Thyroid Hormone and Modulation of Bipolar Disorder

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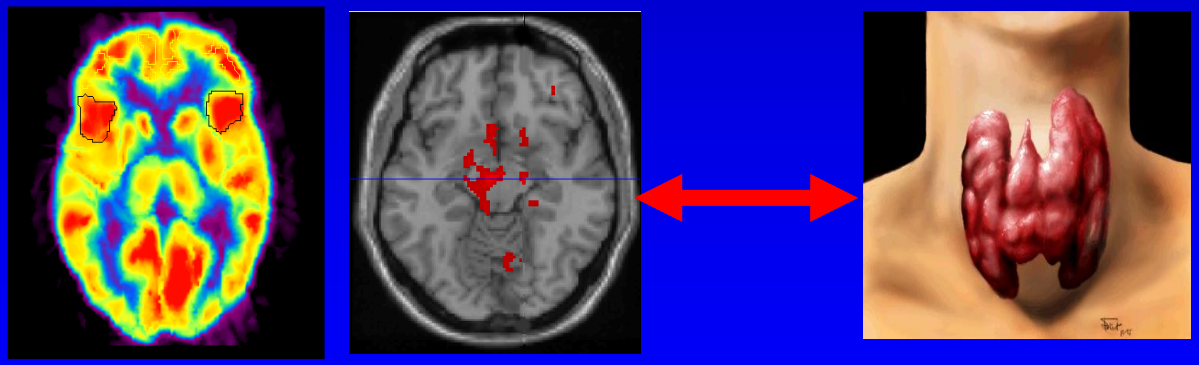


Santiago de Chile, Sept 27, 2018

FIG. 1.1. Large goiter in a woman from an area with a high rate of endemic goiter (Bern, Switzerland). The woman was a patient of the Bern surgeon E. Theodor Kocher, a Nobel laureate. (From Kocher T. Zur Pathologie and Therapie des Kropfes. *Dtsch Z Chir* 1874;4:417.)

E. T. Kocher

Dtsch. Z. Chir, 1874

Thyroid, Brain and Behavior Relationship (1)

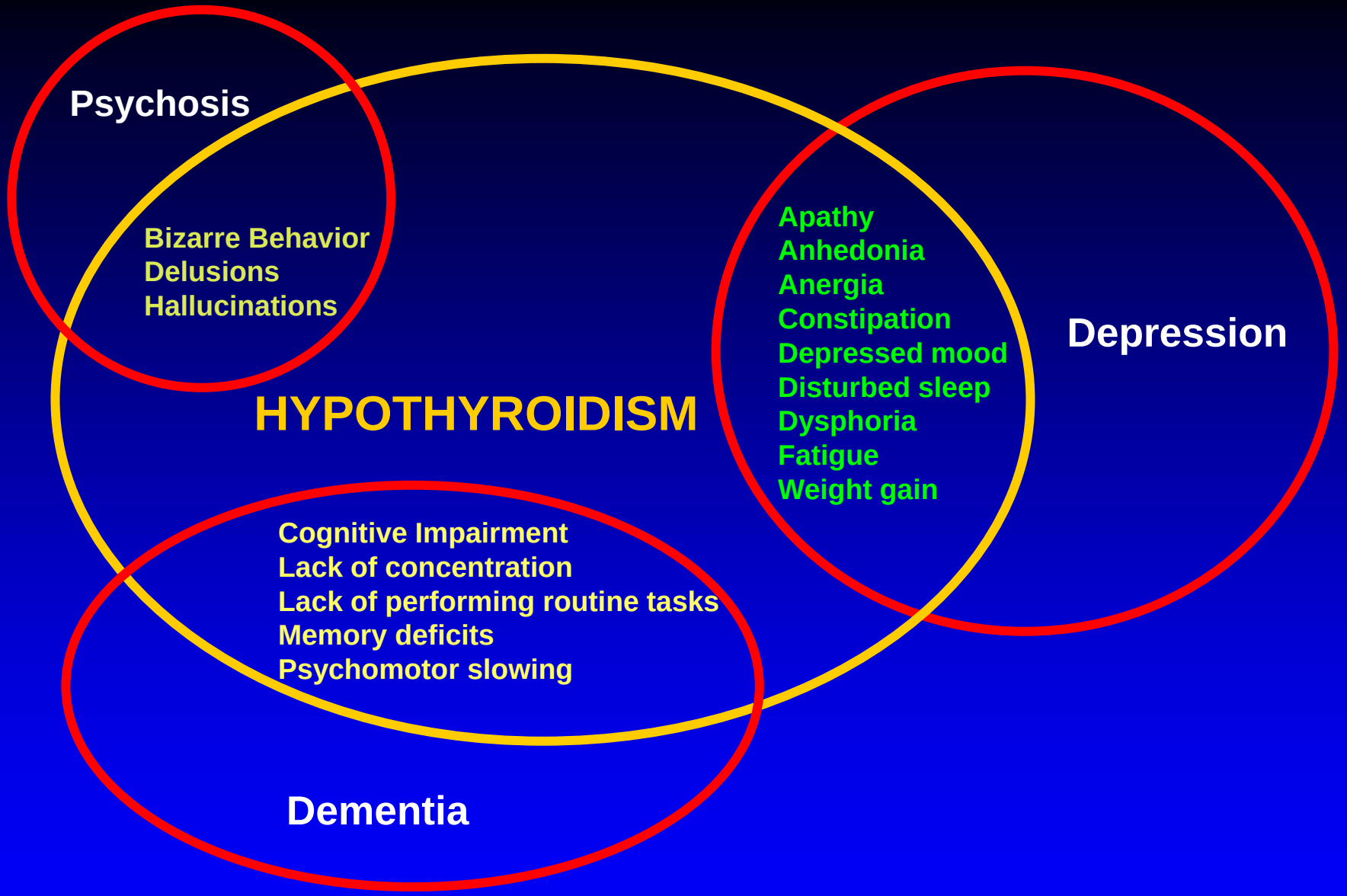
- Thyroid homeostasis critical to normal brain function and development (Clinical Society of London - Report on Myxedema 1888)
- Essential for development & maturation of human brain
- TH deficits during fetal development and early childhood result in mental retardation (cretinism)

Whybrow PC, Bauer M (2005) Behavioral and psychiatric aspects of hypothyroidism. In: Braverman LE, Utiger RD (eds.). The Thyroid. A Fundamental and Clinical Text (9th edition). Lippincott - Raven, Philadelphia, pp. 842-849

Thyroid, Brain and Behavior Relationship (2)

- 1891 Murray (England) – „like to treat like“: Successful treatment of myxoedema with dessicated thyroid (sheep)
- 1936 Gjessing (Norwegen) – successful periodic catatonia with extracts from desiccated thyroid (sheep)

Whybrow PC, Bauer M (2005) Behavioral and psychiatric aspects of hypothyroidism. In: Braverman LE, Utiger RD (eds.). The Thyroid. A Fundamental and Clinical Text (9th edition). Lippincott - Raven, Philadelphia, pp. 842-849



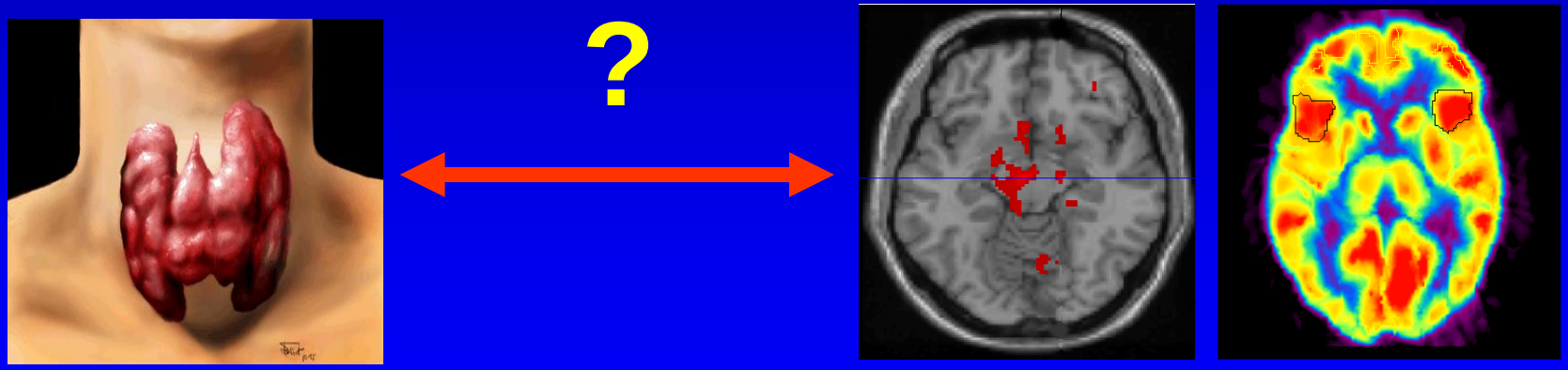
Whybrow PC, Bauer M (2005) Behavioral and psychiatric aspects of hypothyroidism. In: Braverman LE, Utiger RD (eds.). The Thyroid. A Fundamental and Clinical Text (9th edition). Lippincott - Raven, Philadelphia, pp. 842-849

Hypothyroidism - Common Neuropsychiatric Symptoms

- General behavioral: weakness, fatigue, lethargy, lack of energy (90-100%)
- Mood: major depression, psychotic melancholia (50%)
- Cognitive: cognitive slowing, memory deficits, dementia (40%)
- Others: anxiety, insomina

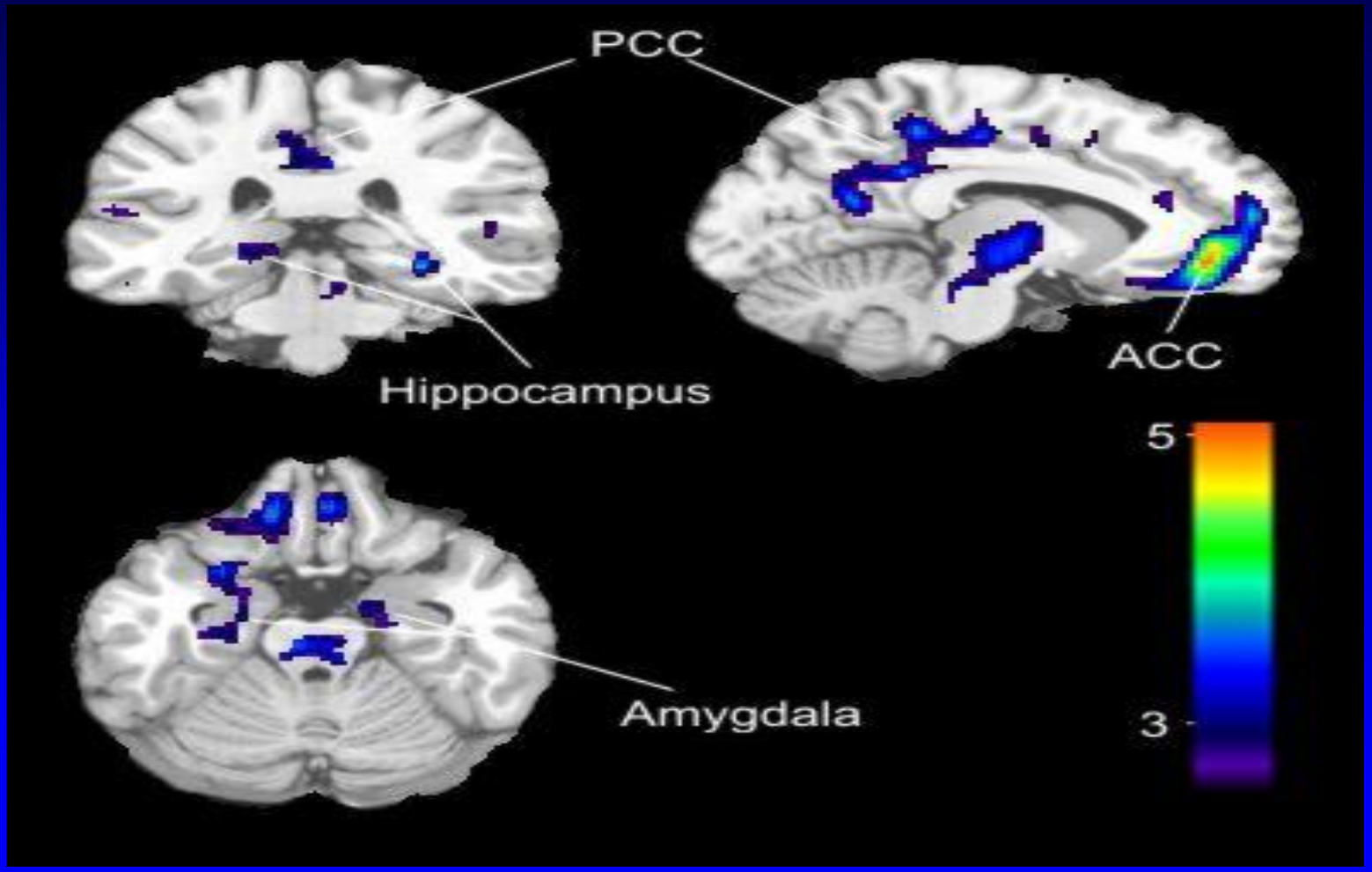
Neuronal Correlates of Hypothyroidism

Functional Neuroimaging with Positron-Emission-Tomography (PET) & [18]Fluorodeoxyglucose (FDG)



Bauer, Silverman, Whybrow et al. (2009) J Clin Endocrin & Metab

FDG-PET Studies in Hypothyroidism:
Lower relative activity in hypothyroid patients vs. controls



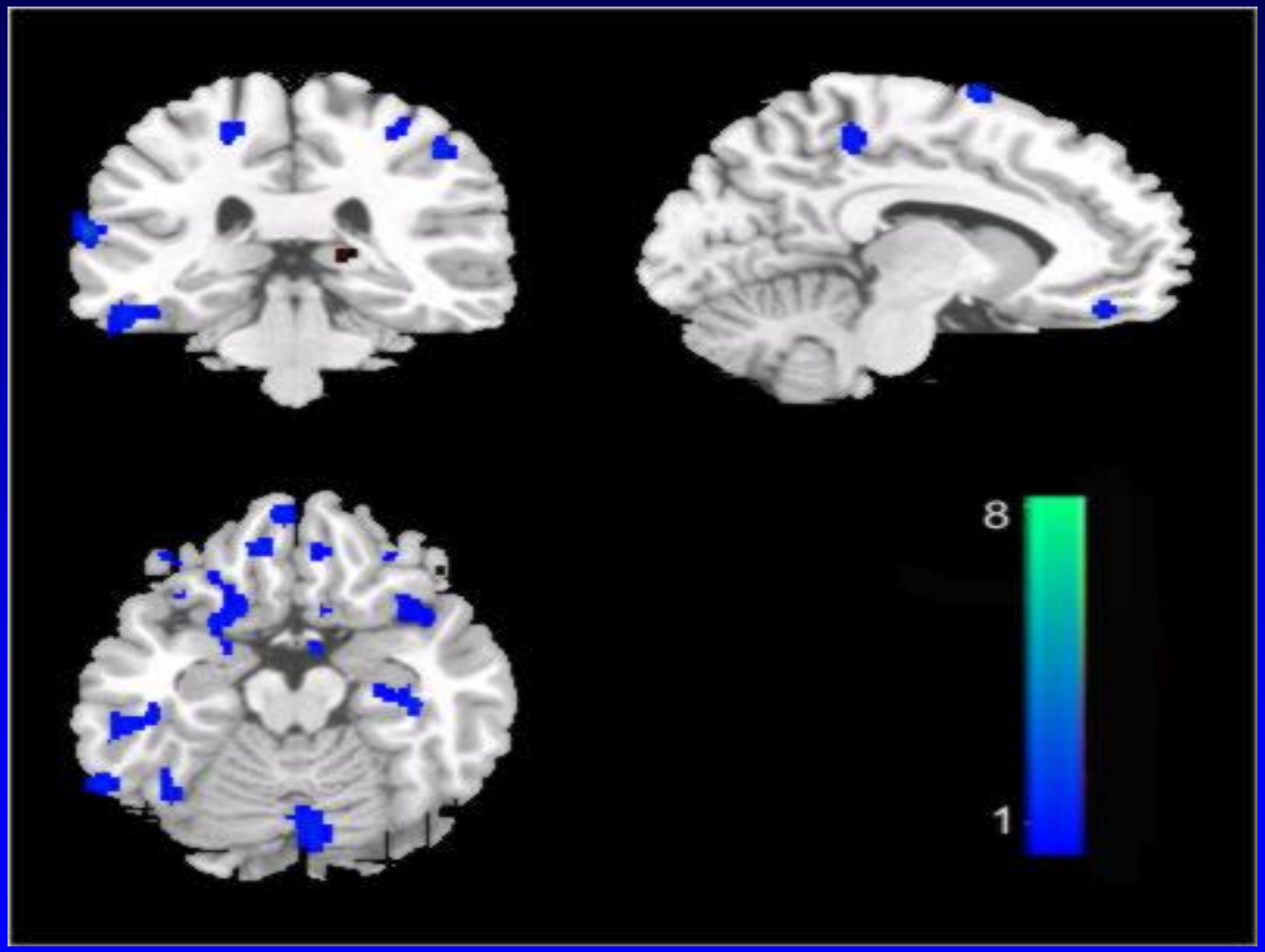
ACC: anterior cingulate cortex

PCC: posterior cingulate cortex

(P<0.01 uncorrected, slices displayed at MNI-coordinates x=-8 y=-32 z=-22).

Bauer et al (2009) J Clin Endocrin & Metab

Normalization after treatment - no significant differences between hypothyroid patients and healthy controls



(P<0.01 uncorrected, slices displayed at MNI-coordinates x=-8 y=-32 z=-22).

Bauer et al (2009) J Clin Endocrin & Metab

The thyroid system and mood disorders: Heuristic model in biological psychiatry

- Low thyroid function: association with depression
- Reversible thyroid condition with thyroid hormone therapy
- Depression typically also relieves

Overview: Use of Thyroid Hormone for Treatment of Mood Disorders

ACCELERATION - Speed response

- T3 (25-50 mcg) in unipolar depression (UP)

AUGMENTATION - Convert nonresponder

- T3 (25-50 mcg) in treatment-resistant UP
- Suprahysiological doses of T4 (300-500 mcg) in treatment- resistant depression

MAINTENANCE - Prophylaxis, prevent episodes

- Suprahysiological doses of T4 (300-500 mcg)
- Rapid cycling & refractory bipolar disorder

Bauer M, Whybrow PC (2002) Thyroid Hormone, Brain and Behavior. In: Pfaff DW et al. (eds.) *Hormones, Brain and Behavior.* Academic Press, San Diego, pp. 239-264

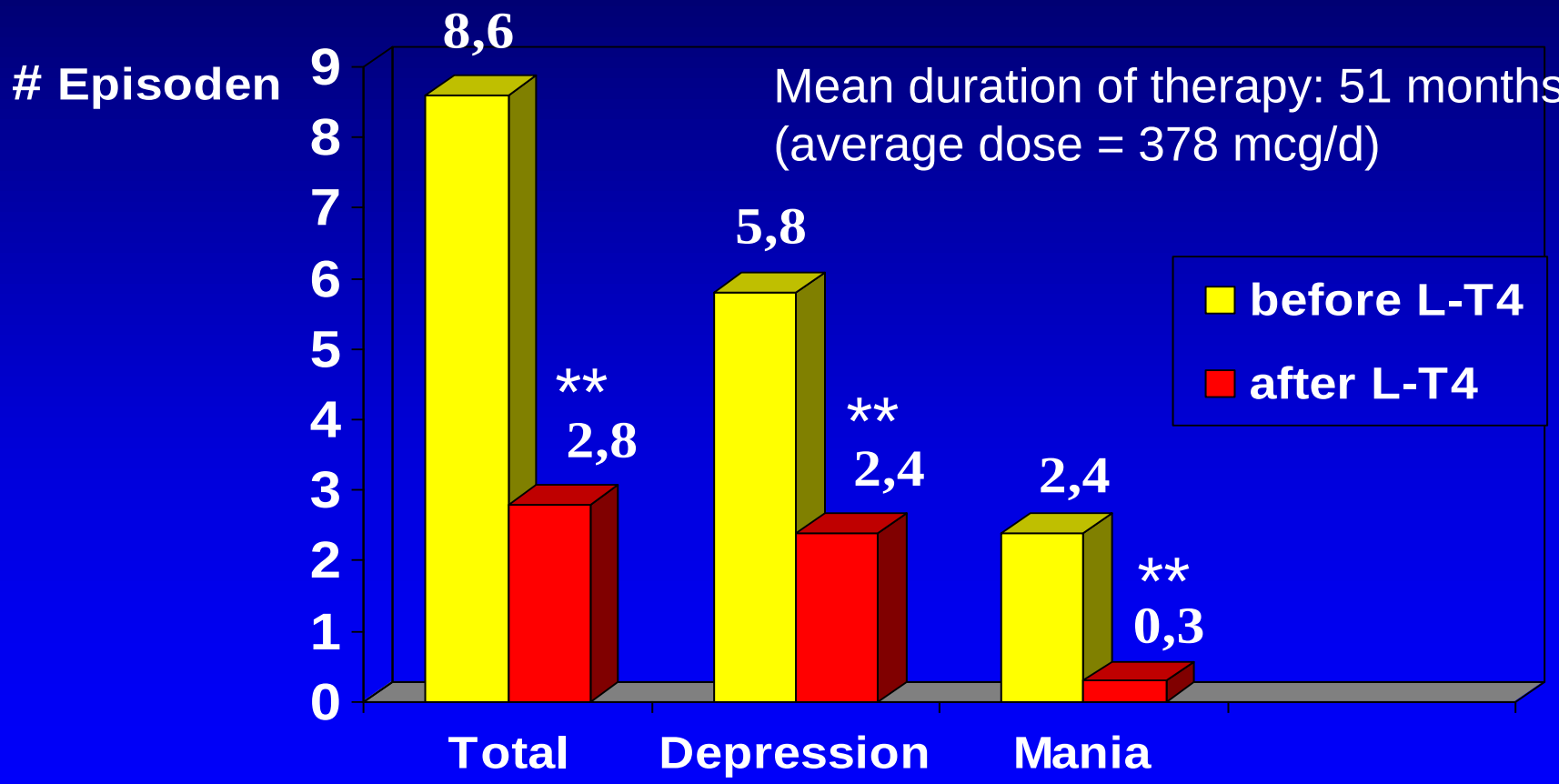
Thyroid Hormone in Mood Disorders

- Studies using supraphysiological doses of L-thyroxine aim at elevating thyroid hormone levels
- Modification of the behavioral expression of mood disorder by a change in thyroid status

Bauer MS & Whybrow 1990, Bauer M et al. 2002, Bauer M et al. 2005

Number of Mood Episodes Before and After Long-Term Treatment with Supraphysiological Doses of L-Thyroxine in Prophylaxis-Resistant Affective Disorders

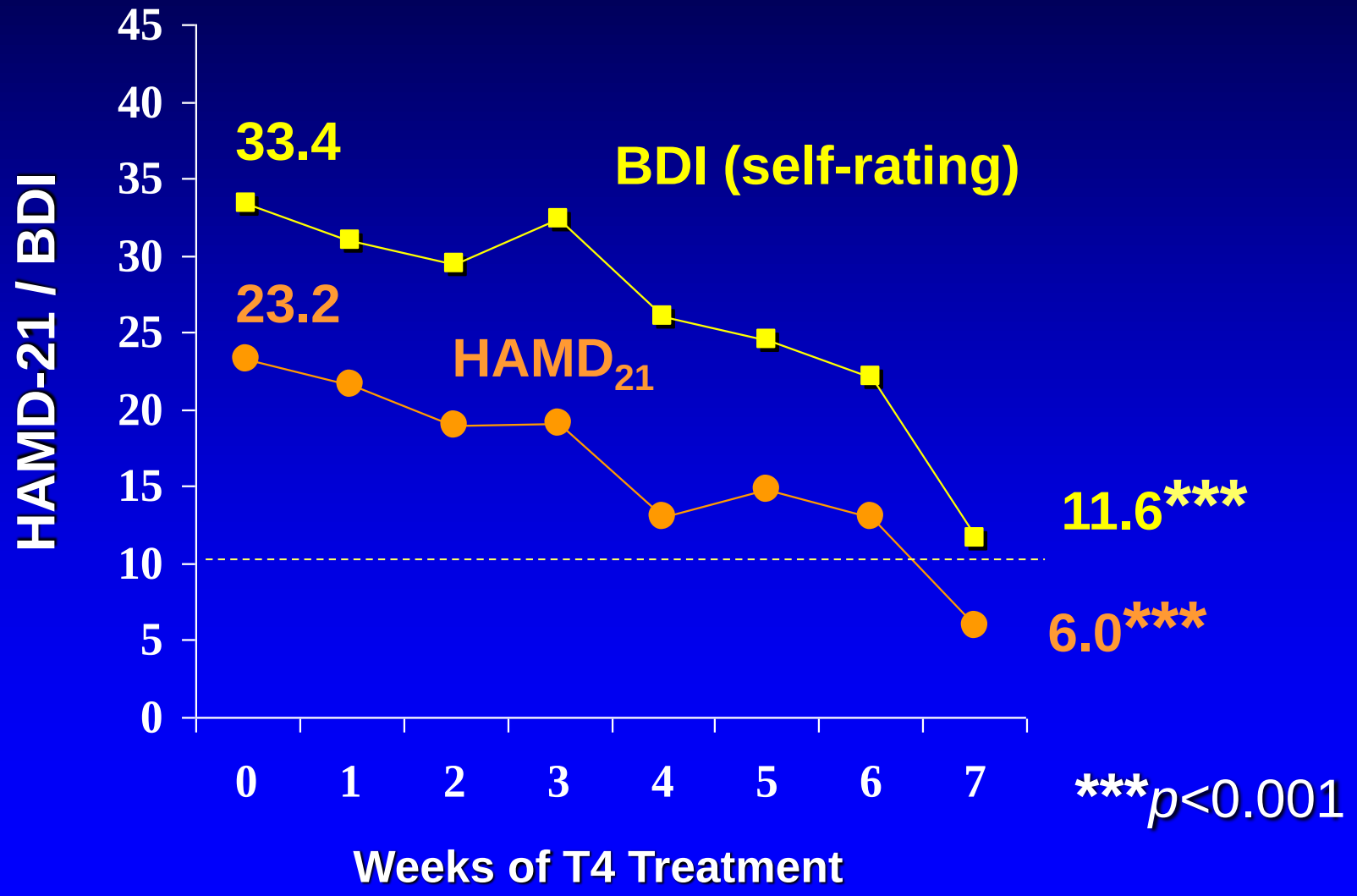
(Mirror-Image Analyse, N=21; 16 F, 5 M; m=47 yrs)



** *p*<0.01 (Wilcoxon test)

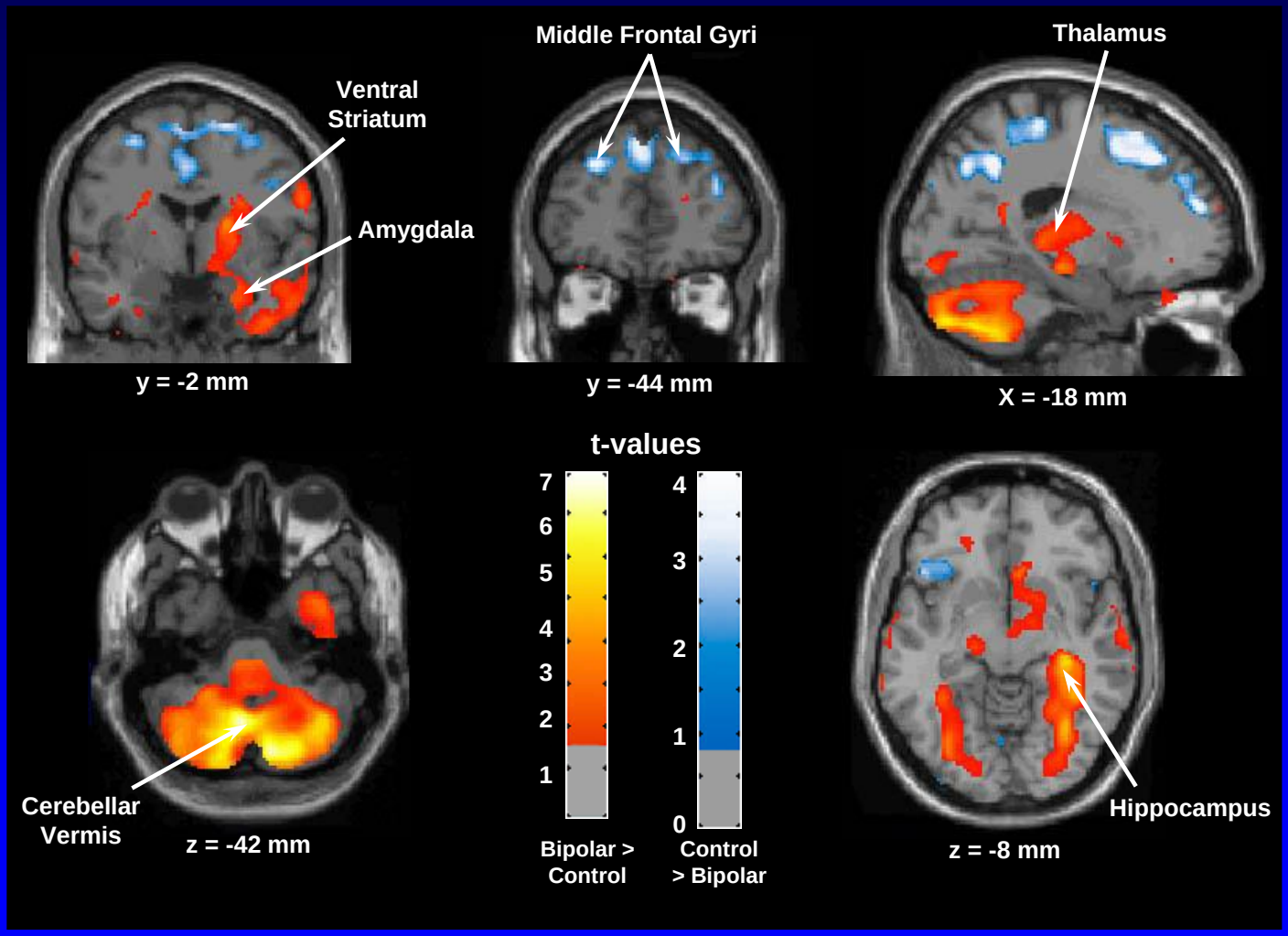
Bauer et al. (2002) *Neuropsychopharmacology*

Improvement of Depression in Female Bipolar Disorder (N=10) with L-T4 Treatment



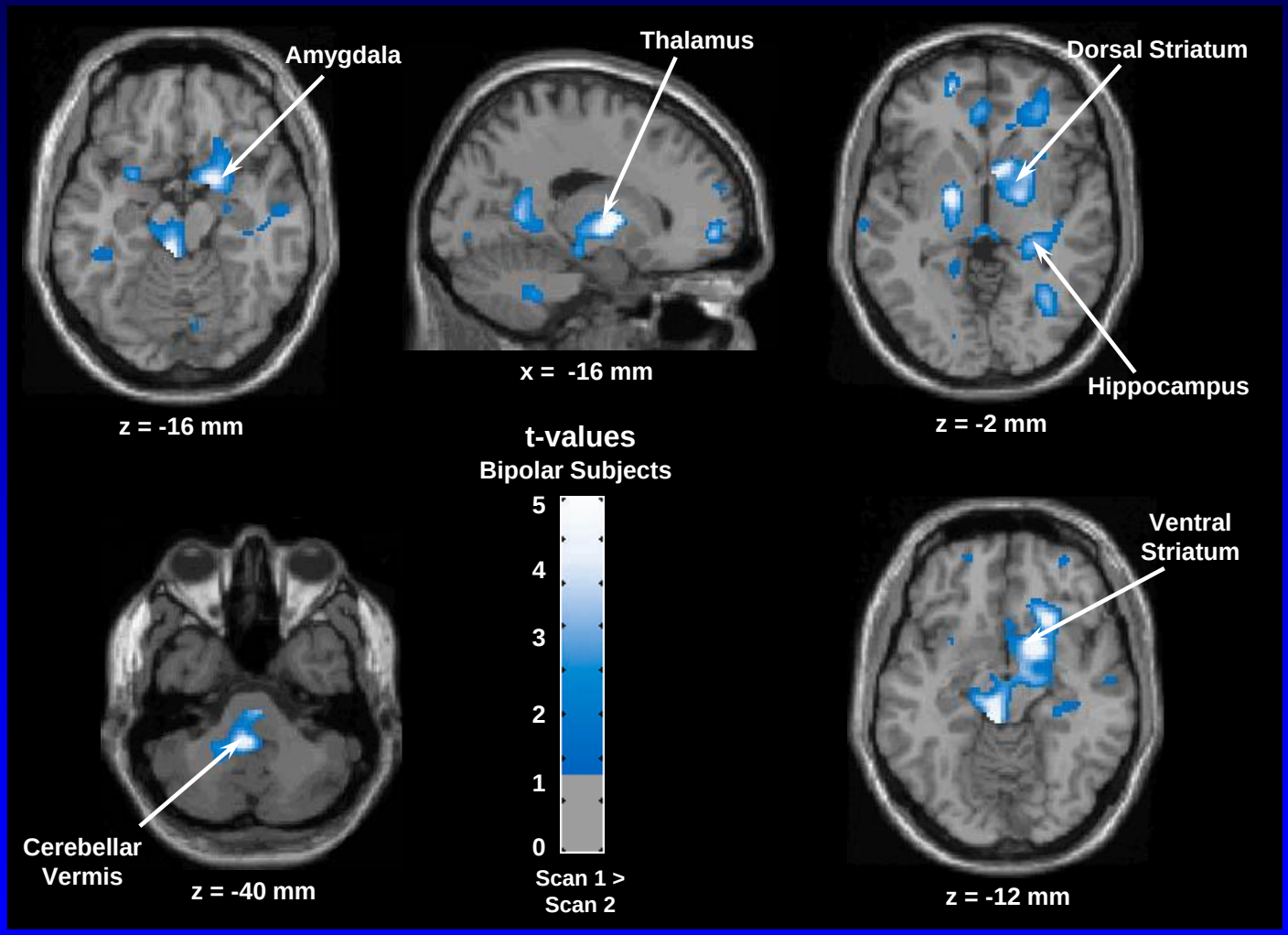
Bauer et al. (2005) *Mol Psychiatry*

FDG-PET in Women (n=10) with bipolar depression: higher regional activity in subcortical-limbic areas – lower activity in middle frontal gyri



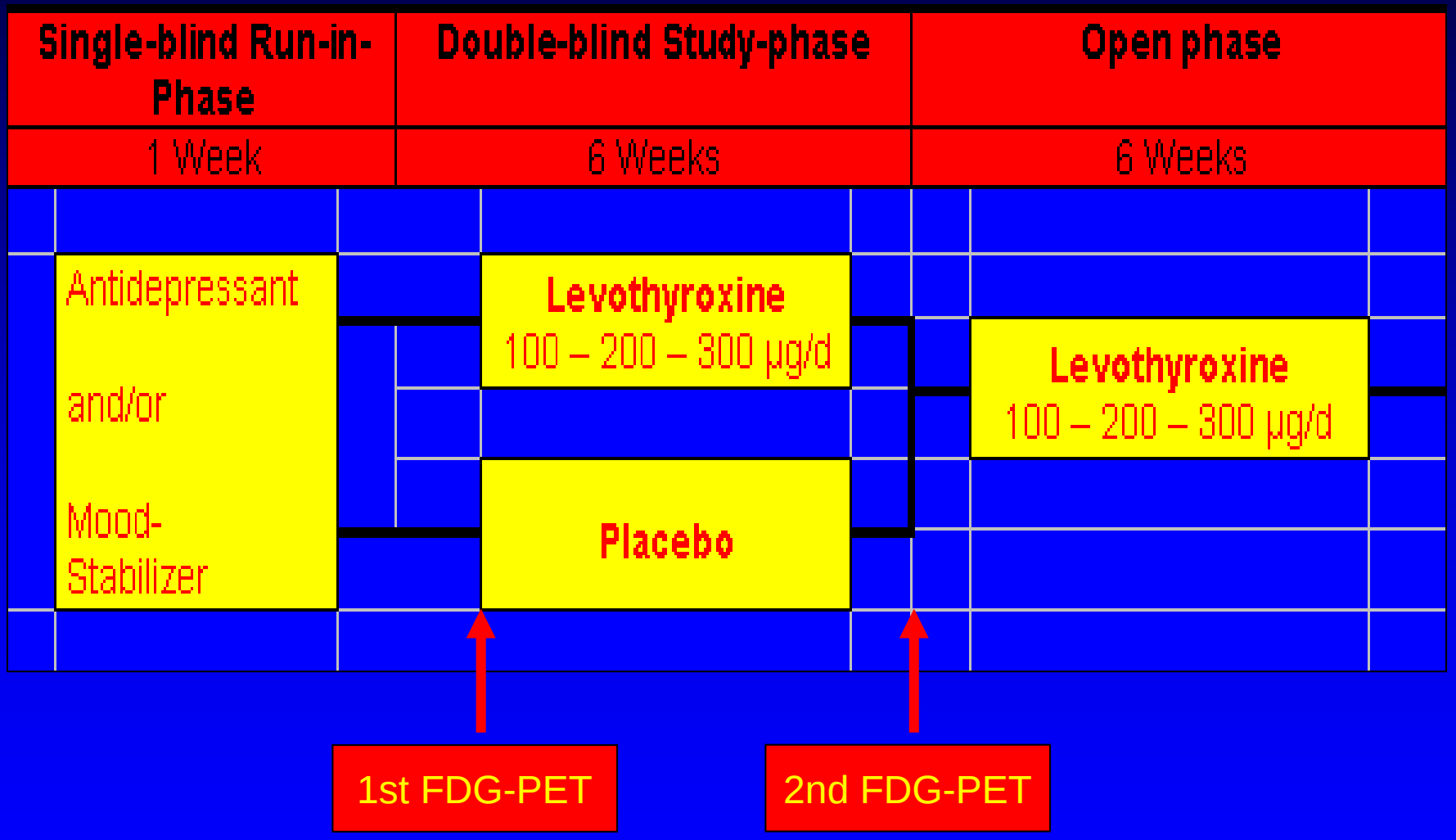
Bauer et al. (2005) *Mol Psychiatry*

FDG-PET in Bipolar Depression: Deactivation in subcortical-limbic areas during treatment with levothyroxine



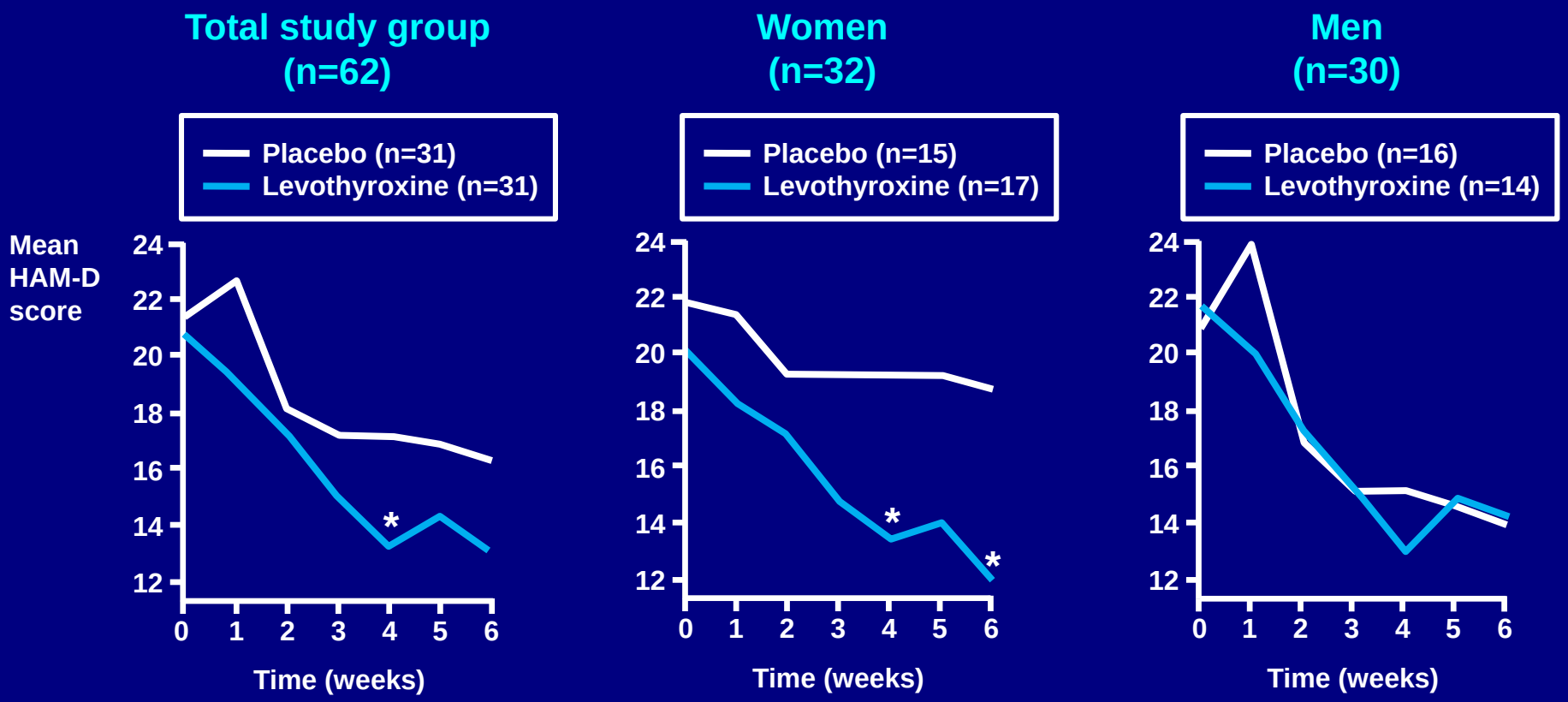
Bauer et al. (2005) *Mol Psychiatry*

Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Levothyroxine (L-T_4 - 300 mcg) as Add-on Treatment in Bipolar Depression – Study Design



The Stanley Medical Research Institute, trial grant # *02T-238*

Adjunctive levothyroxine in bipolar depression: a randomised, double-blind, placebo-controlled study

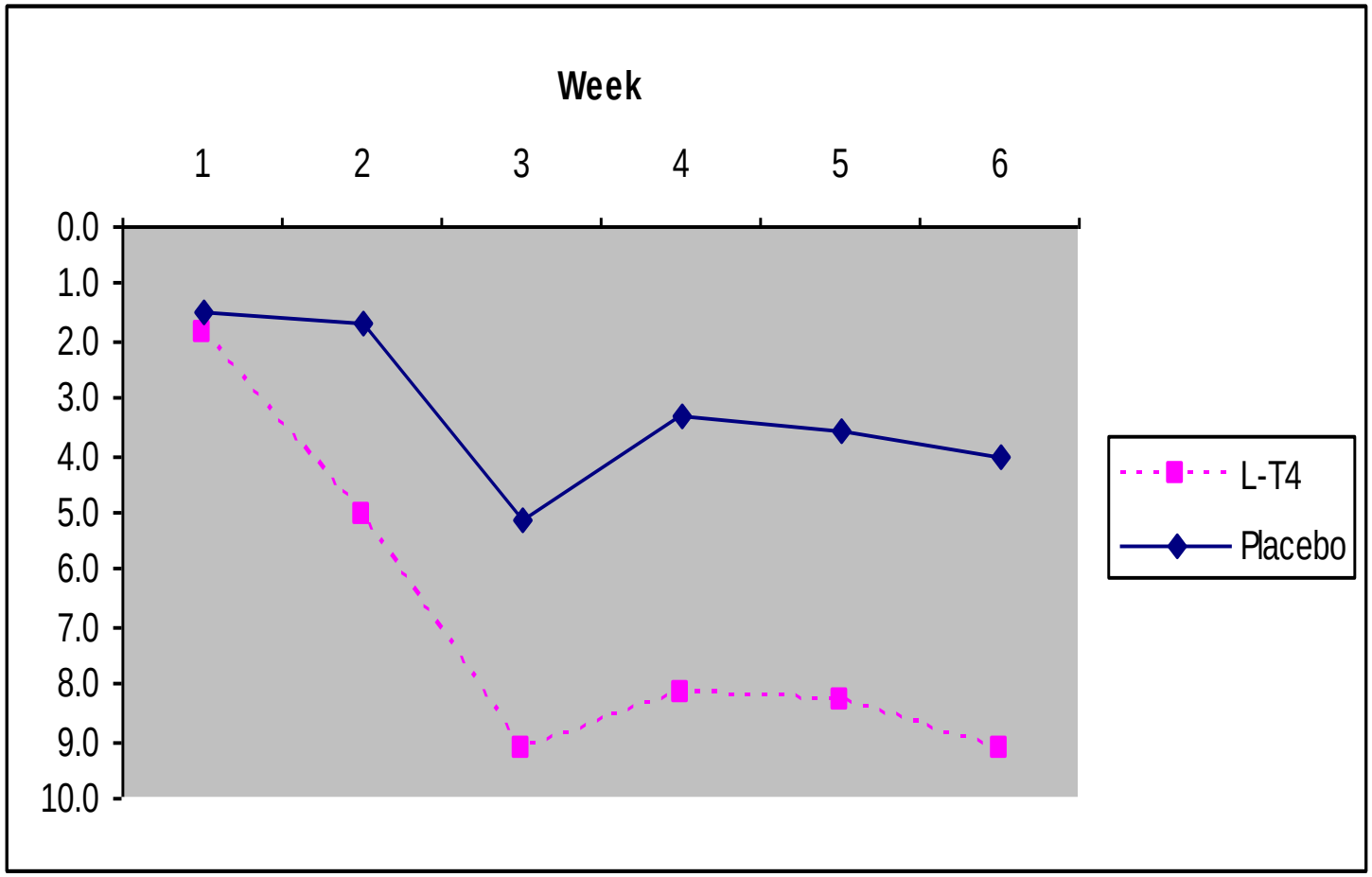


*p<0.05 vs placebo (ITT; LOCF)
Adjunctive levothyroxine (300 µg/day) or placebo in patients with bipolar I or II disorder
HAM-D, Hamilton rating scale for depression

Stamm, Bauer et al 2013; J Clin Psychiatry

Levothyroxine improves mood in bipolar depression: a randomized, placebo-controlled study

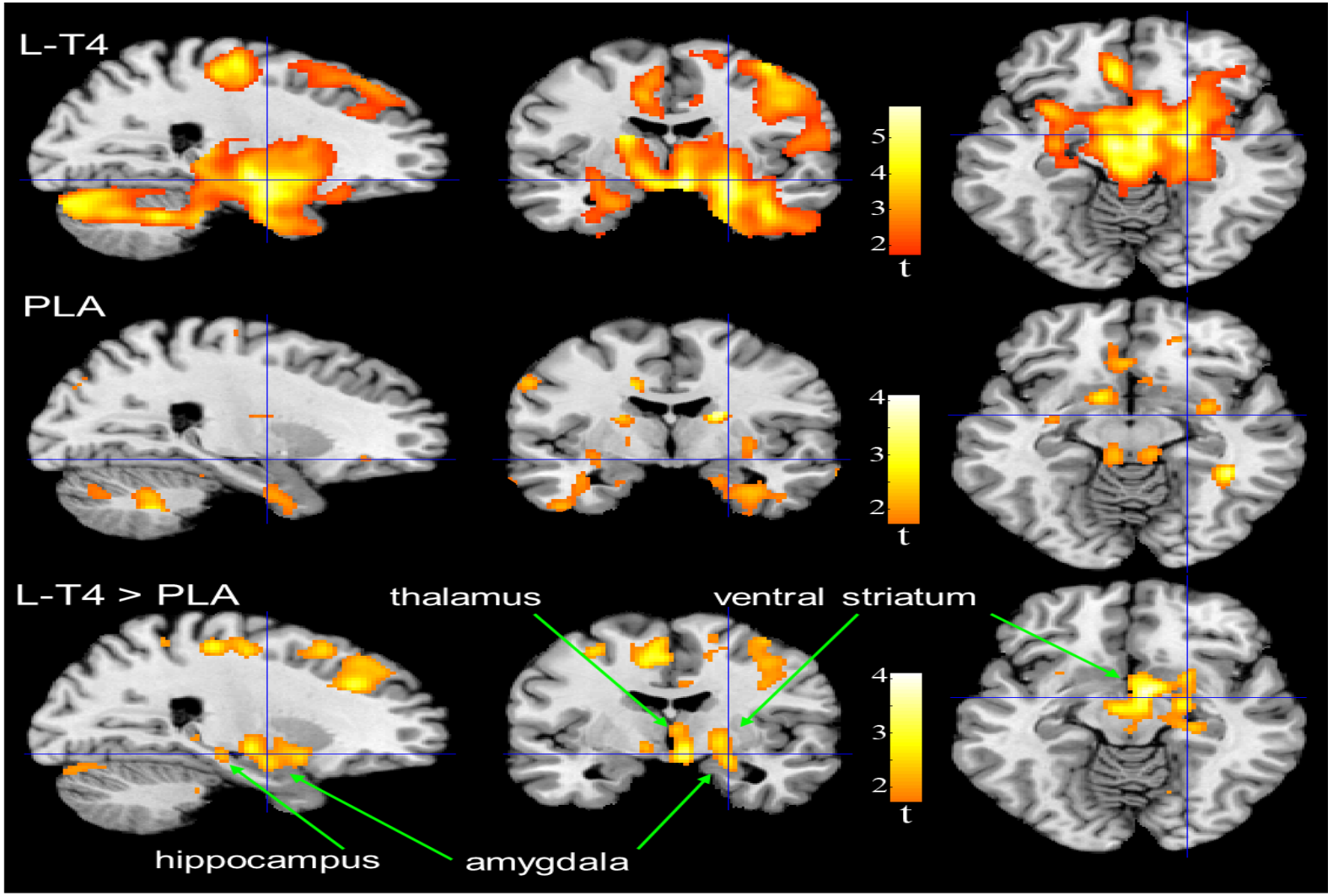
Clinical Improvement during L-T4 treatment



L-T4 n=15; Placebo n=10

Bauer et al. (2016) Molecular Psychiatry

Brain areas where activity changed with L-T4 treatment



Bauer et al (2016) Molecular Psychiatry

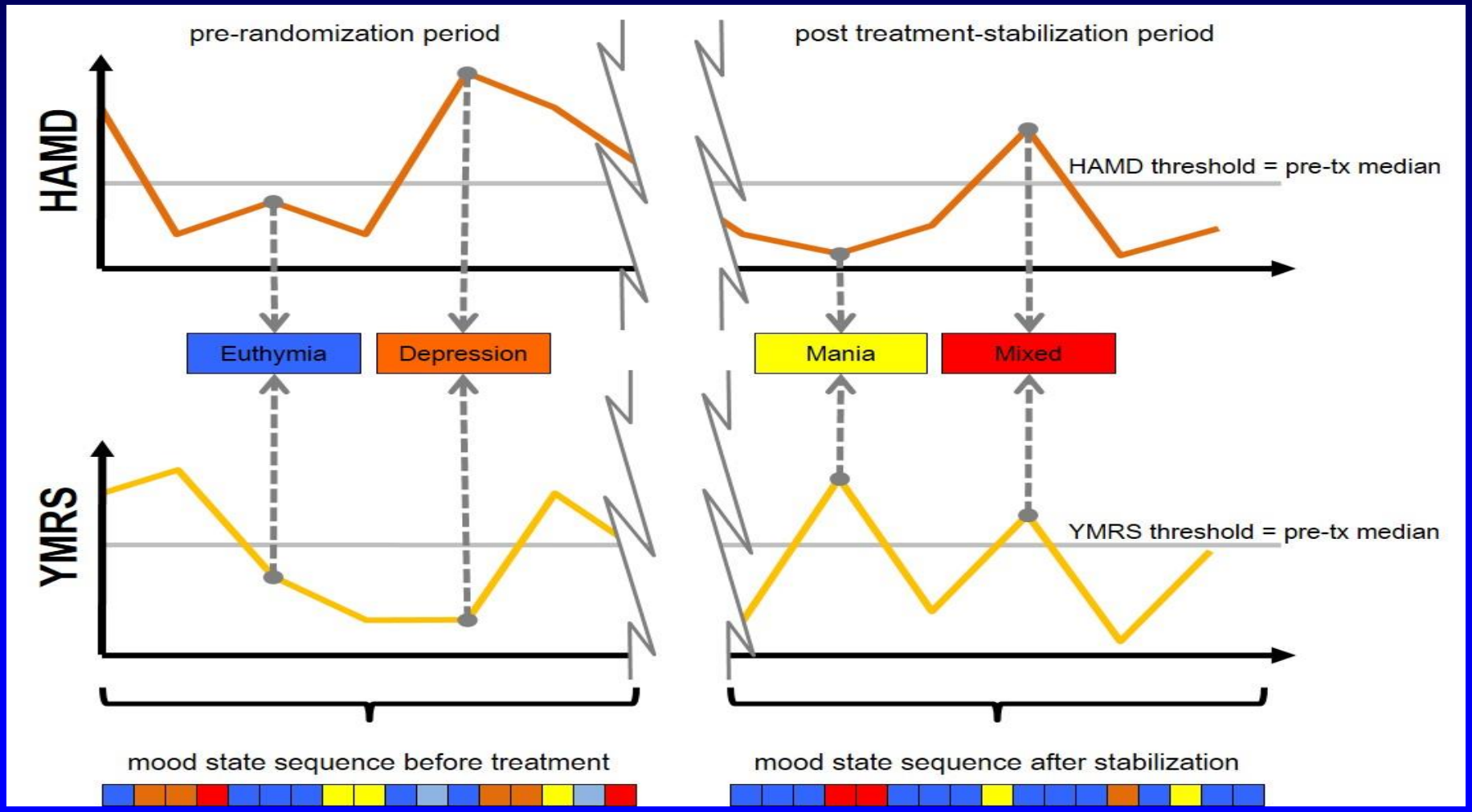
Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: a randomized, double-blind, placebo-controlled trial of levothyroxine (T4) and triiodothyronine (T3)

Bipolar Disorders, 2018

Patricia D. Walshaw (1), Laszlo Gyulai (2), Michael Bauer (3), Mark S. Bauer (4), Brian Calimlim (1), Catherine Sugar (1), Peter C. Whybrow (1)

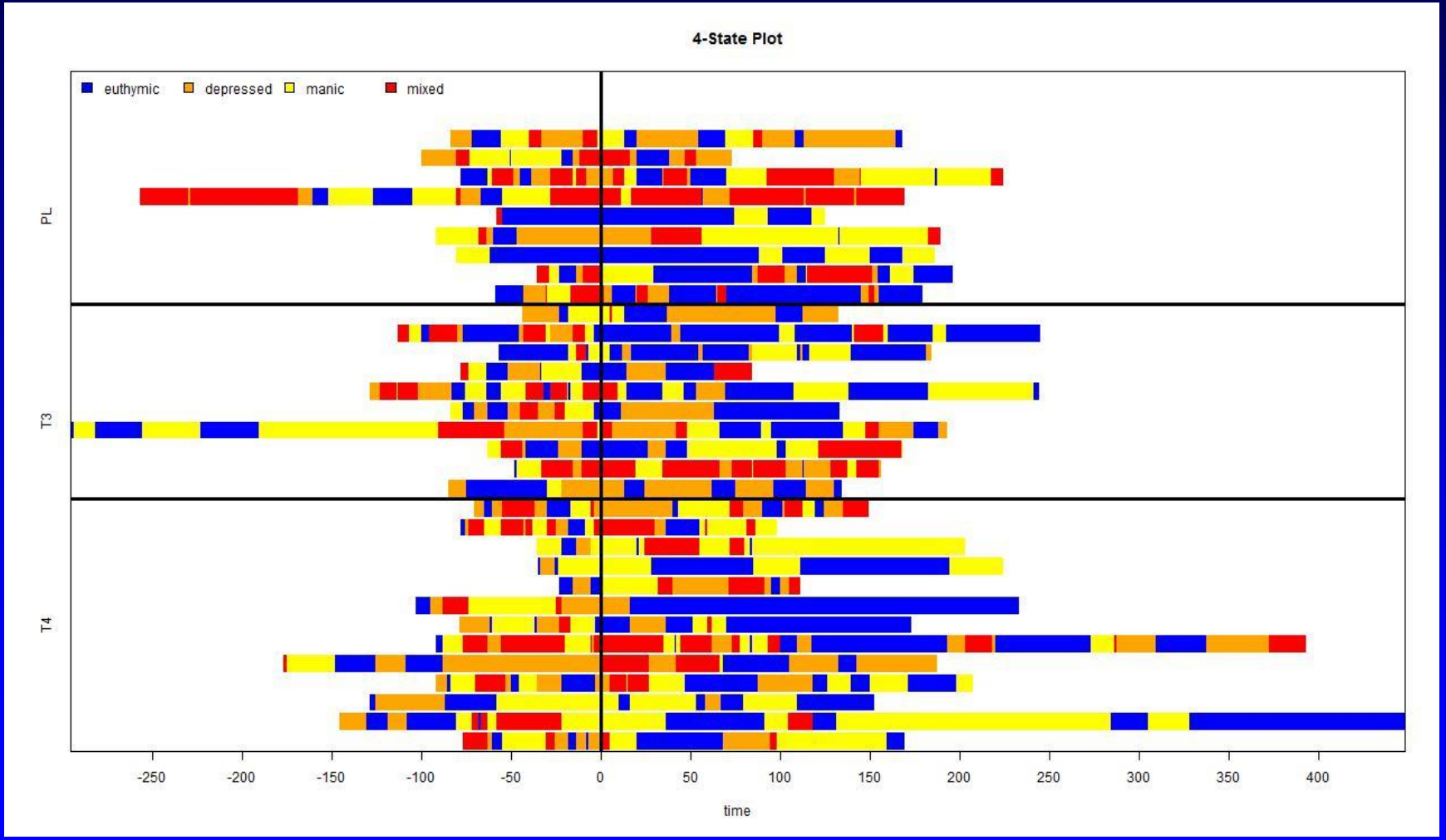
1 Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles (UCLA), Los Angeles, CA, USA
2 Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA
3 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
4 Center for Organization, Leadership, and Management Research, VA Boston Healthcare System, Boston, MA, USA

Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder: Creating mood-state sequences



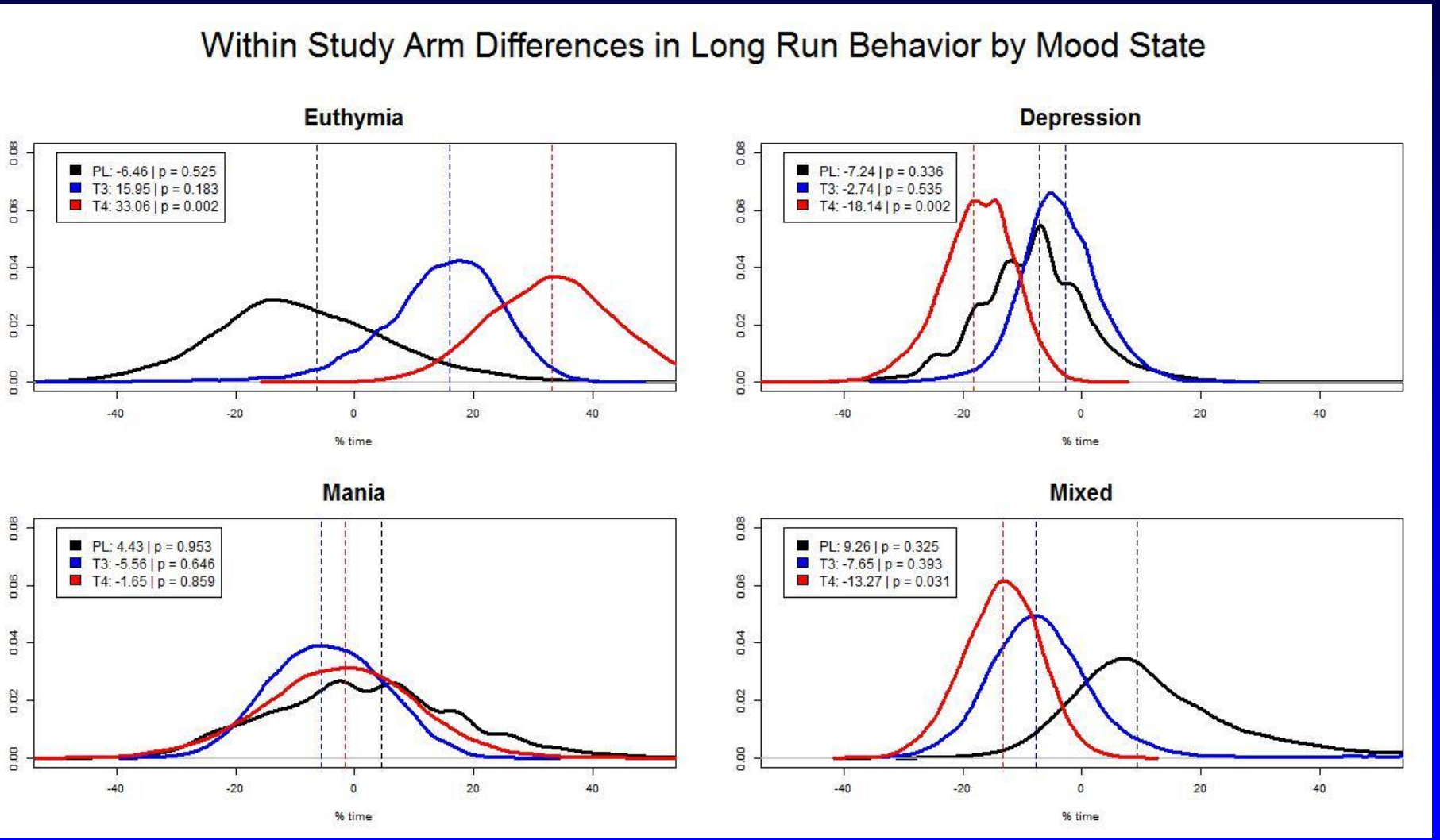
Walshaw et al. 2018

Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder:
Four-state mood plot by patient for 3 treatments



Walshaw et al. 2018

Adjunctive thyroid hormone treatment in rapid cycling bipolar disorder



Walshaw et al. 2018

Conclusions

- Disturbances of thyroid system function may complicate diagnosis & treatment of mood disorder
- Hypothyroidism: brain is a target organ of thyroid hormones & heuristic model for depression
- Treatment with (supra 300 mcg) levothyroxine is a treatment option for women (better than for men) in bipolar disorder/depression
- Supraphysiologic thyroid hormone improves depressive symptoms in patients with bipolar disorder by modulating function in components of the anterior limbic network

Thank your for your attention

Dresden

Journal of Affective Disorders 238 (2018) 213–217

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Journal of Affective Disorders

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

Research paper

Long-term treatment with supraphysiologic doses of levothyroxine in treatment-refractory mood disorders – A prospective study of cardiovascular tolerability

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[g] Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior University of California Los Angeles (UCLA), Los Angeles, CA, USA

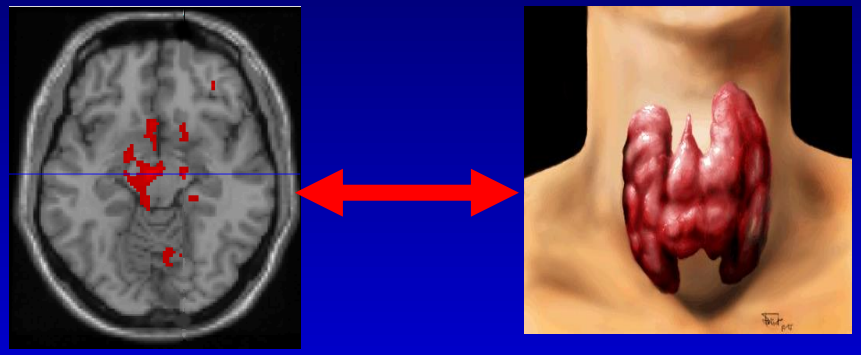
ARTICLE INFO

Keywords:
Levothyroxine
Thyroid
Treatment-refractory mood disorders
Cardiovascular risk assessment

ABSTRACT

Background: To investigate long-term effects of adjunctive prophylactic treatment with supraphysiologic doses of levothyroxine (L-T4) on cardiovascular tolerability in 23 patients with treatment-refractory mood disorders.
Methods: Starting point for a comprehensive cardiovascular assessment in patients was the indication for long-term maintenance treatment with L-T4 (mean dose 463 mcg/day). Prospective longitudinal assessment of the cardiovascular risk profile included in addition to a physical examination and blood pressure measurement, several technical investigations: resting electrocardiogram, transthoracic echocardiogram, cardiac stress test, and holter electrocardiogram. Statistical analysis was performed by linear mixed effects models (LMM) for evaluation of longitudinal changes in various heart measures.
Results: During the mean observational period of 20.4 months none of the heart measures reached statistical significance in change over time. None of the assessed cardiac parameters of each single patient was in a range predictive for cardiac dysfunction.
Limitations: Small sample size, no technical cardiac investigations prior to L-T4 initiation, no patient control group with mood disorders who did not receive L-T4.
Conclusions: Results of this study indicated no increased risk for cardiovascular disorders during treatment with supraphysiologic L-T4 doses in patients with refractory mood disorders.

Thyroid – Brain



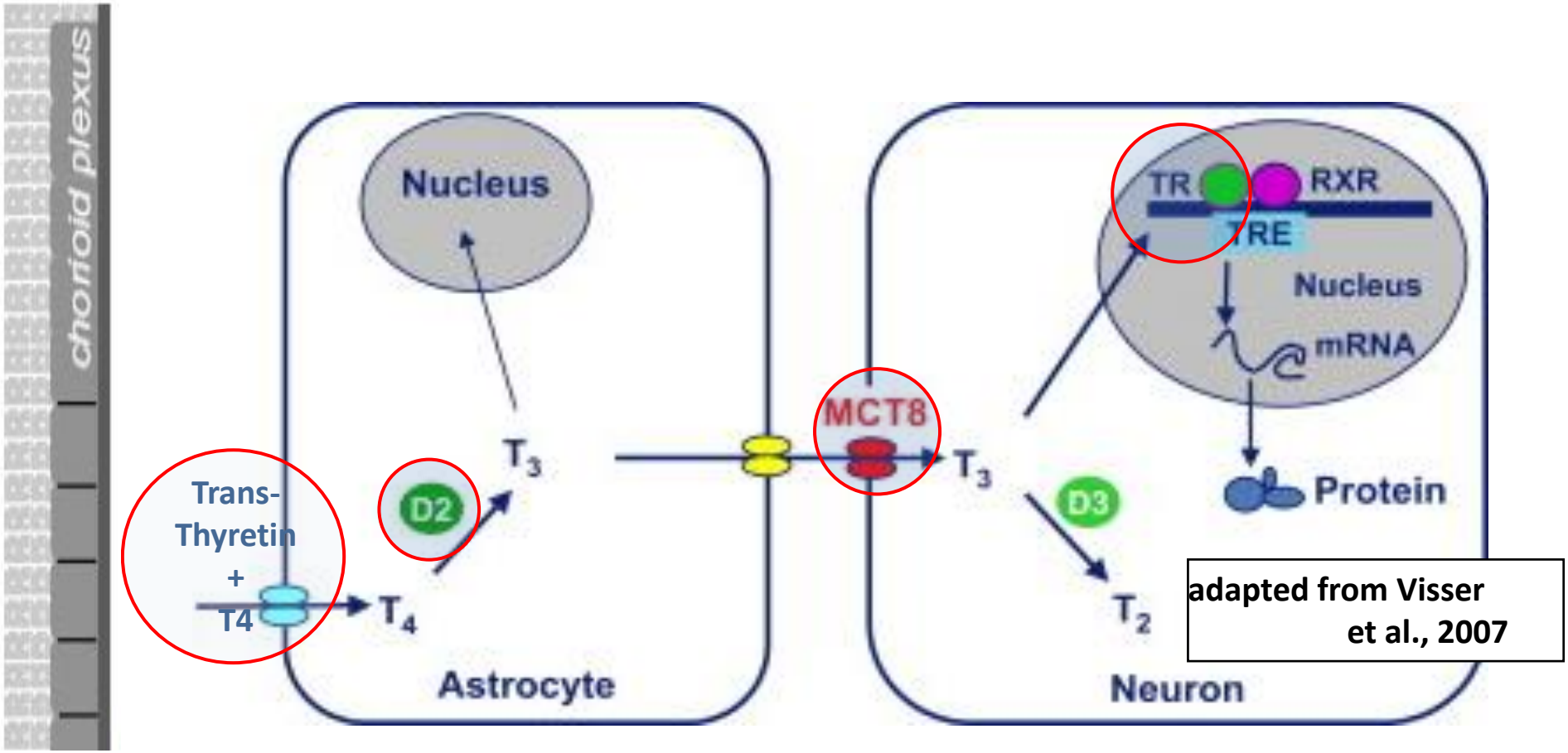
Molecular and neurotransmitter interactions

Adult Mammalian Brain: Site of TH Action

Identification of

- Significant amounts of T4 and T3 in various brain regions
- Nuclear T3 receptors ($\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$)
- Region-specific expression of deiodinase isoenzymes (type II) in brain and pituitary
- Identification and molecular analysis of thyroid-responsive genes in brain
  (e.g., neurotrophic factors, BDNF, NGF, RC3/neurogranin, CRH)

Hypotheses of action
“central hypothyroidism”



Compensating central hypothyroidism could explain antidepressive efficacy of high-dose T4 treatment

Molecular Psychiatry (2002) 7, 140–156

www.nature.com/mp

REVIEW ARTICLE

Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain

M Bauer[1], A Heinz[2], and PC Whybrow[1]

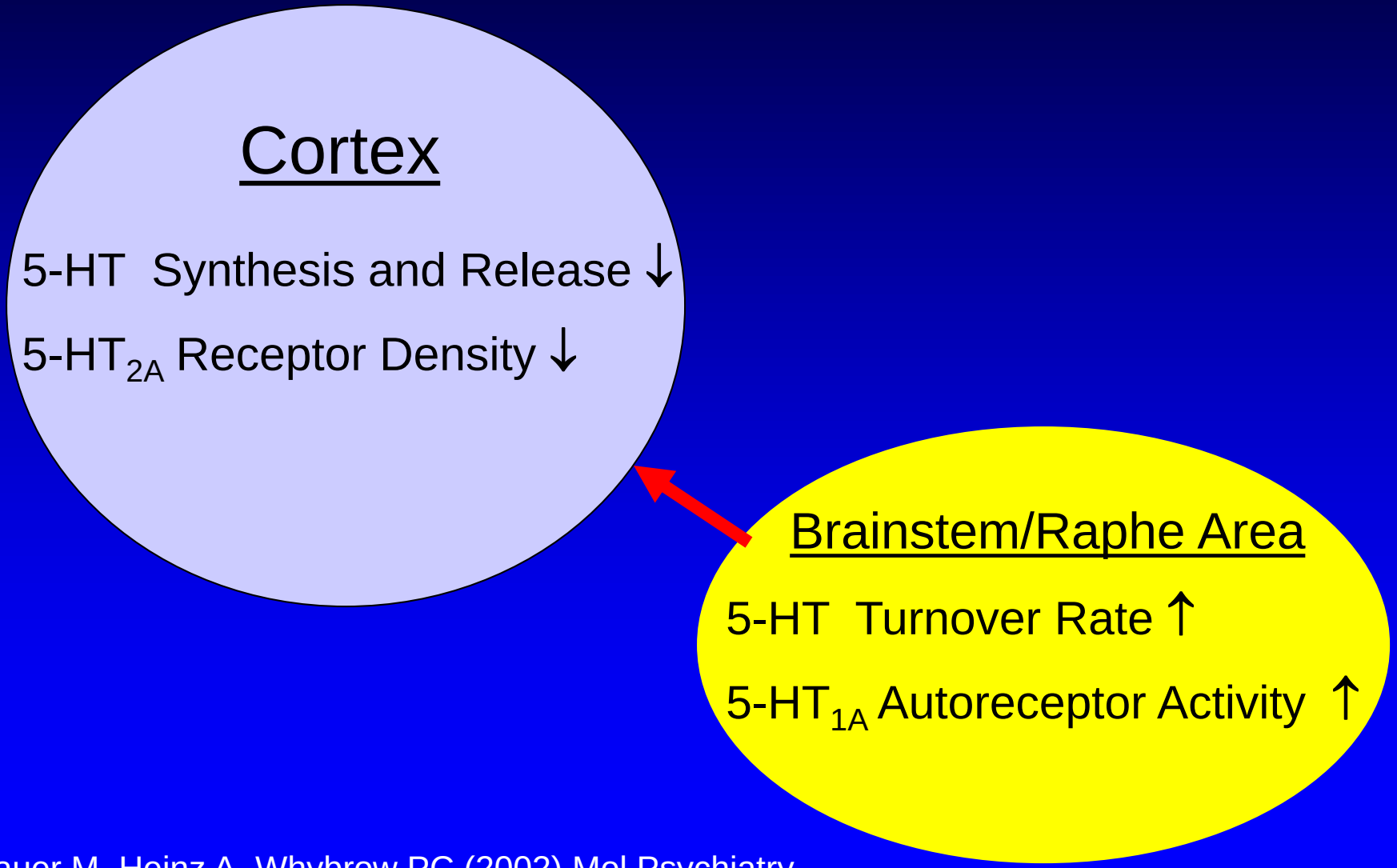
[1]*University of California Los Angeles (UCLA), Neuropsychiatric Institute & Hospital, Department of Psychiatry and Biobehavioral Sciences, 760 Westwood Plaza, Los Angeles, CA 90024, USA;* [2]*Central Institute of Mental Health, Department of Addictive Behavior and Addiction Research, 68159 Mannheim, Germany*

The use of thyroid hormones as an effective adjunct treatment for affective disorders has been studied over the past three decades and has been confirmed repeatedly. Interaction of the thyroid and monoamine neurotransmitter systems has been suggested as a potential underlying mechanism of action. While catecholamine and thyroid interrelationships have been reviewed in detail, the serotonin system has been relatively neglected. Thus, the goal of this article is to review the literature on the relationships between thyroid hormones and the brain serotonin (5-HT) system, limited to studies in adult humans and adult animals. In *humans*, neuroendocrine challenge studies in hypothyroid patients have shown a reduced 5-HT responsiveness that is reversible with thyroid replacement therapy. In adult *animals* with experimentally-induced hypothyroid states, increased 5-HT turnover in the brainstem is consistently reported while decreased cortical 5-HT concentrations and 5-HT_{2A} receptor density are less frequently observed. In the majority of studies, the effects of thyroid hormone administration in animals with experimentally-induced hypothyroid states include an increase in cortical 5-HT concentrations and a desensitization of autoinhibitory 5-HT_{1A} receptors in the raphe area, resulting in disinhibition of cortical and hippocampal 5-HT release. Furthermore, there is some indication that thyroid hormones may increase cortical 5-HT_2 receptor sensitivity. In conclusion, there is robust evidence, particularly from animal studies, that the thyroid economy has a modulating impact on the brain serotonin system. Thus it is postulated that one mechanism, among others, through which exogenous thyroid hormones may exert their modulatory effects in affective illness is via an increase in serotonergic neurotransmission, specifically by reducing the sensitivity of 5-HT_{1A} autoreceptors in the raphe area, and by increasing 5-HT_2 receptor sensitivity.
Molecular Psychiatry (2002) **7**, 140–156. DOI: 10.1038/sj/mp/4000963

Keywords: thyroid system; T_4; T_3; serotonin system; adult brain; 5-HT receptor; mood modulation; affective disorders; depression

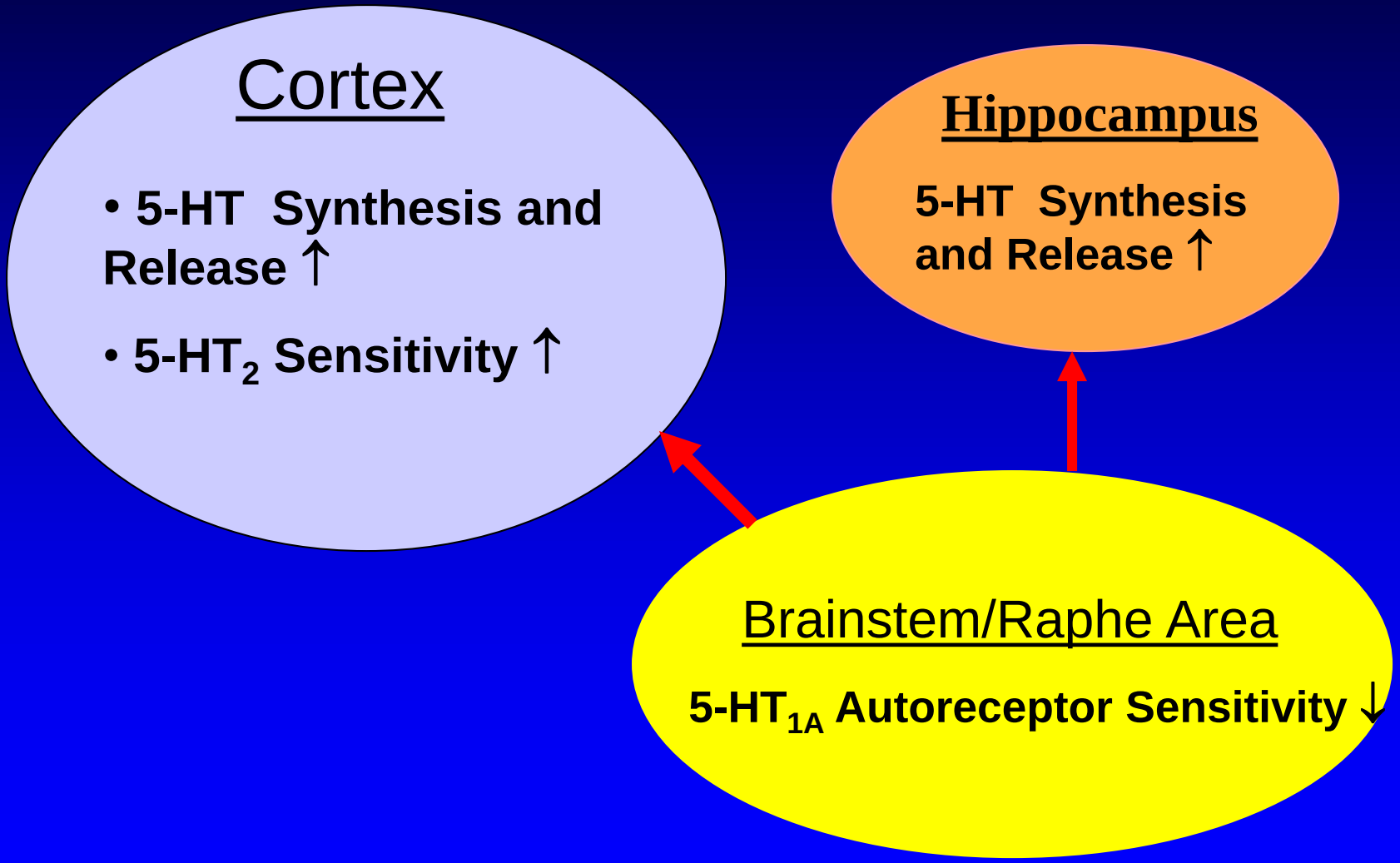
Fig. 1a

The Brain Serotonin System in Experimentally-Induced Hypothyroidism



Bauer M, Heinz A, Whybrow PC (2002) Mol Psychiatry

Effects of Thyroid Hormone on the Brain Serotonin System



Bauer M, Heinz A, Whybrow PC (2002) *Mol Psychiatry* 7:140-156

Conclusions

- Disturbances of thyroid system function may complicate diagnosis & treatment of mood disorder
- Hypothyroidism: brain is a target organ of thyroid hormones & heuristic model for depression
- Treatment with (supra 300 mcg) levothyroxine is a treatment option for women (better than for men) in bipolar disorder/depression
- Supraphysiologic thyroid hormone improves depressive symptoms in patients with bipolar disorder by modulating function in components of the anterior limbic network

Thank your for your attention

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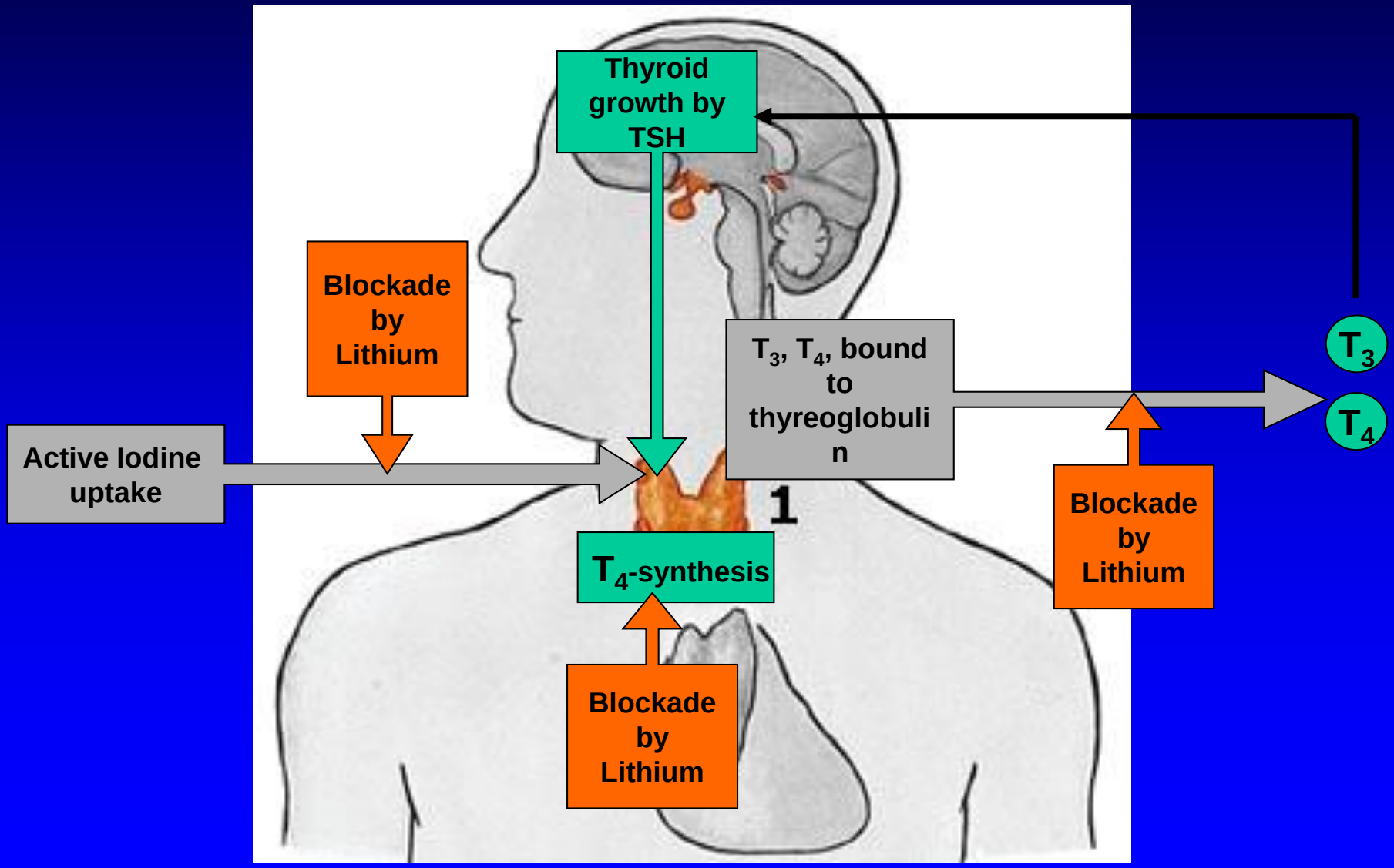
When lithium comes into place

Hypothesis on the lithium – thyroid interaction

Lithium inhibits peripheral thyroid physiology



Prevalence of hypothyroidism in lithium-treated patients

- Wide range in literature 3-40%
- Largest study N=4681, 3.4 % hypothyroid
- Other studies up to 40%
- Women at greater risk
- Age another risk factor

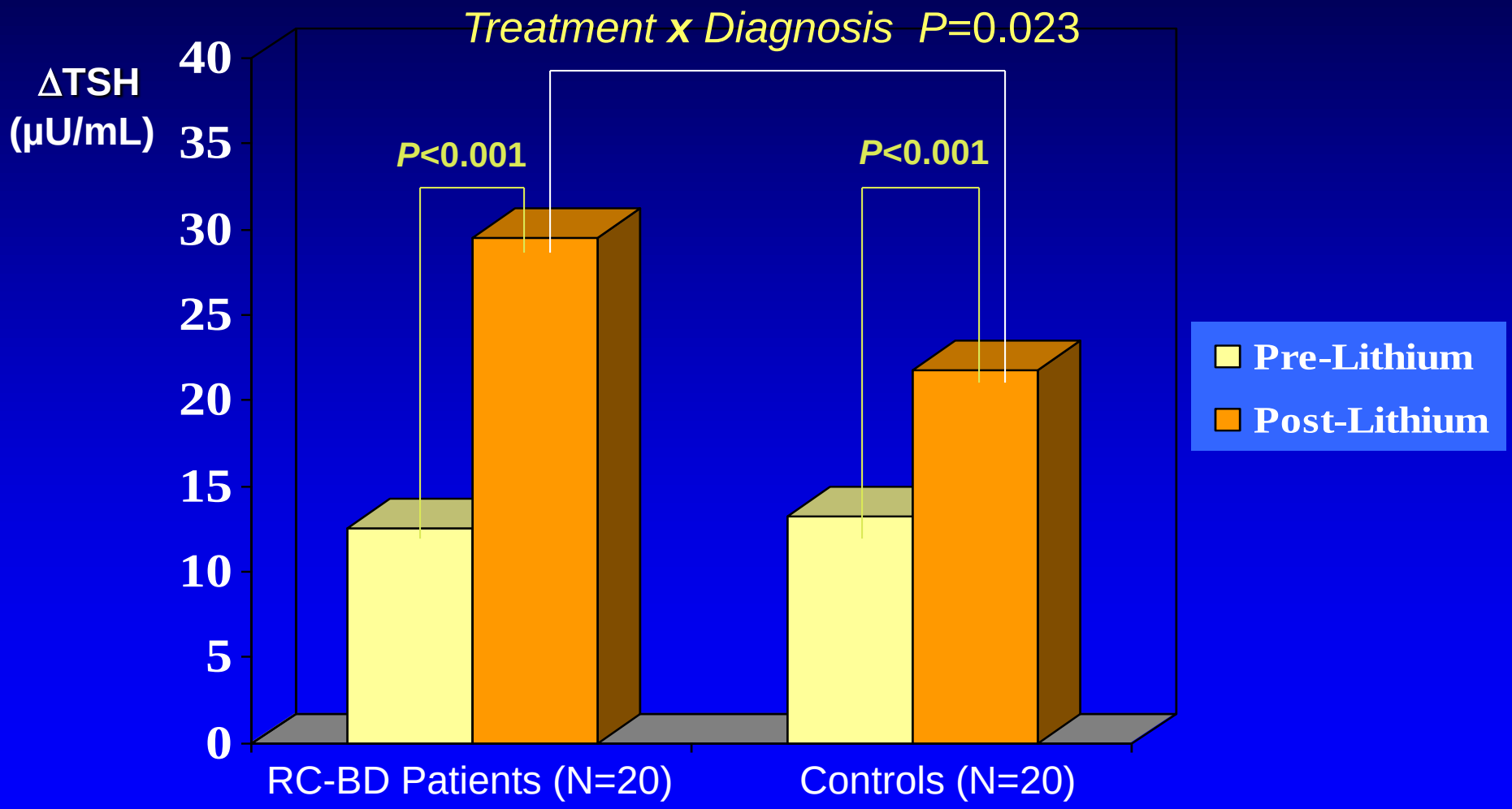
Lazarus et al. (2006) in: Lithium in Neuropsychiatry

Thyroid Function in Rapid Cycling Bipolar Disorder After Lithium Challenge

- Long debate on the relationship between rapid cycling bipolar disorder (RC-BD) and thyroid hypofunction
- Unmedicated Patients with RC-BD (N=20)
- Age-gender matched healthy controls
- 4 weeks challenge with lithium (0.7-1.2 mEq/L)
- Thyroid function tests (TRH stimulation test) before and after lithium treatment

Gyulai, Bauer, Whybrow et al. (2003) Biol Psychiatry

TRH Test: ΔTSH Before and After Lithium Challenge in Rapid Cycling Bipolar Disorder and Healthy Controls: Unmasking Latent Hypothyrodism



Gyulai, Bauer, Whybrow et al. (2003) Biol Psychiatry

Lithium Challenge Study - Conclusion

- Exaggerted TSH response in TRH test: association of Rapid Cycling Bipolar Disorder with latent hypofunction of the thyroid system
- Dysfunction becomes manifest (“unmasking”) with short-term lithium challenge to the thyroid system
- If a latent “central” hypothyroid state exists in RC-BD, increasing the availability of thyroid hormone to the brain may be therapeutic

Gyulai, Bauer, Whybrow et al. (2003) Biol Psychiatry

Conclusions (2)

- Advise to careful monitoring of women with mood disorders (aged > 40 years!) for thyroid abnormalities and changes of thyroid function
- Especially relevant during lithium treatment because lithium may impair vital thyroid metabolic pathways due to its “anti-thyroid” activity
- Treatment with (high dose 300 mcg) L-thyroxine may be a better treatment option for women than for men in bipolar disorder/depression

Summary Lithium & Thyroid

- Anti-thyroid effects of lithium are common & may negatively influence the mood stabilizing effects of lithium
- Goal to increase thyroid hormone levels in lithium-treated patients
- Lithium non-responders do benefit from thyroid hormone (levothyroxine) treatment in longer-term therapy

Thyroid & Brain Interactions

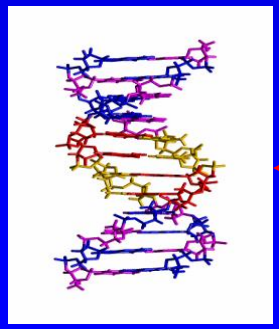
Imaging and genetic technology

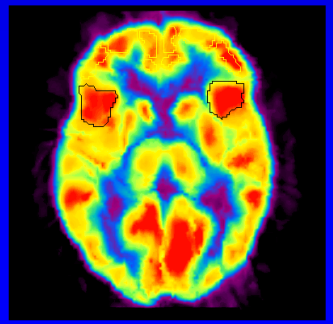
Mood Disorders

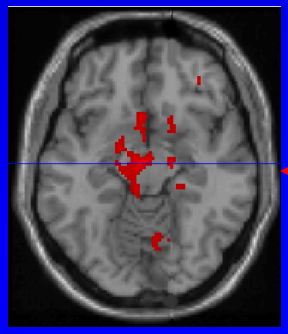
Lithium

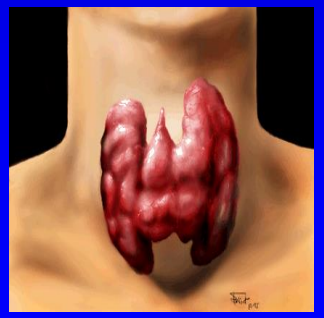
Thyroid Hormone

T3, T4









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

Regional cerebral glucose metabolism and anxiety symptoms in bipolar depression: Effects of levothyroxine

Michael Bauer[a,b,*], Steven M. Berman[b], Florian Schlagenhauf[c], Bradley Voytek[b], Natalie Rasgon[d], Mark A. Mandelkern[e], Peter C. Whybrow[b], Edythe D. London[b]

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Levothyroxine
Bipolar disorder
Anxiety
Positron emission tomography
Depression

ABSTRACT

We examined the relationships between regional brain activity and anxiety in bipolar depressed patients receiving adjunctive treatment with levothyroxine. Regional brain activity was assessed with positron emission tomography and [^{18}F]fluorodeoxyglucose in 10 euthyroid, depressed bipolar women before and after 7 weeks of adjunctive therapy with levothyroxine. The primary biological measures were relative (to global) regional radioactivity as a surrogate index of glucose metabolism in pre-selected brain regions. Relationships were assessed between regional brain activity and anxiety symptoms while controlling for depression severity. At baseline, Trait Anxiety Inventory measures covaried positively with relative brain activity bilaterally in the dorsal anterior cingulate, superior temporal gyri, parahippocampal gyri, amygdala, hippocampus, ventral striatum, and right insula; state anxiety showed a similar pattern. After treatment anxiety was improved significantly. Change in trait anxiety covaried positively with changes in relative activity in right amygdala and hippocampus. Change in state anxiety covaried positively with changes in relative activity in the hippocampus bilaterally and left thalamus, and negatively with changes in left middle frontal gyrus and right dorsal anterior cingulate. Results indicate that comorbid anxiety symptoms have specific regional cerebral metabolic correlates in bipolar depression and cannot only be explained exclusively by the depressive state of the patients.

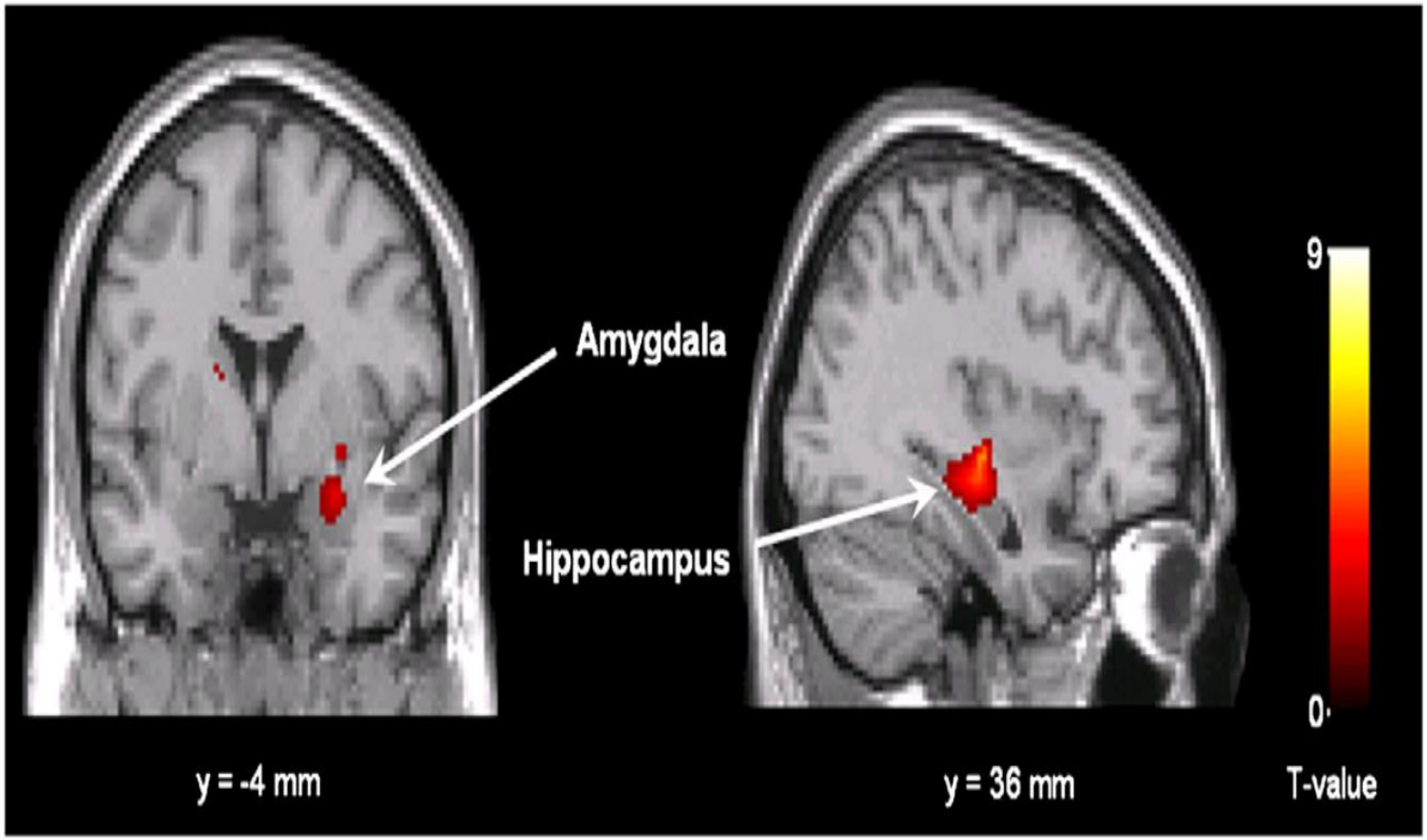
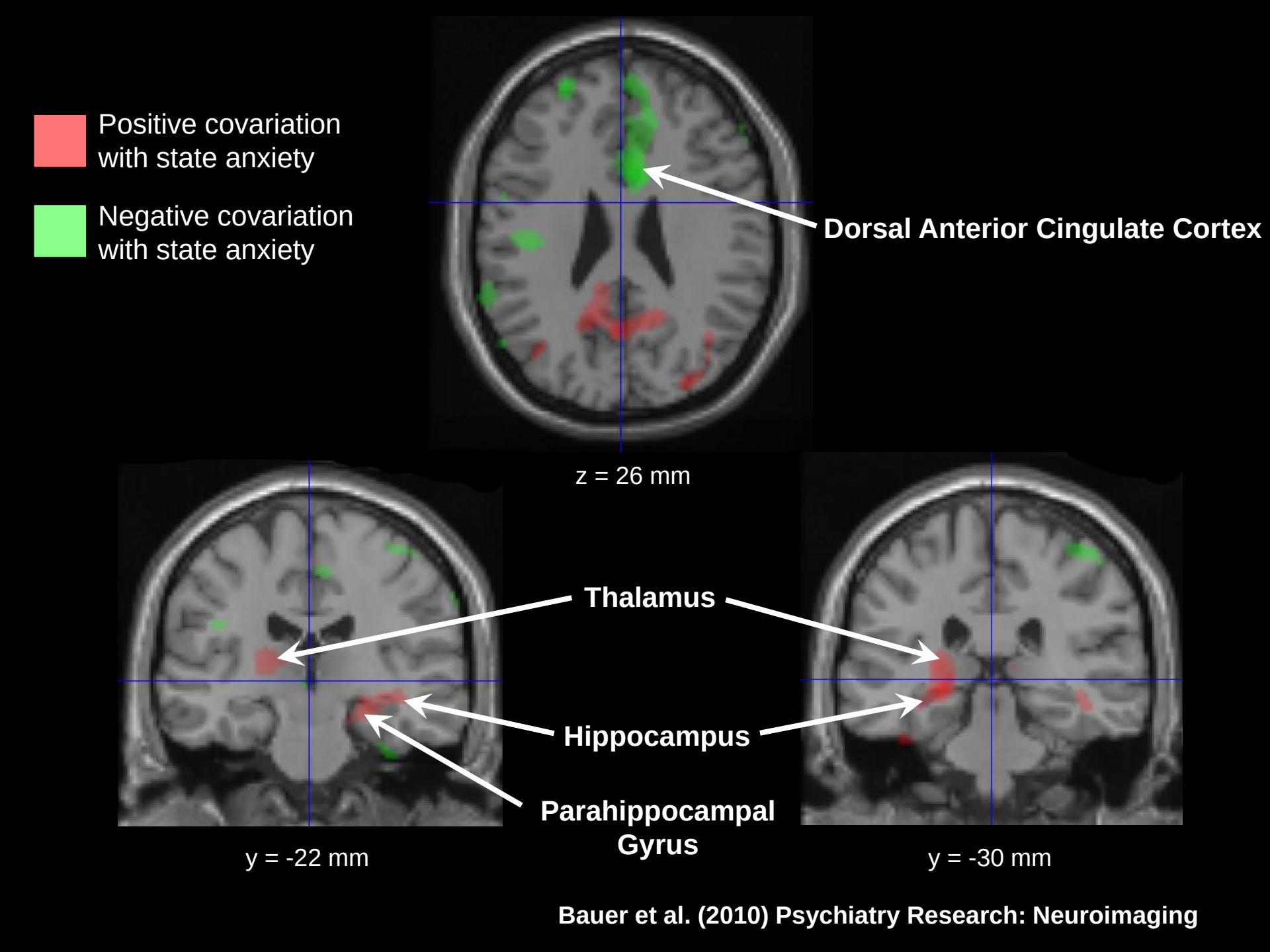


Fig. 1. Brain areas where changes in regional activity were positively correlated with changes in trait anxiety after treatment with levothyroxine in bipolar depression. Statistical parametric maps were generated using SPM99. Colors superimposed on the gray-scale structural MR template indicate areas where the height threshold for the contrast (whole-brain) was $t \geq 1.69$ ($P = 0.05$). Arrows indicate locations where clusters exhibited $P < 0.05$ for spatial extent (corrected for search volume of the relevant VOI but not the number of regions). Coordinates are in MNI space.

Bauer et al. (2010) Psychiatry Research: Neuroimaging



Bauer et al. (2010) Psychiatry Research: Neuroimaging

TRH

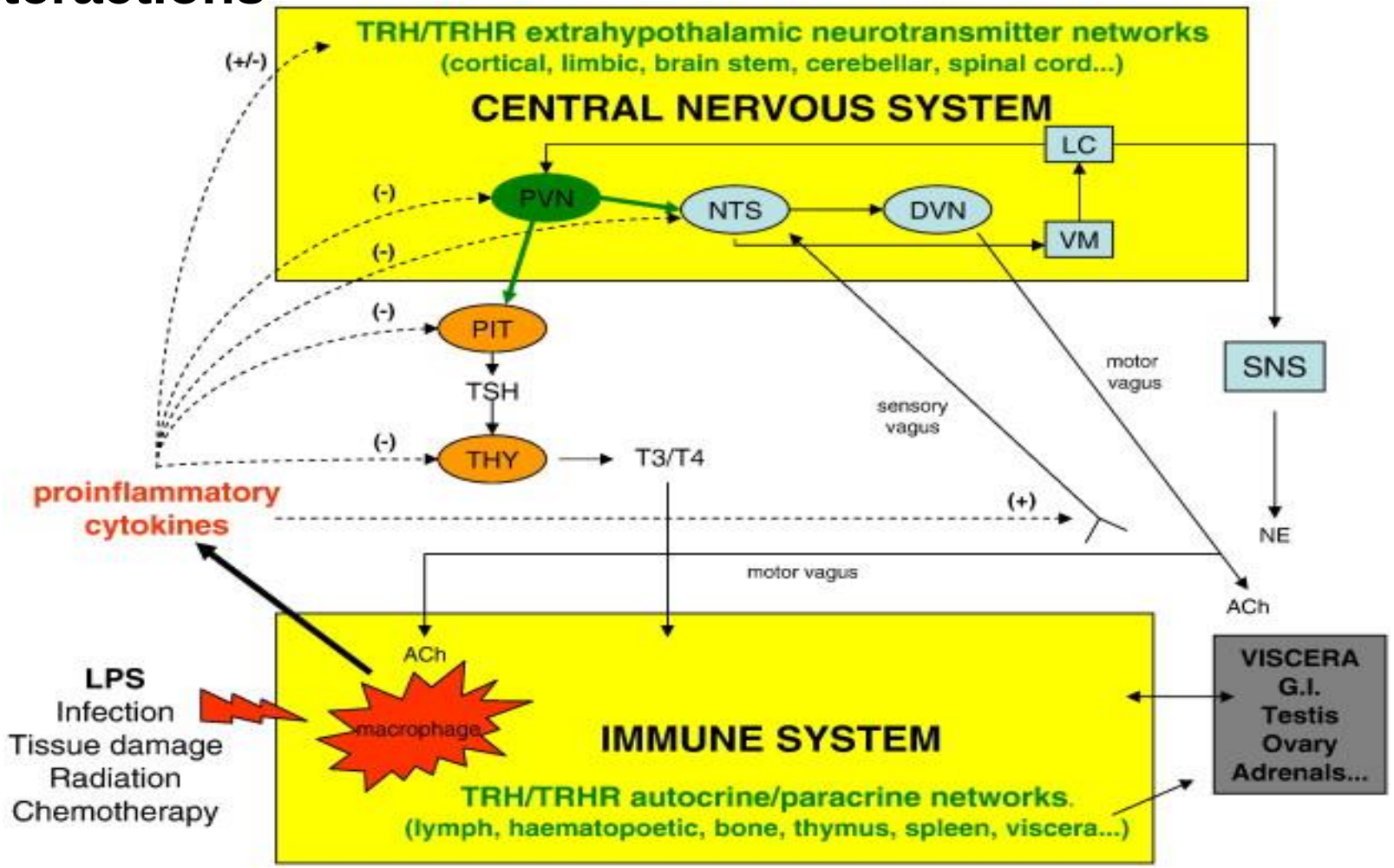
TRH and TRH-Receptor System in Brain: Link to Behavior and Mood

- TRH, thyrotropin-releasing hormone, 1st hypothalamic hormone
- Tripeptid, produced in paraventricular nucleus
- central regulator of HP-thyroid axis: stimulates synthesis & release of pituitary TSH – peripheral thyroid hormone synth & release
- Pharmacological studies with TRH and analogues: array of actions
  - Promote homeostasis
  - Modification of autonomic nervous function
  - Food intake
  - Cognition, locomotion and activation of arousal
  - Mood: antidepressant and anxiolytic effects

Rabeler et al. (2004) Mol Endocrinol; Zeng et al. (2007) Mol Endocrinol;

Sun et al. (2009) Neuropsychopharm

Overview of documented TRH and immune system interactions



J. Kamath , G.G. Yarbrough , A.J. Prange Jr. , A. Winokur

The thyrotropin-releasing hormone (TRH)?immune system homeostatic hypothesis

Pharmacology & Therapeutics Volume 121, Issue 1 2009 20 - 28

TRH and TRH-Receptor System in Brain: Link to Behavior and Mood

- TRH receptor type 1 (TRH-R1) and type 2 (TRH-R2): G-protein coupled receptors
- TRH R1/R2 like TRH also expressed extra-hypothalamically in various brain regions (incl. limbic regions and cortex) although highly expressed differentially
- TRH-R2 has not been identified in humans

Rabeler et al. (2004) Mol Endocrinol; Zeng et al. (2007) Mol Endocrinol; Sun et al. (2009) Neuropsychopha

Table 1 Comparison of the distributions of TRH-R1 and TRH-R2 in rat brain

Region	TRH-R1	TRH-R2
Cortex		
Rhinal cortex	+	
Piriform cortex	+	
Frontoparietal cortex	+	+
Primary visual cortex		+
Primary olfactory cortex	+	+
Anterior cingulate area		+
Posterior cingulate area		+
Retrosplenium		+
Striate areas		+
Subiculum	+	+
Thalamus		
Paraventricular nucleus	+	+
Centromedial nucleus		+
Anteroventral nucleus		+
Ventroposterior nucleus		+
Posterior medial nucleus	+	
Laterodorsal nucleus		+
Lateroposterior nucleus		+
Ventromedial nucleus		+
Medial habenular nucleus		+
Medial reuniens nucleus		+
Medial/lateral geniculate nucleus		+
Subthalamic area		
Subthalamic nucleus		+
Hypothalamus		
Anterior hypothalamic area	+	+
Lateral hypothalamic area	+	+
Posterior hypothalamic area	+	
Medial preoptic area	+	+
Lateral preoptic area	+	
Dorsomedial hypothalamic nucleus	+	
Paraventricular nucleus	+	+
Periventricular nucleus	+	
Suprachiasmatic nucleus	+	
Mammillary nucleus	+	+
Hippocampus		
Dentate gyrus	+	
Ammon's horn	+	
Amygdala		
Amygdaloid nuclei	+	+
Septal region		
Stria terminalis	+	+
Medial septal nucleus	+	
Lateral septal nucleus	+	
Septohippocampal nucleus	+	
Nucleus of the diagonal band	+	+
Corpus striatum		
Caudate putamen		
Globus pallidus	?	+
Nucleus accumbens	+	
Midbrain and hindbrain		
Superior colliculus	+	+
Inferior colliculus		+
Periaqueductal gray	+	+
Mesencephalic reticular nucleus		+
Ventral tegmental area		+
Pontine gray		+
Pontine reticular nucleus		+
Central/rostral linear raphe nuclei		+
Periolivary nucleus	+	
Nucleus sagulum		+
Parabrachial nucleus	+	+
Motor trigeminal nucleus	+	
Facial nucleus	+	
Hypoglossal nucleus	+	
Dorsal motor nucleus of vagus	+	
Pituitary		
Anterior lobe	+	?

+, expression of mRNA.

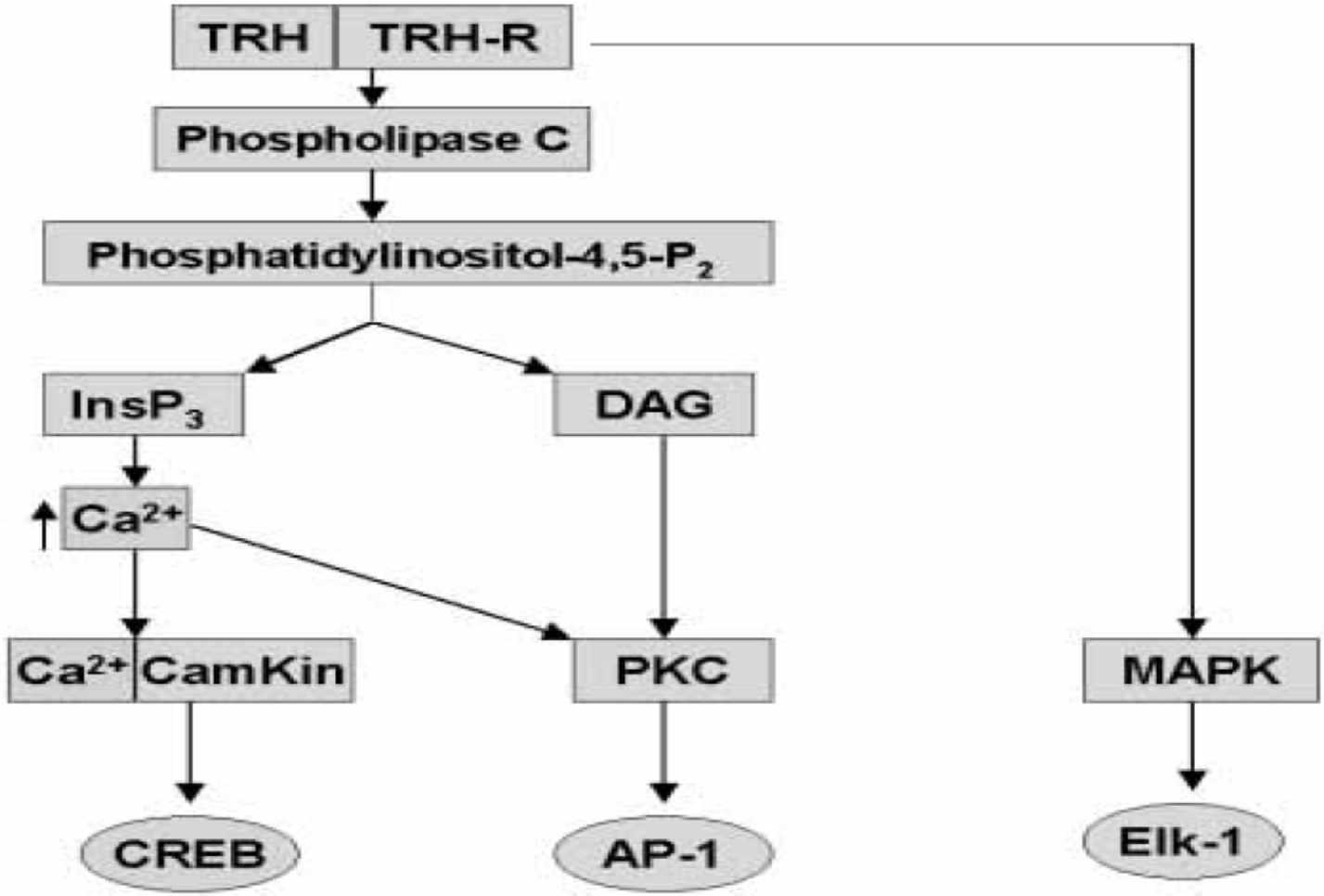


Figure 1 An overview of the intracellular signaling pathways activated by binding of TRH to its receptors. As indicated in the text, activation of TRH-Rs leads to activation of calcium/calmodulin-dependent protein kinase (Ca^{2+}/CamKin), PKC and MAPK, and induces gene transcription via transcription factors CREB, AP-1, and Elk-1. $InsP_3$, inositol 1,4,5-triphosphophosphate; DAG, diacyl glycerol.

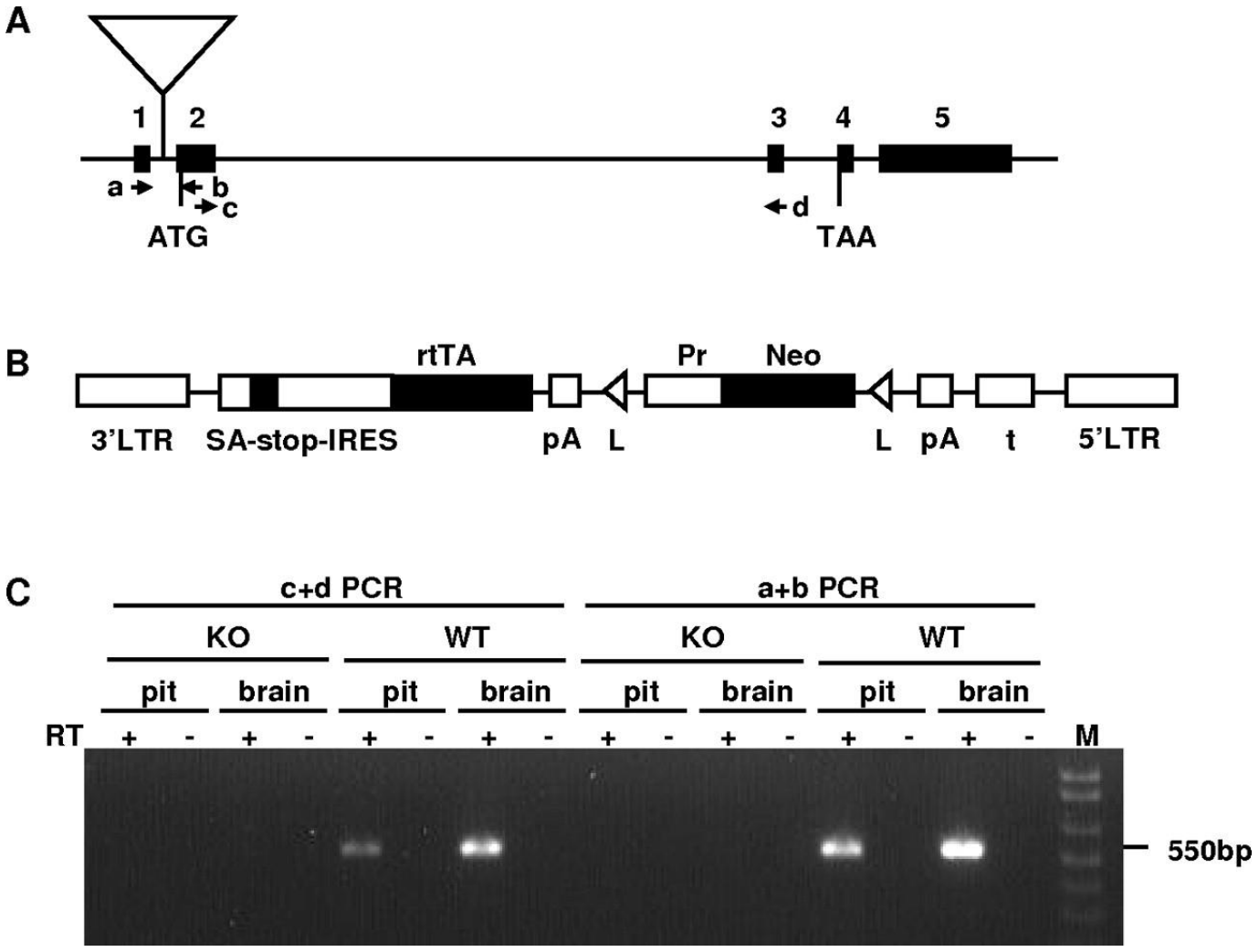
Overview of knock-out mice in prepro-TRH and TRH-R1/R2 genes

- TRH KO:
  - Results in central and peripheral hypothyroidism
  - Normal development
  - no behavioral characterization
- TRH receptor type 1 (TRH-R1) KO
- TRH receptor type 2 (TRH-R2) KO

Rabeler et al. (2004) Mol Endocrinol; Zeng et al. (2007) Mol Endocrinol; Sun et al. (2009) Neuropsychopha

TRH-R1 KO Mice

Schematic diagram of the retroviral vector insertion in the TRH-R1 gene.

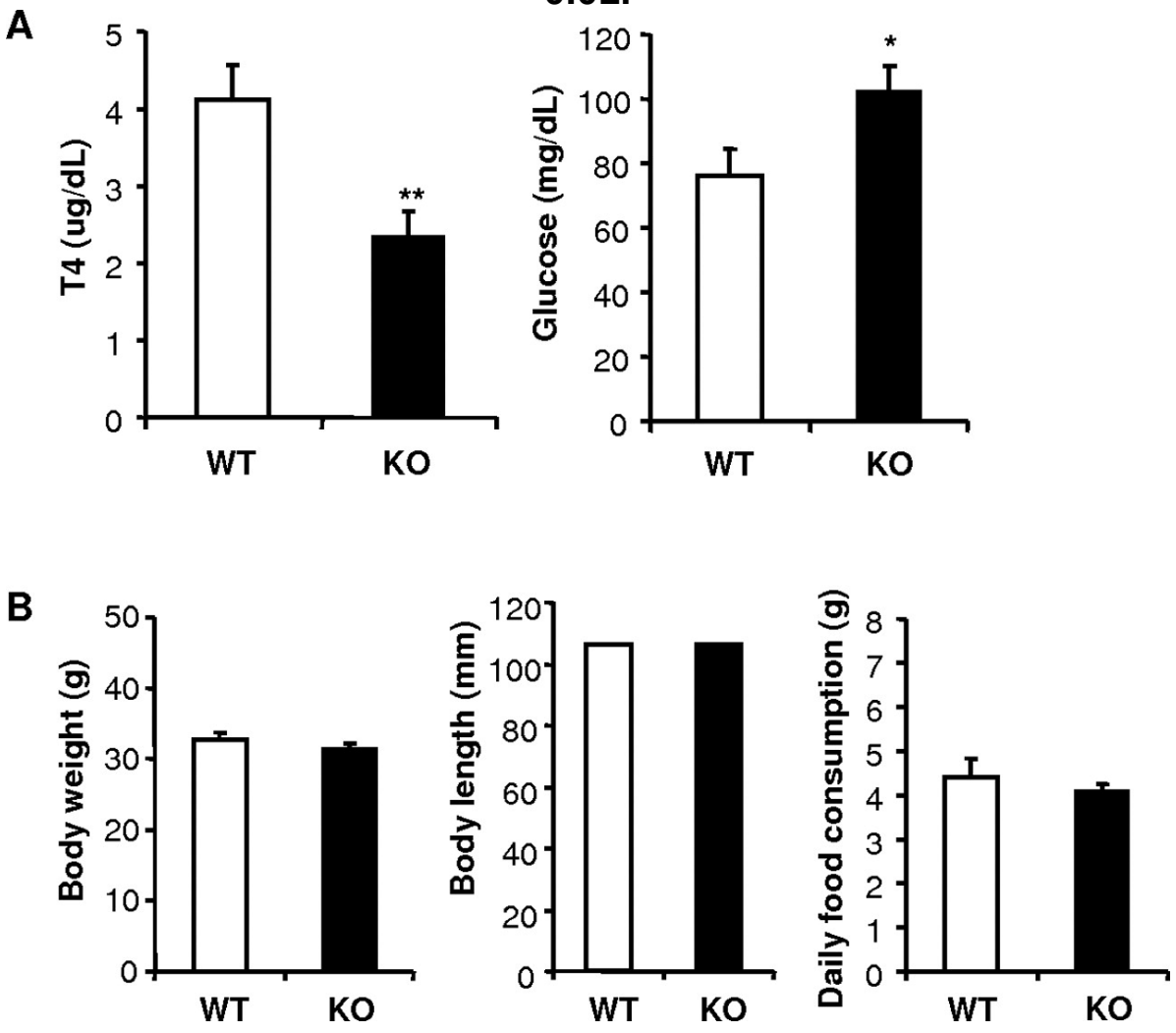


Zeng H et al. Molecular Endocrinology 2007;21:2795-2804

MOLECULAR ENDOCRINOLOGY

TRH-R1 KO Mice Have Hypothyroidism but Normal Body Size and

Food Intake A, TRH-R1 KO mice have decreased plasma T4 level (left panel) *, P < 0.05; **, P < 0.01.

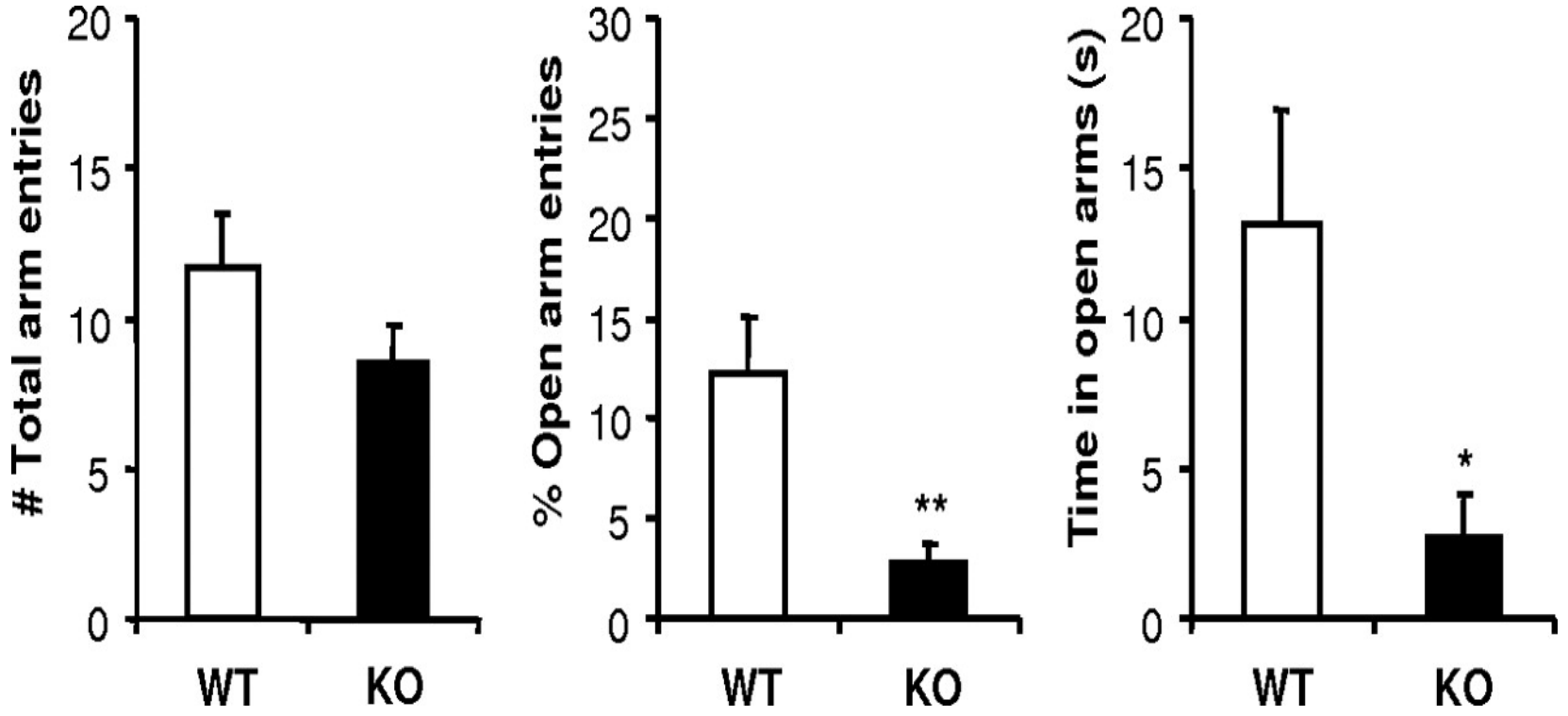


Zeng H et al. Molecular Endocrinology 2007;21:2795-2804

MOLECULAR ENDOCRINOLOGY

TRH-R1 KO Mice Exhibit Increased Anxiety in the Elevated Plus Maze Test

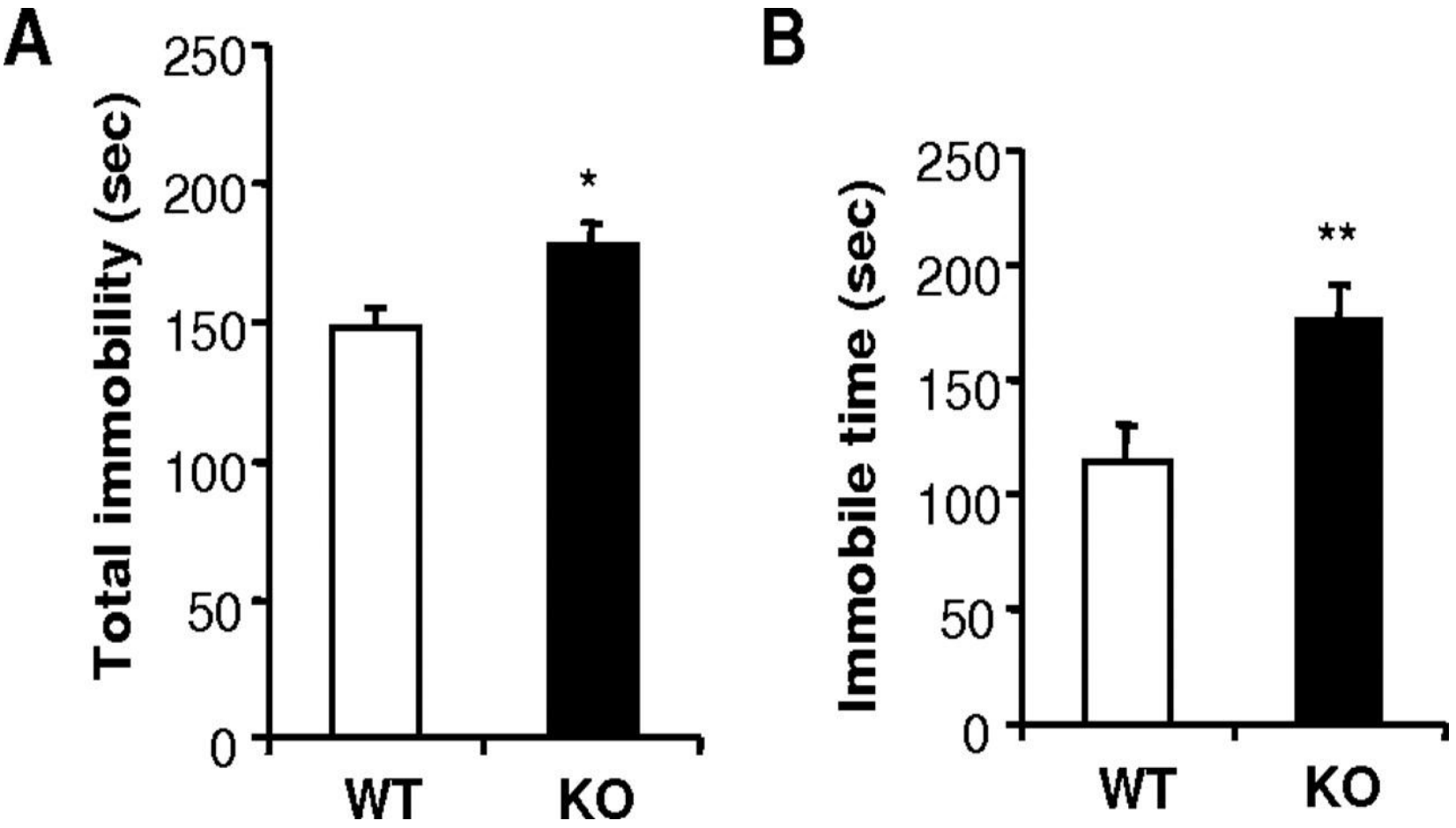
Left panel, Total number of entries into both open and closed arms; middle panel, percentage of entries into the open arms compared with total number of arm entries; right panel, the ti...



Zeng H et al. Molecular Endocrinology 2007;21:2795-2804

MOLECULAR ENDOCRINOLOGY

TRH-R1 KO Mice Exhibit Increased Immobility in Depression Tests (Tail suspension test)



Zeng H et al. Molecular Endocrinology 2007;21:2795-2804

MOLECULAR ENDOCRINOLOGY

TRH-receptor type 2 deficient mice are euthyroid and exhibit increased depression phenotypes

Sun et al. 2009, Neuropsychopharmacology

TRH-R2 KO mice are euthyroid: basal and TRH-stimulated serum TSH levels in mice

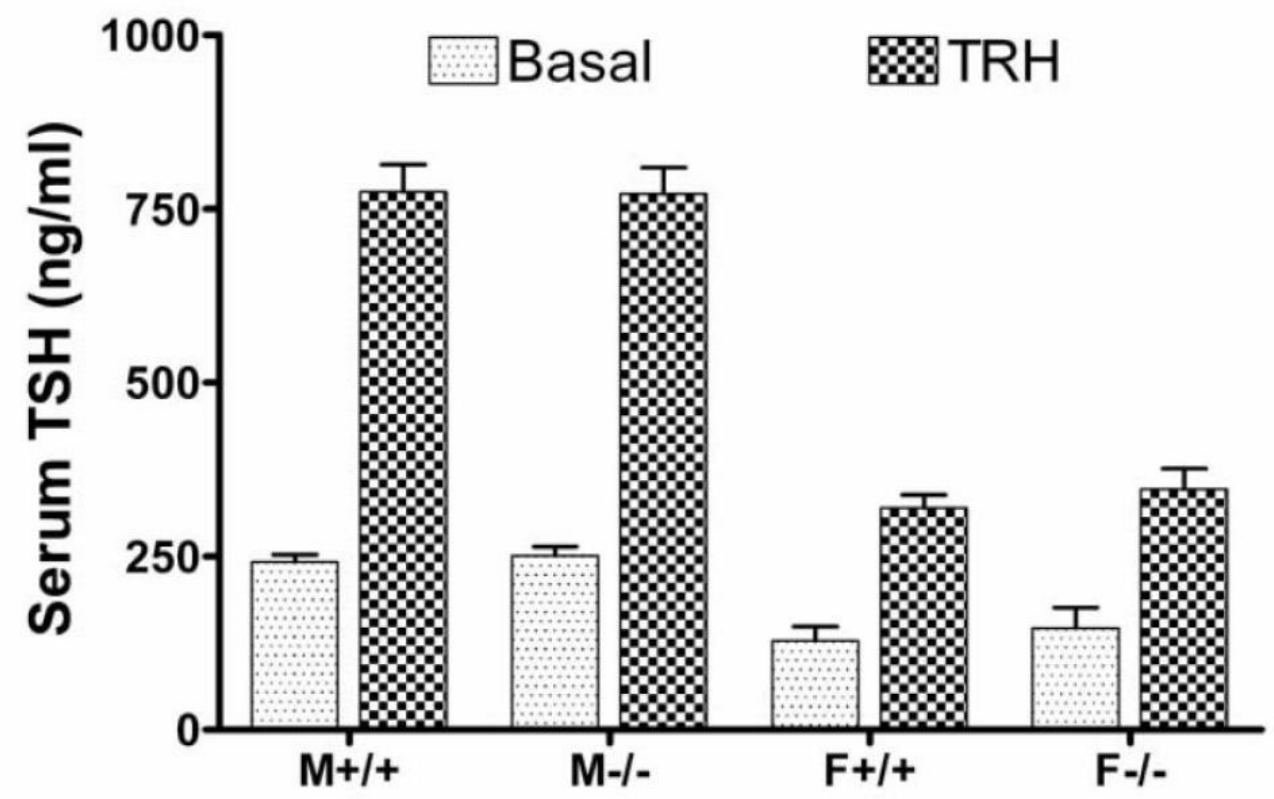


Figure 3.
Basal and TRH-stimulated serum TSH levels in wild type and TRH-R2-deficient mice. Serum for TSH measurements were obtained just before TRH (5 μg/kg) administration i.p. (Basal) and 30 min after (TRH). There was no difference in any of the values in wild type compared to TRH-R2-deficient mice.

Sun et al. (2009) Neuropsychopharmacol

TRH-R2 KO mice: tail suspension (TST) and forced swing tests (FST) different from WT only in female animals

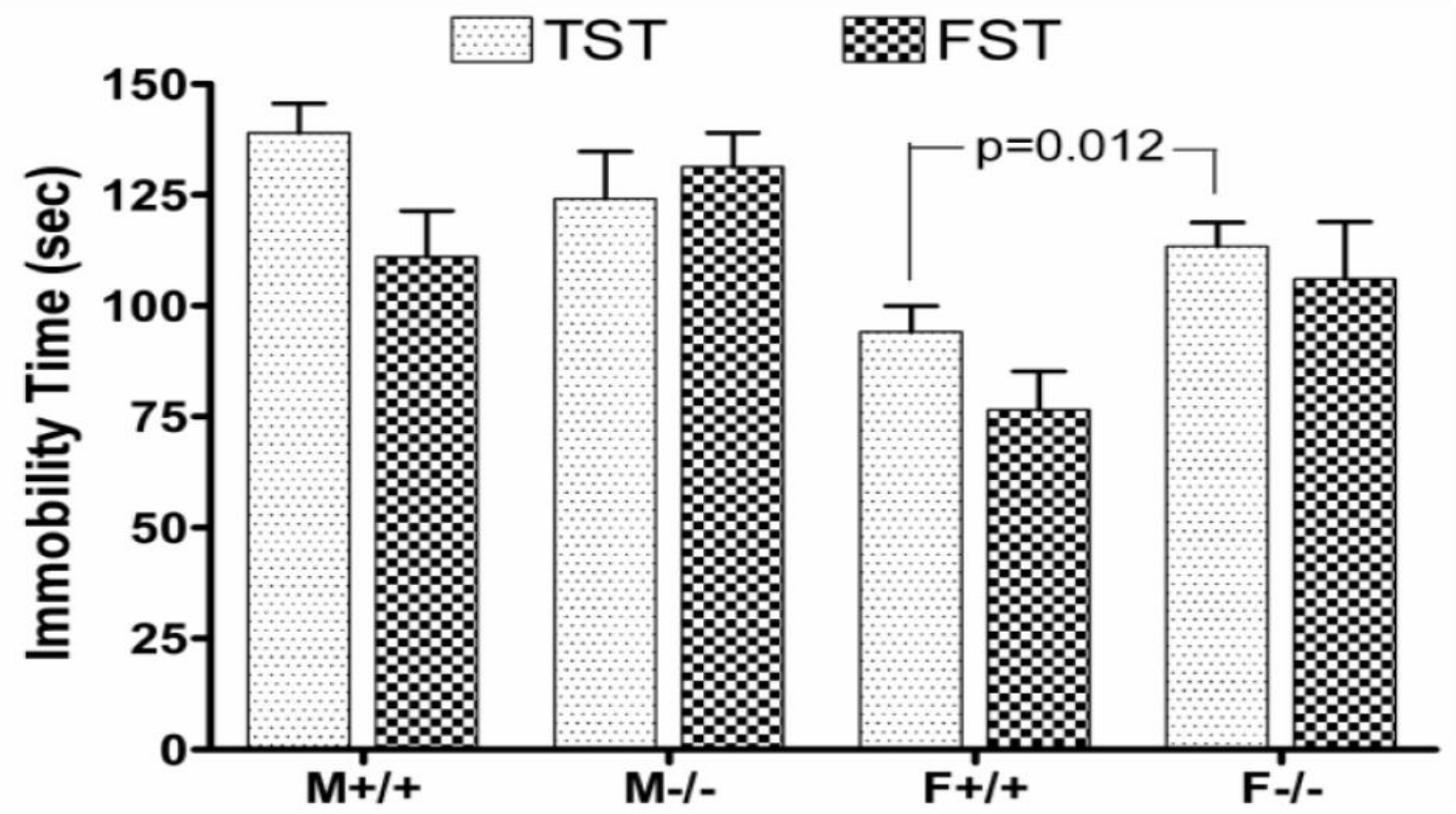
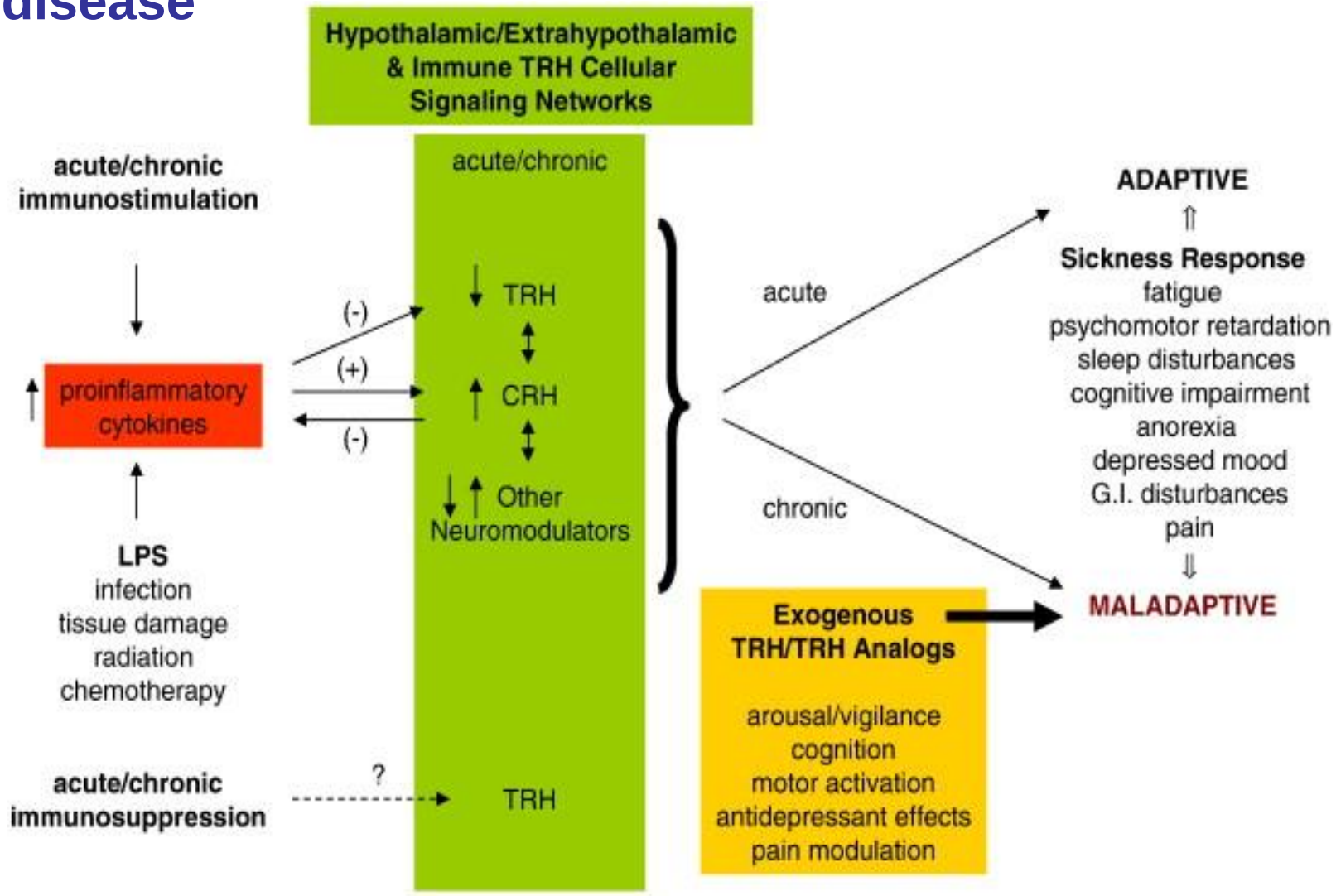


Figure 4.
Results of tail suspension and forced swim tests in wild type and TRH-R2-deficient mice. Forced swim (FST) and tail suspension tests (TST) were performed as described in Experimental Procedures. Male and female data were analyzed separately by *t*-test.

Sun et al. (2009) Neuropsychopharmacol

TRH and immune system interactions in health and disease



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Summary
Thyroid Disorders and Lithium Treatment

- Are the commonest endocrine side effect of lithium therapy
- Hypothyroidism, goitre most often, hyperthyroidism (autoimmune mechanism?)
- Are not contraindication for lithium tx
- Should be monitored by blood test (TSH) and ultrasonography (baseline !)
- Should be consequently treated, particularly hypothyroid states, because they may worsen the clinical course of the mood disorder