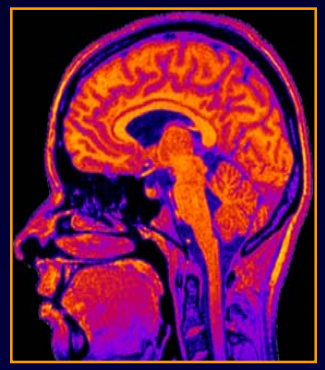


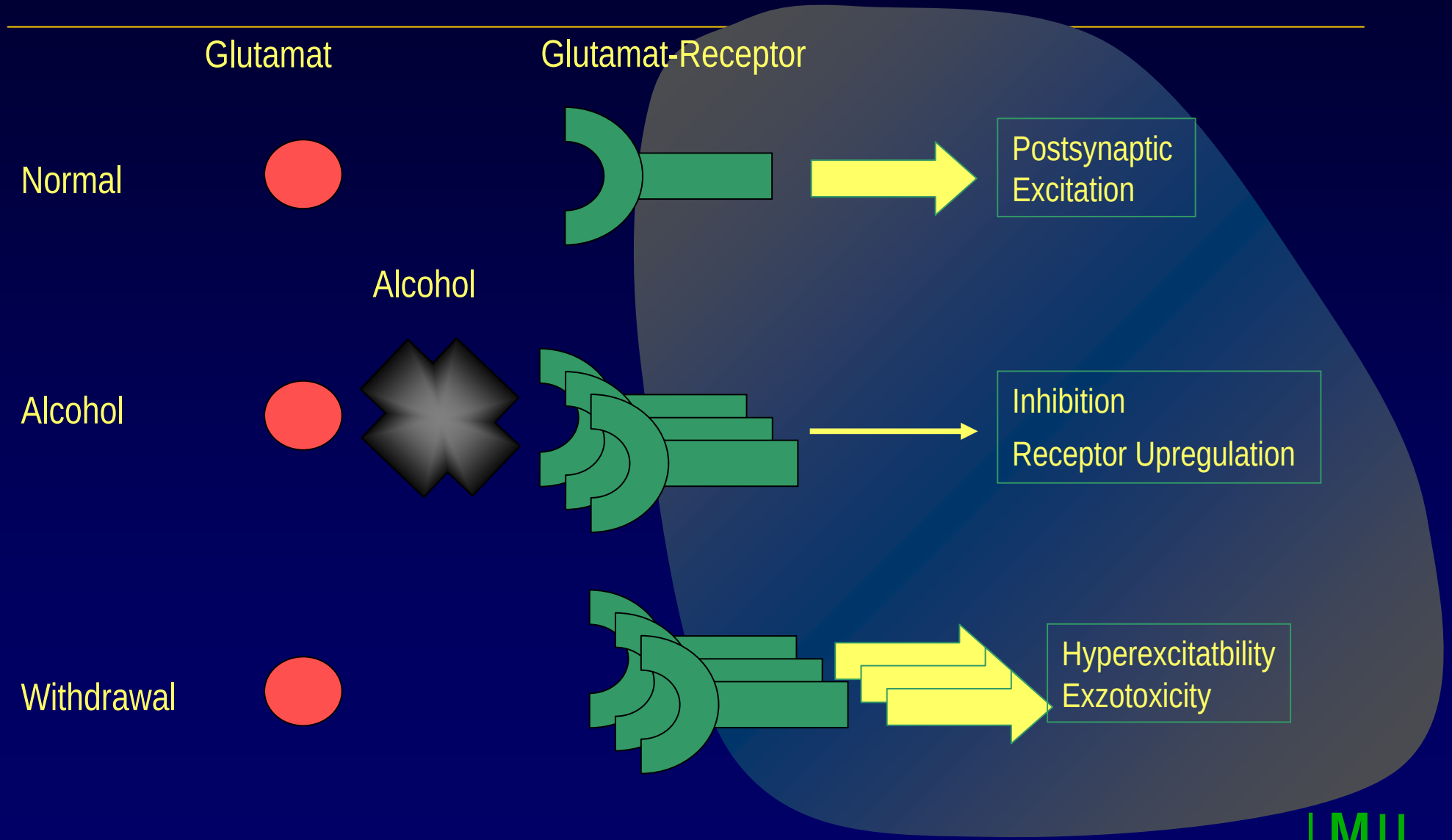
Regional Glucose metabolism after Dextrometorphane-Challenge in Alcoholics and Controls

M. Soyka[1], Rüther[1], CG. Schütz[1], K.Tatsch[2], W.Koch[2],

[1]Psychiatric Hospital

[2] Nuclear Medicine, LMU München

Effects of Alcohol on the glutamatergic Neurotransmission:



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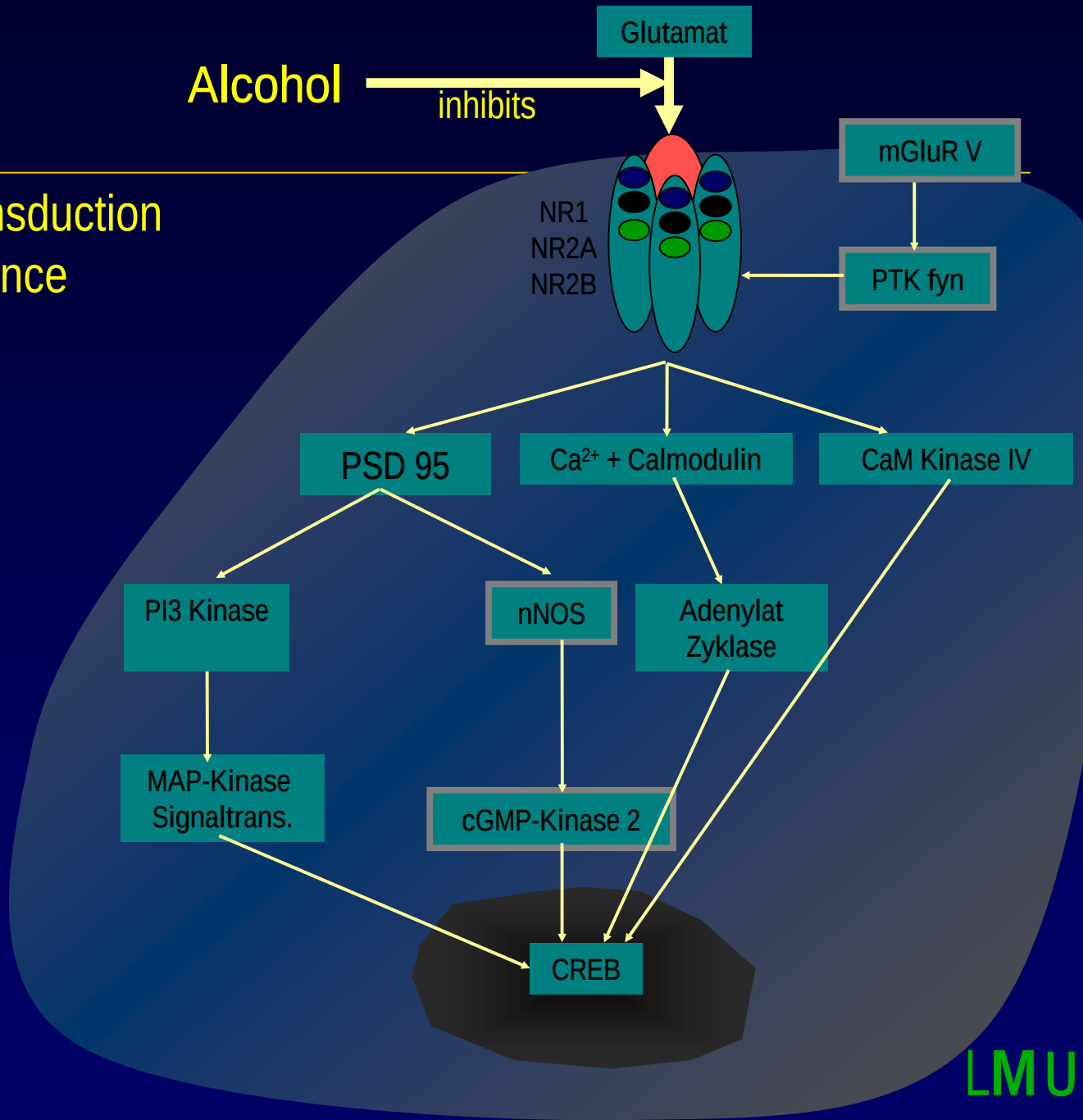
Glutamatergic signaltransduction In alcohol dependence



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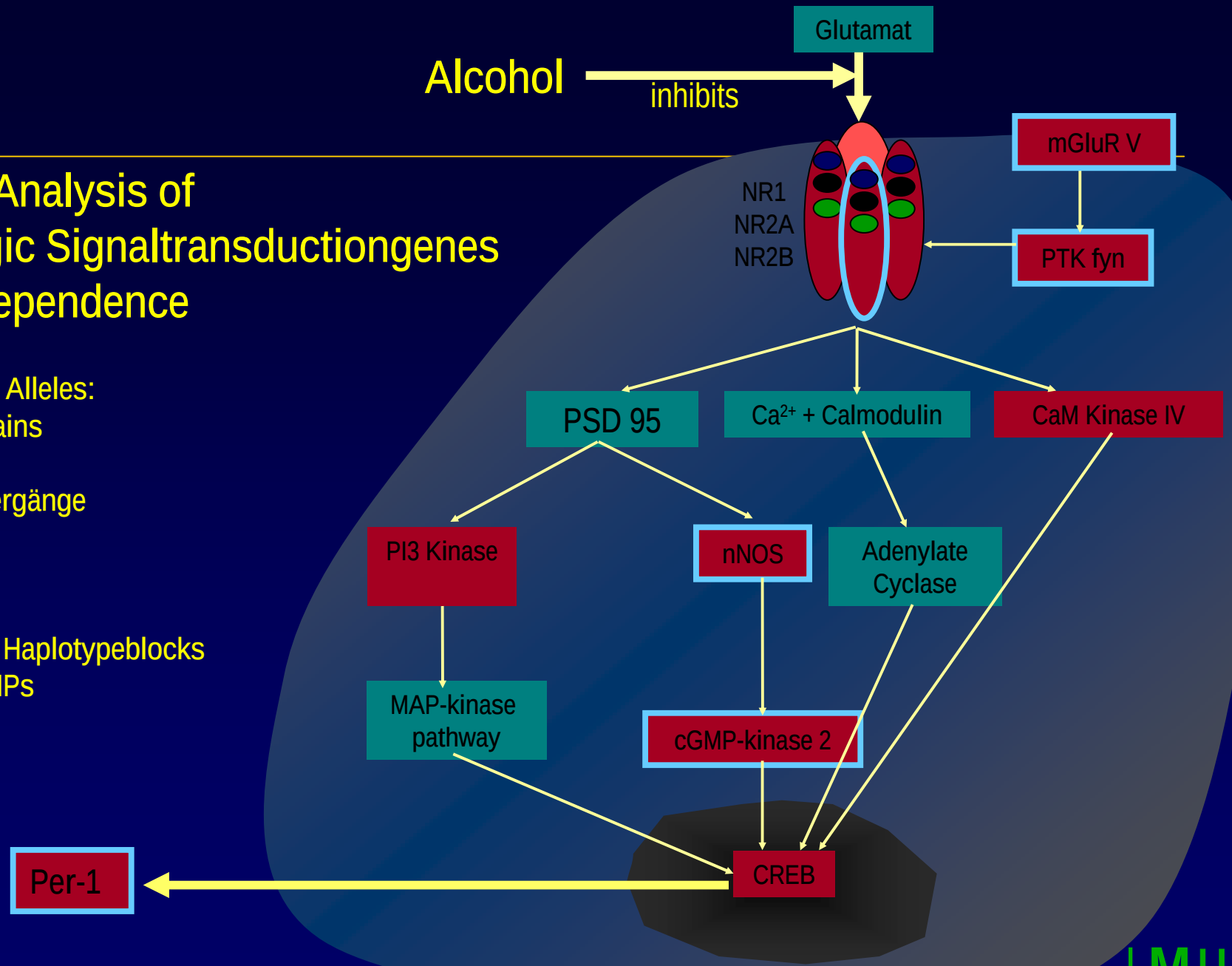
Systematic Analysis of Glutamatergic Signaltransductiongenes In alcohol dependence

Sequencing of 70 Alleles:
- regulatory Domains
- Exon
- Exon-Intron Übergänge

Identification of
- 204 SNPs
- 29 SNPs coding Haplotypeblocks
- 13 functional SNPs



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Regulation of alcohol intake via Glutamatergic signaltransduction genes in animal model

	Alcohol intake	Alcohol Preference	Sensitivity	Tolerance	Relapse
mGluR5	X				X
PTK fyn			X	X	
nNOS	X	X			
cGMP-Kinase 2	X		X		

Bäckström et al., in press; Miyakawa et al., 1997; Spanagel et al., in press; Werner et al., in press;

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Dose-Related Ethanol-like Effects of the NMDA Antagonist, Ketamine, in Recently Detoxified Alcoholics

John H. Krystal, MD; Ismene L. Petrakis, MD; Elizabeth Webb; Ned L. Cooney, PhD; Laurence P. Karper, MD; Sheila Namanworth; Philip Stetson, PhD; Louis A. Trevisan, MD; Dennis S. Charney, MD

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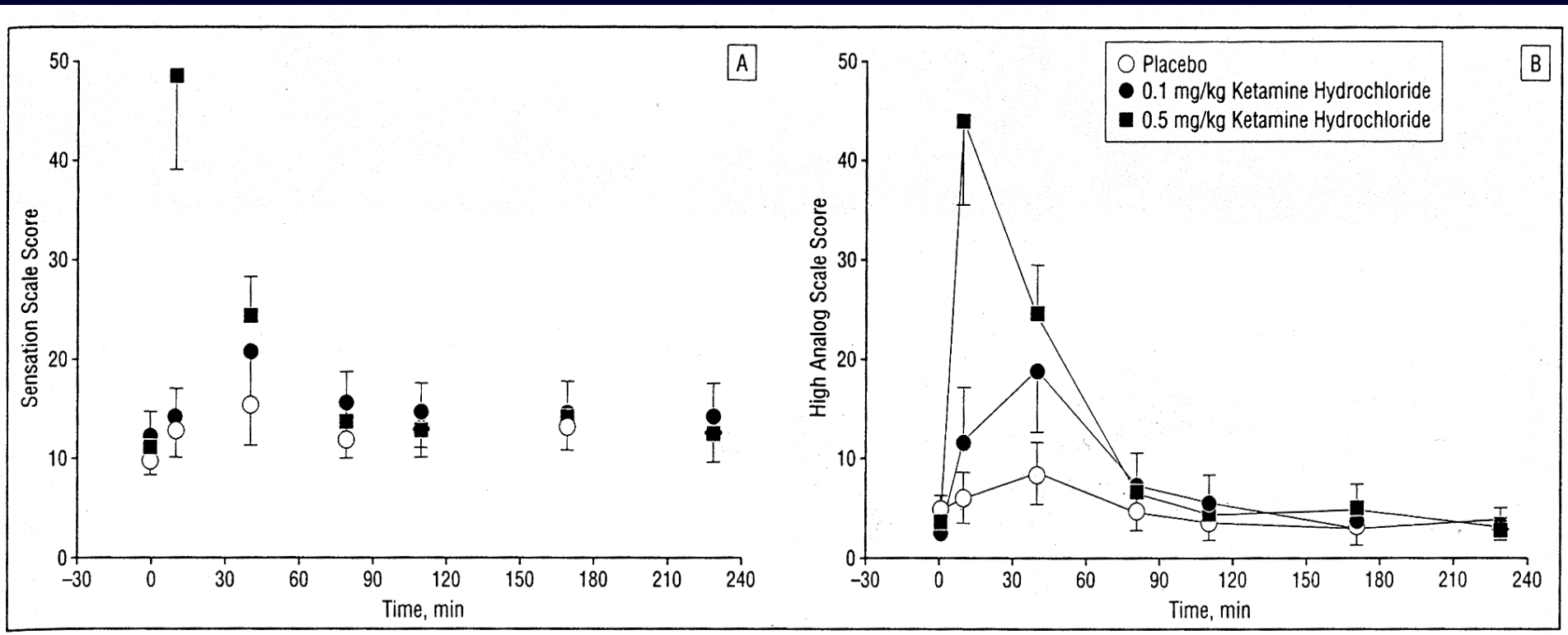

Figure 1. *Effects of placebo, 0.1 mg/kg ketamine hydrochloride, and 0.5 mg/kg ketamine hydrochloride on Sensation Scale Scores (A) and on self-rated "high" (B) in recently detoxified alcoholic patients (N=20). Values are expressed as mean±SEM. See "Patients and Methods" and "Results" sections for explanation of statistical analyses.*

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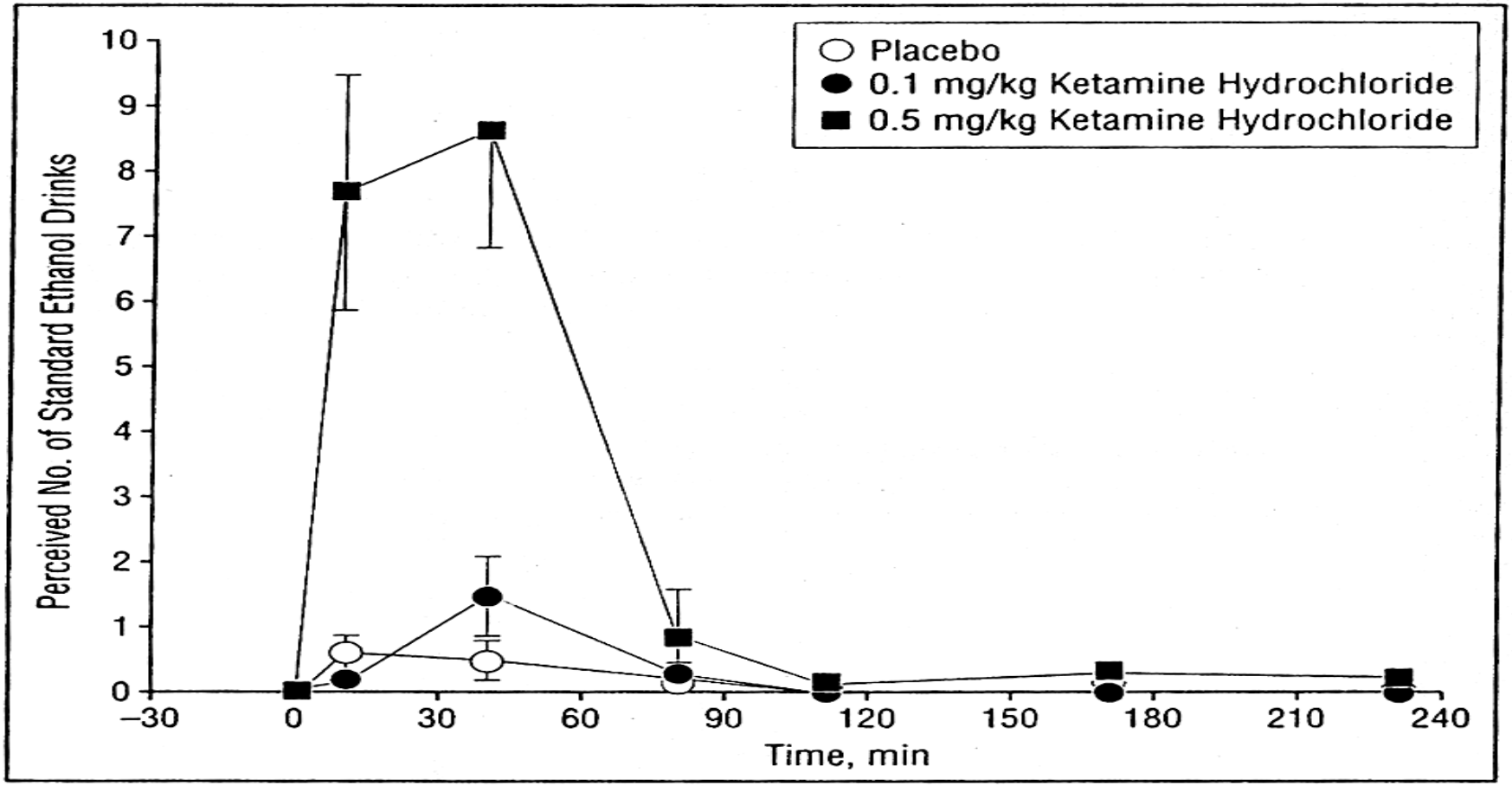

Figure 2. *The number of standard ethanol drinks that recently detoxified alcoholic patients (N=20) determined were similar to the effects of placebo, 0.1 mg/kg ketamine hydrochloride, and 0.5 mg/kg ketamine hydrochloride. Values are expressed as mean±SEM. See "Patients and Methods" and "Results" sections for explanation of statistical analyses.*

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FDG- PET following Ketamine- Challenge

Design	Metabolism	Authors
N=10 Ketamin 1,2mg/kg 1h	Absolut: ↑ ,v.a.frontal ↑↑ parietal,insula, temporal ↑ Relativ: frontolateral ↑ l.anteriores cingulum ↑	Vollenweider et al. (1999)
N= 17 Ketamin 0,65 mg/kg 1h	Absolut: nur prefrontal ↑ (focal), no global increase Relativ: n.a.	Breier et al. (1997)

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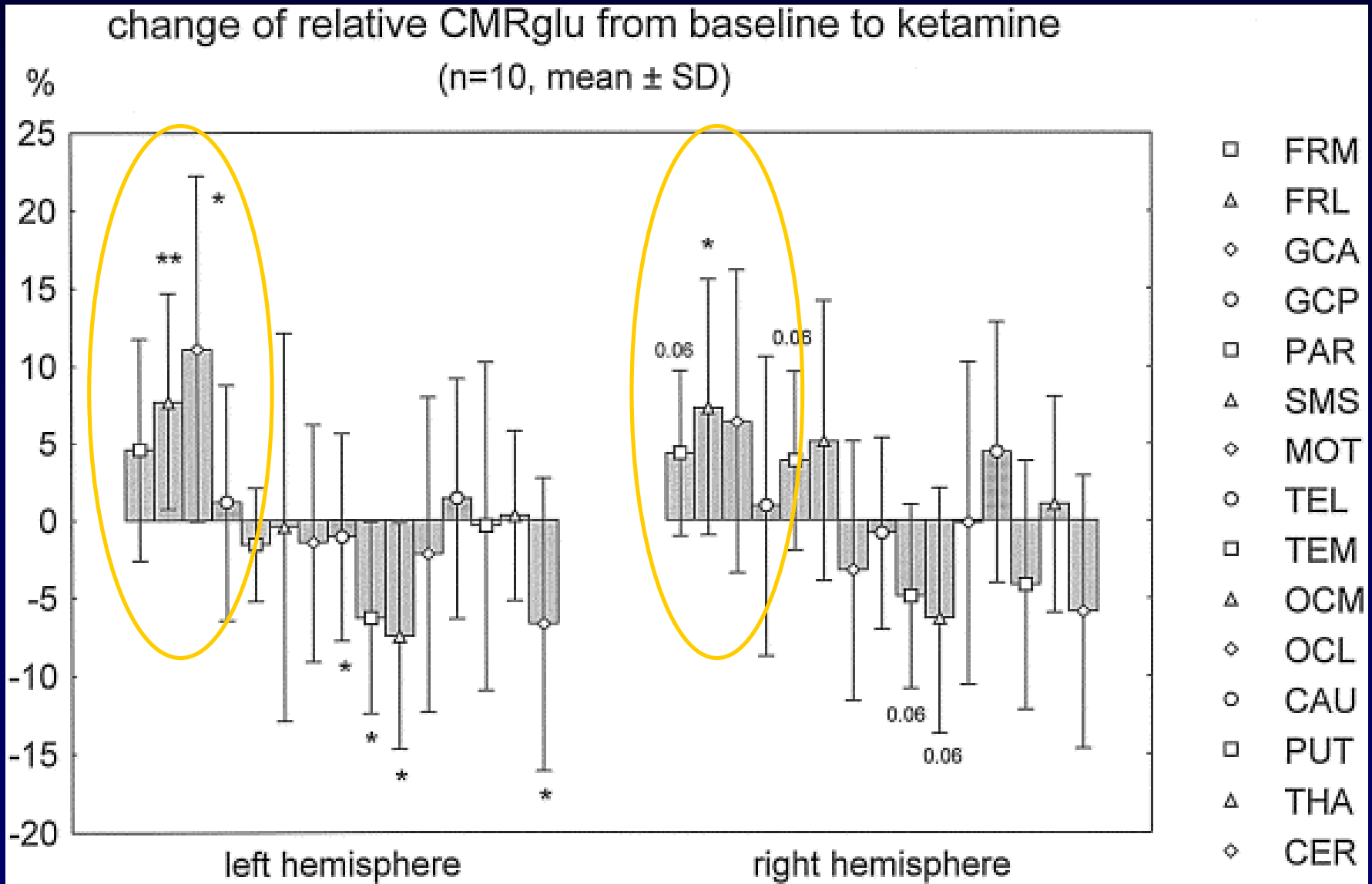
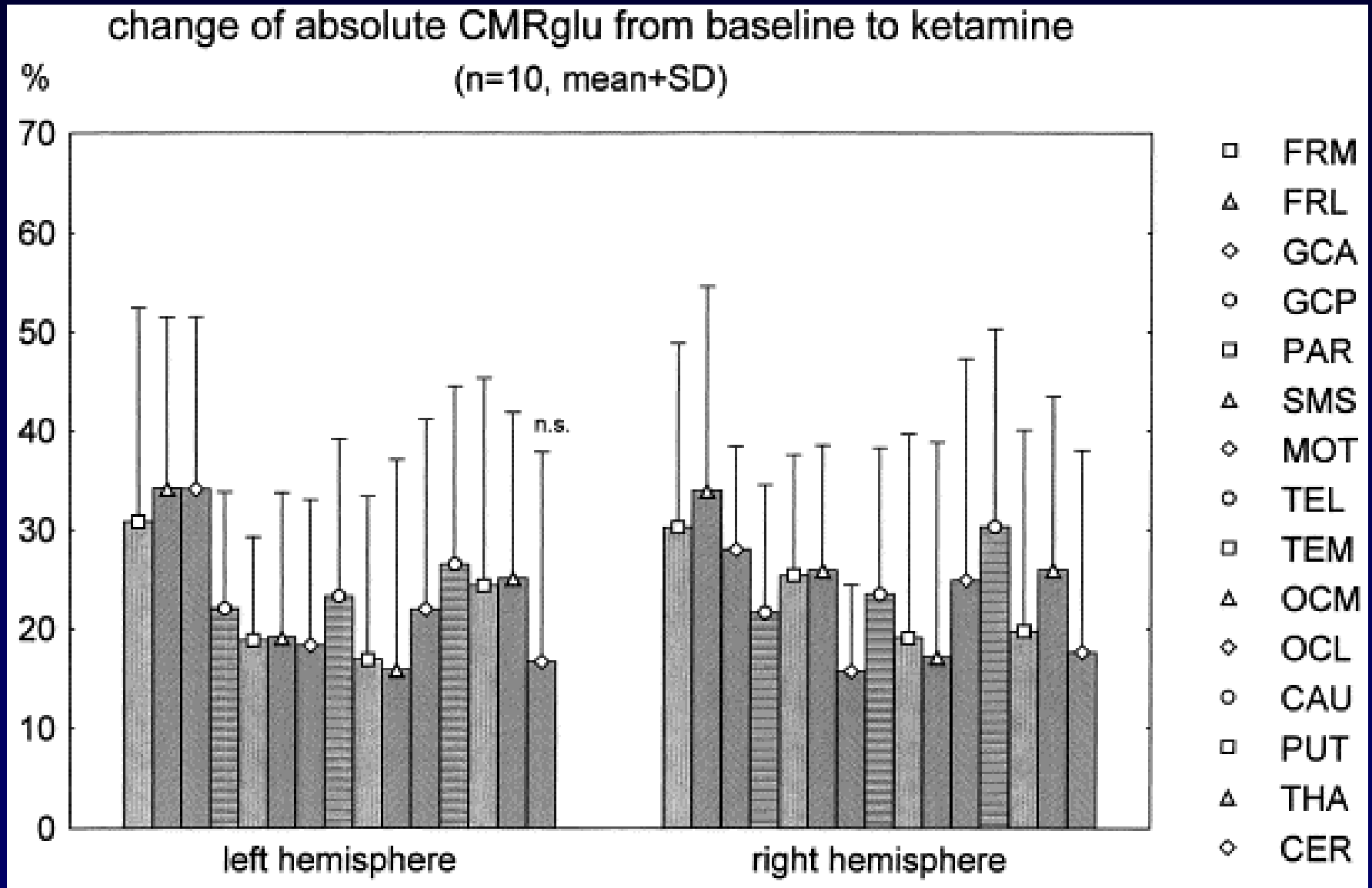
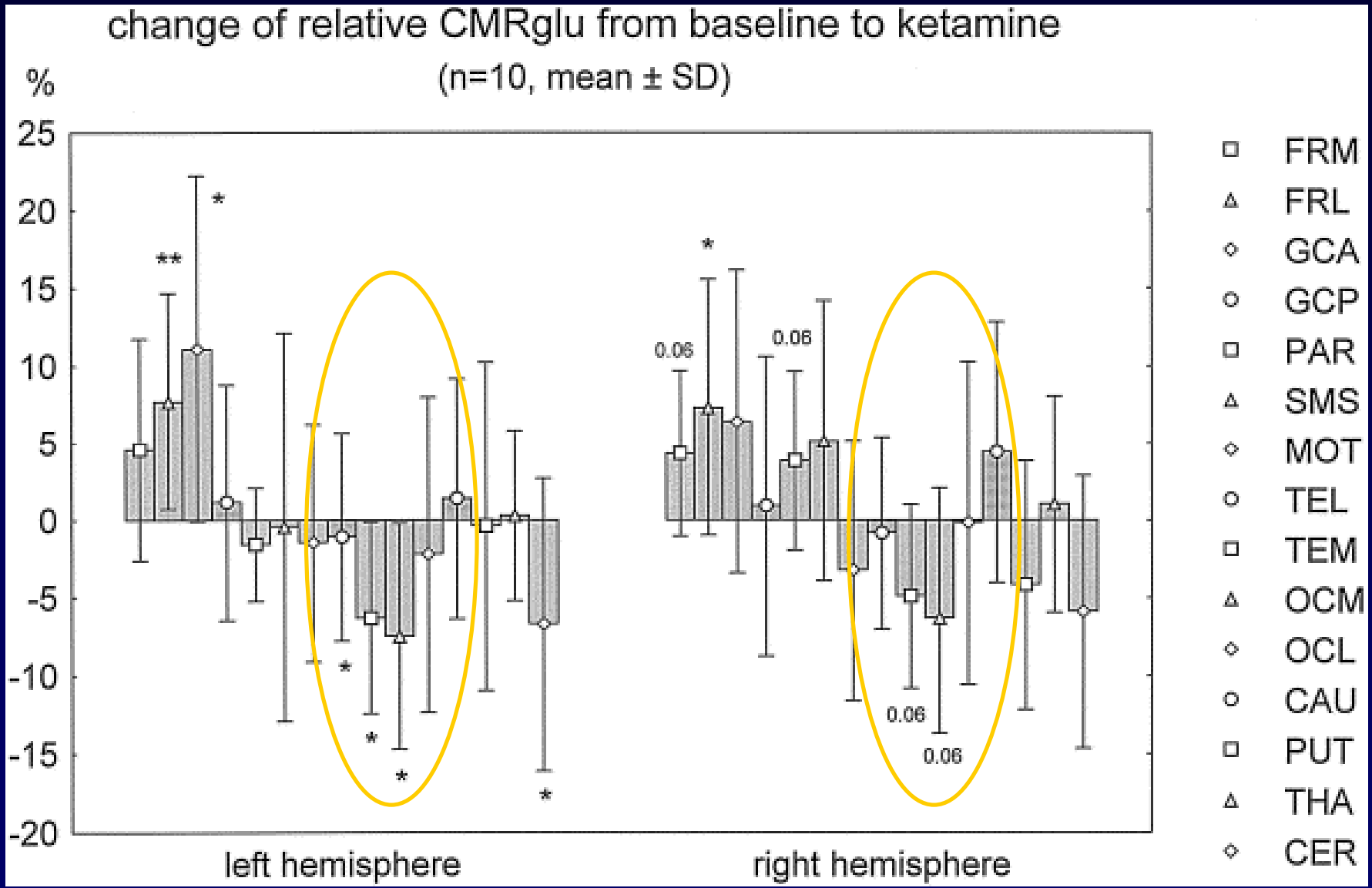
Vollenweider et al.



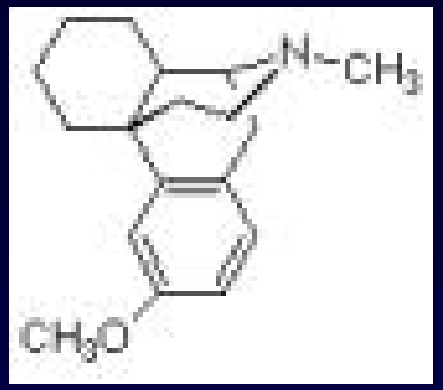
Vollenweider et al.



Vollenweider et al.



Dextromethorphane



- (+)-3-Methoxy-N-methylmorphinan
  specific, non-competitive NMDA antagonist
  (main metabolite Dextrorphan)
- oxidative O-demethylisation (Cytocrom P4502D6) ,
  renal excretion
- in 60 countries for 40 years over-the-counter
- indication: antitussive treatment
- fast absorption from gastrointestinal tract

Binding affinity at the ion channel of the NMDA receptor complex

Compound	K_i [nM]
MK- 801	15
PCP	42
Dextrorphane	222
Ketamine	420
Memantine	540
Dextromethorphane	3.500
Amantadine	10.500

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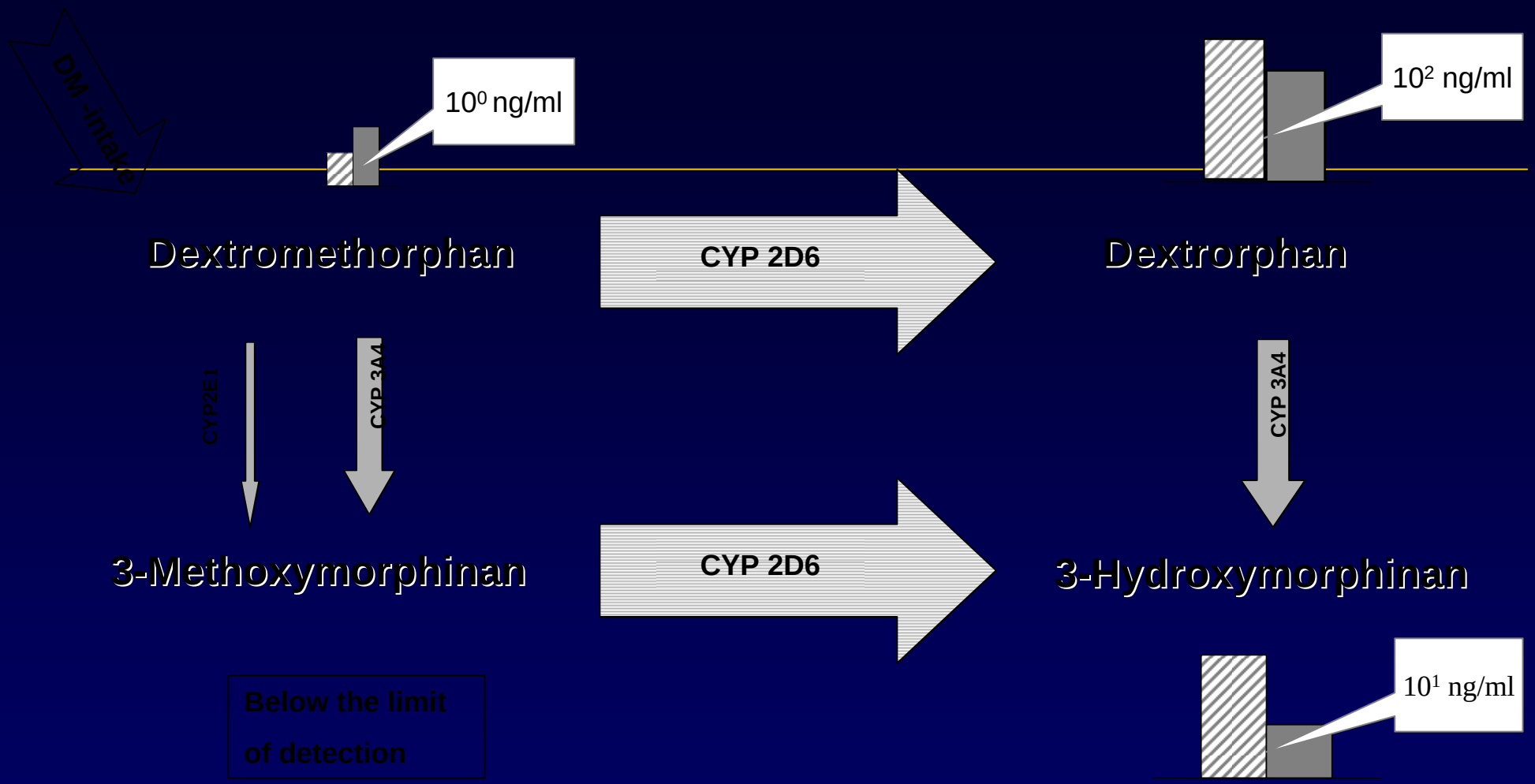
DM -intake
10^0 ng/ml
10^2 ng/ml
Dextromethorphan
CYP 2D6
Dextrorphan
CYP2E1
CYP 3A4
CYP 3A4
3-Methoxymorphinan
CYP 2D6
3-Hydroxymorphinan
10^1 ng/ml
Below the limit of detection
Alcohol dependants
Controls

Fig. 1

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Subtyp binding

Agent	NR1 + NR2A	NR1 + NR2B	NR1 + NR2C	NR1 + NR2D
Alcohol	+	+++	+	+
D-Cycloserine	+	++	+++	+++
Memantine	++	+++	+++	+++
Ketamine	++	++	++	++
Dextrorphan	++	++	+++	+
				Parsons et al. 1998

NMDA receptor challenge with dextromethorphan – subjective response, neuroendocrinological findings and possible clinical implications

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Psychiatric Hospital, University of Munich, Federal Republic of Germany

Received June 30, 1999; accepted October 14, 1999

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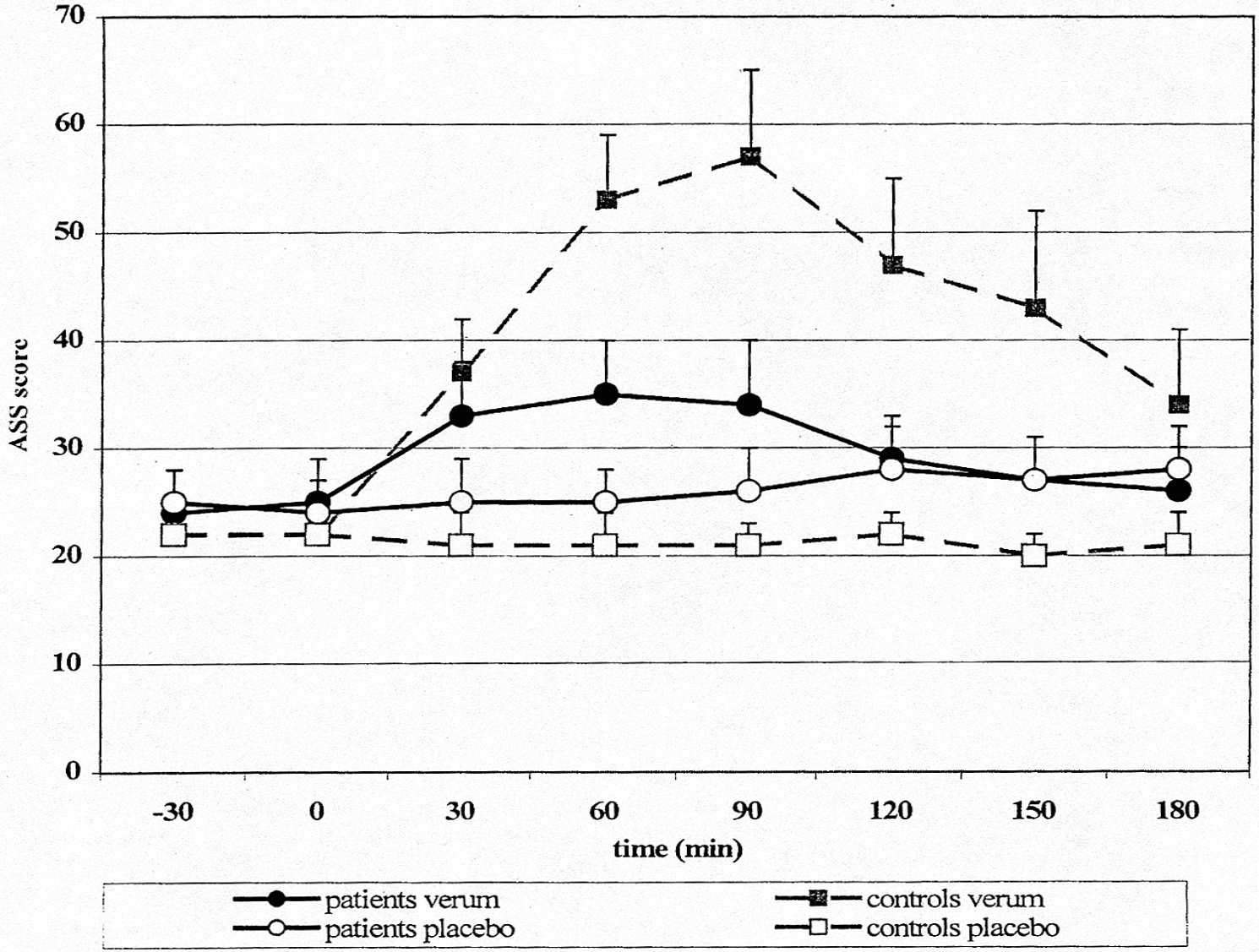
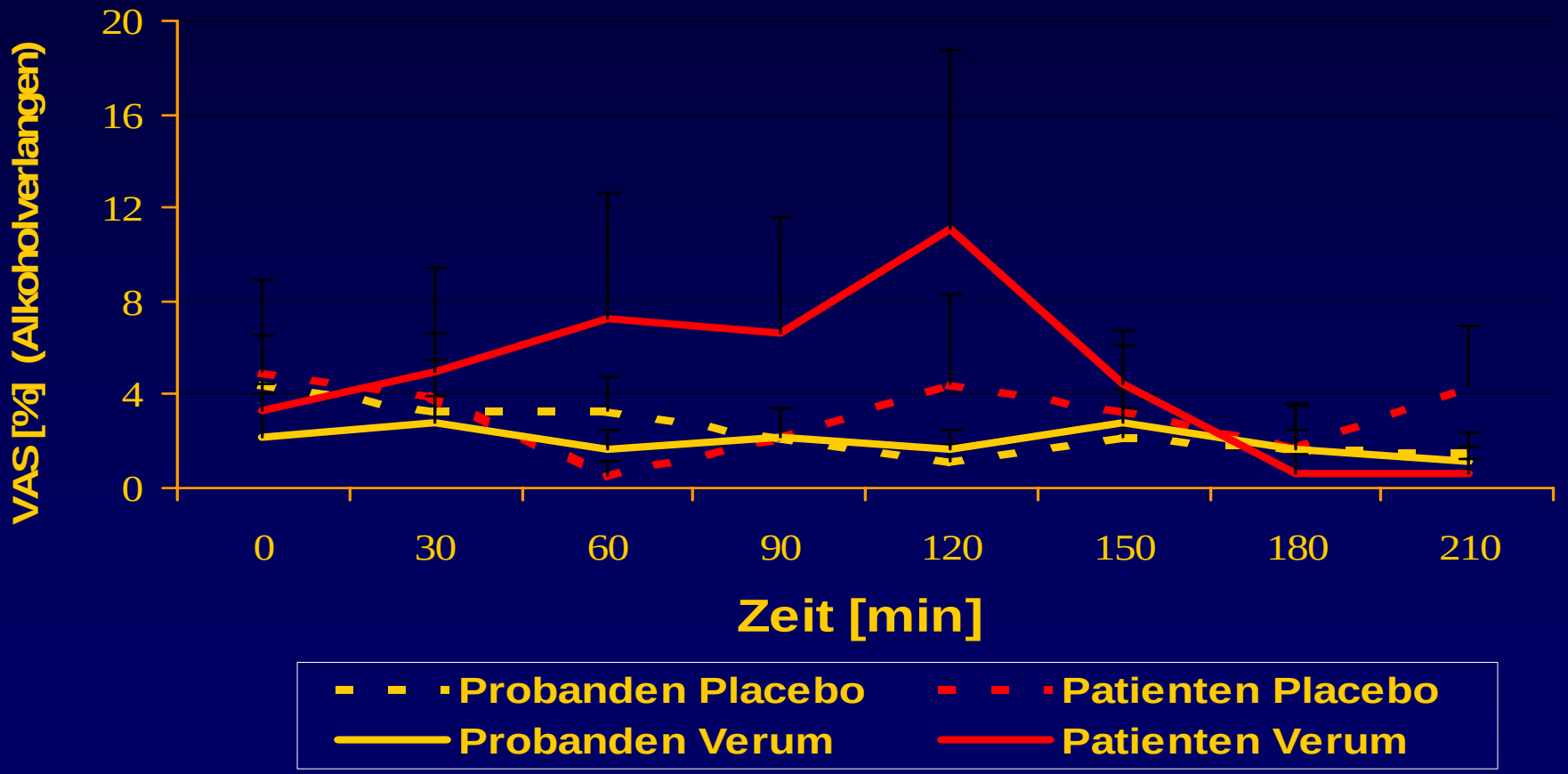


Effects of dextromethorphan 2 mg/kg or placebo on Alcohol Sensation Scale Scores in recently detoxified alcoholics (n = 20) and age-matched healthy controls (n = 10). Values are expressed as mean ± SEM. See "Subjects and methods" and "Results" sections for explanations of statistical analysis

Dextromethorphane-Challenge
Visuelle Analogue Scale – Alcohol craving



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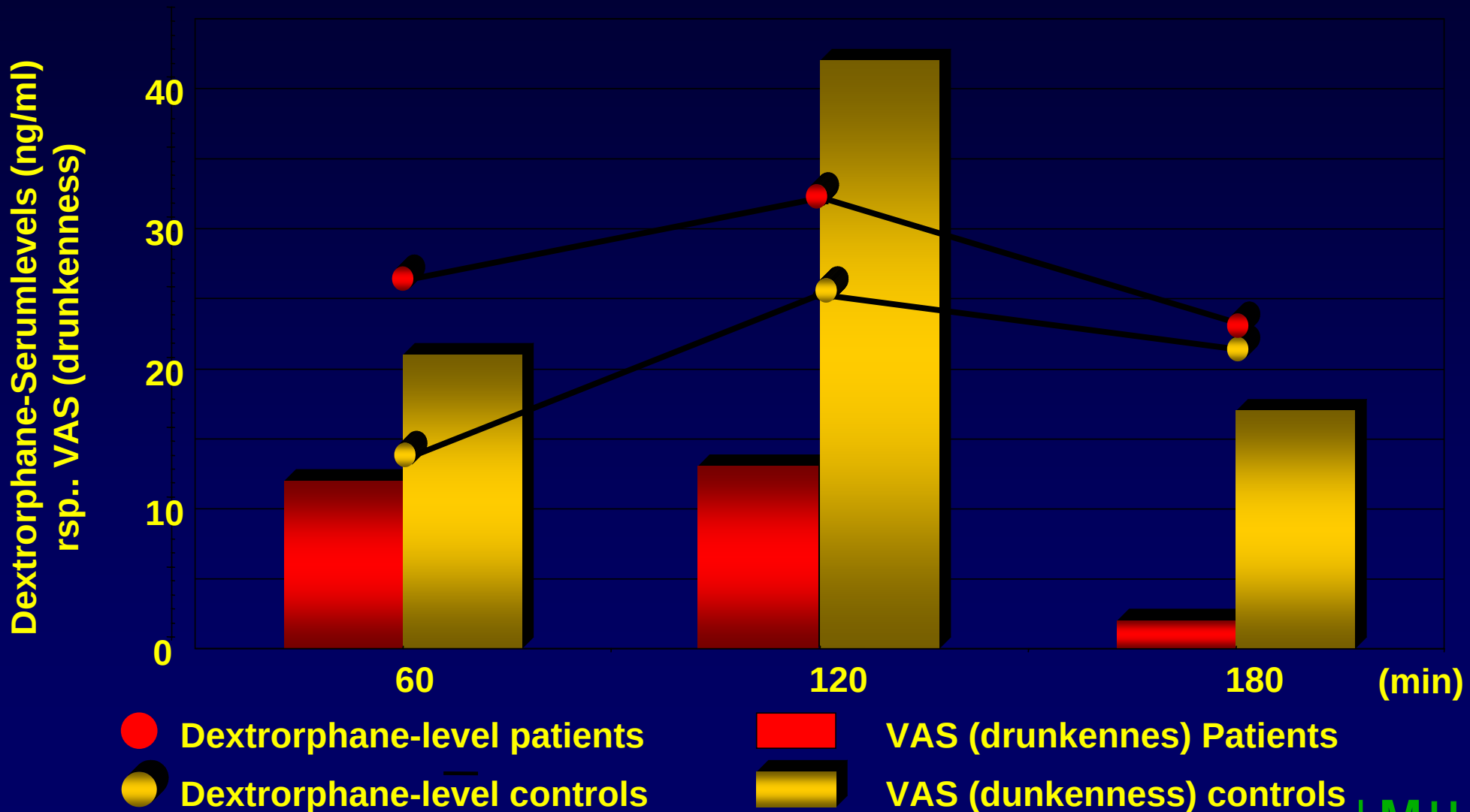
Dextromethorphane-Challenge
subjective alcohol-like effects



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Hypotheses

- **Alcohol effects only mediated by NMDA Antagonism**
  ↑ Metabolic Changes induced by Alcohol and Dextromethorphane are similar.

- **Chronic Alcohol consumption leads to Hypersensitivity of the NMDA System (Animal Model) ↑ Metabolic Changes more marked in alcoholics compared to controls.**

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Inclusion criteria:

Alcoholics	Controls
1. Alcohol dependence (DSM IV)	1. No alcohol dependence or abuse
2. 14 to 26 days of abstinence	2. Irrelevant
3. Males only	3. Males only
4. Informed consent	4. Informed consent

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Study design

- **Placebo-controlled, double blind, double dummy, randomized (S-Plus)**
- **Probands:**
  - **12 alcoholics (ICD 10) male, right-handed Patients, no psychiatric diagnosis**
    - 14 - 26 days post inpatient withdrawal
  - **10 healthy, male, right-handed controls**
    - age and sex matched [31-45]
- **Challenge substances:**
  - **2mg/kg Dextromethorphane**
  - **0,4g/kg Ethanol (n=8, controls only!)**
  - **Placebo**

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Scanning

- ECAT Exact HR + PET-Scanner
- Transmissions-Scan (Ge-68-Quelle: Schwächungskorrektur)
- 120 MBq ^{18}FDG i.v.
- Emission scan over 60 min, aquisition in 3D
- Arterialized bloodsamples (input-function) for absolute metabolic rates
- Reconstruction with filtered back-projektion (Hann-filter)

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Data analysis

- BRASS software (sterotactic normalisation and analysis)

- ROI 63 regions of interest using a 3 D template

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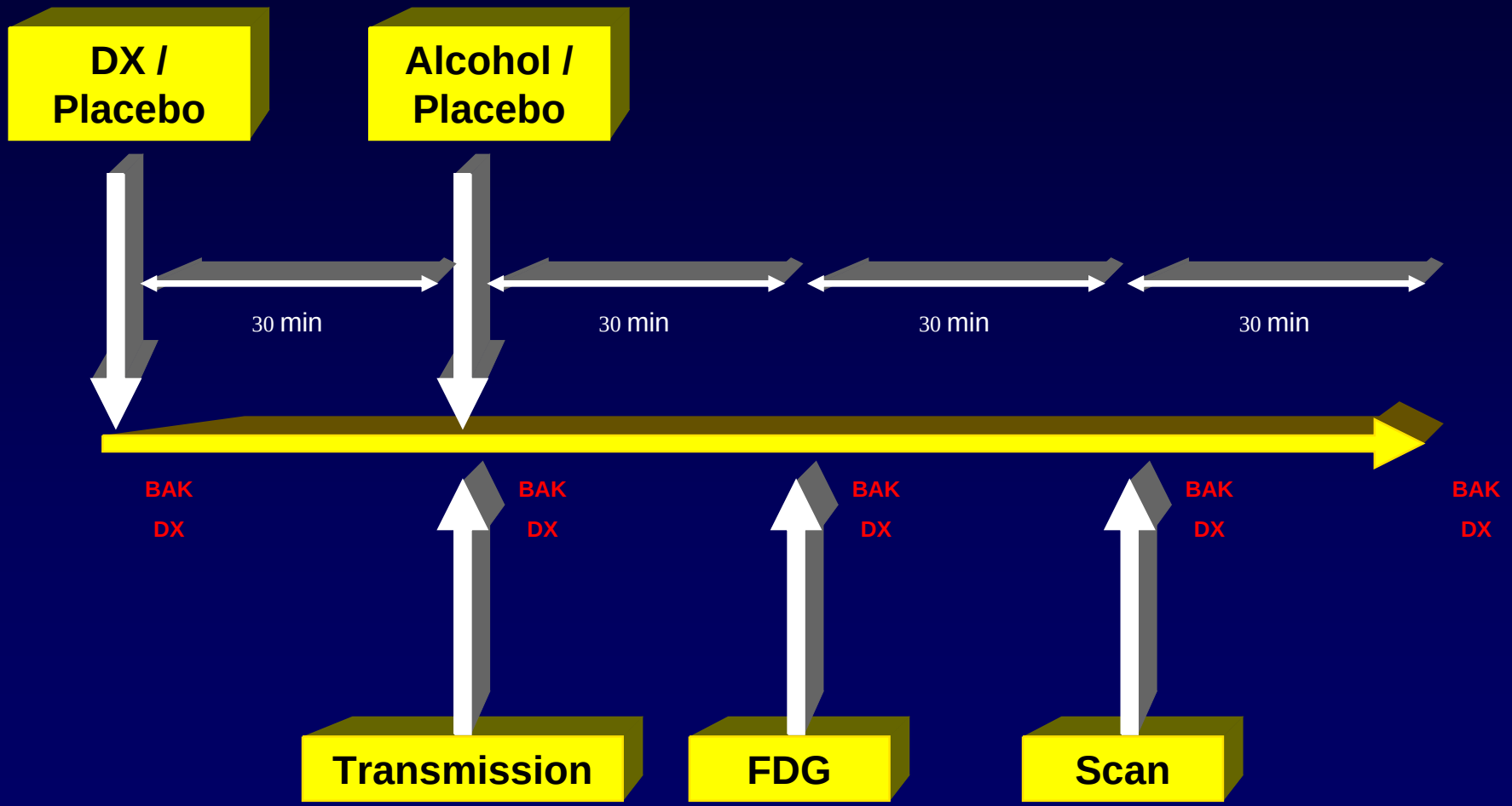
Flow Chart



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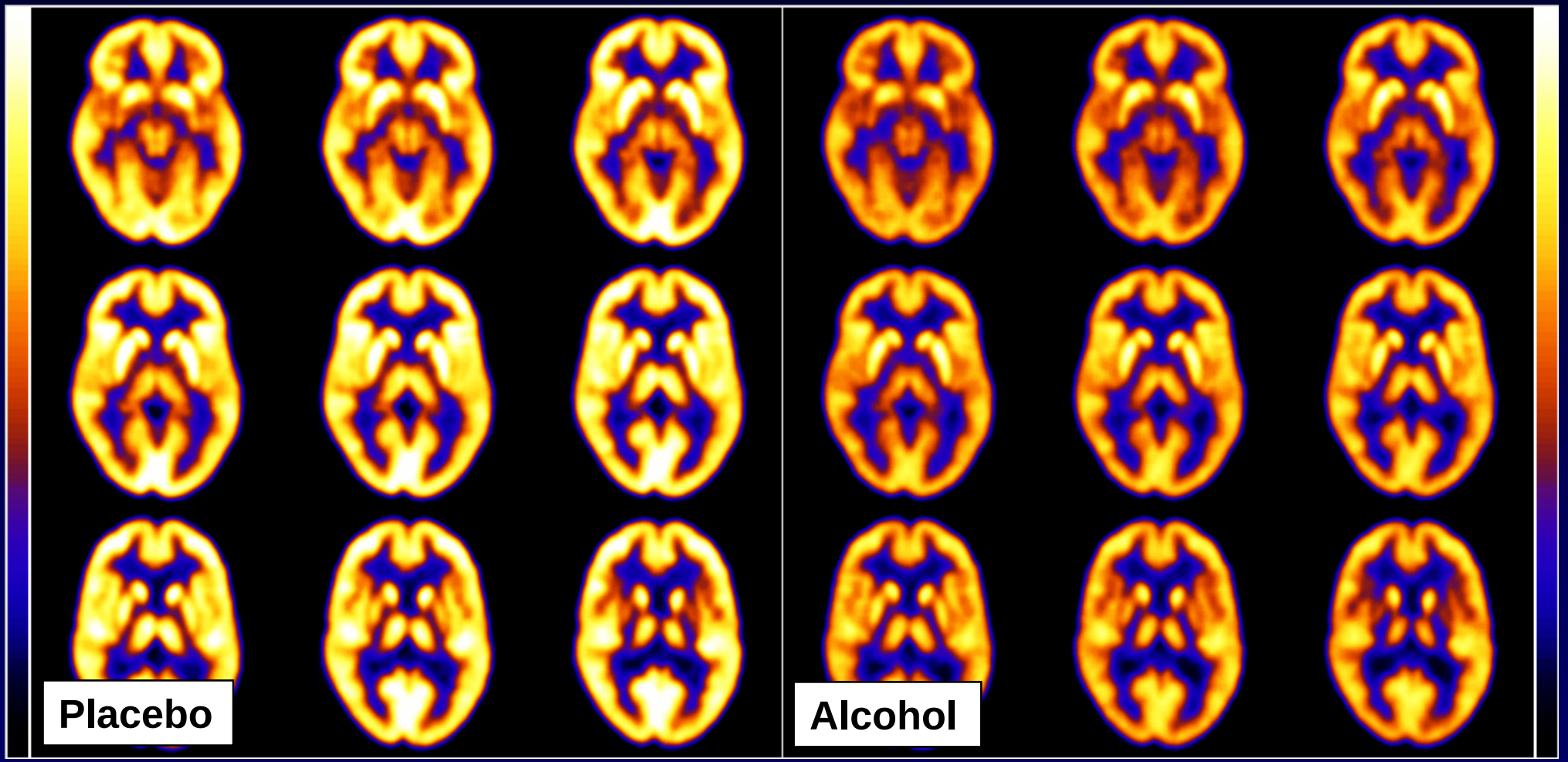
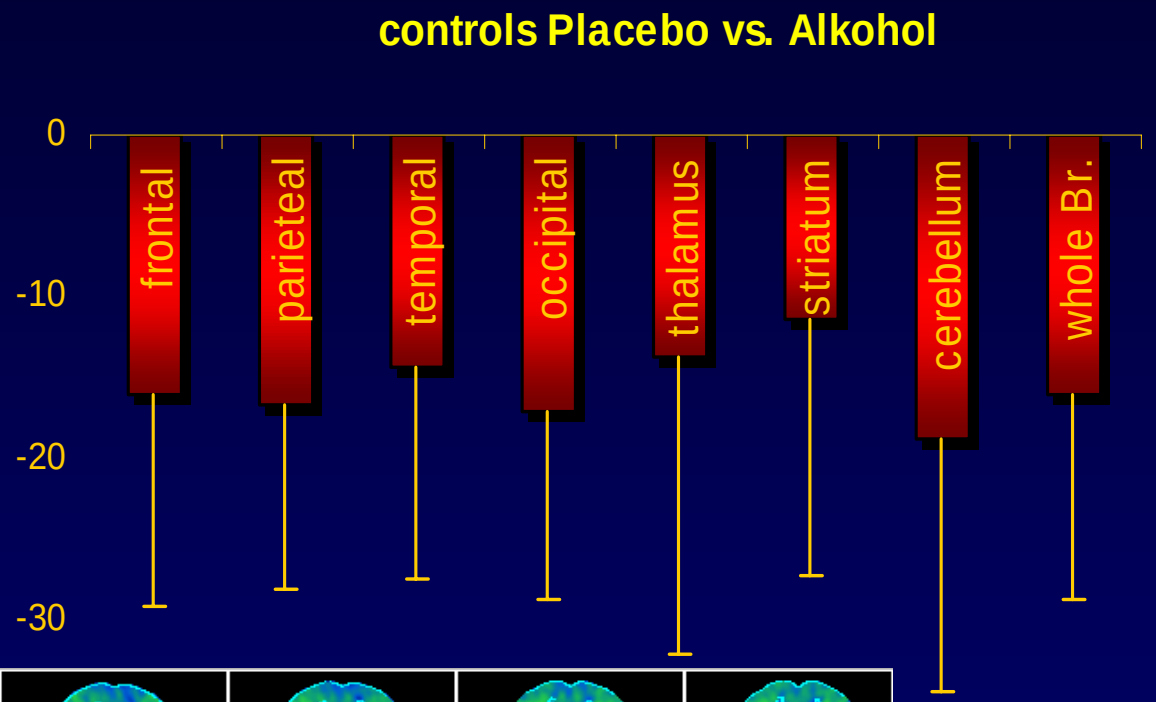
Controls: Influence of alcohol on rCMRglc

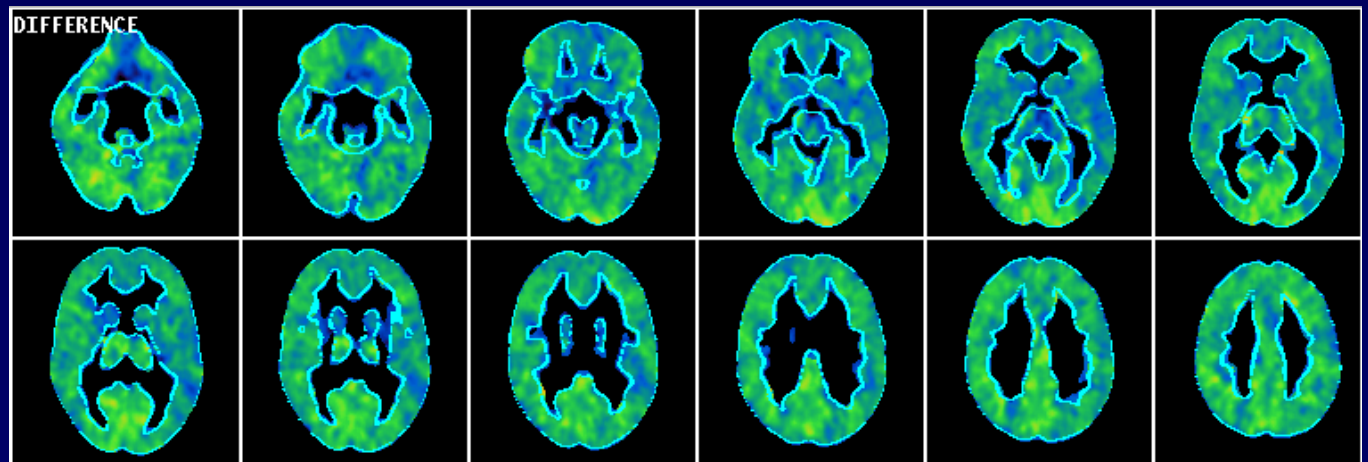


Controls: Alcohol leads to a significant decrease in rCMRglc compared to placebo condition. Data are shown as mean images of the respective conditions.

Controls: Influence of alcohol on rCMRglc

Frontal lobe	- 16%	p < 0.05
Parietal lobe	- 17%	p < 0.05
Temporal lobe	- 14%	p < 0.05
Occipital lobe	- 17%	p < 0.05
Thalamus	- 14%	n.s.
Striatum	- 12%	n.s.
Cerebellum	- 19%	p < 0.05
Whole brain	**- 16%**	**p < 0.05**





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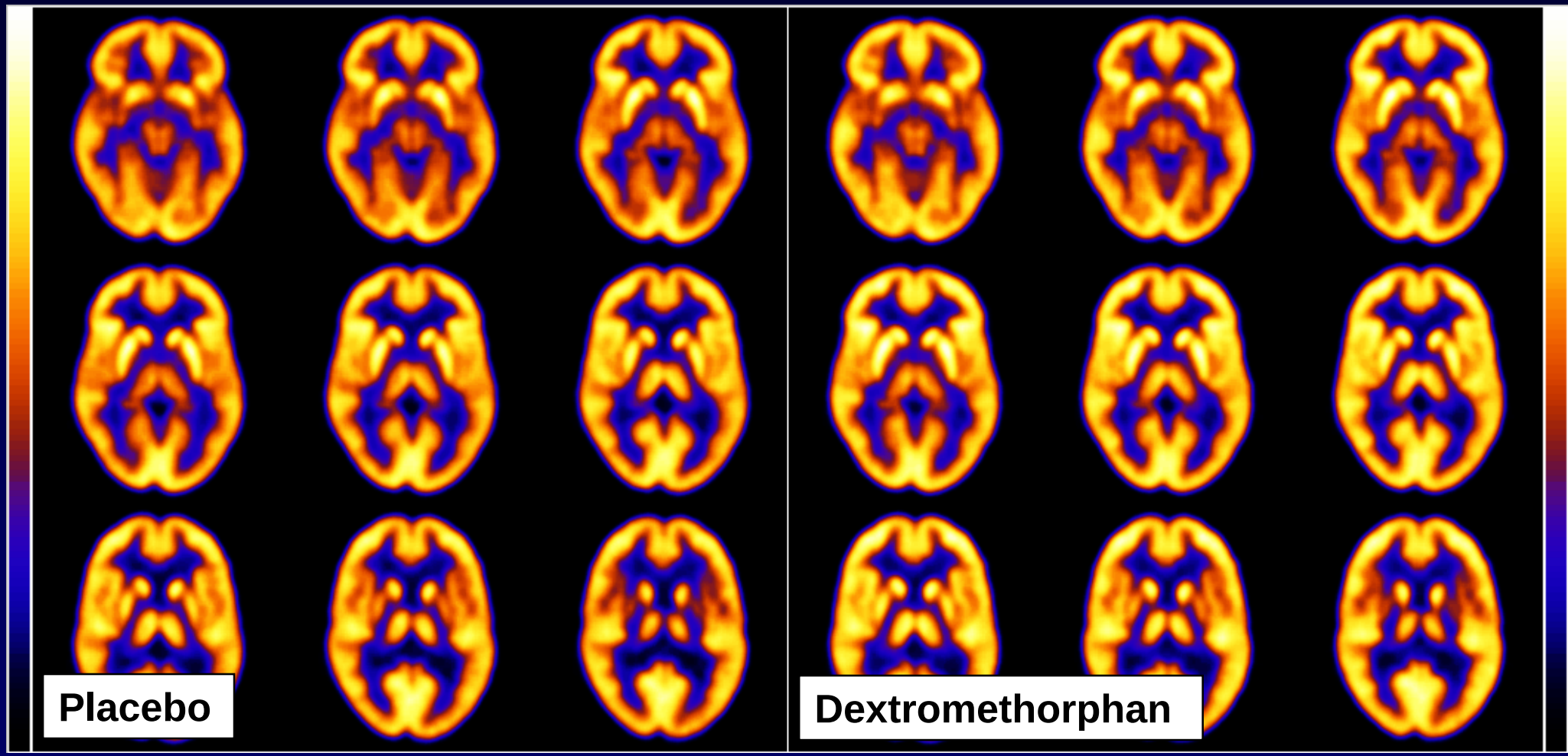
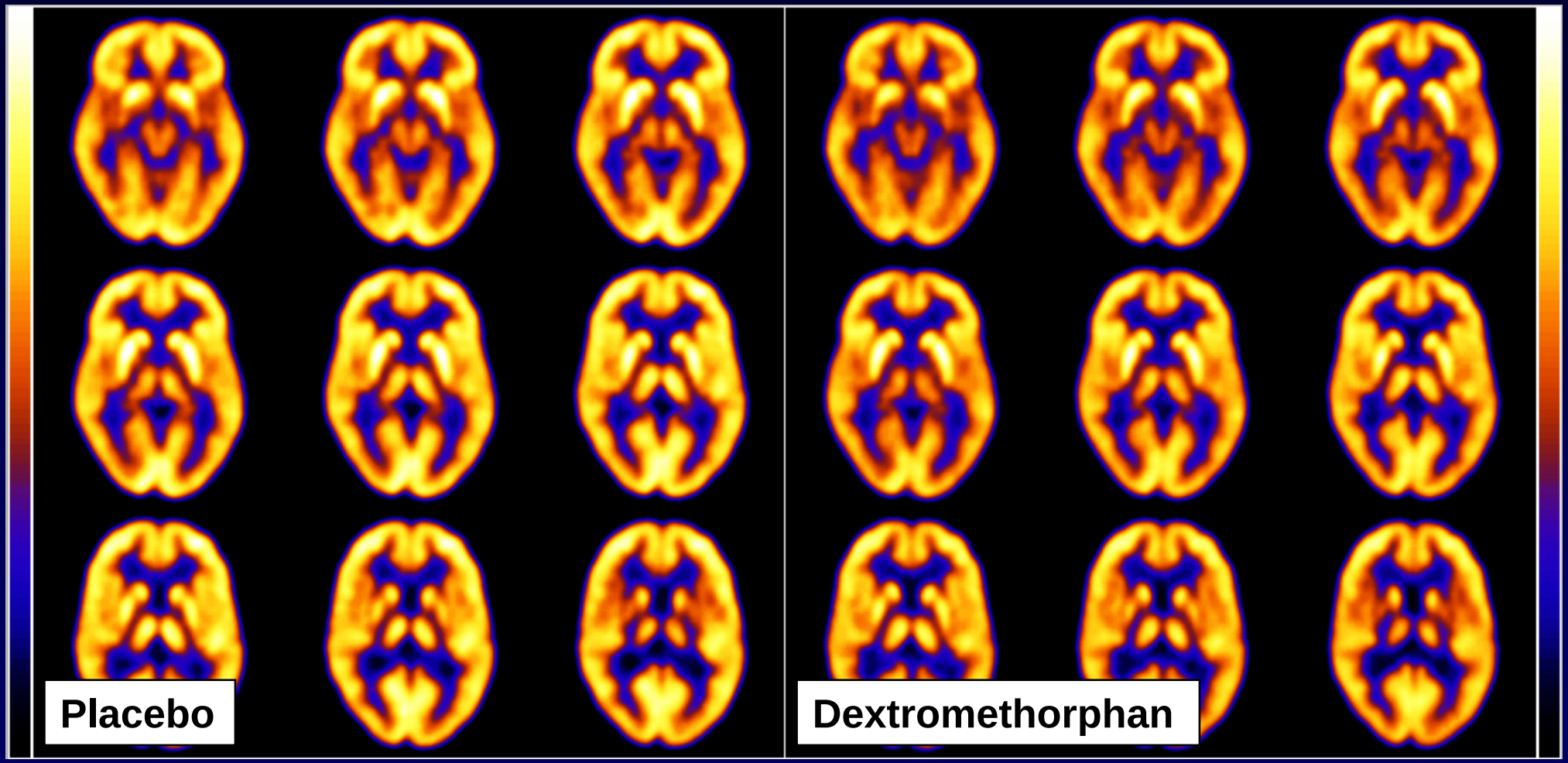
Controls: Influence of Dextromethorphan on rCMRglc



Controls: Dextromethorphane leads to a slight increase in rCMRglc compared to placebo condition.

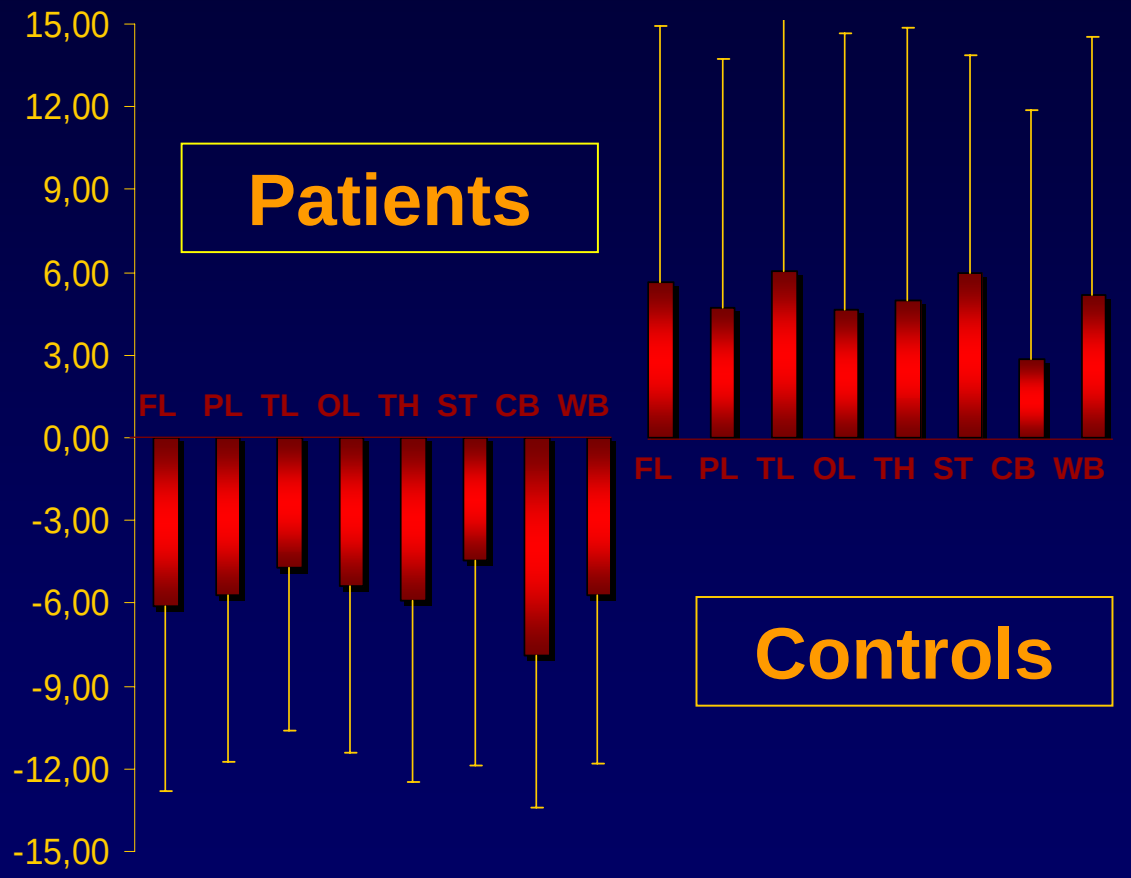
Patients: Influence of Dextromethorphan on rCMRglc



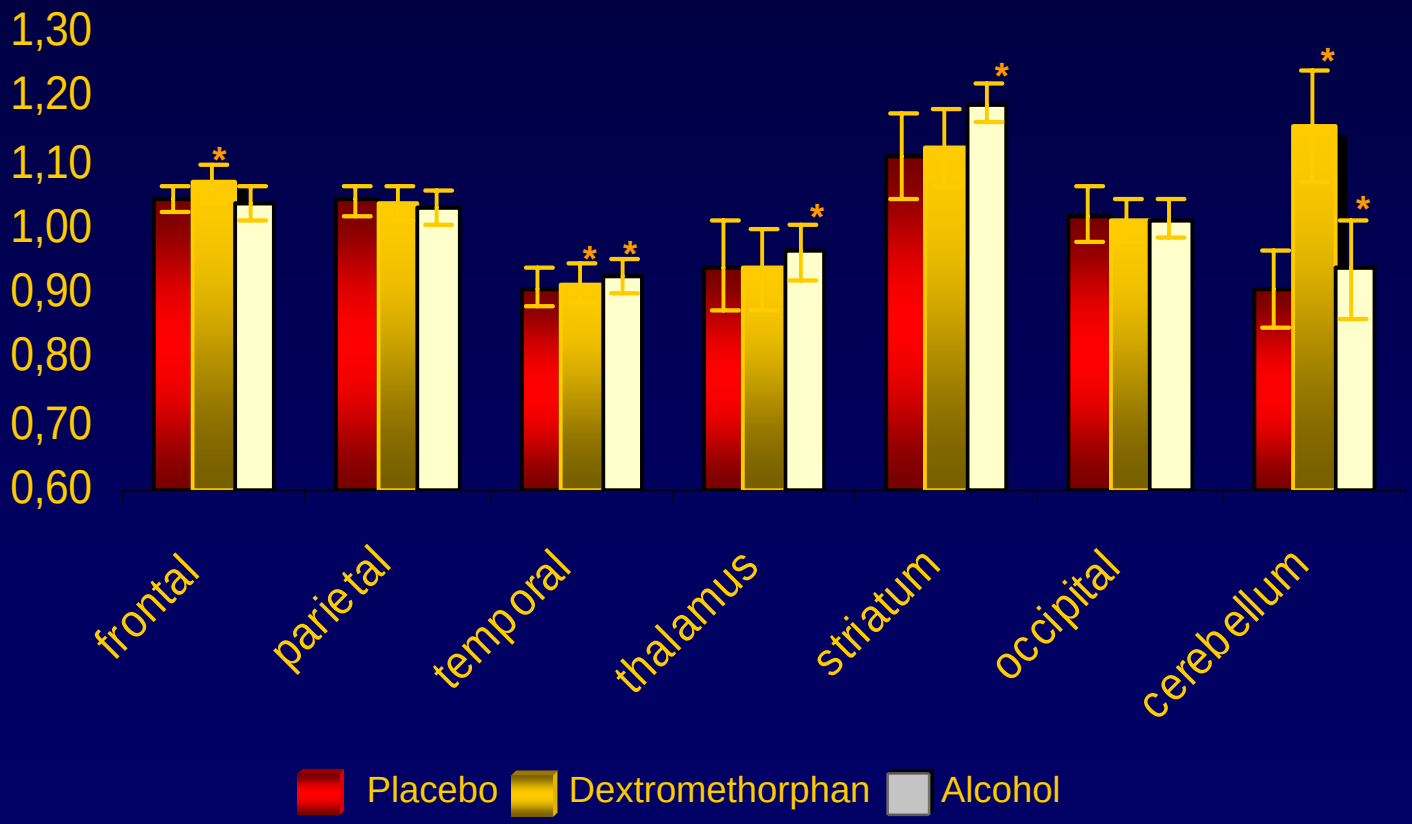
Patients: Dextromethorphan lead to a slight decrease in rCMRglc compared to placebo condition.

Regional effects Placebo vs. Dextromethorphane

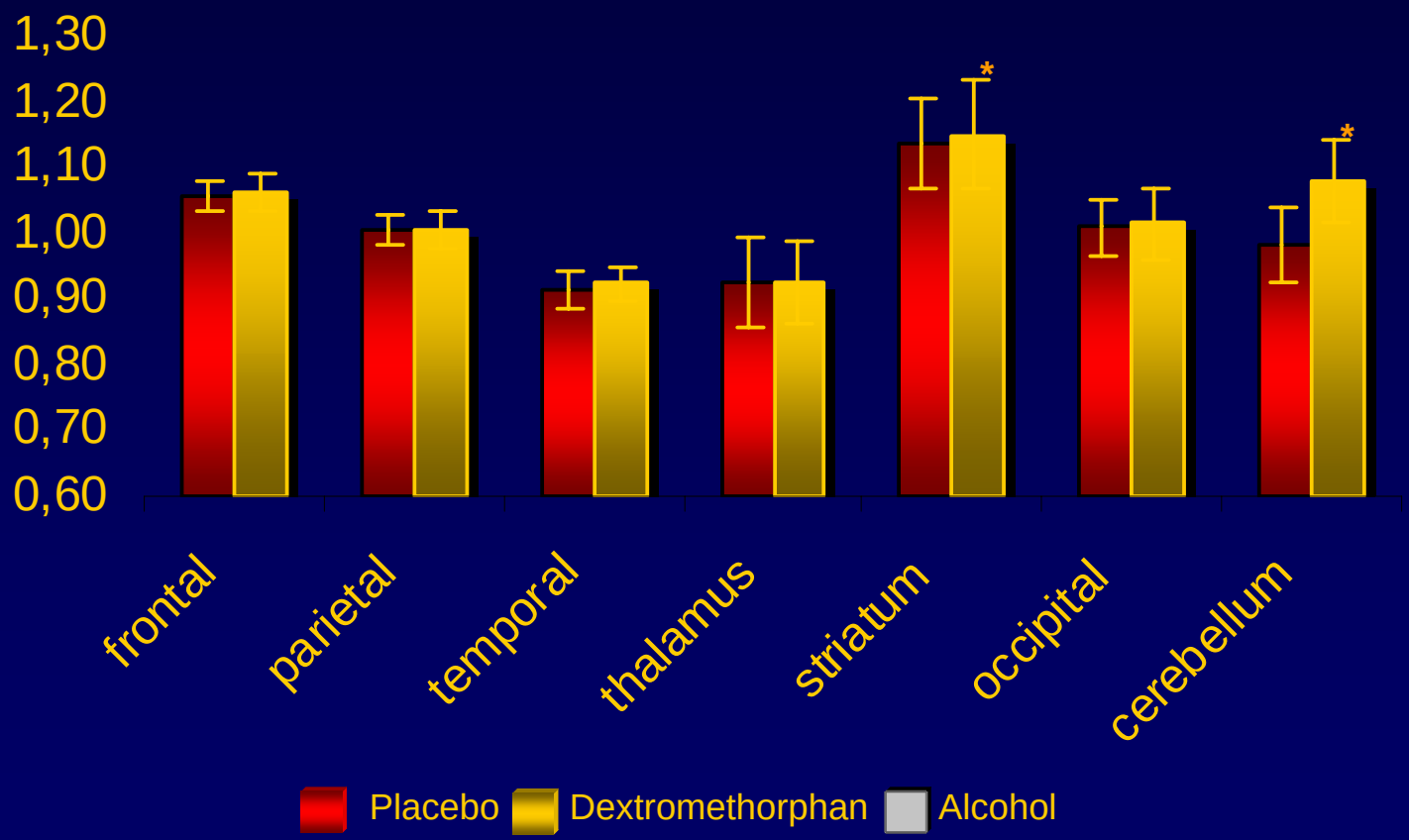
	Patients	Controls	Sign.
Frontal lobe	- 6%	+ 6%	p < 0,05
Parietal lobe	- 6%	+ 5%	p < 0,05
Temporal lobe	- 5%	+ 6%	p < 0,05
Occipital lobe	- 5%	+ 5%	p < 0,05
Thalamus	- 6%	+ 5%	p < 0,05
Striatum	- 4%	+ 6%	p < 0,05
Cerebellum	- 8%	+ 3%	p < 0,05
Whole brain	- 6%	+ 5%	p < 0,05



Controls: relative metabolic rates (hyperfrontality etc)



Patients: relative metabolic rates



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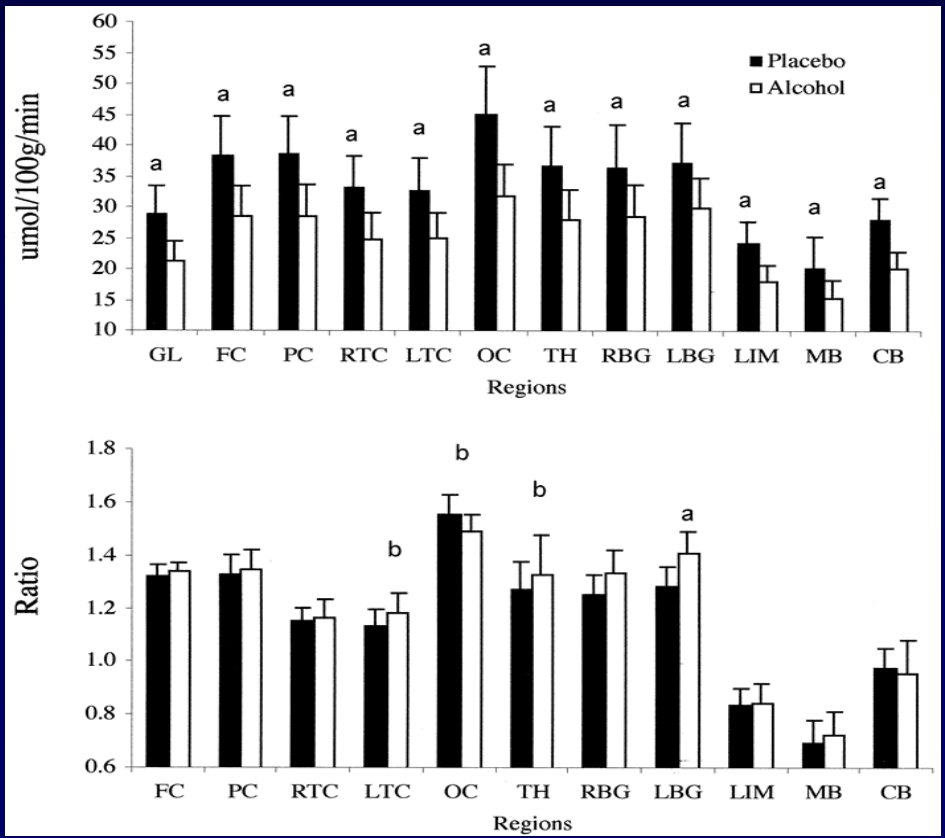
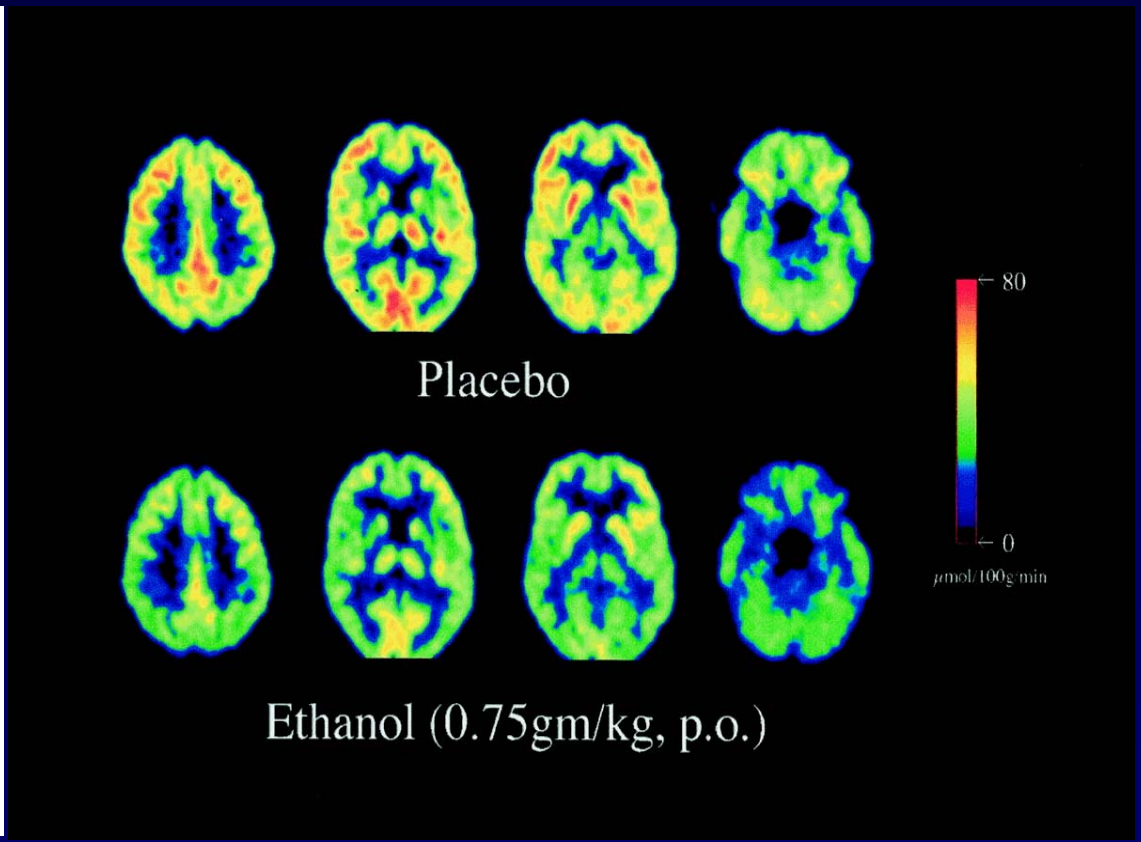
FDG-PET after Alcohol

- Global Reduction of CMRglc, v.a. occipital und cerebella





(Wang et al. 2002)

Summary:

- No significant differences in rCMRglc between alcoholics and controls under placebo condition
- Alcohol-like effects following dextromethorphan – challenge in controls and alcoholics
  (controls > alcoholics)
- Acute effects of alcohol similar to findings in previous studies (Volkow et al. 1990, Wang 2000)

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Summary:

- While in controls dextromethorphan induces a slight increase in rCMRglc (similar to ketamine), in alcoholics rCMRglc decreases.
- Contrary to our hypothesis concerning sensitivity of the NMDA-System: Differences between alcoholics and controls were qualitativ not quantitativ.
- In healthy controls dextromethorphan shows a spezific pattern, similar to ketamine but not other drugs of abuse.

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Ergebnisse: relative Werte Probanden

	PL / DX	PL / AL
Frontal: (re>li)	↑	⇔
Temporal: (re)	↑	⇔
Limb.S.:	⇔	↓
Thalamus:	⇔	↓
Brainstem:	↑	⇔

parietal, occipital, cerebellar no significant differencies

Ziele

Untersuchung des rCMRglc bei

- **gesunden Probanden**

  Placebobedingung
  aktue Wirkung von Dextromethorphan
  akute Wirkung von Alkohol

- **alkoholabhängigen Patienten (2 Wochen nach stationärem Entzug)**

  Placebobedingung
  aktue Wirkung von Dextromethorphan

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NMDA Subunit 2B in Alcohol Dependence

Table 1 Sample characteristics

	Alcohol dependents	Controls
Sex (males/females)	291/86	226/238
Age (years)	42.4±9.1	44.9±14.5
Age of onset (years)	30.1±9.6	
Duration of dependence (years)	11.5±8.5	
Family history positive	119 (31.6)	
Alcohol withdrawal-induced epileptic seizures (n°; %)	57 (15.1)	
Alcohol withdrawal-induced delirium tremens (n°; %)	64 (16.9)	

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NMDA Subunit 2B in Alcohol Dependence

Table 1a Alcohol dependents characteristics and NR2B polymorphisms genotype

	SNP 1806191			SNP 1806201		
	AA	AG	GG	CC	CT	TT
Sex (m/f), n=377	78/22	143/43	70/21	153/48	120/32	18/6
Age (ys.)	41.7±8.5	42.7±9.2	42.3±9.6	42.3±8.8	42.9±9.4	40.3±9.9
Age of onset (ys.)	29.2±9.3	30.4±9.4	30.5±10.2	30.3±8.9	30.0±10.6	29.5±9.0
Duration of dependence (ys.)	11.9±9.0	11.4±8.3	11.2±8.5	10.9±8.2	12.4±8.5	11.2±10.4

No differences were detected between genotype groups of each polymorphism (one-way ANOVA, $p<0.05$).

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NMDA Subunit 2B in Alcohol Dependence

Table 2 SNP1806201 genotype distribution and allele frequencies in controls and patient subgroups

Sample	Genotype distribution					Allele frequencies			
	CC n (%)	CT n (%)	TT n (%)	P^1 *(df=2)*	P^2 *(df=2)*	C n (%)	T n (%)	P^3 *(df=1)*	P^4 *(df=1)*
Controls – total group	256 (55.2)	179 (38.6)	29 (6.3)			691 (74.5)	237 (25.5)		
Patients									
- total group	201 (53.3)	152 (40.3)	24 (6.4)	.86		554 (73.5)	200 (26.5)	.65	
- age of onset ≤ 25 ys.	49 (51.6)	39 (41.1)	7 (7.4)	.79		137 (72.1)	53 (27.9)	.50	
- age of onset ≥ 26 ys.	92 (55.4)	60 (36.1)	14 (8.4)	.59	.73	244 (73.5)	88 (26.5)	.73	.73
- seizures positive	32 (56.1)	24 (42.1)	1 (1.8)	.38		88 (77.2)	26 (22.8)	.53	
- seizures negative	150 (54.2)	105 (37.9)	22 (7.9)	.68	.24	405 (73.1)	149 (26.9)	.56	.37
- delirium positive	39 (60.9)	22 (34.4)	3 (4.7)	.66		100 (78.1)	28 (21.9)	.37	
- delirium negative	132 (55.2)	92 (38.5)	15 (6.3)	1.0	.69	356 (74.5)	122 (25.5)	.99	.40
By gender									
Males									
Controls	119 (52.7)	88 (38.9)	19 (8.4)			326 (72.1)	126 (27.9)		
Patients	153 (52.6)	120 (41.2)	18 (6.2)	.59		426 (73.2)	156 (26.8)	0.70	
Females									
Controls	137 (57.6)	91 (38.2)	10 (4.2)			365 (76.7)	111 (23.3)		
Patients	48 (55.8)	32 (37.2)	6 (7.0)	.60	.79	128 (74.4)	44 (25.6)	.55	.75

[1] χ^2-test to compare patient groups and patient subgroups with corresponding control group, df=2

[2] χ^2-test to compare corresponding patient subgroups, df=2

[3] χ^2-test to compare patient groups and patient subgroups with corresponding control group, df=1

[4] χ^2-test to compare corresponding patient subgroups, df=1

NMDA Subunit 2B in Alcohol Dependence

Table 3 SNP1806191 genotype distribution and allele frequencies in controls and patient subgroups

Sample	Genotype distribution AA n (%)	AG n (%)	GG n (%)	P^1	P^2	Allele frequencies A n (%)	G n (%)	P^3	P^4
Controls – total group	117 (25.2)	235 (50.6)	112 (24.1)			469 (50.5)	459 (49.5)		
Patients									
- total group	100 (26.5)	186 (49.3)	91 (24.1)	.90		386 (51.2)	368 (48.8)	.79	
- age of onset ≤ 25 ys.	28 (29.5)	45 (47.4)	22 (23.2)	.69		101 (53.2)	89 (46.8)	.51	
- age of onset ≥ 26 ys.	40 (24.1)	81 (48.8)	45 (27.1)	.75	.59	161 (48.5)	171 (51.5)	.52	.31
- seizures positive	18 (31.6)	24 (42.1)	15 (26.3)	.44		60 (52.6)	54 (47.4)	.67	
- seizures negative	72 (26.0)	137 (49.5)	68 (24.5)	.95	.57	281 (50.7)	273 (49.3)	.95	.71
- delirium positive	18 (28.1)	32 (50.0)	14 (21.9)	.86		68 (53.1)	60 (46.9)	.58	
- delirium negative	63 (26.4)	115 (48.1)	61 (25.5)	.82	.83	241 (50.4)	237 (49.6)	.97	.59
By gender									
Males									
Controls	56 (24.8)	111 (49.1)	59 (26.1)			223 (49.3)	229 (50.7)		
Patients	78 (26.8)	143 (49.1)	70 (24.1)	.81		299 (51.4)	283 (48.6)	.52	
Females									
Controls	61 (25.6)	124 (52.1)	53 (22.3)			246 (51.7)	230 (48.3)		
Patients	22 (25.6)	43 (50.0)	21 (24.4)	.91	0.98	87 (50.6)	85 (49.4)	.80	0.85

[1] χ^2-test to compare patient groups and patient subgroups with corresponding control group, df=2

[2] χ^2-test to compare corresponding patient subgroups, df=2

[3] χ^2-test to compare patient groups and patient subgroups with corresponding control group, df=1

[4] χ^2-test to compare corresponding patient subgroups, df=1