POSTGRADUATE PROGRAM IN NEUROSCIENCE
Molecular Aspects of Neurological Diseases
Basel 2009

Bipolar Disorders

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Artists with mit Manic-Depressive Illness

Diagnostic Criteria for Major Depressive Episode

For > 2 weeks five (or more) of the following symptoms and at least one is either depressed mood or loss of interest or pleasure:

- depressed mood most of the day.....
- markedly diminished interest or pleasure in all, or almost all activities most of the day ....
- significant weight loss....or weight gain..or decrease or increase in appetite....
- insomnia or hypersomnia...

Continued....

Diagnostic Criteria for Major Depressive Episode (continued)

- psychomotor agitation or retardation fatigue or loss of energy
- feelings of worthlessness or excessive or inappropriate guilt
- diminished ability to think or concentrate
- recurrent thoughts of death, recurrent suicidal ideation...or a suicude attempt...

Diagnostic Criteria for Manic Episode

For >1 week (or any duration if hospitalization is necessary):

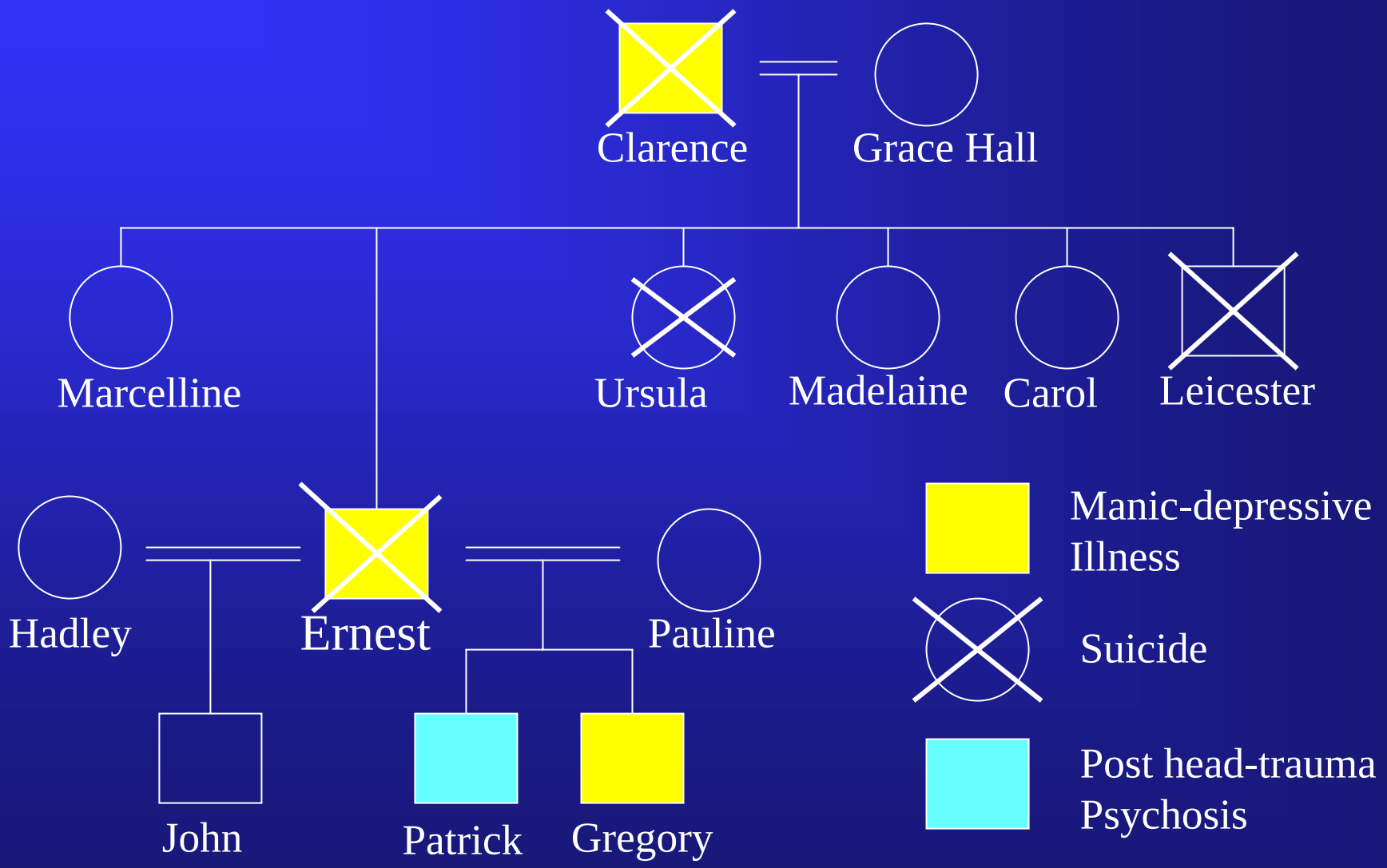
- inflated self-esteem or grandiosity
- decreased need for sleep
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e. attention tooe easily drawn to unimportant or irrelevant external stimuli)
- increase in goal directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences

Pathophysiologie Bipolarer Störungen?

„The root of the evil lies in the constitution itself, in the fatal weakening of families from generation to generation.....The root of the evil certainly lies there, and there is no cure for it.“

Vincent van Gogh

Ernest Hemingway: Partial Family History



Genetic Data of Affective Disorders

- Bipolar: Concordance rate MZ 80%
  DZ 20%
- Unipolar: Concordance rate MZ 50%
  DZ 20%
- Most concordant MZ are concordant also in course of illness
- First degree relatives of bipolar index cases:
  morbidity risk: 15 - 20 %
- First degree relatives of bipolar index cases
  morbidity risk: 10 - 15 %
- Children of two affected parents: morbidity risk 55 %
- Bipolar: female : male = 1:1
- Unipolar: female : male = 2:1

Molecular Genetic Data of Bipolar Disorders

- Complex pattern of inheritance
- no single gene of major effect
- Association studies (Looking for polymorphisms that are more common in patients than controls)
- $\Rightarrow$ disease gene of linkage disequilibrium (e.g. 5 HT-transporter, TH, D2, D3, MAOA, COMT)
- Linkage studies (Looking for genetic markers that cosegregate with the disease in affected individuals in large families): „Hot spots“ e.g. at 4p16, 10q25-26, 12q23-24, 18p11, 18q21-23, 21q22

Two Roads in the Quest for the Pathophysiology of Bipolar Disorder:

- Neurobiological mechanisms of action of drugs that improve or provoke altered mood (Antidepressants, antipsychotics, mood stabilizer, drugs of abuse)
- Neurobiological abnormalities associated with the illness?

Treatment of Bipolar Disorders

- Antidepressants:

  Treat the depressive episode but may induce mania or cycle acceleration
- Antipsychotics:

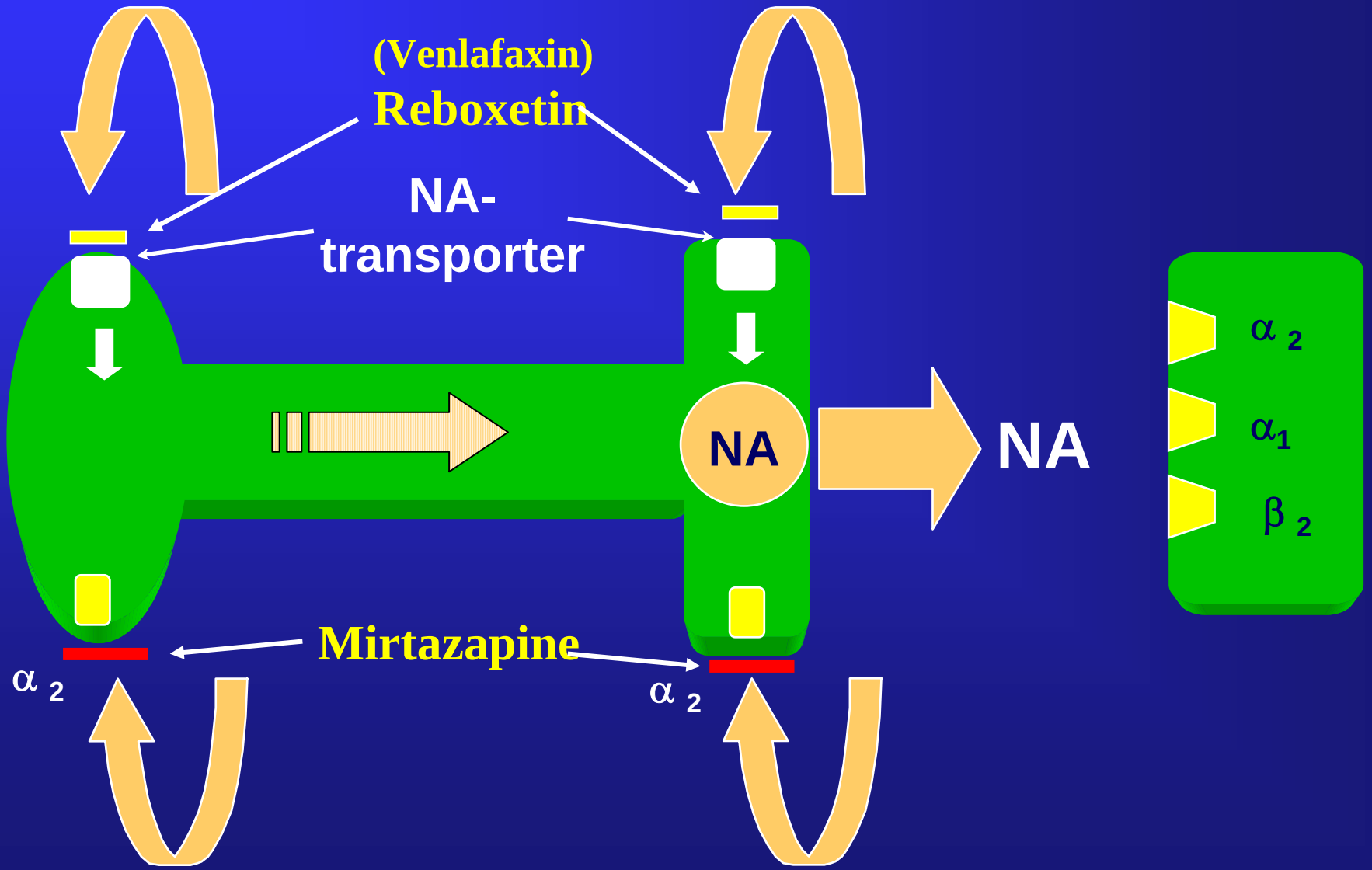
  „Treat“ the manic episode but may induce depression
- Mood Stabilizer:

  Treat mania (or depression). Prevent recurrences of mania and/or depression!

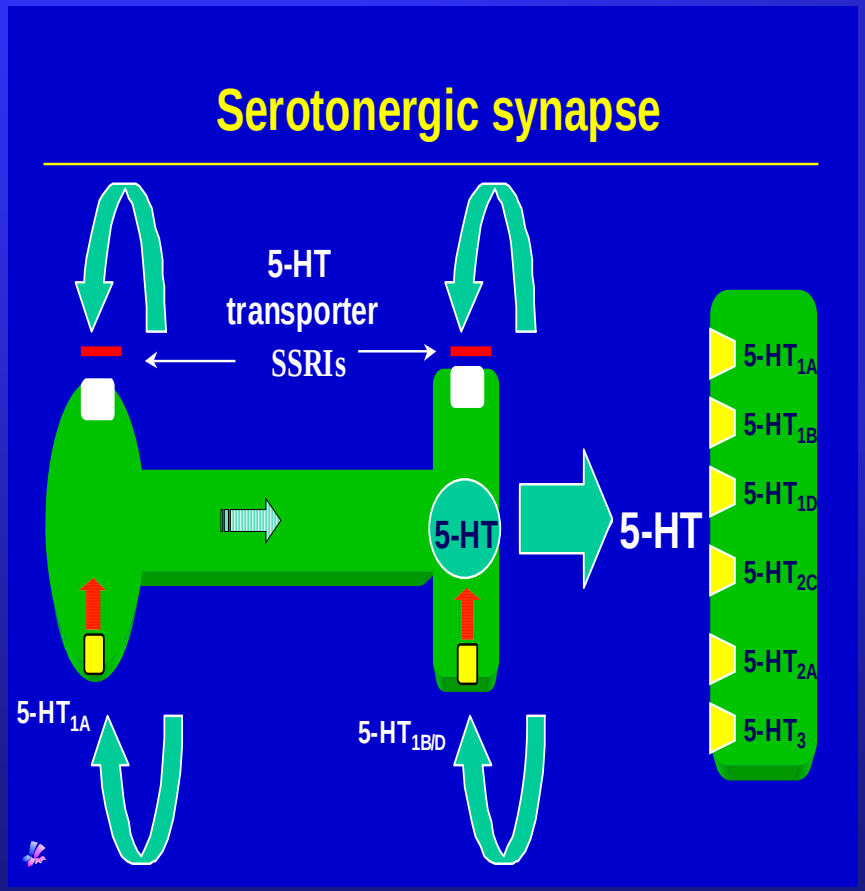
Mechanism of Action of Antidepressants

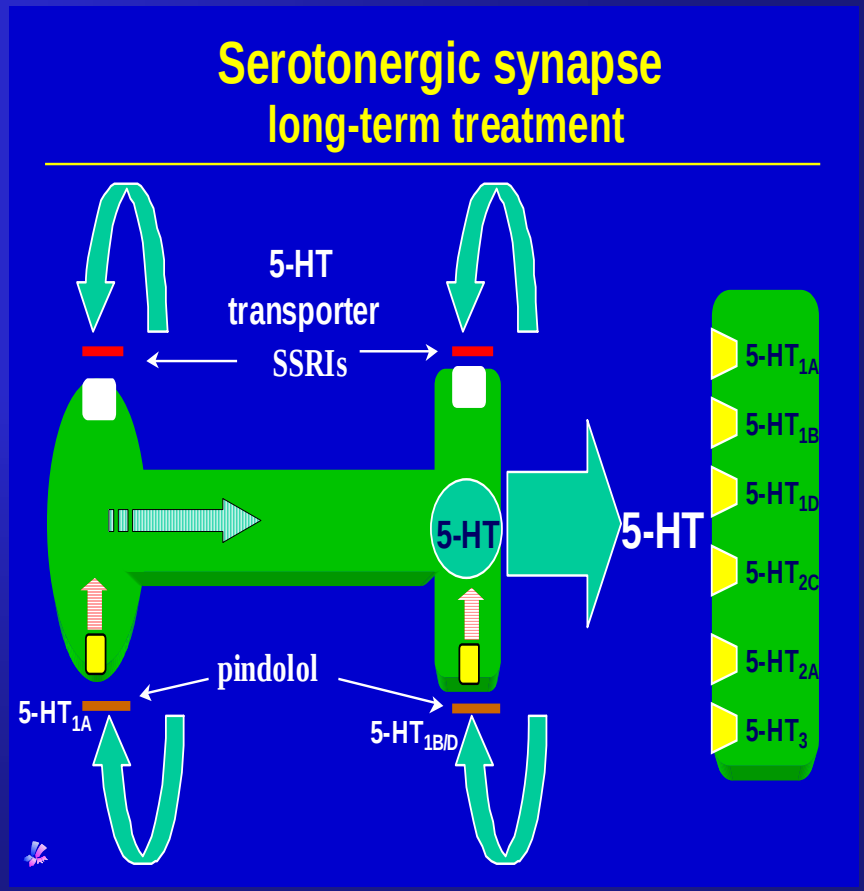
- AD increase 5HT and/or NA in the synaptic cleft by inhibition of re-uptake, inhibition of metabolism or by blockade of presynaptic α_2 -receptors that inhibit 5HT or NA release
- Types of AD:
  - TCA (unspecific)
  - SSRI‘s (specific for 5HT)
  - SNRI‘s (specific for noradrenalin)
  - SSNRI‘s (specific for 5HT and noradrenalin)
  - MAOI‘s
  - presynaptic α_2-Blocker

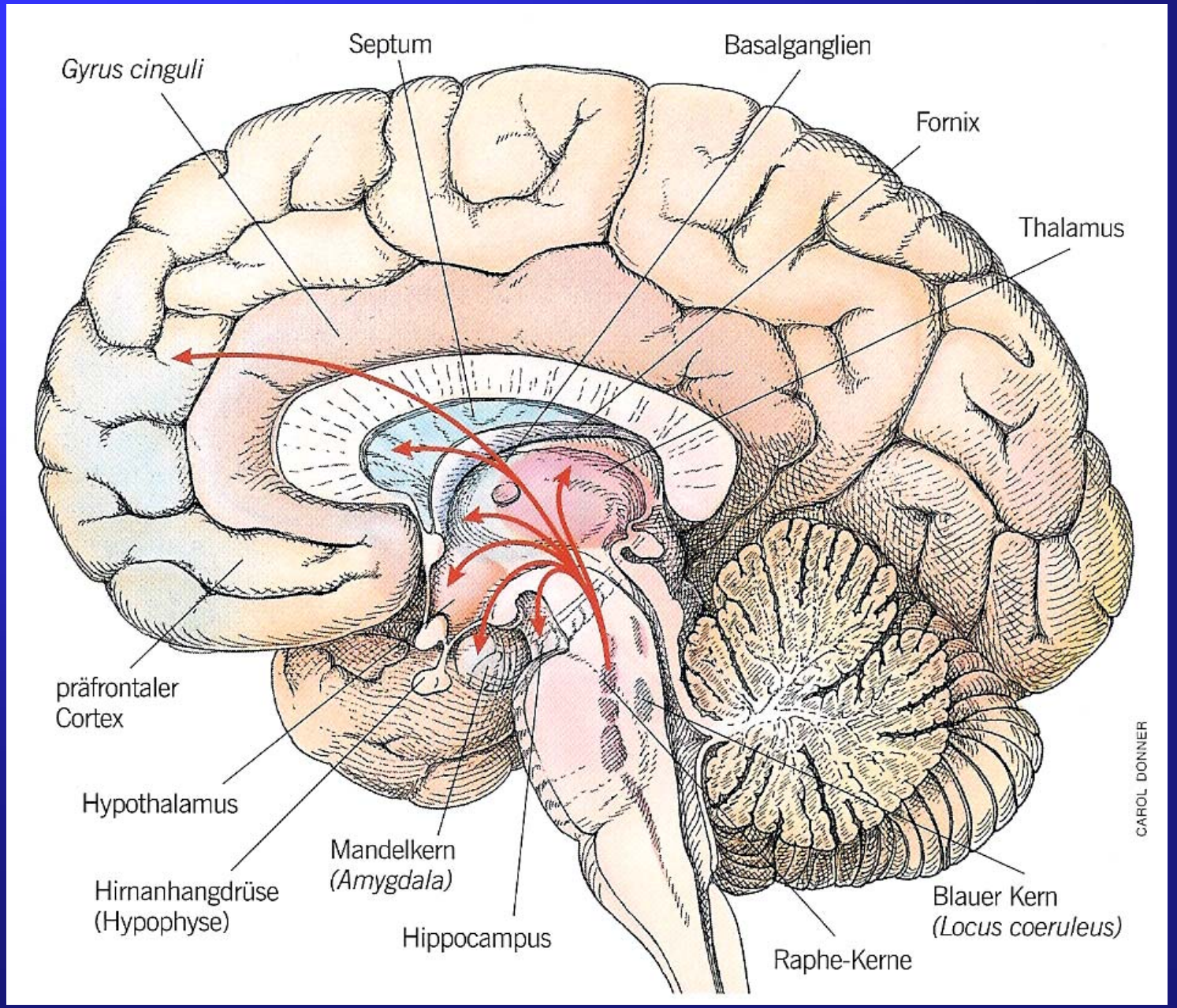
Noradrenergic synapse



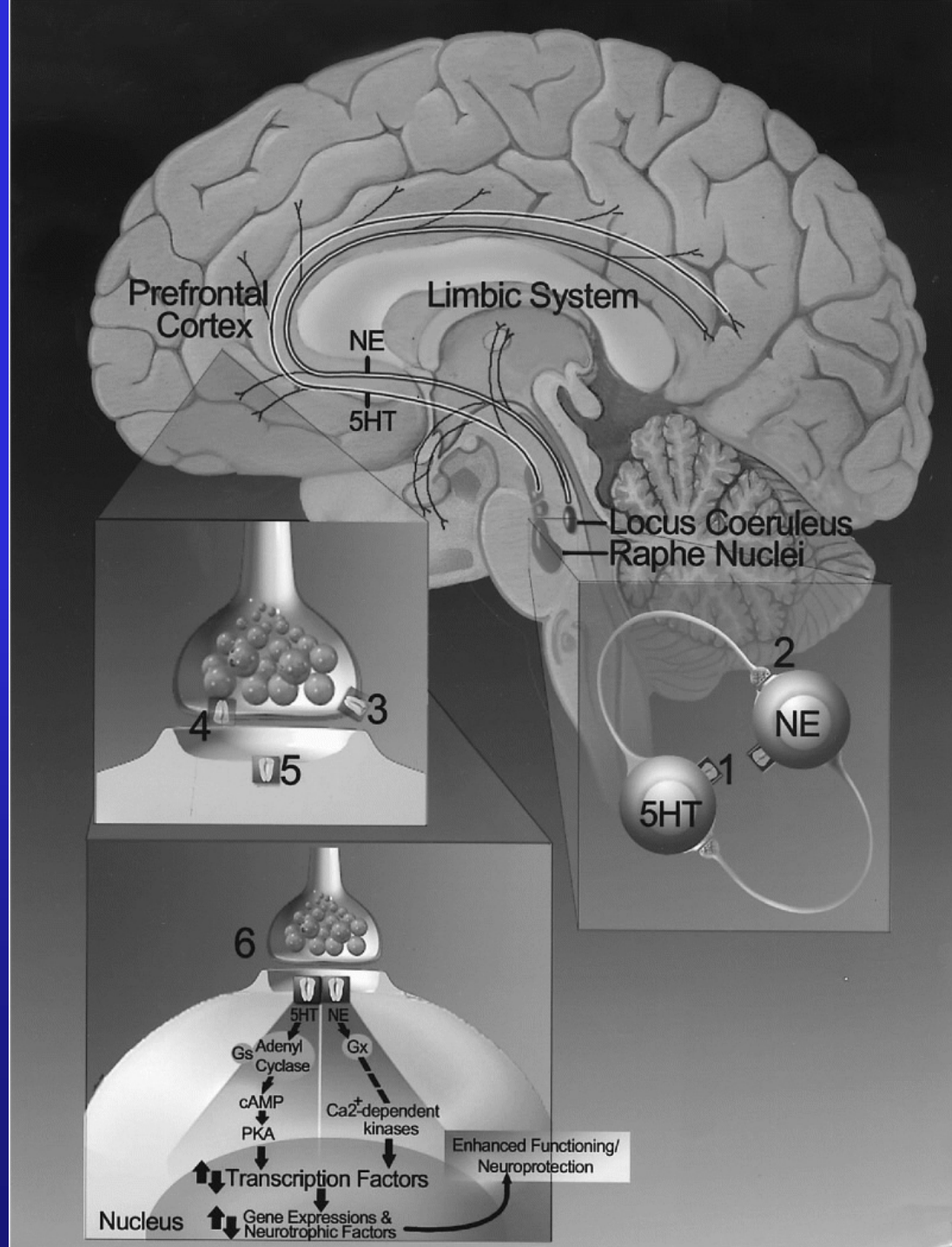
Effects of SSRI-treatment on synaptic efficacy






Gyrus cinguli
Septum
Basalganglien
Fornix
Thalamus
präfrontaler Cortex
Hypothalamus
Hirnanhangdrüse (Hypophyse)
Mandelkern (Amygdala)
Hippocampus
Raphe-Kerne
Blauer Kern (Locus coeruleus)
CAROL DONNER

Interactions of noradrenergic and serotonergic neurotransmission



„Mono-Amine“-Hypothesis of Affective Disorders

- Depressive symptoms are due to a pathological low catecholaminergic and/or serotonergic neurotrans-mission, manic symptoms to a pathologically increased neurotransmission via these pathways.

Empirical Basis:

- (Almost) all antidepressants increase the concentration of monoamines in the synaptic cleft.
- Agents that decrease aminergic neurotransmission (e.g. reserpin) may induce depressive symptoms, agents that increase aminergic neurotransmission (e.g. amphetamine) may induce mania-like symptoms.

Methods for Depletion of Neurotransmitters in the Brain

- α-Methylparatyrosin (AMPT) (Inhibition of tyrosine-hydroxylase und thus inhibition of noradrenaline and dopamine synthesis)
- Tryptophan-depleted diet + TRP-free aminoacid-drink (Depletion of Trp, inhibition of serotonine synthesis)

Effects of Neurotransmitter-Depletion-Studies

(Review: Delgado & Moreno 2000)

Subjects	5HT-Depletion	Catecholamine-Depletion
healthy	--	+/-
previous episode of depresssion, remitted without medication	+++	+++
depressive, no medication	--	--
remitted with SSRI	++++	+
remitted with NRI	+	++++
remitted with NaSSa	++++	++++

Mechanism of Action of Antidepressants (AD) -Implications for Pathophysiology-

- Effects of AD on neurotransmitters are rapid, but antidepressant action is delayed by 7-14 d

  $\Rightarrow$ downstream effects are important!

- Reversal by neurotransmitter-depletion of AD-induced remission is specific for the type of AD used. No effect in healthy controls or acutely depressive patients!

  $\Rightarrow$ AD do not correct deficiency in monoamines but act via compensating downstream dysfunctions!

Aminergic-Cholinergic Dysbalance-Hypothesis of Affective Disorders

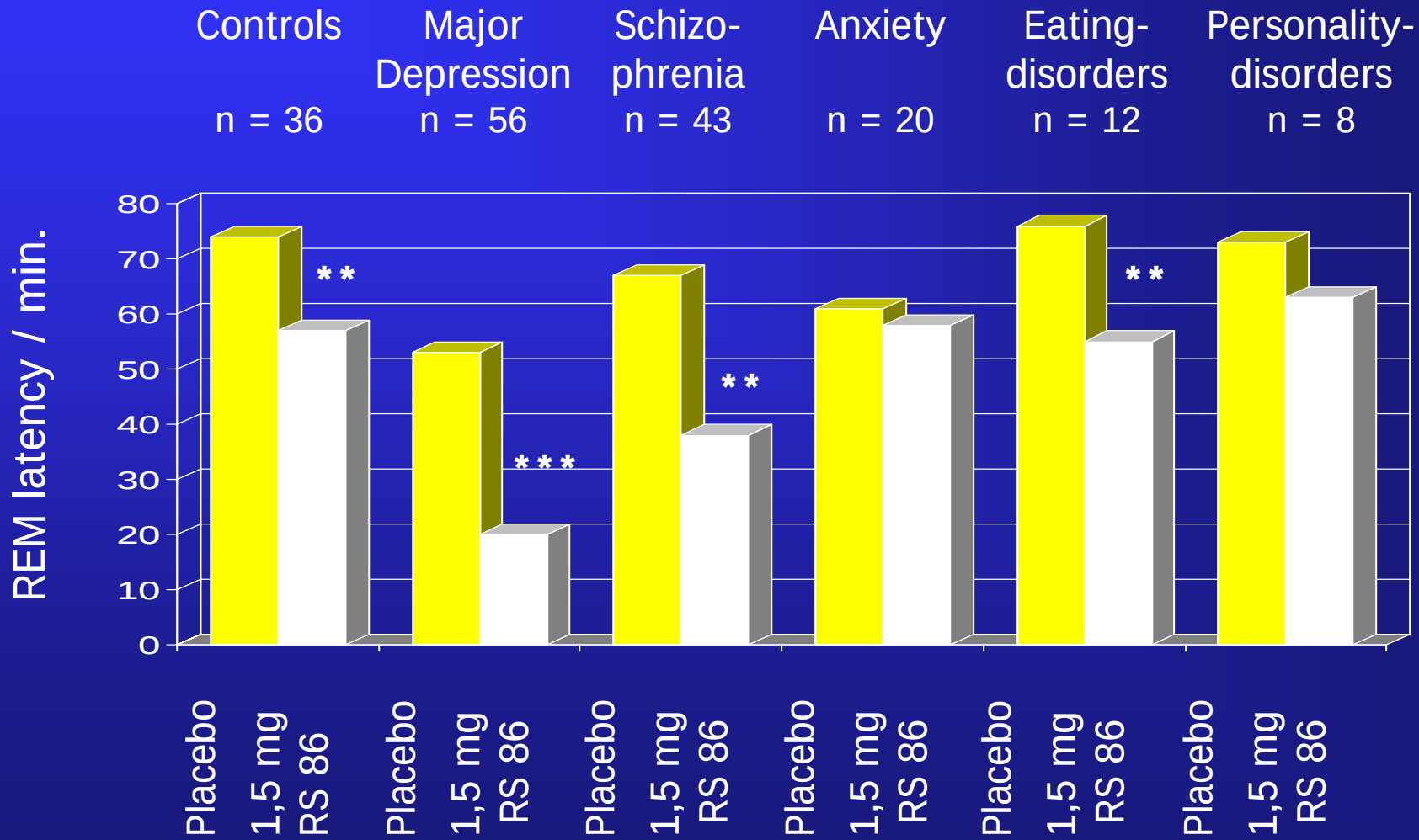
- Preponderance of aminergic over cholinergic neurotransmission leads to manic symptoms, preponderance of cholinergic over aminergic neurotransmission to depressive symptoms.
- Empirical Basis:

  -Effects of antidepressants on monoamines

  -Depressiogenic effect of physostigmin

  -Increased sensitivity of REM-sleep to cholinergic stimulation in depressive patients

Impact of RS 86 in psychopathology I



** p < 0.01 in comparison to placebo / *** p < 0.001 in comparison to placebo

Neurobiological Alterations in Affective Disorders - Sleep-Disturbances-

- Decreased slow-wave (Delta) sleep
- Increased REM-sleep pressure
- Increased sensitivity of REM-sleep to cholinergic stimulation (due to alterations of receptor sensitivity?)
- Increased cerebral glucose-metabolism (CGM) in ant. cingulate (normalized by sleep deprivation)

Other Treatment Options
-Implications for Pathophysiology-

- Sleep Deprivation (SD):
  - transitory antidepressive, triggers mania!
  - Increases Delta-Power (correlation with clinical antidepressant response?)
  - Reduces CGM: correlates with antidepressant response to SD (Wu et al 1992, 1999; Ebert et al 1994; Ho et al 1996)

Other Treatment Options
-Implications for Pathophysiology-

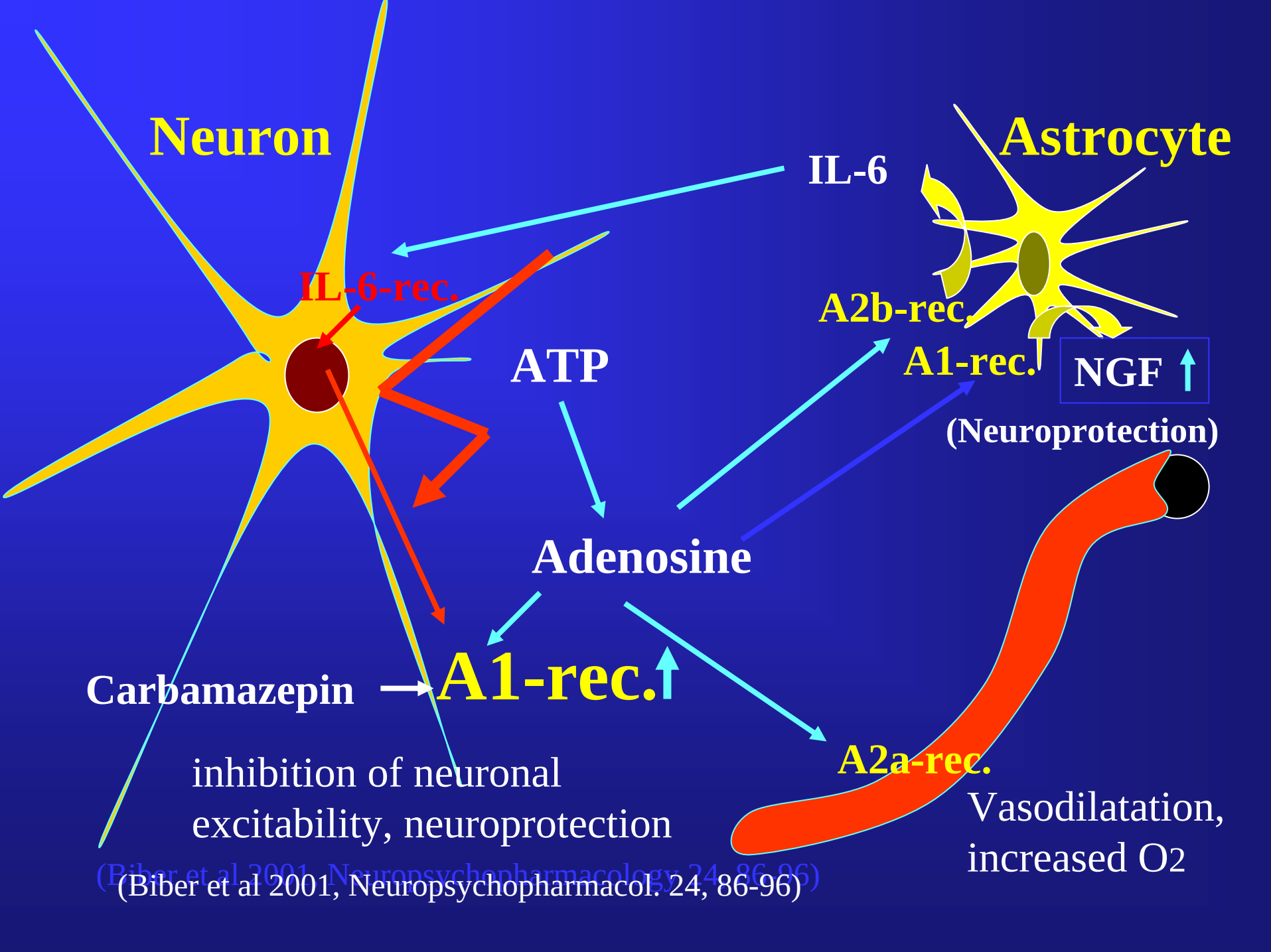
- Electroconvulsive Therapy (ECT):
  - Very effective antidepressant and antimanic
  - Increase of Delta-Power after ECT correlates with the response to ECT (Sackheim et al 1996)
  - Reduction of CGM after ECT correlates with response to ECT (Nobler et al 1994)

Indicators for enhanced Adenosine A_1-Receptor-Activation in the Brain

- Increase in EEG Delta-Power (Benington et al 1995; Landolt et al 1995)
- Reduction of Cerebral Glucose Metabolismus (Ho et al 1996)

Function of adenosine in the brain

- Inhibitory neuromodulator
- Signalizes und antagonizes O_2 -Deficit:
  - A1-Receptors (inhibition of neuronal Excitability)
  - A2a-Receptors (vasodilatation)
  - A2b-Receptors (Glycogenolysis in astroglia)
- Antiepileptic a. neuroprotective effects

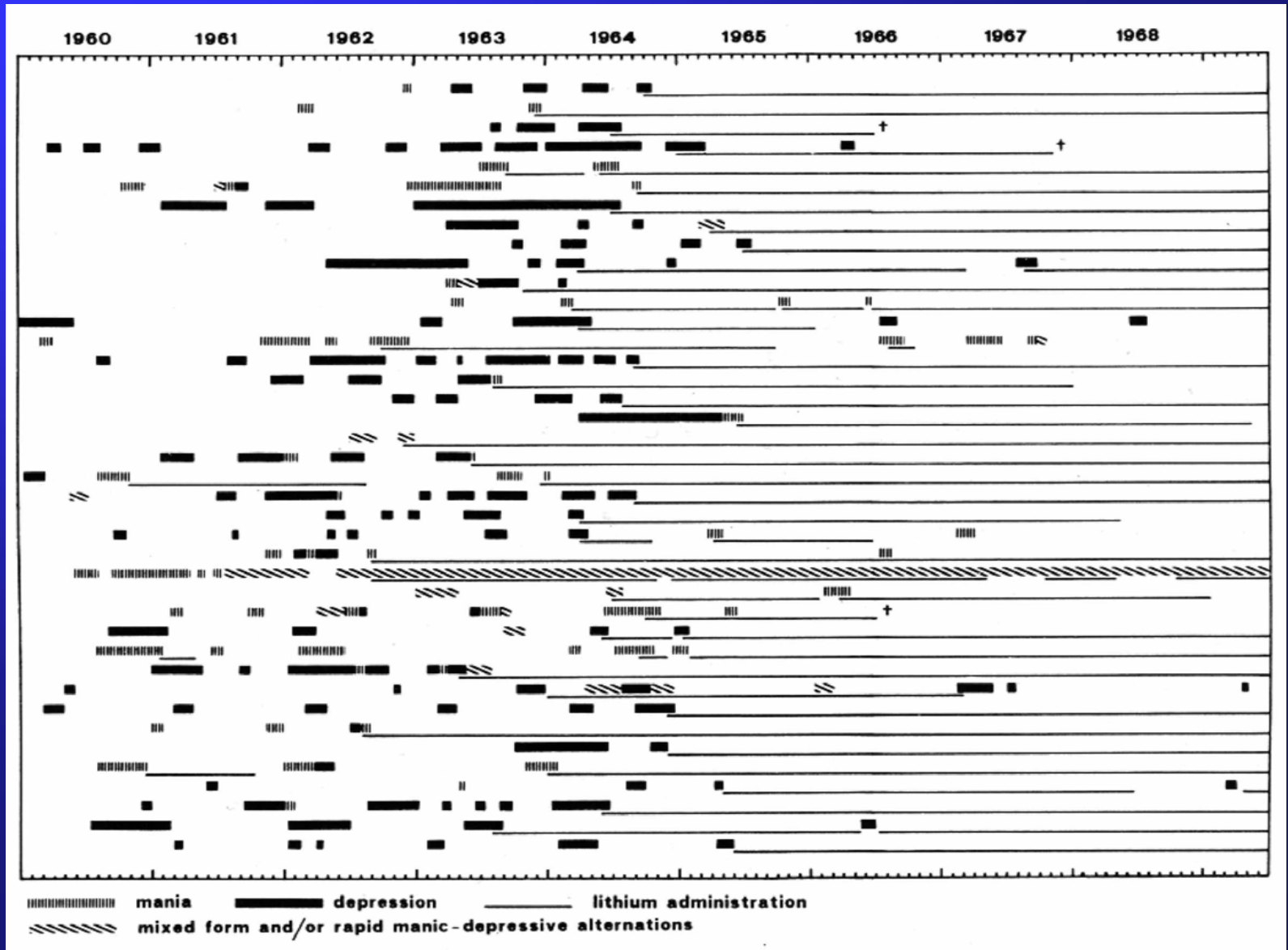

Neuron
Astrocyte
IL-6
IL-6-rec.
A2b-rec.
A1-rec.
NGF
(Neuroprotection)
ATP
Adenosine
Carbamazepin
A1-rec.
A2a-rec.
inhibition of neuronal
excitability, neuroprotection
Vasodilatation,
increased O2
(Biber et al 2001, Neuropsychopharmacol. 24, 86-96)

The antidepressive effects of sleep deprivation, ECT and carbamazepine may be due to upregulation of adenosin A1-receptors in the brain and consequent inhibition of cholinergic neurotransmission

Antibipolar Medications („Mood Stabilizer“)

- Lithium salts
- Carbamazepine
- Valproate
- Lamotrigine
- other new Antiepileptics (?)
- „atypical“Antipsychotics(?)

Early studies of the prophylactic effect of lithium therapy (Baastrup & Schou 1967; Schou 1973)

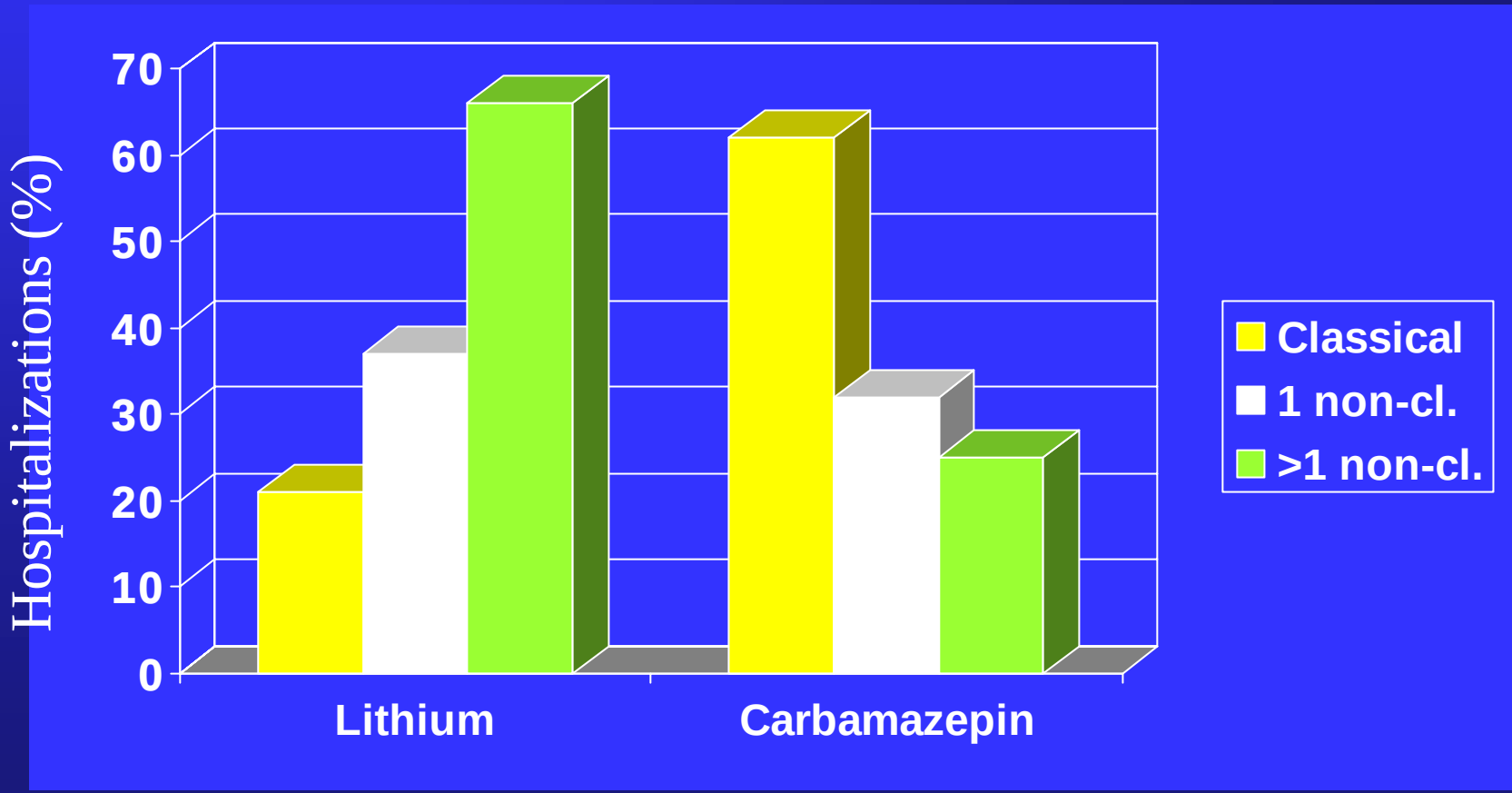


Differential Indications of Mood Stabilizer?

- „Typical“ Euphoric Mania
- „Atypical“ Dysphoric Mania
- Mixed States
- „Rapid Cycling“
- Psychotic Symptoms
- „Bipolar Depression“
- Continuation and Maintenance Therapy

Hospitalizations (%) during maintenance treatment with lithium or carbamazepine

(Greil et al 1998)

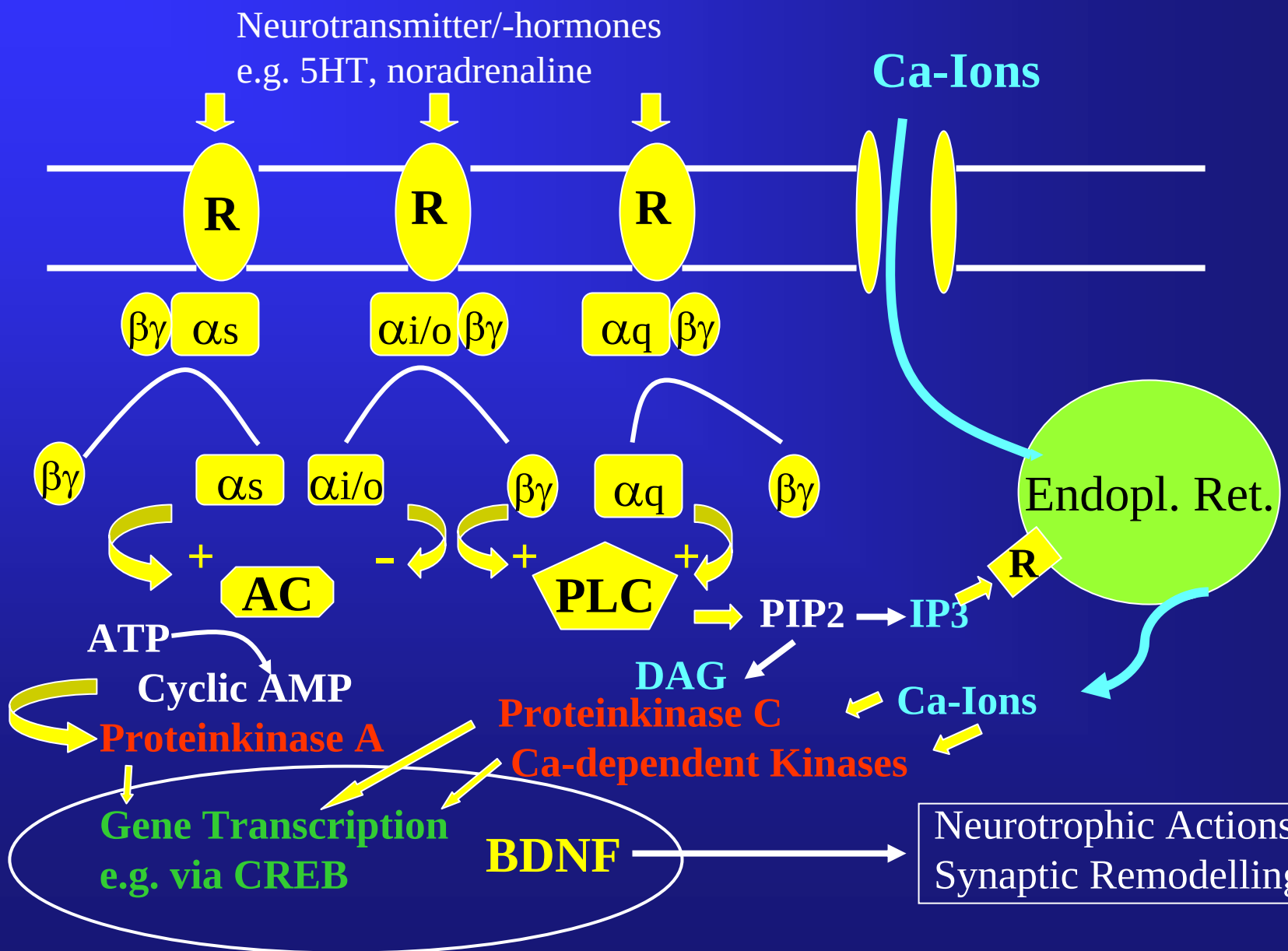


Cellular Signaling Pathways: Arguments for their Role in Bipolar Disorder

(modified from Manji & Lenox 2000, Biol. Psychiatry 48, 518-530)

- Regulate multiple neurotransmitter systems and their functional balance
- Dynamic regulation of signaling networks forms the basis for higher order brain function (mood and cognition)
- Critical role in fine-tuning of signals
- Critical role in neuroplastic events and cellular resiliency
- Major targets for actions of hormones (thyroid, steroids)
- Ubiquitously expressed, but brain regional dysregulation and circumscribed symptomatology is possible.
- Targets of mood stabilizers

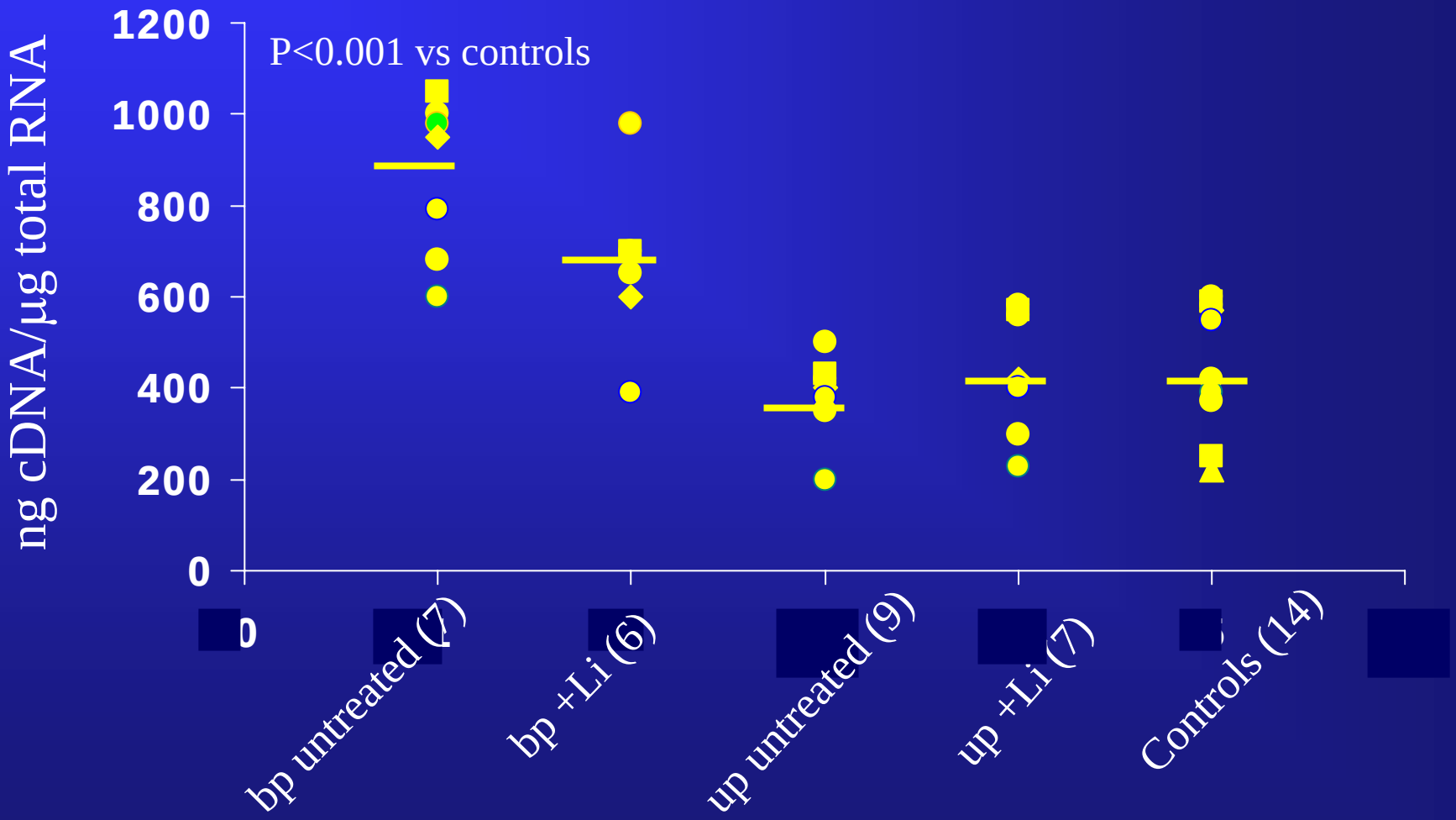
Signaltransduction Systems



G-Proteins in Bipolar Disorder and in the Mechanism of Action of Lithium

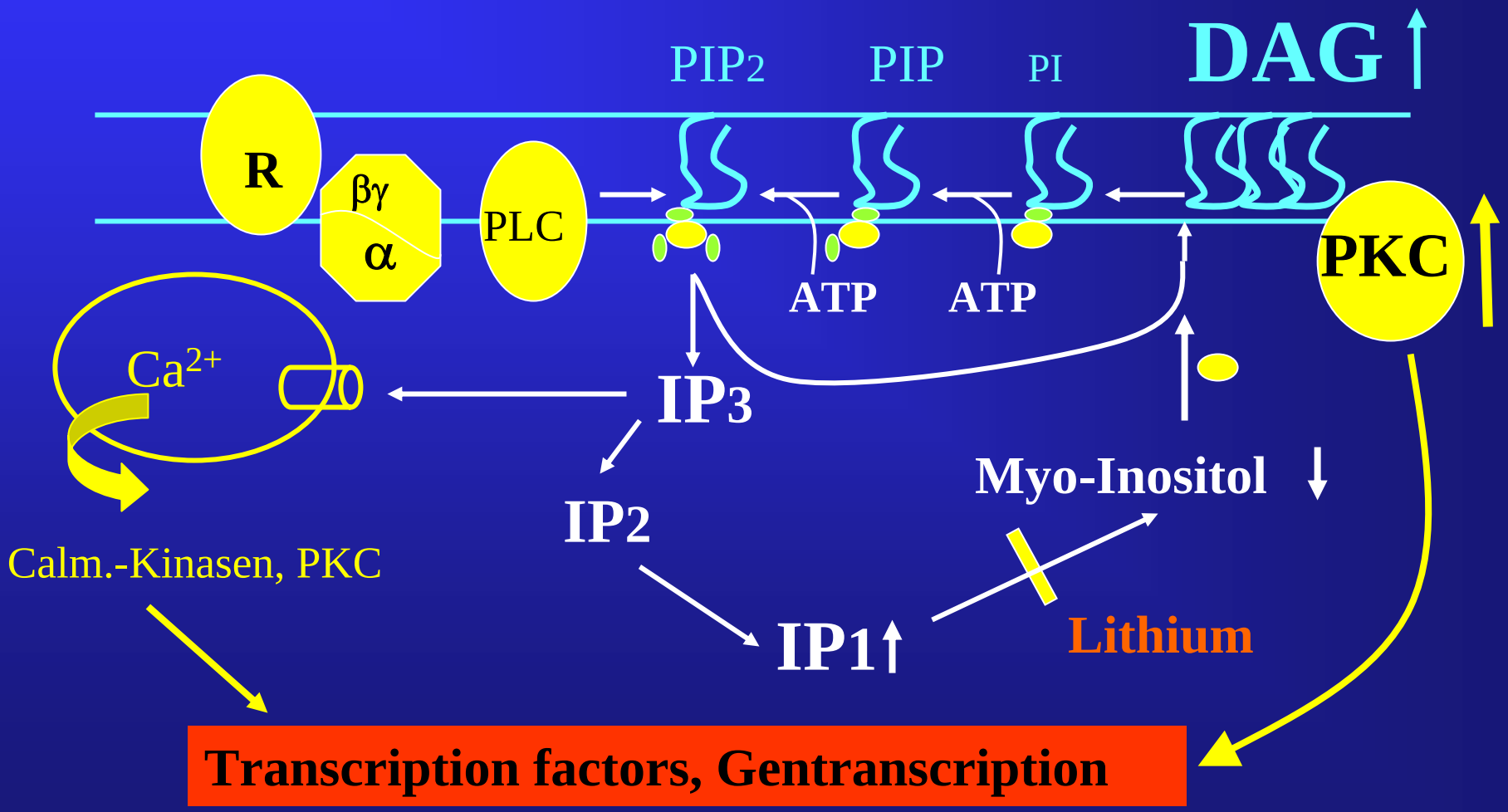
- Increase of $G\alpha_s$-protein in post-mortem brain and peripheral blood cells of bipolar patients (Young et al 1993, 1994; Manji et al 1995; Mitchell et al 1997)
- Various, sometimes localized effects of chronic lithium on mRNA expression of α-subunits, e.g. downregulation of α_s and α_i (Lenox et al 1998; Jacobsen et al 1998)

Content of Gαs-mRNA in neutrophils of patients and controls



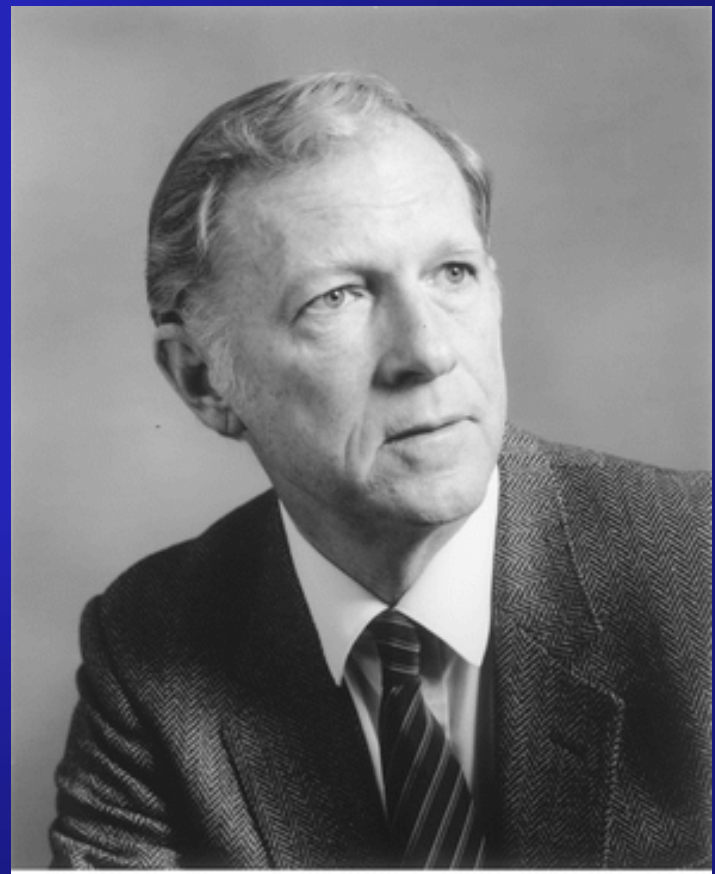
Lithium Ions	Valproate	Carbamazepine
Neurotr.-Metabolis.	?	?
Receptor Sensitivity	?	?
G-Proteins	?	?
IP1-Phosphatase	IP1-Synthase	--
--	--	Adenosine-Recept.
GSK-3	GSK-3	?
--	Na-channels,	Na-channels,
--	Ca-channels	Ca-channels
--	GABA	GABA-B
Adenylylcyclase	--	Adenylylcyclase
Proteinkinase C	Proteinkinase C	--
Inositoltransport	Inositoltransport	Inositoltrans
β-Catenin, AP-1	β-Catenin, AP-1	port
Neuroprotection	Neuroprotection	I.E. Genes ?
		Neuroprotection?

PI-Signaltransduction - Effect of Lithium



The Inositol-Depletion-Hypothesis
(Berridge et al 1989)

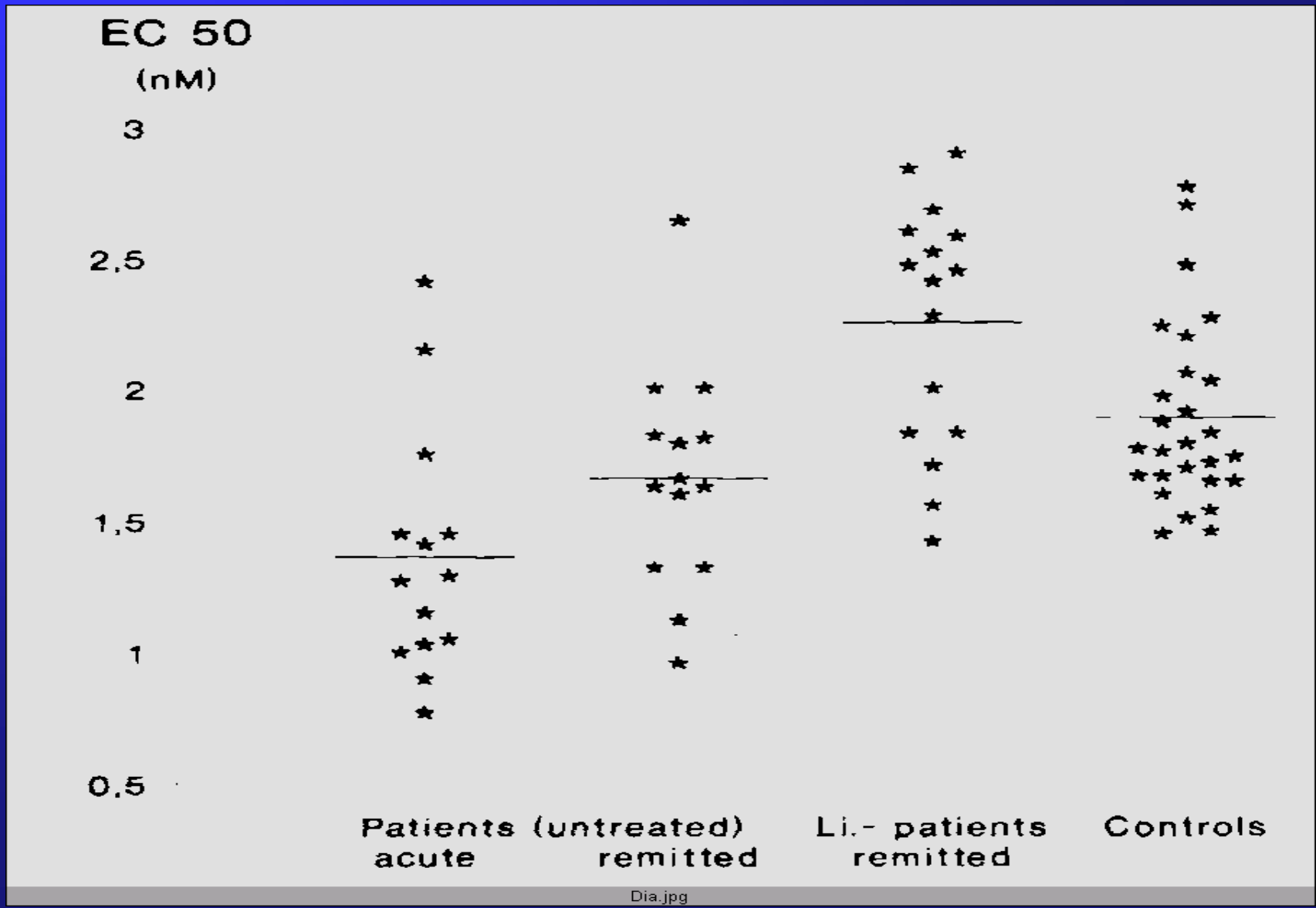
- Li inhibits InositolmonophosphataseInositolmonophosphatase
- ⇒ Depletion of sensitive brain areas of inositol
- ⇒ Inhibition of the PI-second messenger-system in „pathologically overactivated neural circuits“.



Effects of Lithium on Myo-Inositol Content in the Brain

- Acute treatment of rats with high doses: appr. 35% reduction in inositol content (Sherman et al 1981, 1985).
- Chronic treatment of rats with „therapeutical“ doses: Reduction (20%) limited to hypothalamus (Lubrich et al 1997).
- Therapeutic treatment of manic-depressive patients: Reduced inositol content in frontal lobe after 5-7 d (Moore et al 1999).

Ca-Response to fMLP in Neutrophils of Patients and Controls



PI-Signalling in Peripheral Cells of Manic-Depressive Patients: Effect of Lithium Therapy

- Increased activity of the PI-system in platelets and neutrophils of depressive or manic patients (state marker).
- Decreased activity of the PI-system in neutrophils under chronic lithium therapy.

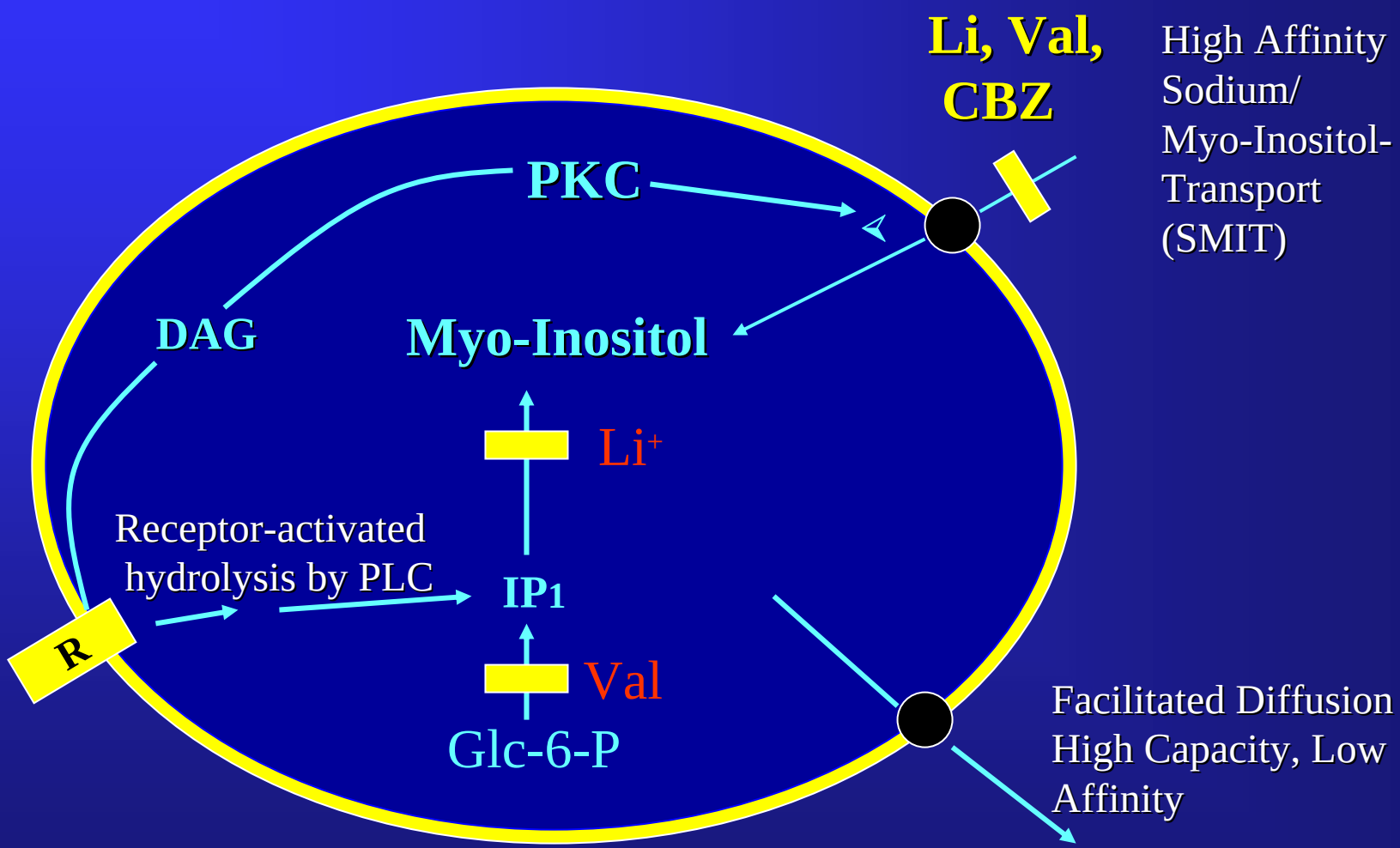
Effects of Lithium on PI-signalling in Brain Slices

- Inhibition of activity in brain slices from species (rats, mice) which readily deplete of inositol.
- Potentiation of activity in species (guinea pig, primate) relatively resistent to inositol depletion (Dixon et al 1992).

Later Modifications of the Inositol Depletion Hypothesis

- Lithiums effects on PI-signalling may differ in various brain areas and even different brain cells
- Inositol depletion is only the initial trigger of more downstream effects such as:
  - Activation and later downregulation of PKC-isoenzymes
  - Modulation of gene transcription

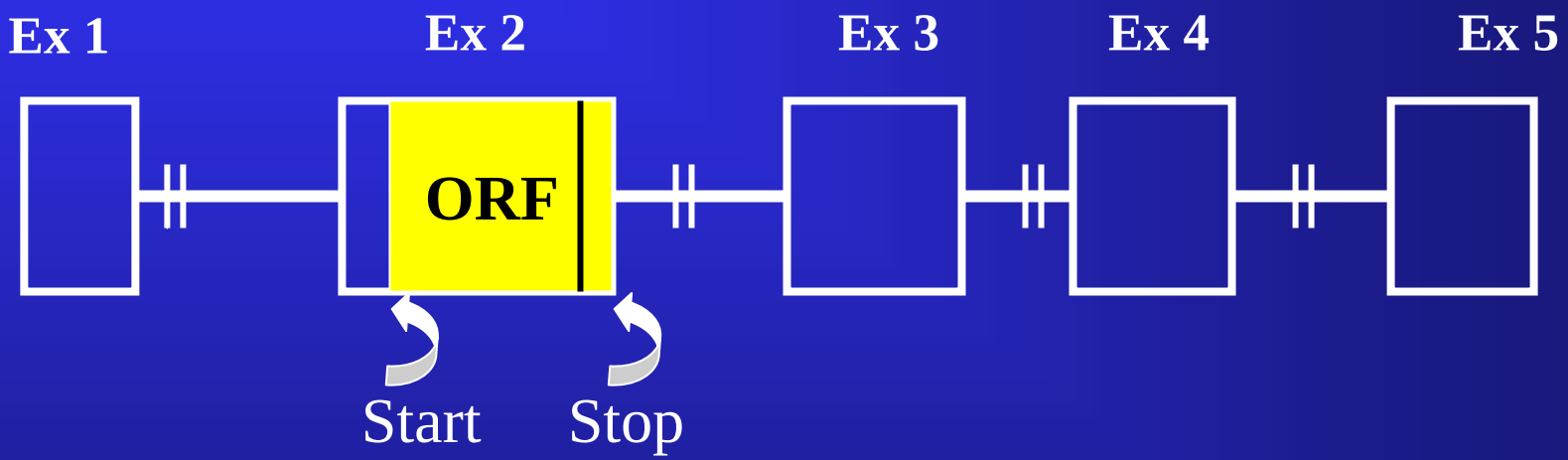
Factors Determining Myo-Inositol Levels in Brain Cells



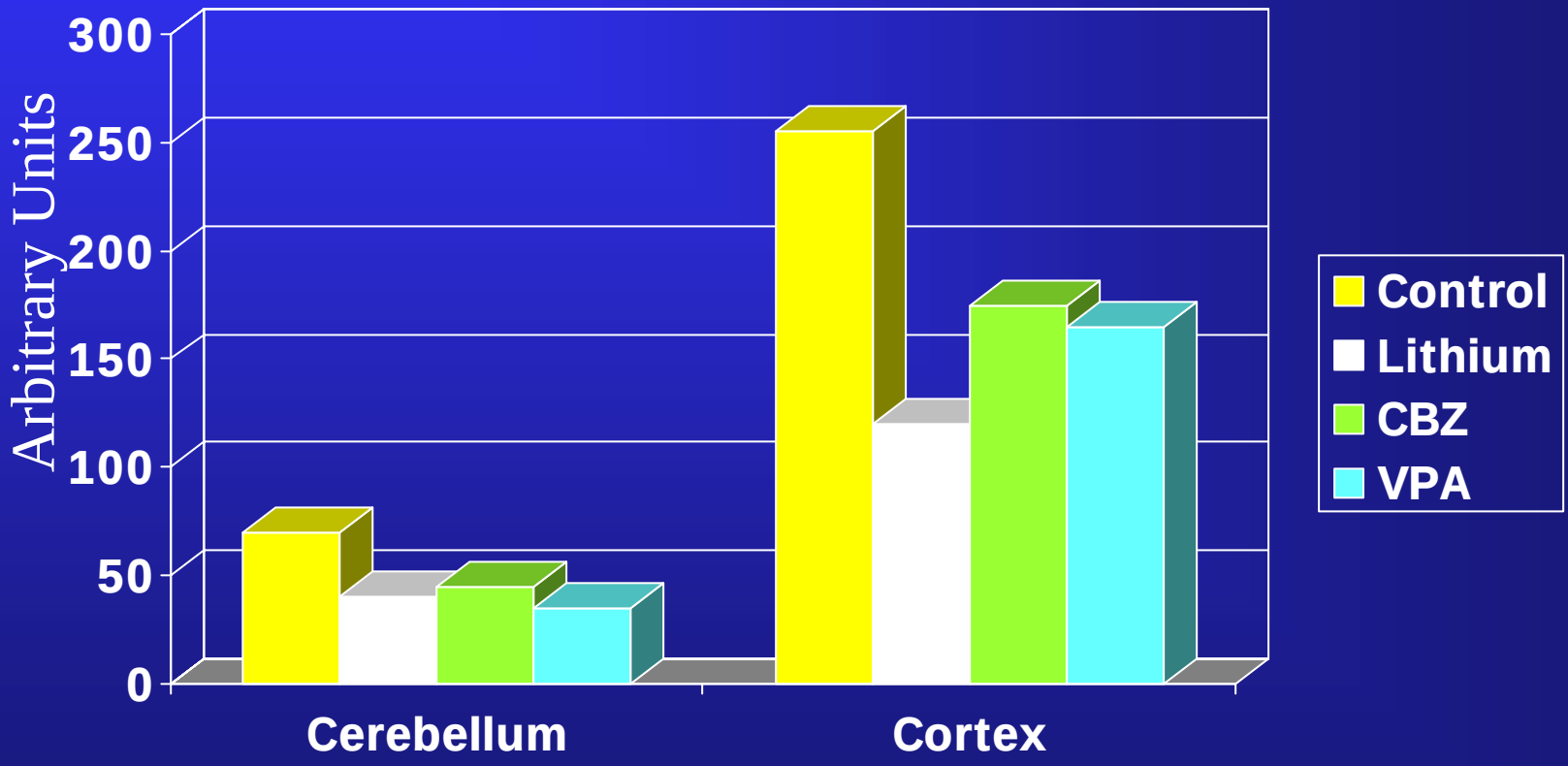
The High Affinity Sodium/Myo-Inositol-Co-Transporter (SMIT)

- The human gene (SCL5A3) is localized on chromosome 21q22.1
- Atypical gene structure: $\geq$ 5 exons, intronfree ORF in the unusual large exon 2.
- Alternative splicing (Porcellati et al 1999).
- Differential expression and regulation in distinct areas of the brain (Yamashita et al 1998; Nonaka et al 1999; Lubrich et al 2000).

Structure of SLC5A3



SMIT-mRNA Expression in Astrocytes after Chronic Treatment (14 d) with Mood Stabilizers



Lubrich & van Calker 1999, Neuropsychopharmacology 21, 519

Effects of Mood Stabilizer on neurons in Cell Culture

(Williams et al (2002) A common mechanismof action for three mood-stabilizing drugs. Nature 417, 292-295)

All three established mood stabilizer (lithium, valproat, carbamazepin) alter the growth of axons in cell culture. These effects are counteracted by yo-inositol.

⇨ Inositol depletion: Important common mechanism of action of mood stabilizer

⇨ Most likely cause of inositol depletion: Inhibition of SMIT?

Determination of Myo-Inositol by MRS - in Brain Areas of Bipolar Patients

- Untreated, acutely manic adolescent patients: Increased content of myo-inositol in anterior cingulum and frontal cortex (Davanzo et al 2001, 2003; Cecil et al 2003)
- Adult patients: No difference as compared to controls (Moore et al 2000, Cecil et al 2002; Silverstone et al 2002; Dager et al 2004).
- Treatment with lithium: In bipolar patients (Moore et al 1999) decrease of the myo-inositol signal in frontal cortex.

➡ Increased content of myo-inositol in frontaler cortex/ant. cingulum in untreated patients? Reduced (and thus normalized) under therapy with mood stabilizers?

Neurotrophic Effects of Mood Stabilizers - More Evidence for Alterations in Gene Transcription

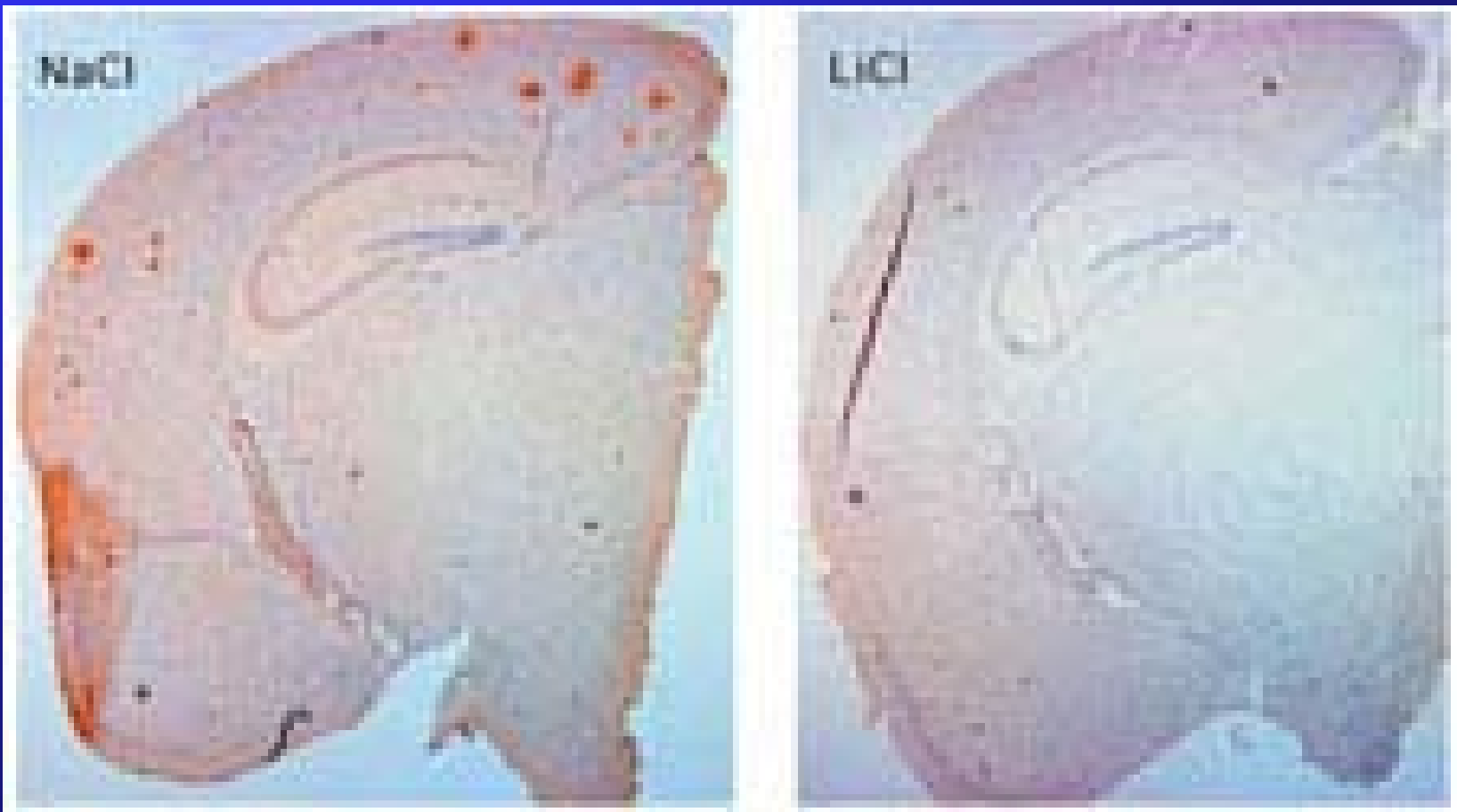
- Chronic lithium (14 d) increases hippocampal neurogenesis in mice (BrdU immunohistochemistry) (Chen et al 2000)
- Chronic (4 w) lithium or valproate increase bcl-2 immunoreactive neurons in the frontal cortex of the rat (Chen et al 1999)
- Increase in brain gray matter volume in BPD patients after 4 weeks of lithium treatment (Moore et al 2000)
- Chronic lithium therapy increases NAA in human brain (Moore et al 2000)

Neuromorphological Alterations in Bipolar Disorders

- Reduced volume of brain regions that appear to be invoved in the pathophysiology of mood disorders (e.g. hippocampus) (Review: Manji & Duman 2000)
- Reduced numbers of glia-cells in the post-mortem frontal cortex and cingulate of patients with bipolar disorder (Rajkowska et al, Biol Psychiatry in press; Ongur et al 1998, PNAS 95, 13290)

Lithium inhibits accumulation of Alzheimer's disease amyloid-β in the brain of mice that overproduce APP

(P. Klein, C. Wilson & V. Lee 2003)



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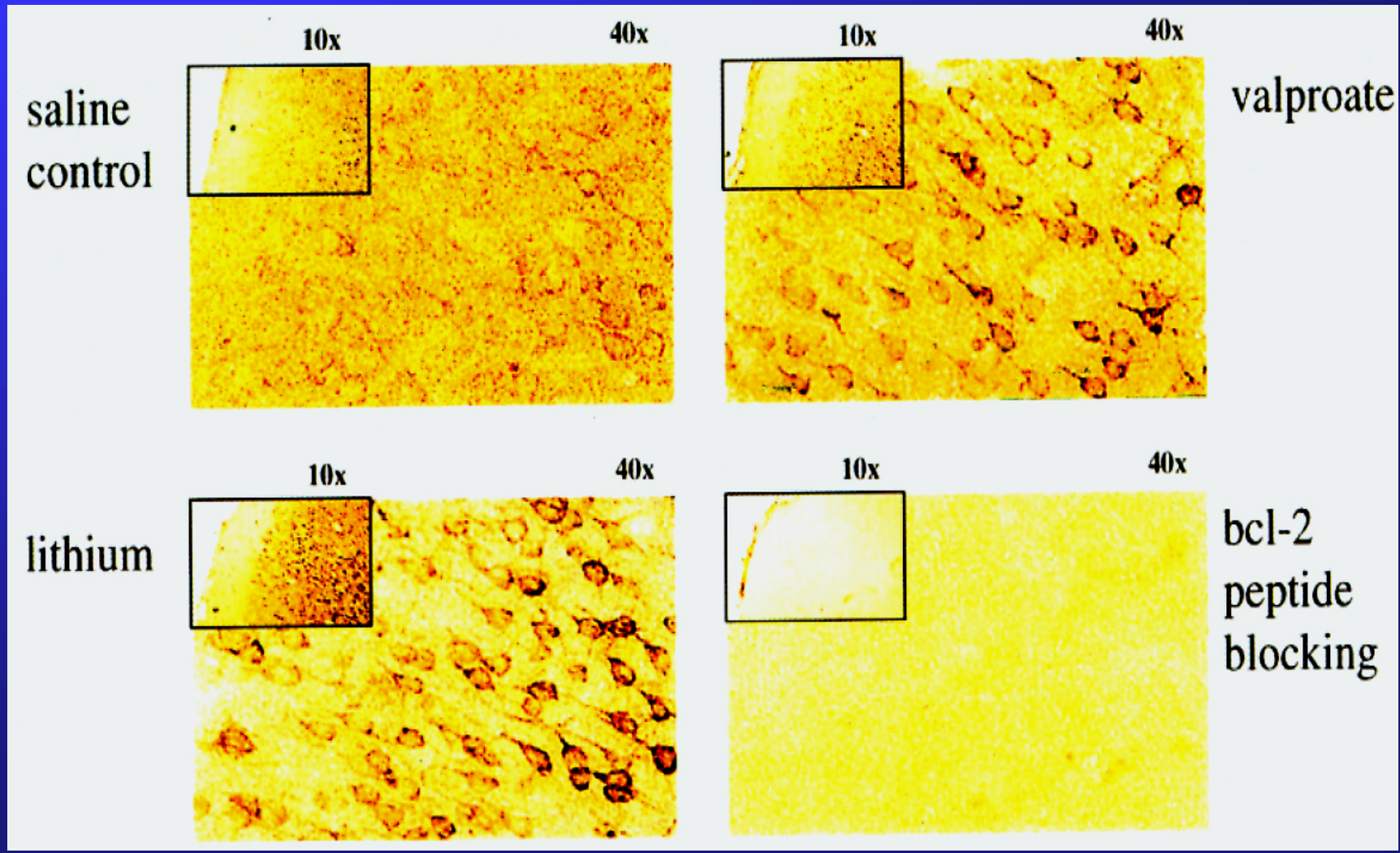
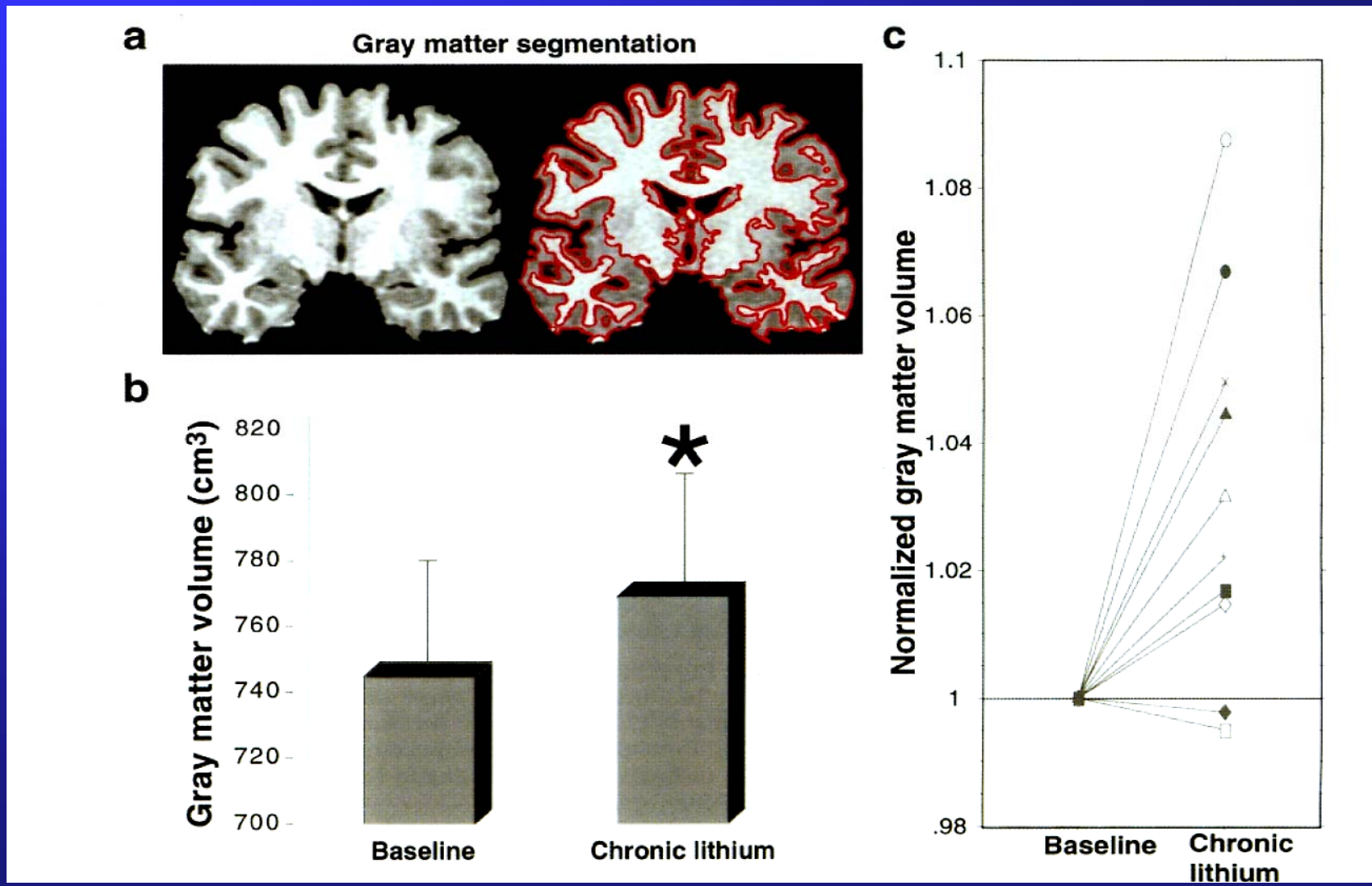


Increase in brain gray matter volume in BPD patients after 4 weeks of lithium treatment (Moore et al 2000)



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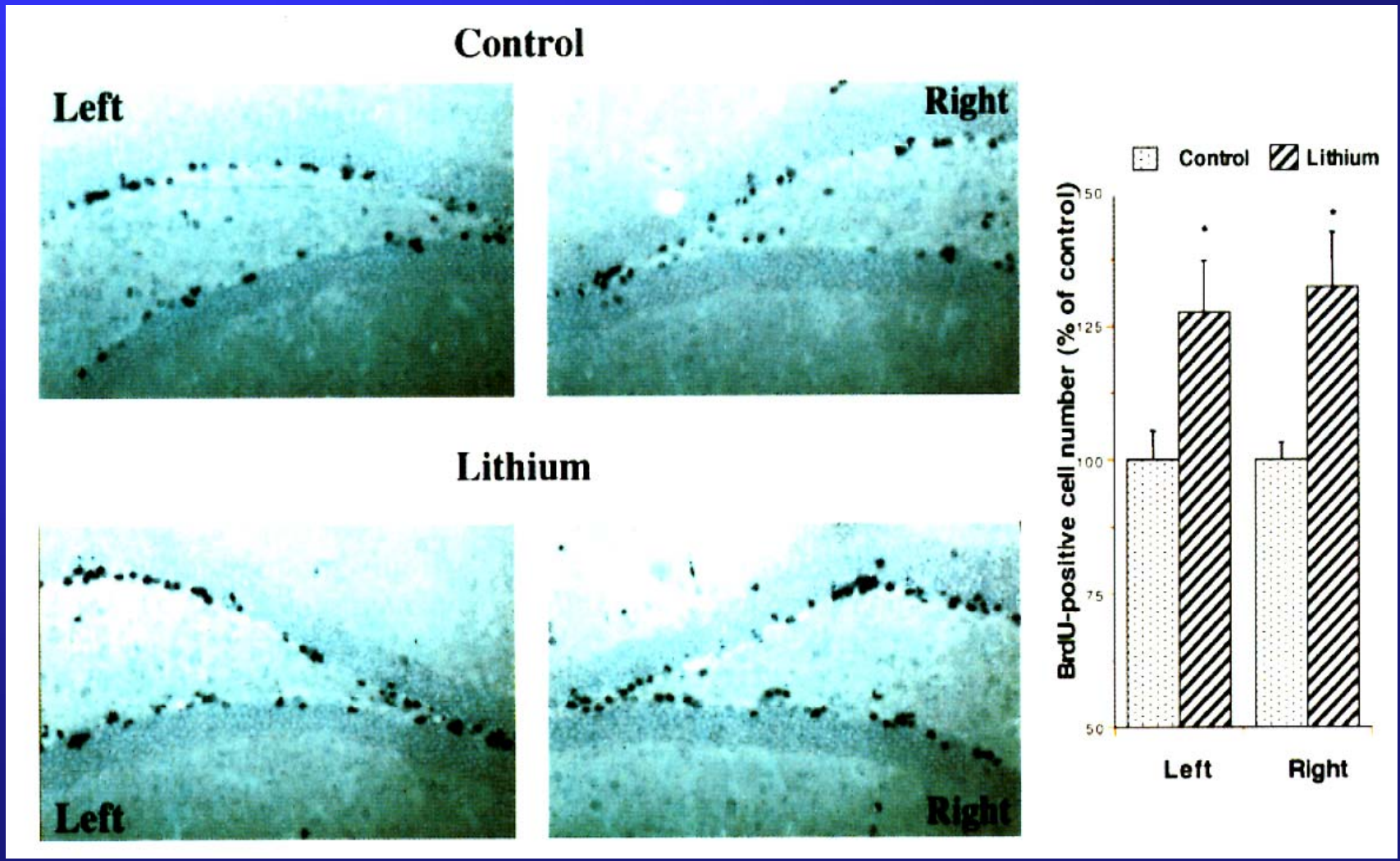
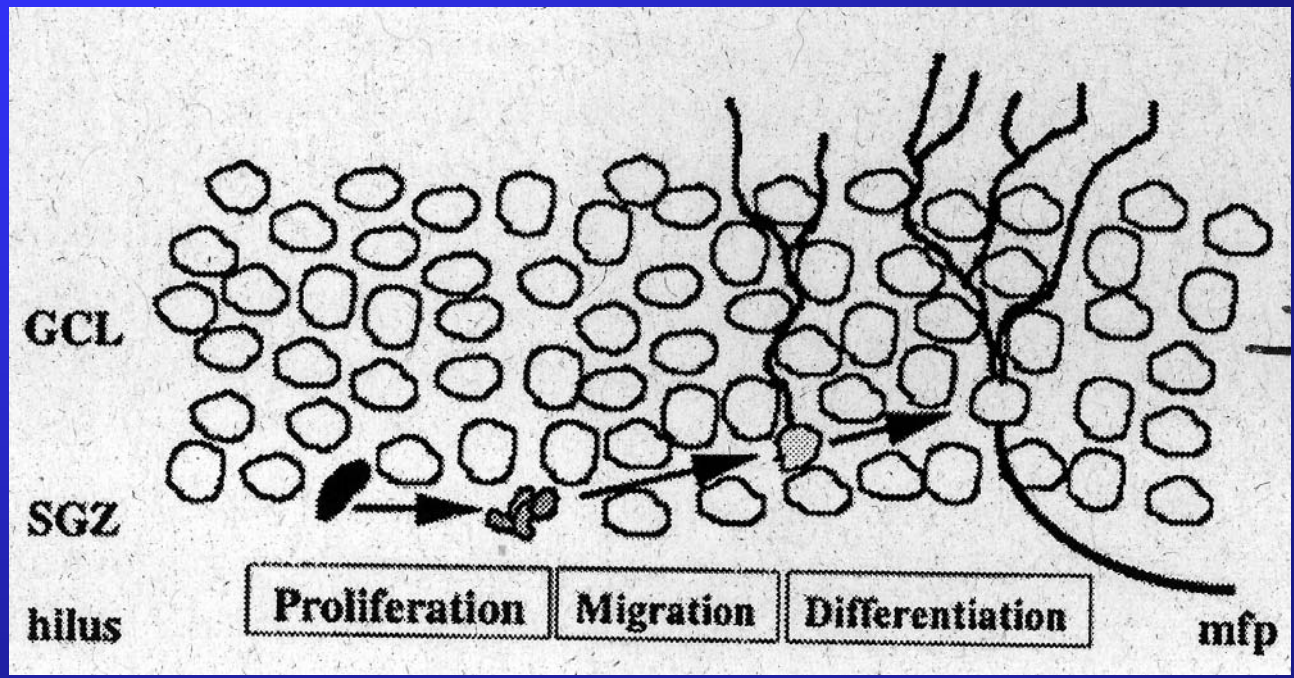


Adult Neurogenesis in the Hippocampus
(Duman et al 2001)

9000/day

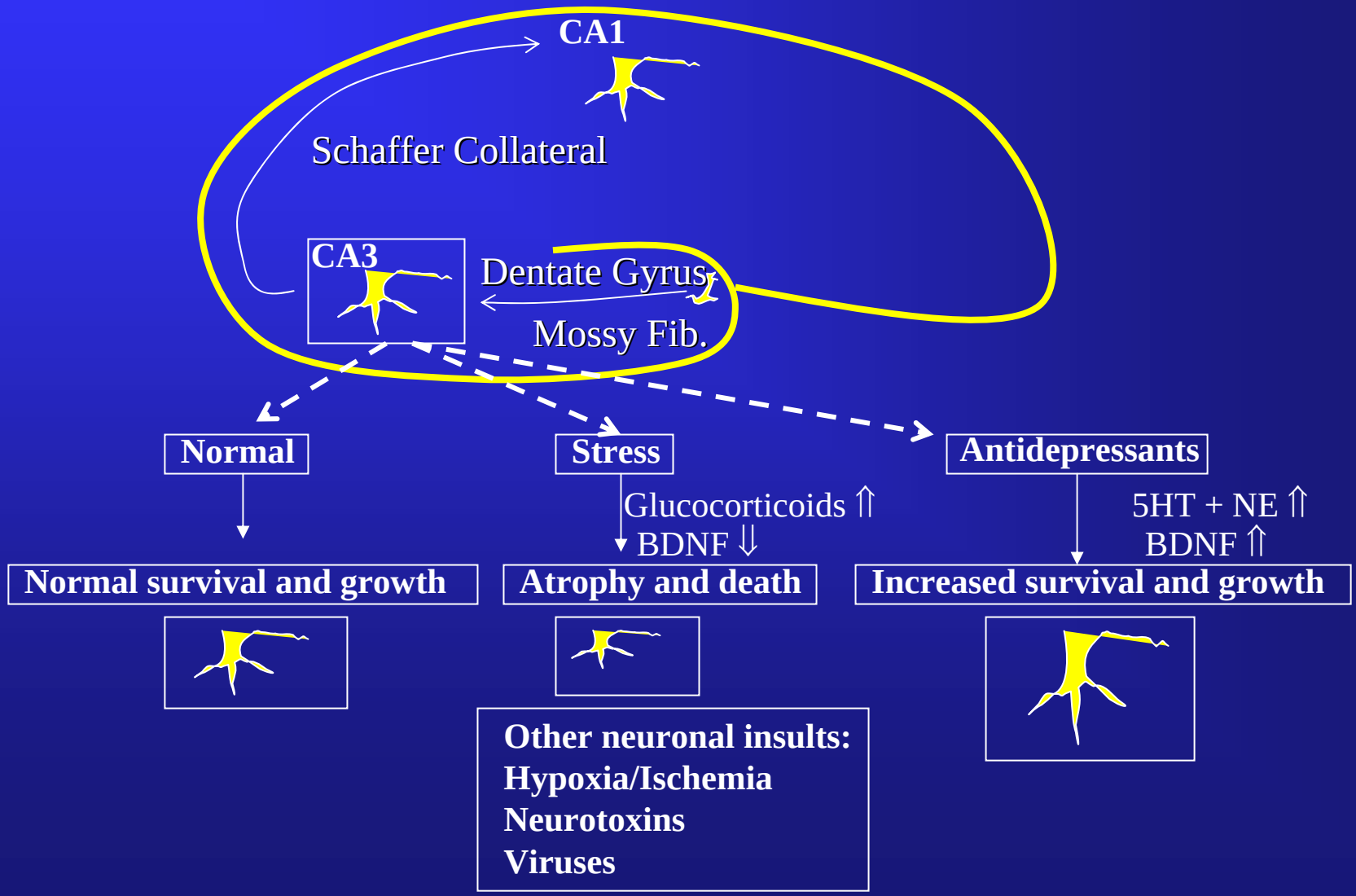


270 000/month

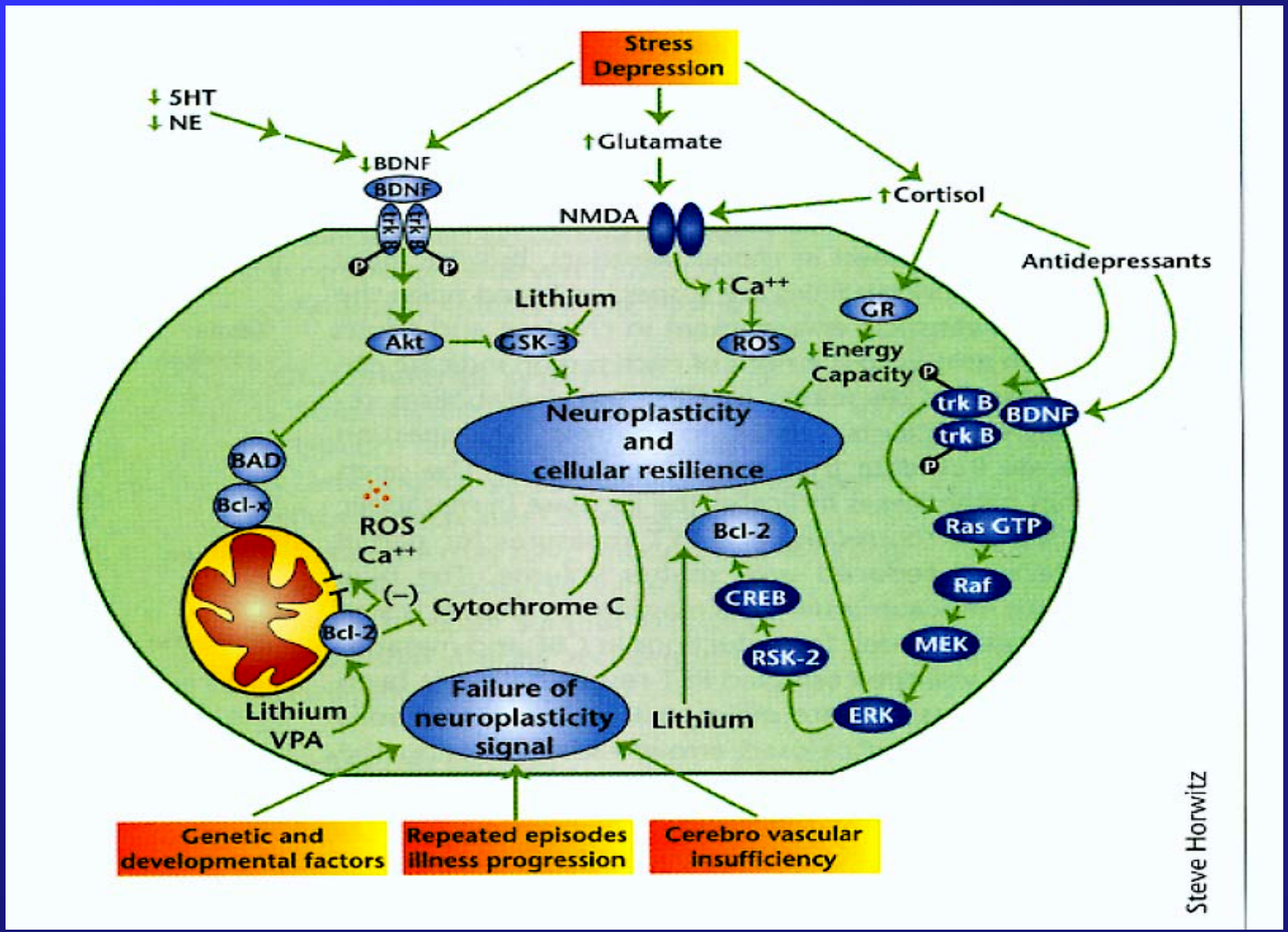
Neurogenesis is upregulated by:
stimulating environment
endurance training
learning
Estrogen
Antidepressivs
Lithium
Valproate

Neurogenesis is downregulated by
Stress
Glukocortikoids
Age
Opiates
Excitatory Aminoacids

A molecular and cellular model of depression and the action of antidepressants (Duman et al 1997)



Neuroplasticity and cellular resilience in mood disorders
(Manji et al 2000)



Summary

Abnormalities in bipolar disorder („Endophänotypes“)

- structural a. functional alterations in the brain (volumen, glia number, NAA, CBF, CGM) (state, trait or scar?)
- polysomnographic alterations, cholinergic supersensitivity (state or trait?)
- enhanced $G\alpha_s$-expression (trait)
- enhanced sensitivity of PI-signaling (trait?)
- SMIT (??)

Prospects - From Basis Science to Clinical Applications?

- Clinical trials of PKC-Inhibitors such as tamoxifen (Bebchuk et al 2000)?
- High thru-put screening for compounds that inhibit GSK-3 and/or SMIT activity and subsequent clinical trials?
- Early and agressive treatment with mood stabilizers may be necessary to prevent progression of neuromorphological alterations.

Questions

- Which alterations of sleep patterns are typically found in depression?
- How do they relate to theories of the pathophysiology of affective disorders?
- What is the principal assumption of the inositol-depletion hypothesis of lithium action?
- How are the neuromorphological findings in bipolar disorder related to potential mechanisms of action of mood stabilizers?

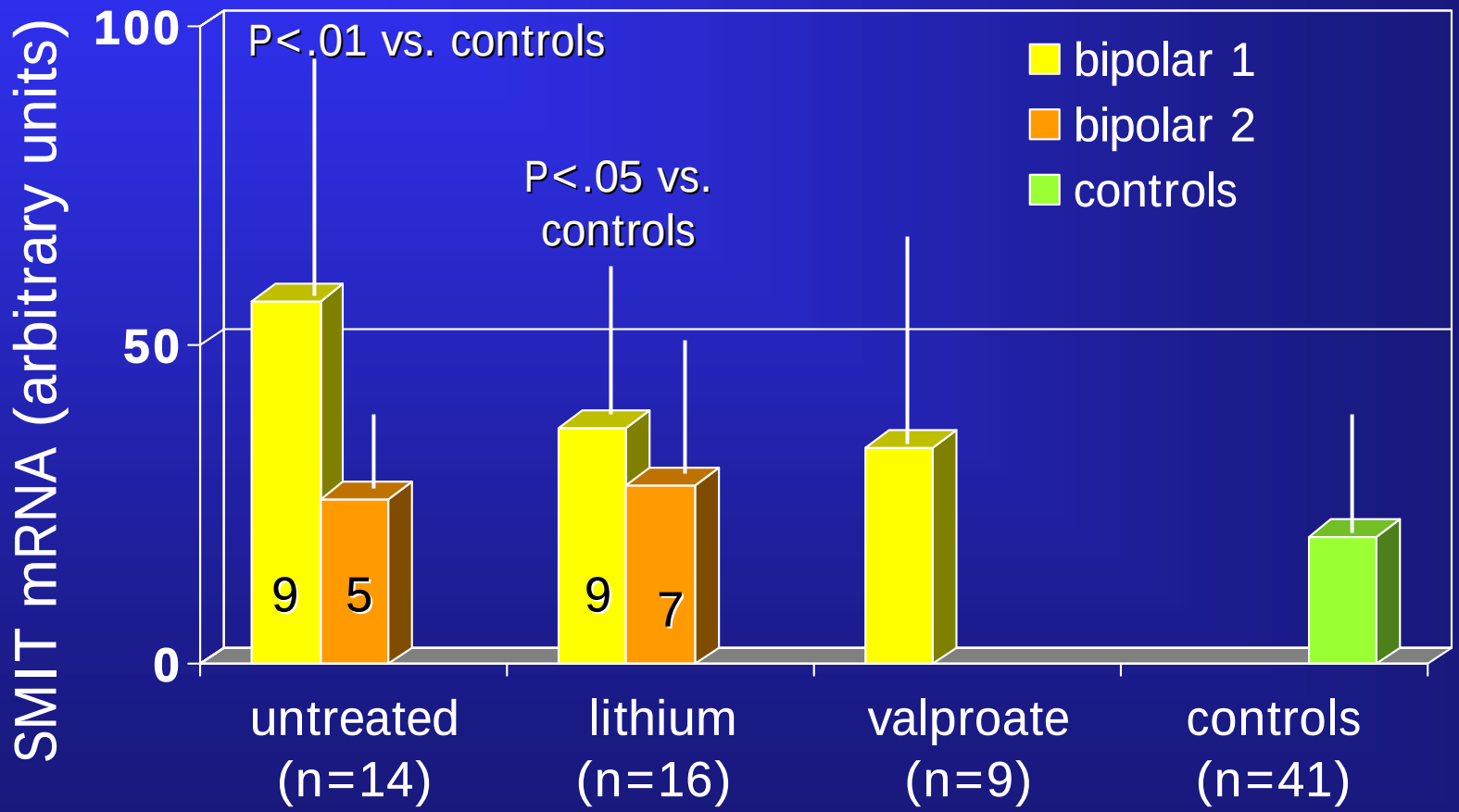
Sigmund Freud:

Bei dem innigen Zusammenhang von körperlichen und seelischen Dingen darf man vorhersehen, dass der Tag kommen wird, an dem sich Wege der Erkenntnis und Beeinflussung von der Biologie der Organe und ihrer Chemie zu dem Erscheinungsgebiet der Depression eröffnen werden. Dieser Tag scheint noch ferne, gegenwärtig sind uns diese Krankheitszustände von der medizinischen Seite her unzugänglich.

1926

$G\alpha_s$-mRNA Expression in Neutrophils of bp-Patients and Controls (Real-Time PCR)

(Willmroth et al unpublished)

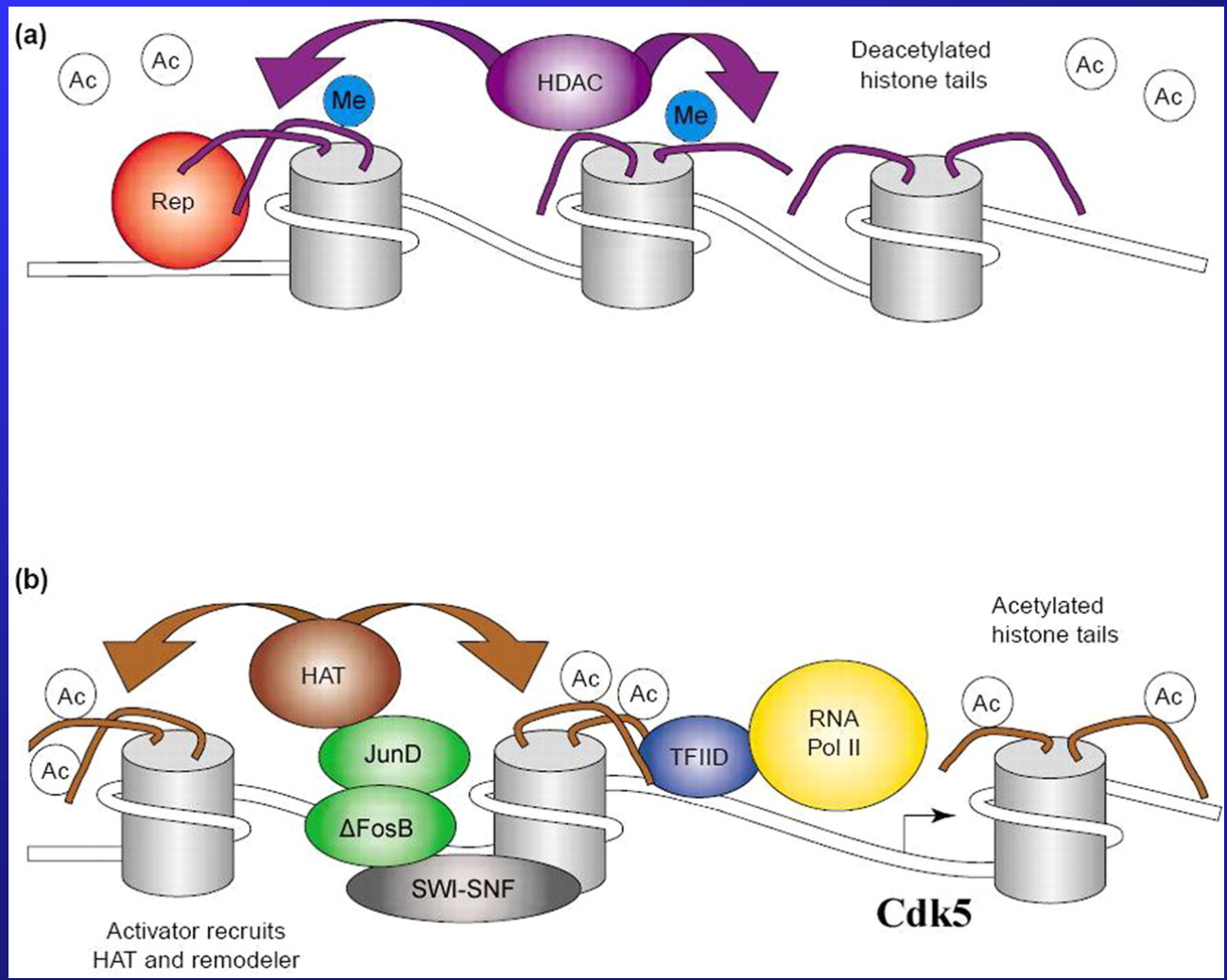


Direct Targets of Mood Stabilizers

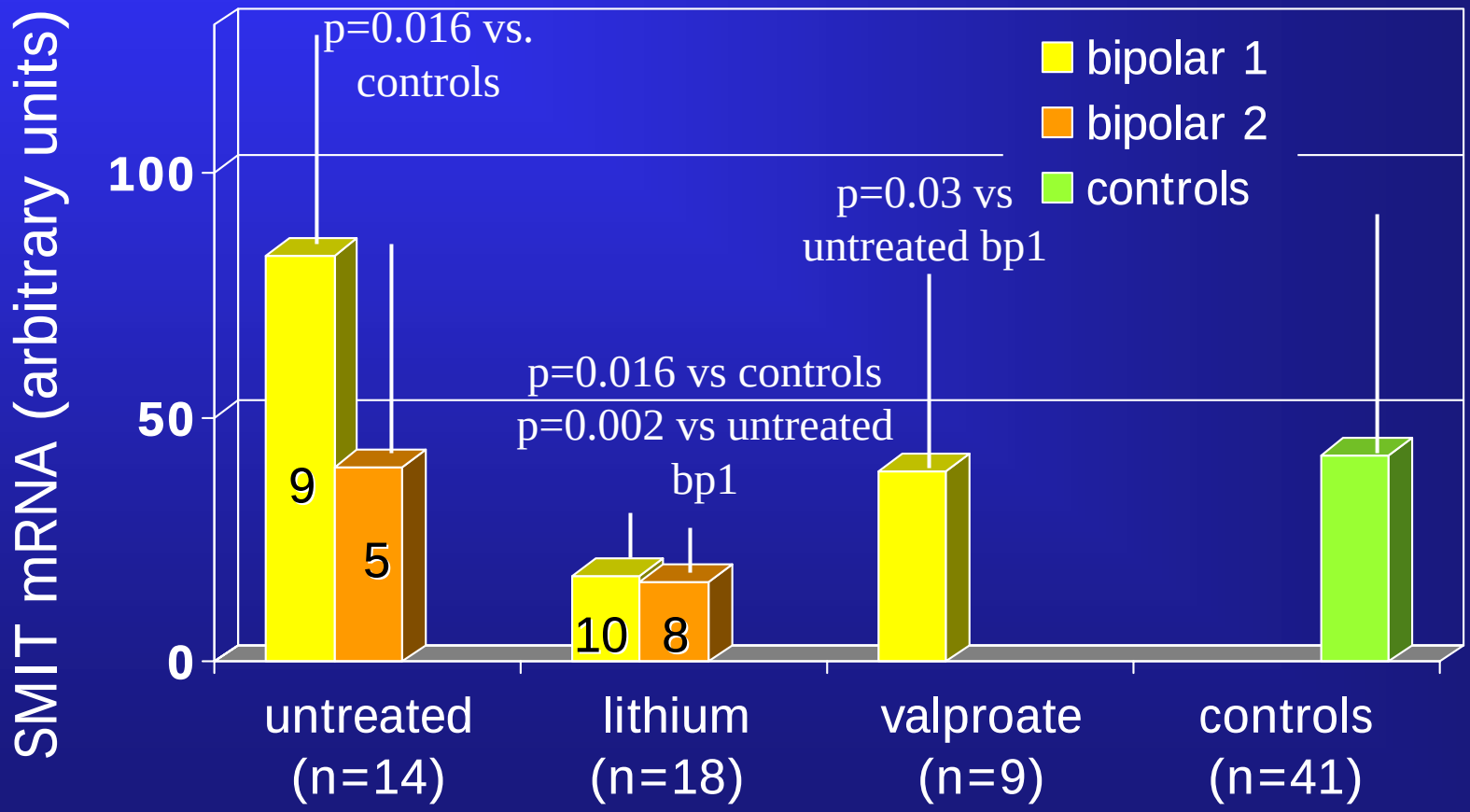
- Lithium ions: Inhibit by competition with Mg^{2+}
  - Adenylylcyclase
  - Phosphomonoesterases (IMPase, IPPase, PAP-Phosphatase)
  - Glycogen-Synthase-Kinase-3 (GSK-3)
- Valproate
  - GABA-Metabolism (?)
  - Inhibition of Na^{+}-channels
  - Inhibition of Histon-Deacetylase ($\Rightarrow$ Epigenetics)
- Carbamazepine
  - Inhibition of Na^{+}-channels
  - Inhibition and Upregulation of Adenosine A_1-Rezeptors

Regulation of Gentranscription by epigenetic Mechanisms

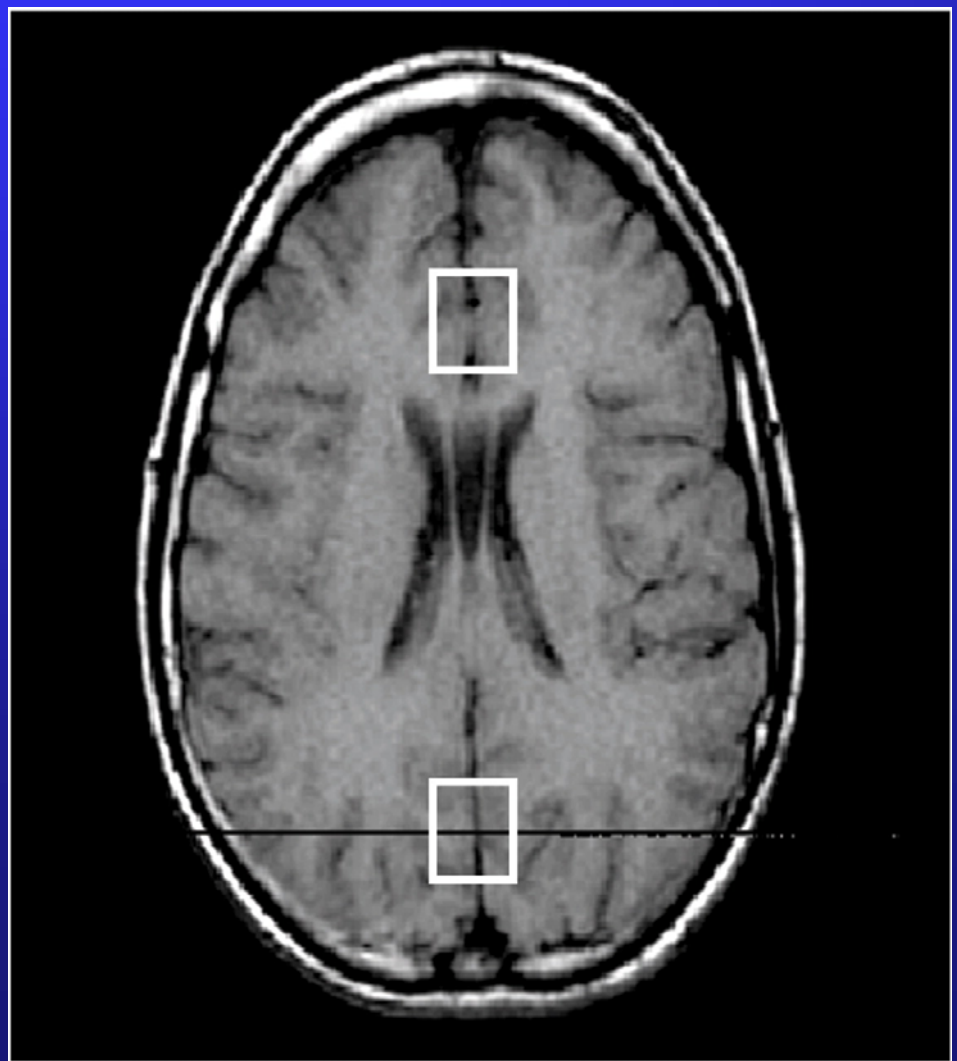
(Colvis, C. M. et al. J. Neurosci. 2005;25:10379-10389)

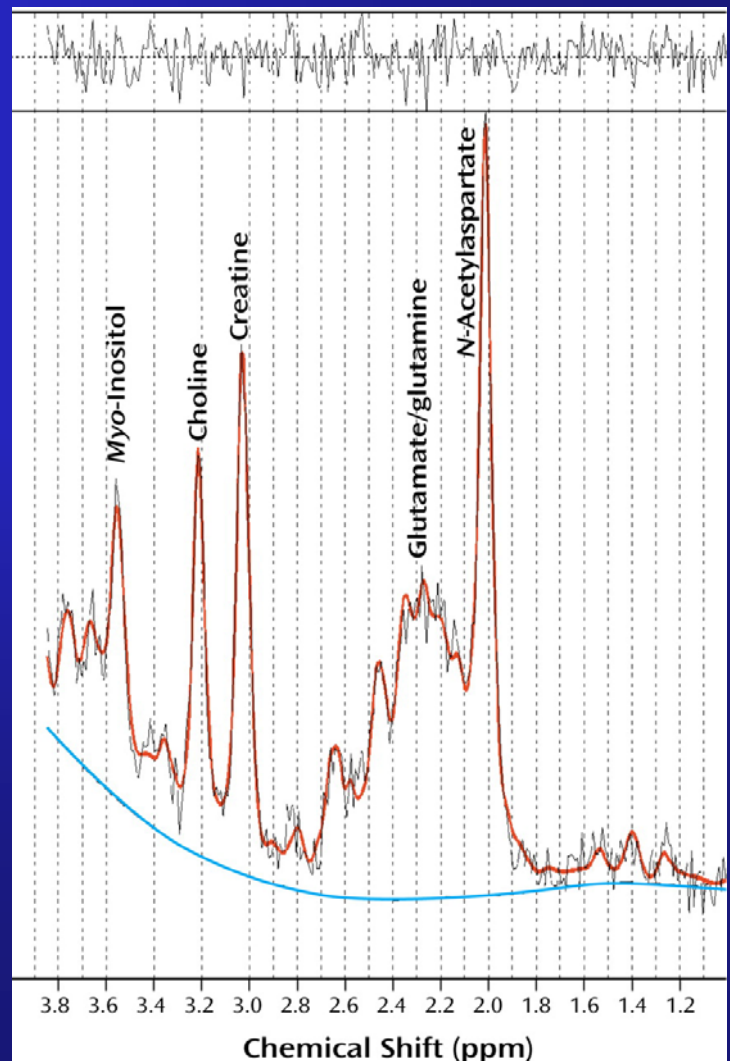


SMIT1-mRNA Expression in Neutrophils of bp-Patients and Controls (Willmroth et al 2007)



MR Spektroskopie bei bipolaren Störungen (Davanzo et al 2003)



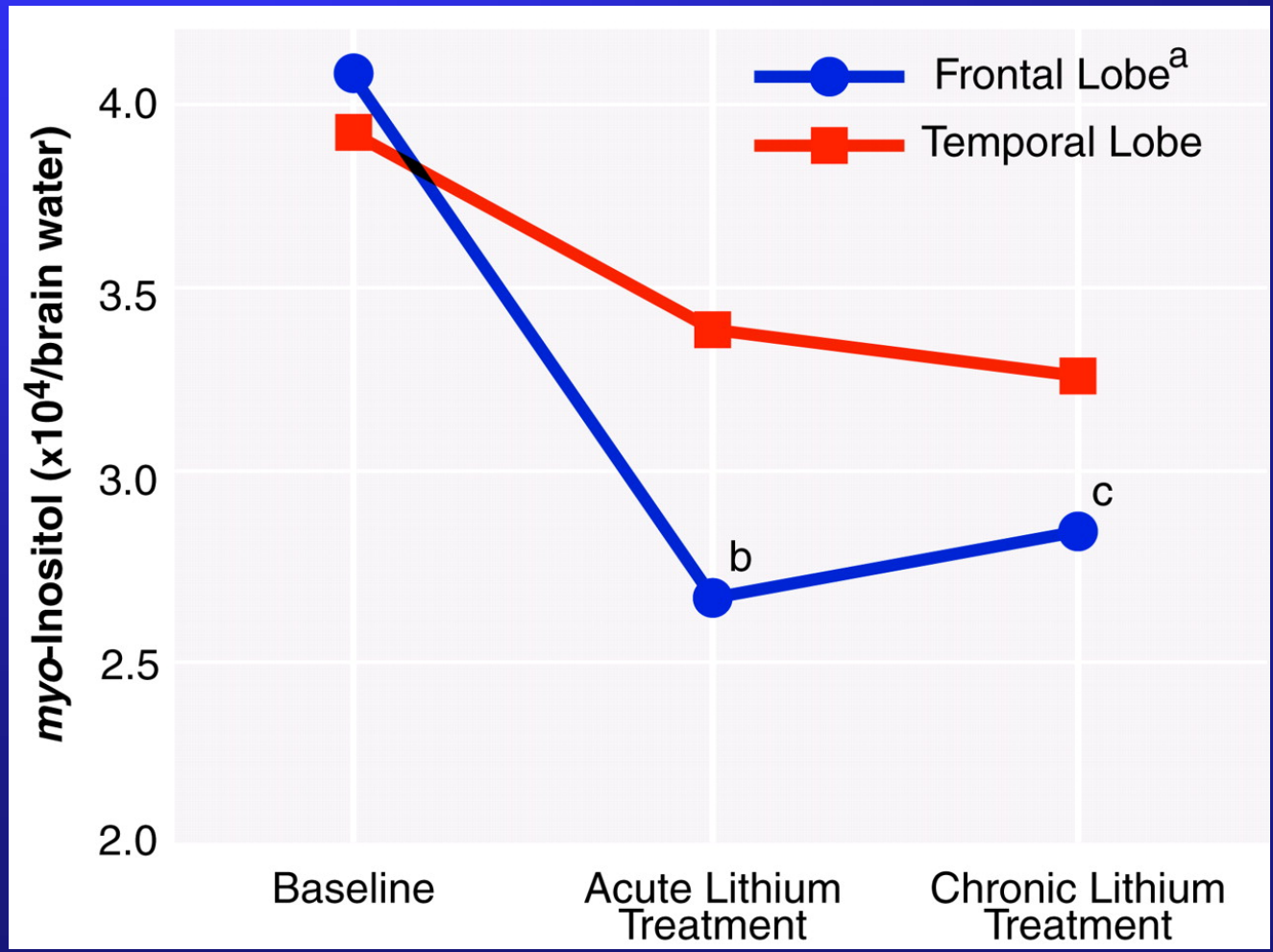


Myo-Inositol-Gehalt im ant. Cingulum bei juvenilen Patienten mit bp-Störung
(Davanzo et al 2003)

TABLE 2. Brain Proton Spectroscopy Metabolite Measures in Children and Adolescents With Bipolar Diso tent Explosive Disorder and in Normal Comparison Subjects

Brain Area and Group	Creatine-Phosphocreatine (mmol/liter)		*Myo*-Inositol (mmol/liter)		*Myo*-Inositol/Creatine-Phosphocreatine	
Anterior cingulate cortex						
	Mean	SD	Mean	SD	Mean	SD
Bipolar disorder (N=10)	6.16	0.85	4.55	0.50	0.75	0.12
Intermittent explosive disorder (N=10)	6.21	0.47	4.08	0.55	0.66	0.08
Comparison group (N=13)	6.13	0.41	4.05	0.38	0.66	0.06
	p		p		p	
Bipolar disorder versus intermittent explosive disorder (Wilcoxon test)	0.88		0.02		0.05	
Comparison versus bipolar disorder (Wilcoxon test)	0.85		0.02		0.02	
Comparison versus intermittent explosive disorder (Wilcoxon test)	0.58		0.71		0.90	

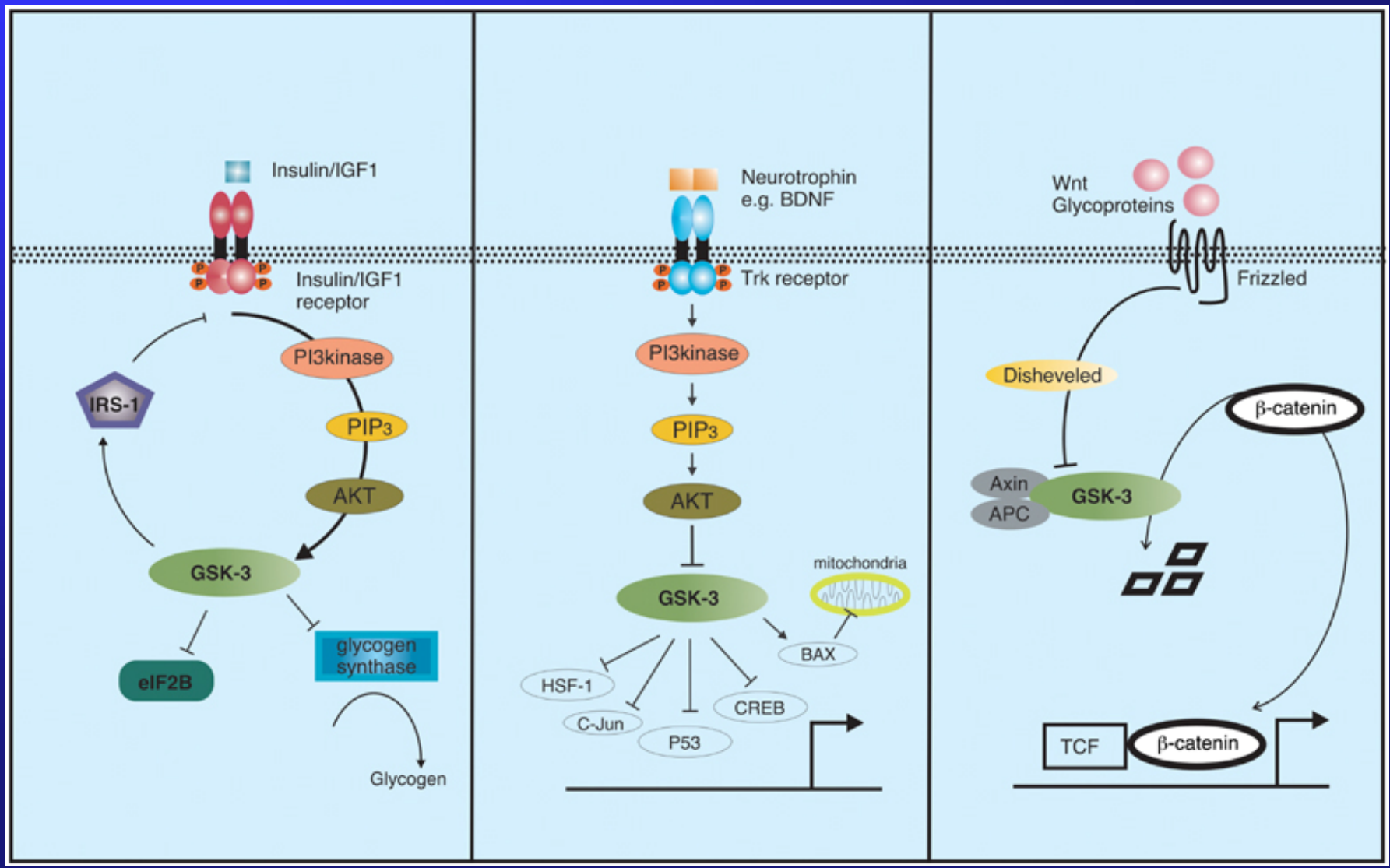
Effect of Lithium Treatment on Brain Myo-Inositol (Moore et al 1999)



Funktional Alterations in Bipolar Disorders

- Increased CBF and Glc-Metabolismus (PET) in limbic und prefrontal Areas
- Reduced NAA-Content in Hippocampus und dorsolateral prefrontal Cortex
- Increasing Evidence for Mitochondria-Dysfunction! (Kato et al 2000; Konradi et al 2004; Iwamoto et al 2005; Sun et al 2006)

Glycogen-Synthase-Kinase-3 in cellular signaling



Glykogen-Synthase-Kinase-3-Beta (GSK-3β).

(review: Li et al 2002 Bipolar Disorders 4, 137)

- Inhibition by Li^+ (in vitro und in vivo, K_i 1-2 mM)
- Inhibition by Valproat (Chen et al 1999)? (controversial!)
- Central role in the regulation of apoptosis, plasticity and resilience of neural cells
- Higly expressed in brain
- Gen localised on 3q21.1

Induction of hippocampal neurogenesis by chronic valproate treatment in adult mice.

Hao et al J Neurosci. 2004 Jul 21;24(29):6590-9.