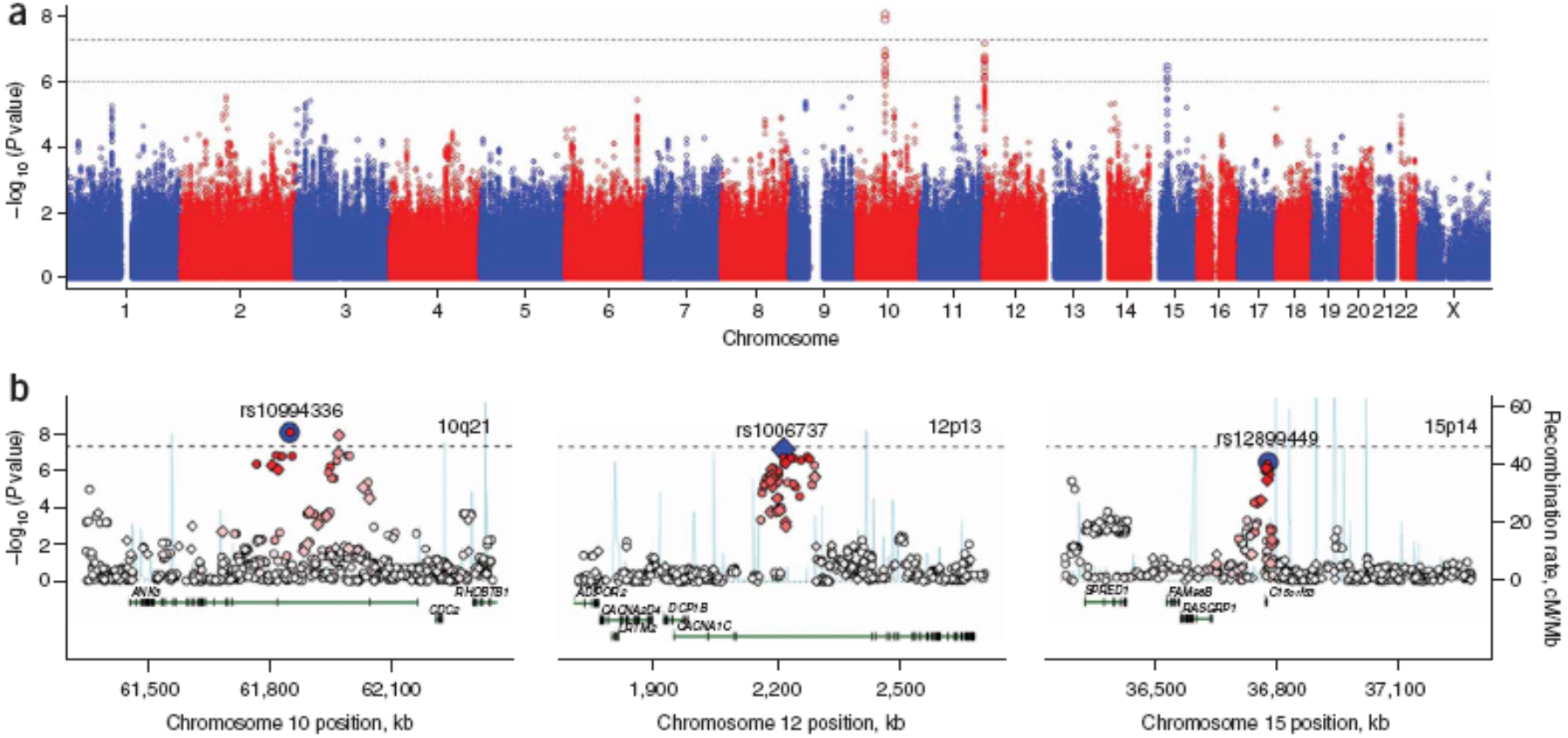


CACNA1C

Alpha subunit L-type Calcium channel

Sklar et al. Molecular Psych 2008:13;558

Ankyrin 3 and alpha subunit of L-type Calcium Channel



Ferriera et al. Nature Genetics 2008;40:1056

Table 2 Summarizing studies of neuroprotection against oxidative damage by mood-stabilizing drugs

Mood stabilizers	Tissue	Results	References
VPA	Primary cultured rat cerebral cortical cells	↓ FeCl3-induced oxidative damage to lipid and protein	Wang et al[77]
Li+, VPA	Primary cultured rat cerebral cortical cells	↓ Glutamate-induced oxidative damage to lipid and protein	Shao et al[78]
Li+, VPA	Human neuroblastoma SH-SY5Y cells	↓ Rotenone- and H2O2-induced cytochrome c release, caspase-3 activation and cell death.	Lai et al[79]
Li+	SH-SY5Y cells	↓ Rotenone- and H2O2-induced activation of caspase-2 and -3	King and Jope[80]
Li+, VPA	Primary cultured rat cerebral cortical cells	↑ GSH levels, ↑GCL expression, ↓ H2O2-induced cell death	Cui et al[81]
LTG, CMZ	SH-SY5Y cells	↑ GSH levels, ↑ GCL expression	Cui et al[81]
Li+	Mouse hippocampal HT-22 cells	↓ H2O2- and glutamate-induced cell death	Schafer et al[82]
OLP	Rat Pheochromocytoma PC-12 cells	↓ β-amyloid-induced cell death, caspase-3 activation, ROS overproduction	Wang et al[85]
OLP	PC-12 cells	↓ H2O2-induced cell death,↑SOD enzyme activity	Wei et al[84]
Li+, VPA	Rat hippocampus	↓ Amphetamine-induced lipid peroxidation	Frey et al[86]
Li+, VPA	Primary cultured rat cerebral cortical cells	↑ GST-M1 and A4 expression, ↑GST enzyme activity	Wang et al[87,88]
Li+	Rat brain	↑ SOD activity	Shukla[90]
Li+	Rat brain	↑ Total antioxidant reactivity levels, ↑ activities of SOD and GPx	De Vasconcellos et al[91]
OLP	PC-12 cells	↑ SOD mRNA levels	Li et al[92]

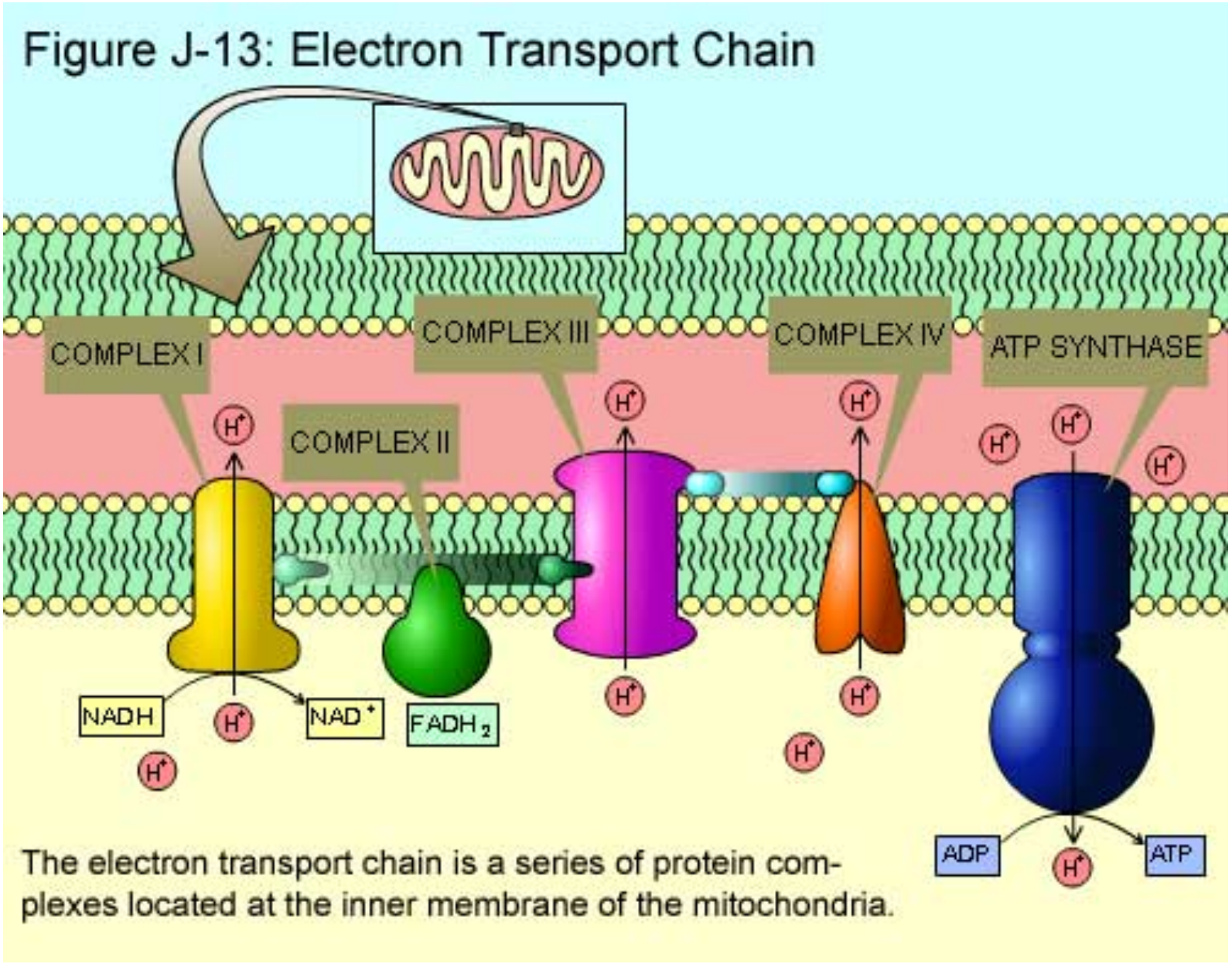
Li+ = lithium; VPA = valproate; OLP = olanzapine; LTG = lamotrigine; CMZ = carbamazepine; GSH = glutathione; GCL = glutamate-cysteine ligase; SOD = superoxide dismutase; GPx = glutathione peroxidase

Wang et al. Canadian J Psychiatry 2007:52:753

Can bipolar relapse be decreased by modulating mitochondria?

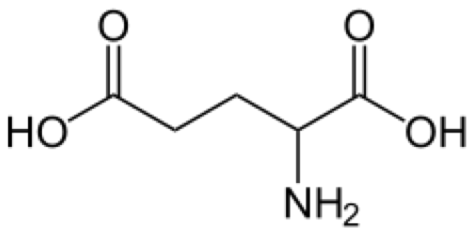
Mitochondrial Modulators

- N-acetyl-cysteine (NAC)
- Acetyl-L-carnitine (ALCAR)
- Alpha lipoic acid
- Coenzyme Q10
- S-adenosylmethionine (SAMe)

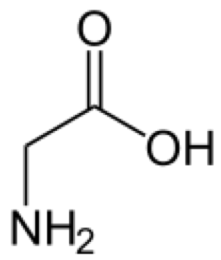


hopes.stanford.edu/treatmts/ebuffer/j1.html

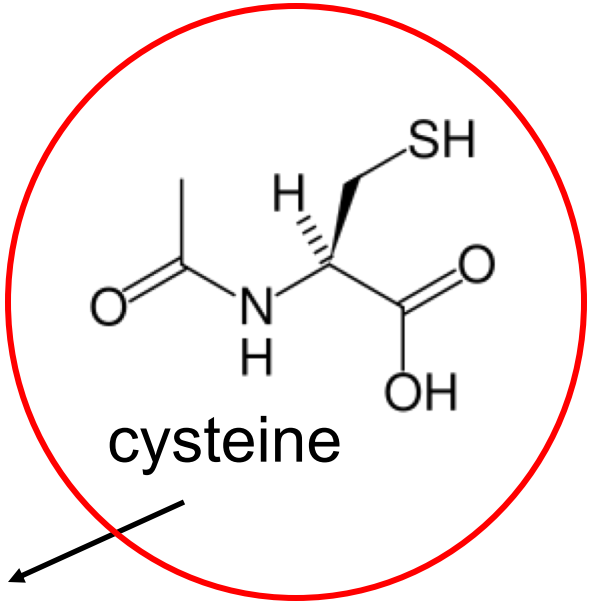
n-acetyl-cysteine (NAC)



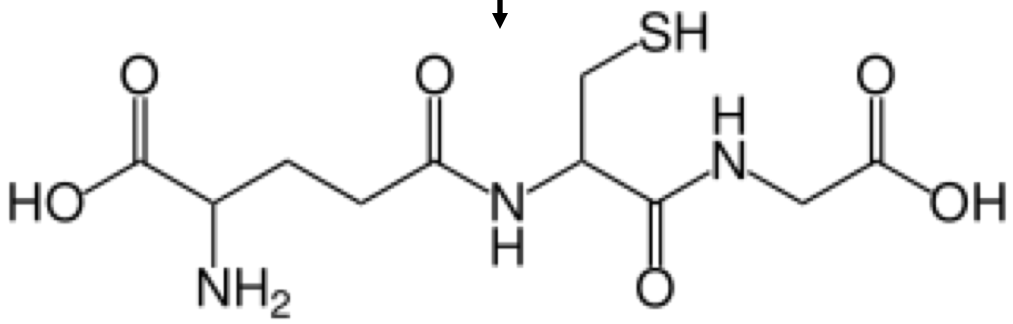
glutamate



glycine



cysteine



glutathione

NAC

- Increases synthesis of glutathione (GSH)
- GSH
  - reacts with hydrogen peroxide H_2O_2 to form H2O
  - conjugates with oxidized products, catalyzed by glutathione-s-transferase (GST) to further reduce oxidative stress.
- Lithium and valproate neuroprotective effects
  - mediated by increasing GSH and glutamate-cysteine ligase levels
  - lithium increases gene expression of GST isoenzymes

Atkuri KR, et al. Current Opinion in Pharmacology 2007;7(4):355-359.
Shao L, et al. Neuroscience 2008;151(2):518-524.

NAC

- Neuroprotective
- Prevents oxidative damage in complex
- Broad efficacy
  - Bipolar depression
  - Schizophrenia
  - OCD spectrum
  - Autism
  - Cocaine, marijuana, smoking

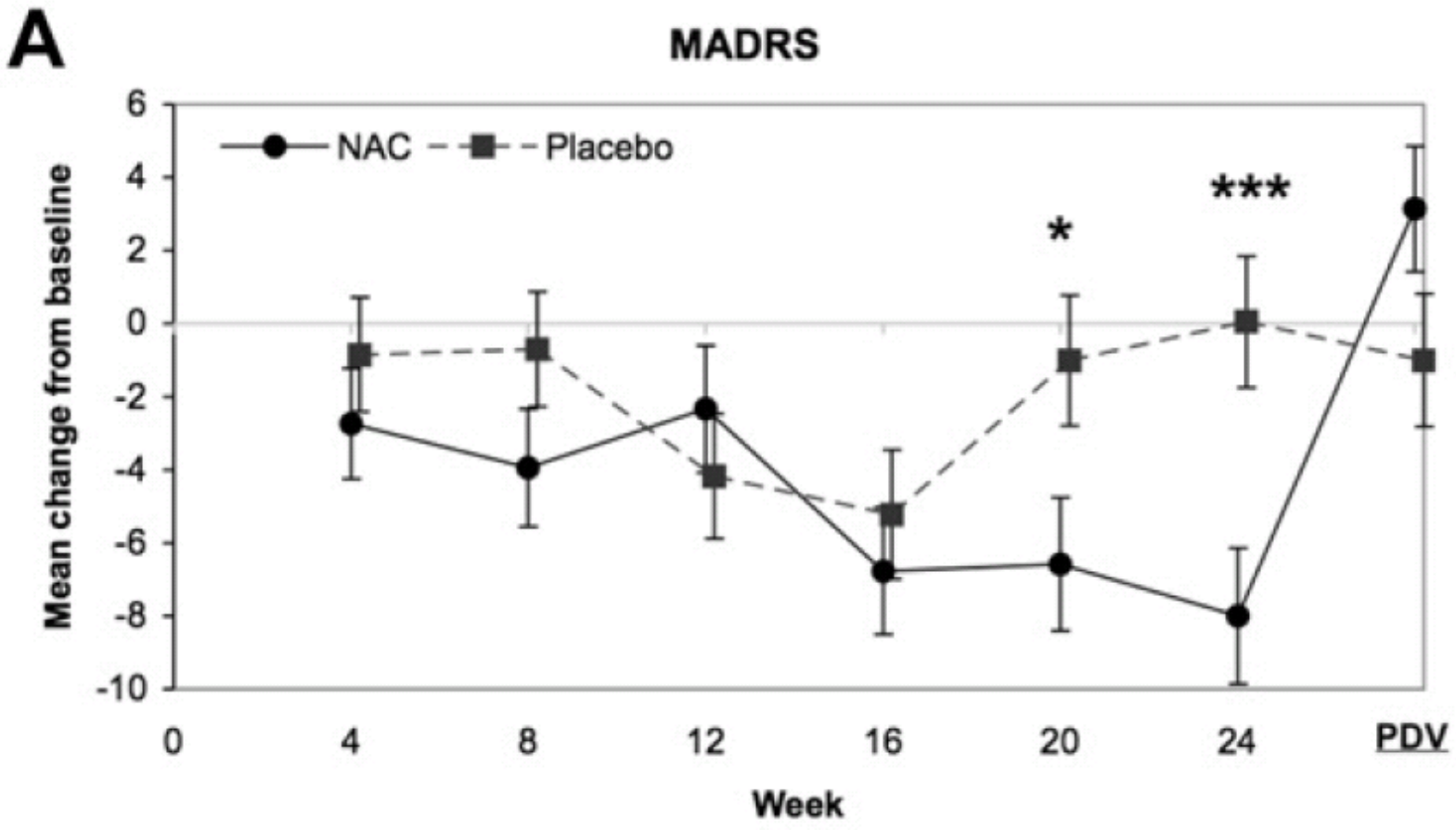
Mayer M, Noble M. Proc Natl Acad Sci 1994;91:7496 -7500.
Nicoletti et al. Neurochemical Research 2005;30:737-752.
Grant JE, et al. Biological Psychiatry 2007;62(6):652-657.

N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder—A Double-Blind Randomized Placebo-Controlled Trial

Michael Berk, David L. Copolov, Olivia Dean, Kristy Lu, Sue Jeavons, Ian Schapkaitz, Murray Anderson-Hunt, and Ashley I. Bush

Biological Psychiatry 2008

N-acetyl-cysteine RCT



Acetyl-L-Carnitine (ALCAR)

- Carnitines
  - transport fatty acids into mitochondria
    - beta-oxidation
    - energy generation
  - scavenge ROS
  - fatty acids
    - enter mitochondria as acyl-carnitines,
    - when oxidized, release energy
    - form acetyl-coenzyme a, which then enters the citric acid cycle

Hoppel C. American Journal of Kidney Diseases 2003;41(Supplement 4):S4-S12.
Al-Majed AA, et al. Clin Exp Pharmacol Physiology 2006;33(8):725-733.
Rebouche et al. Annals of the NY Academy of Sciences 2004;1033(1):30-41.

Acetyl-L-Carnitine (ALCAR)

- ALCAR absorbed better than L-carnitine
- able to cross the blood-brain barrier
- neuroprotective and antiapoptotic properties
- block glutamate-induced over-expression of glutamic acid decarboxylase GAD67
- reverse age-related degeneration in animal models
- decrease oxidative stress?
- may slow down or reverse age-related cognitive and motoric decline in rats
- reverse diminished reactivity to the environment

Ames BN, Liu J. Annals New York Academy of Sciences 2004;1033(1):108-116.

Acetyl-L-Carnitine (ALCAR)

- Alzheimer's Disease,
- ADHD inattentive type
- Fatigue and peripheral neuropathy
  - HIV infection
  - Chemotherapy,
  - Diabetic neuropathy
  - Fibromyalgia
  - may prevent or reverse valproate-induced hepatotoxicity
- equivalent to amisulpride for dysthymic disorder

Rossini M, et al. Clinical and Experimental Rheumatology 2007;25:182-188.
Elmslie JL et al. Bipolar Disorders 2006;8:503-507.

Alpha Lipoic Acid

- Cofactor for pyruvate dehydrogenase complex
- Increase cellular uptake of glucose
- Scavenge ROS

Soczynska. *Expert Opin. Investig. Drugs (2008) 17(6):827-843*

Summary

- Mitochondria and the brain
- Psychiatric Disorders in Mitochondrial Diseases
- Mitochondrial Dysregulation in Psychiatric Disorders