

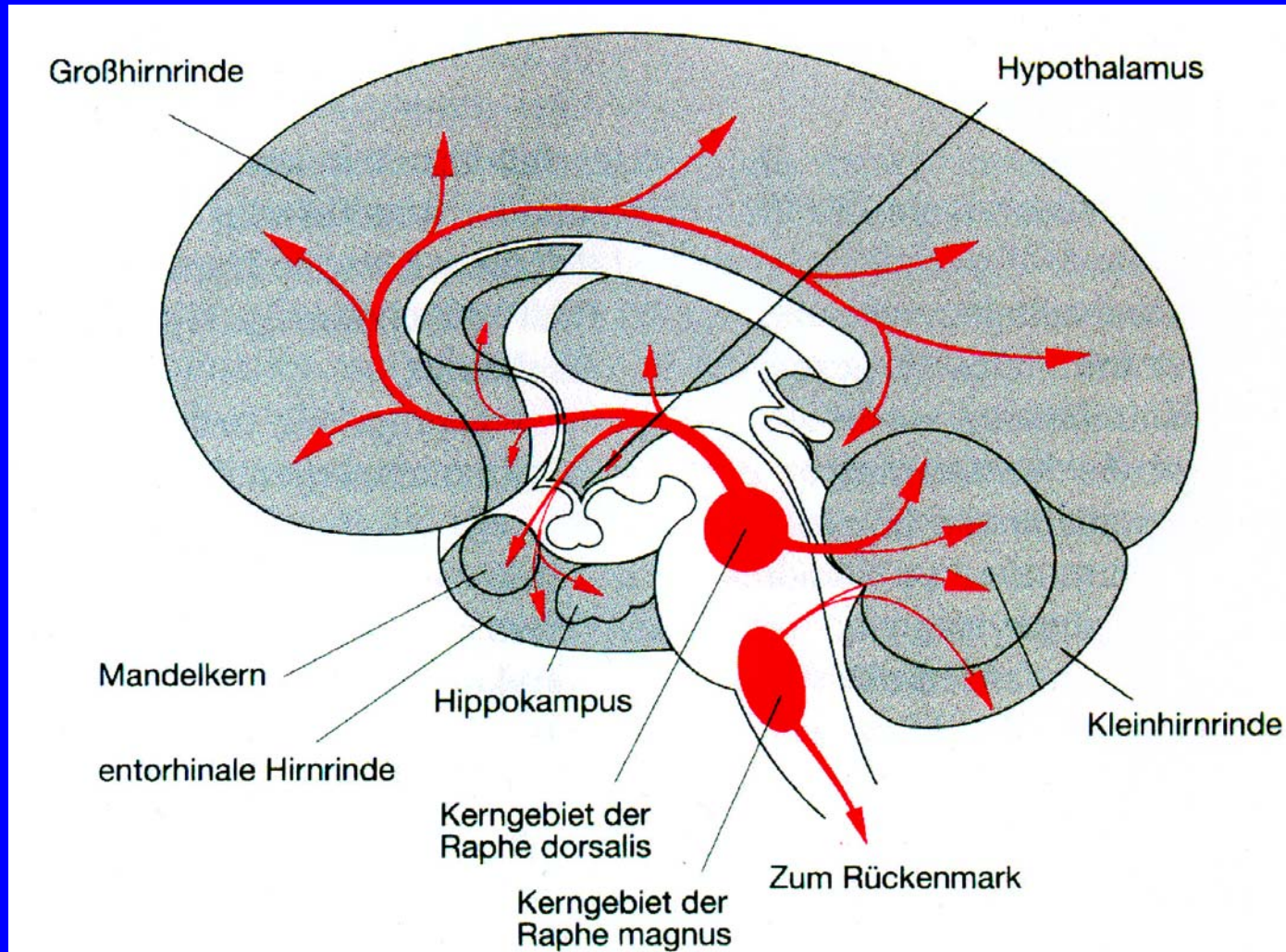
Neurophysiologischen Untersuchungen des Serotonin- Systems

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Universitätsklinikum der Ruhr-Universität Bochum



Zentrales Serotoninsystem (zu trennen vom peripheren im Darm)

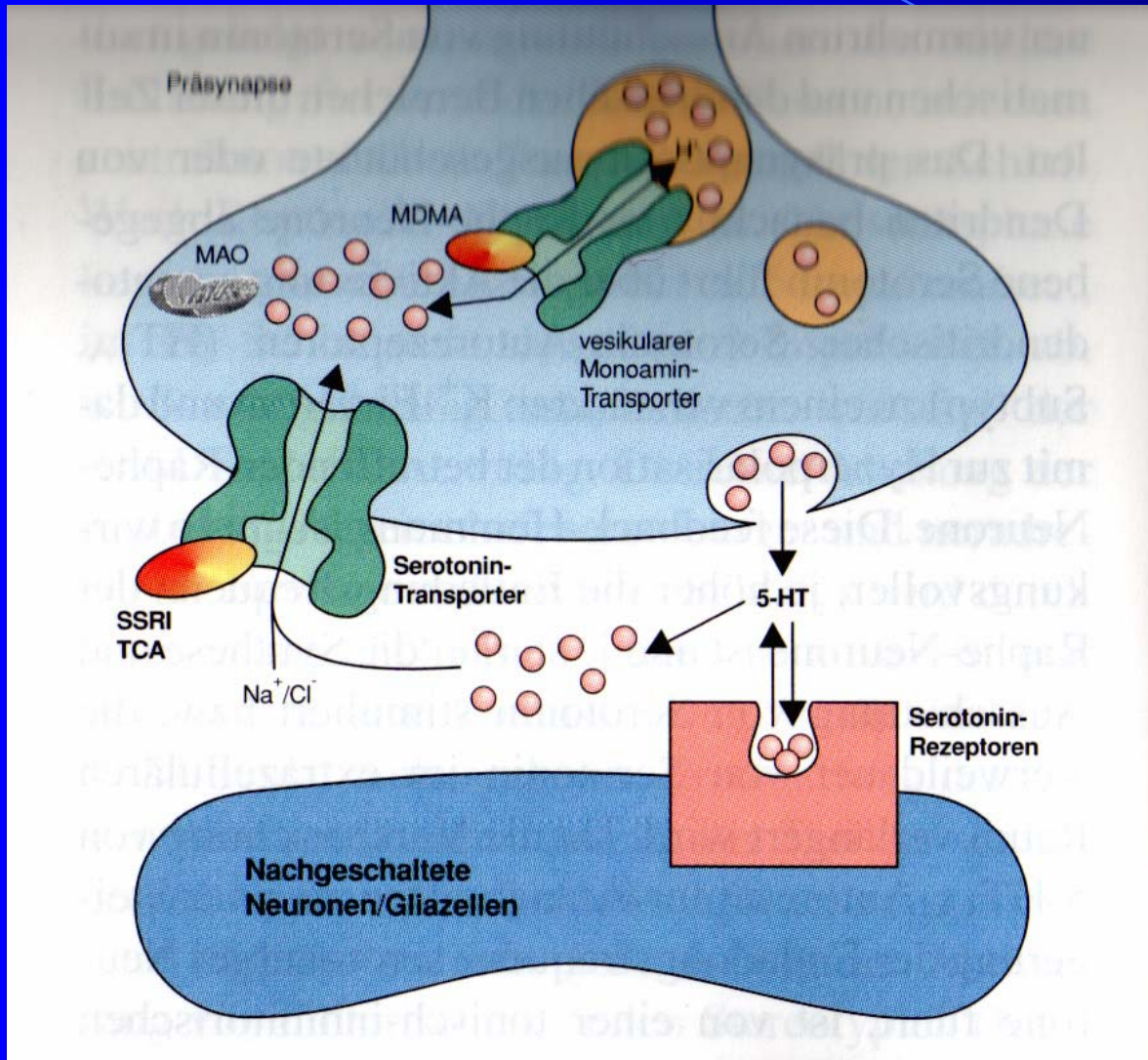


Ursprungsorte und Zielgebiete des serotonergen Neurotransmitter-Systems

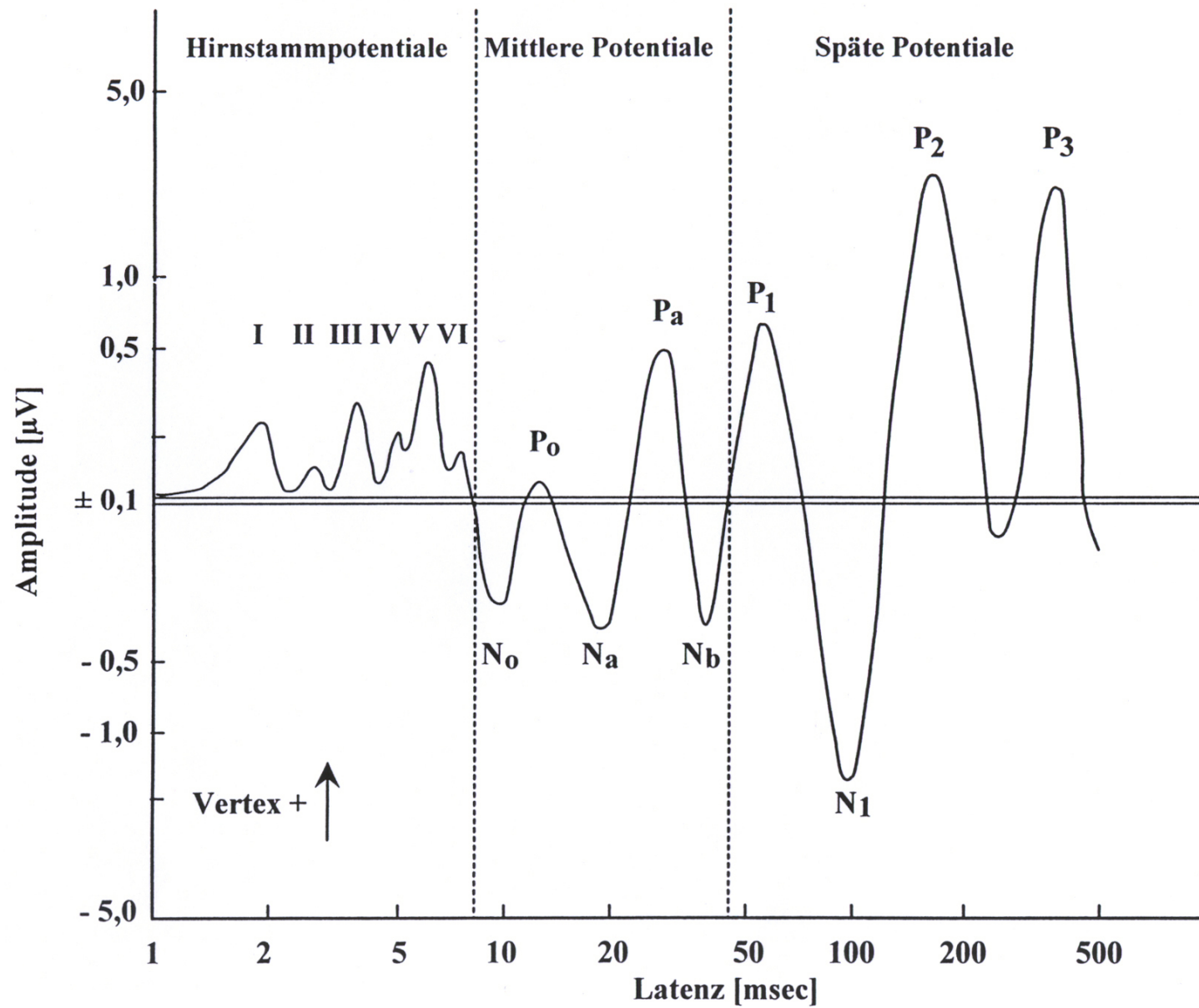
Biochemische Indikatoren für das zentrale serotonerge System

- Serotonin im Vollblut, Serum, Plasma oder Thrombozyt
- Serotonintransporter (Uptake), serotonerge Rezeptoren an der Thrombozytenmembran
- 5-HIES im Liquor
- Cortisol, Prolaktin im Blut nach Fenfluramin, m-CPP oder Citalopram-Gabe
- Tryptophan-Depletion

PET/SPECT-Liganden für 5-HTT: Metabolische versus Release-Seite des serotonergen Systems



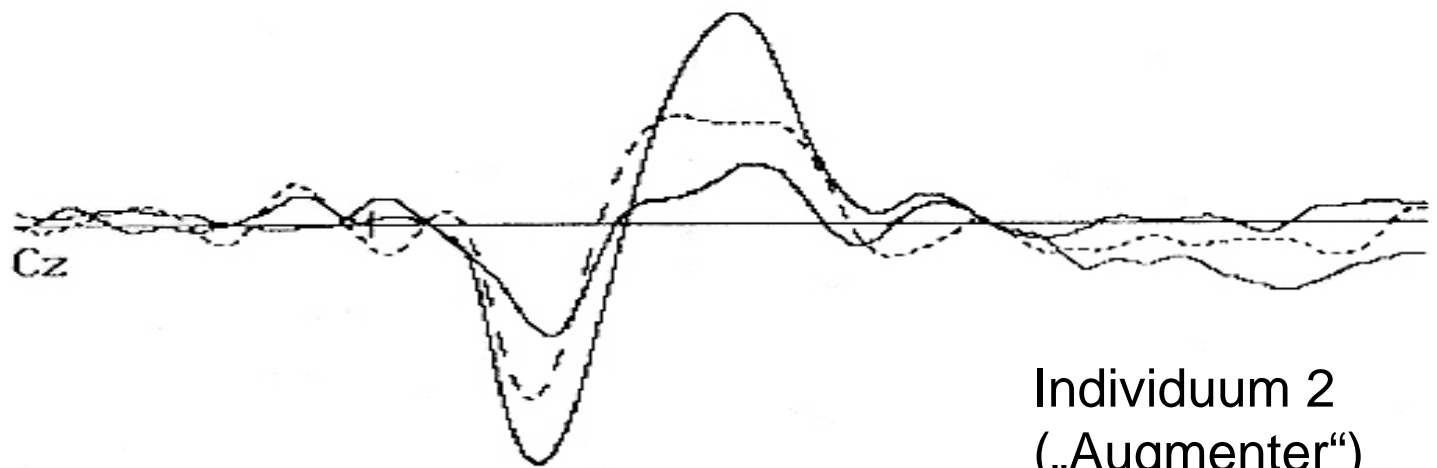
- Uptake: indirektes Maß für Release
- 5-HTT nicht alleine, OCT1-3 (MAO)
- 5-HIES $r < 0.5$
- Rolle der Autorezeptoren
- Gegenregulationsprozesse, Feedbackkreisläufe
- Bindung hoch/niedrig: 5-HT hoch/niedrig ?





Cz

Individuum 1
(„Reducer“)



Cz

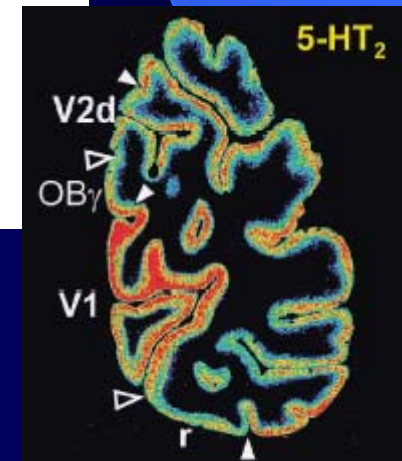
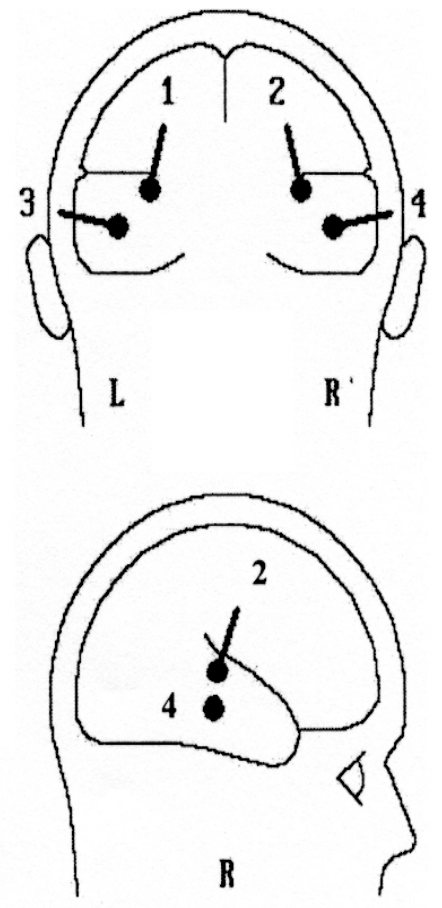
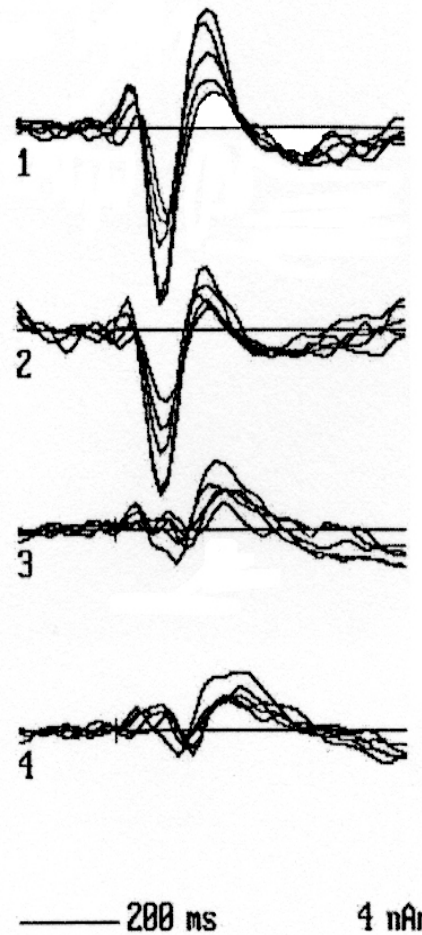
Individuum 2
(„Augmenter“)

100 ms

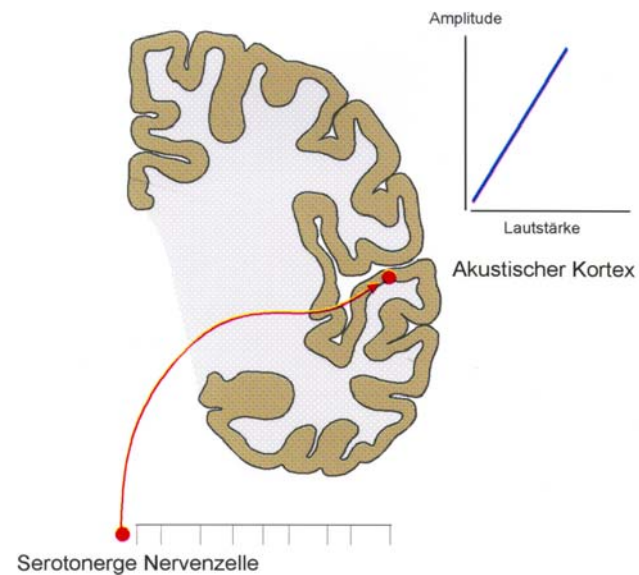
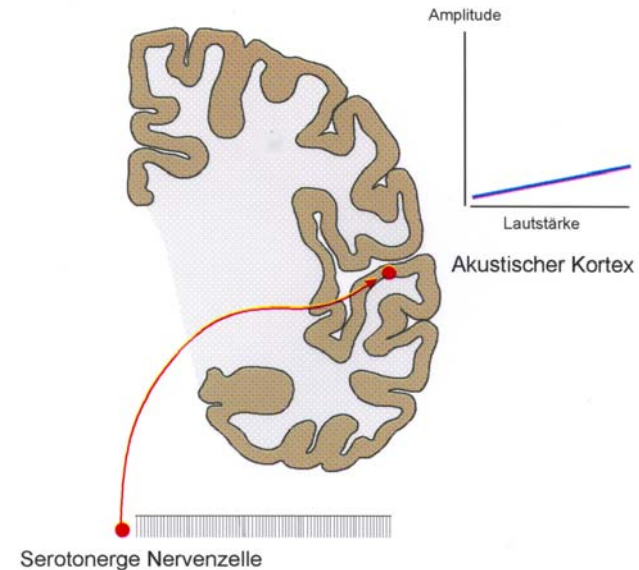
aver.ref.

15 μ V

left
tangential dipole
right
left
radial dipole
right

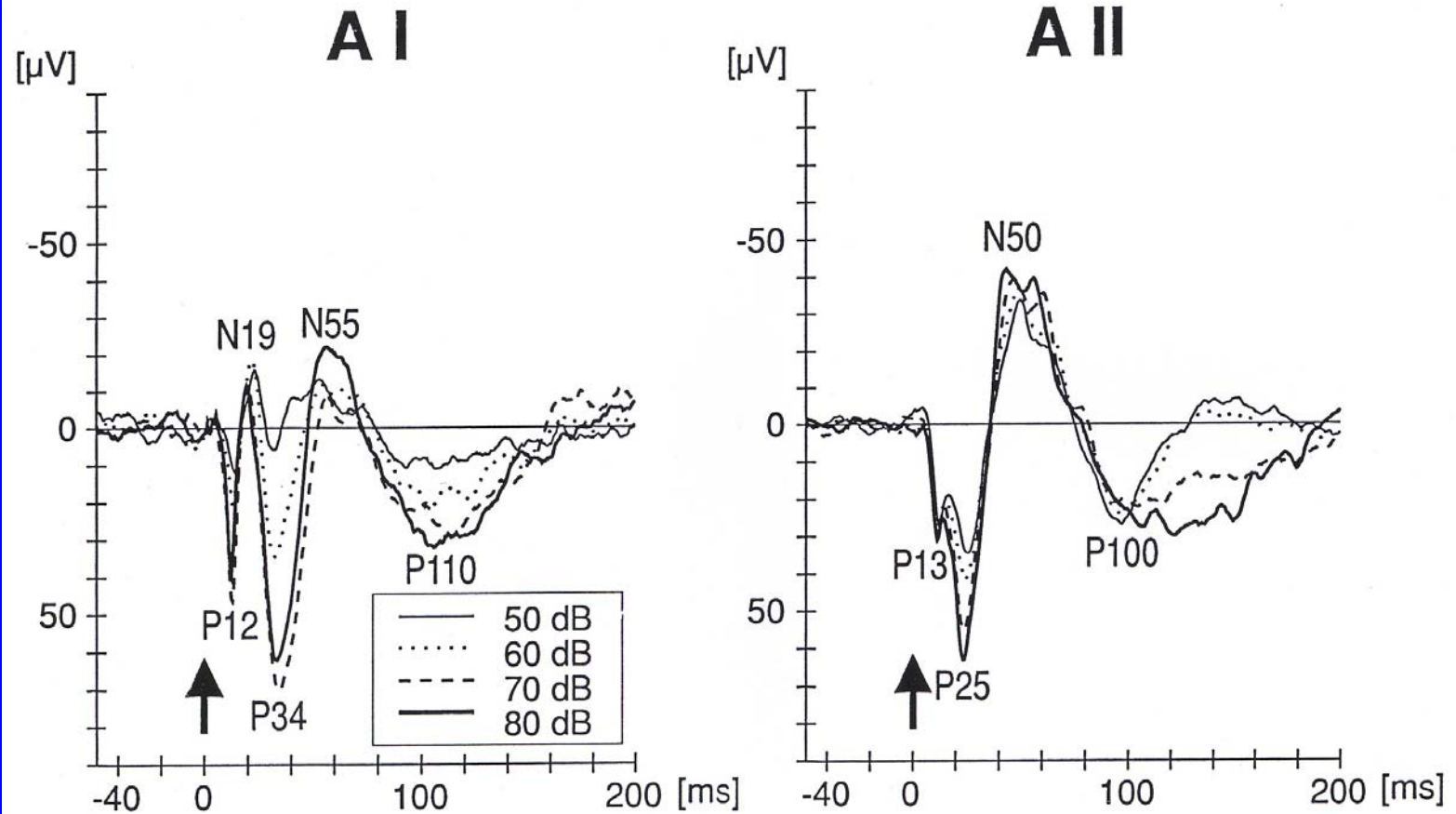


Lautstärkeabhängigkeit
akustisch evozierter Potentiale
(LAAEP) als Indikator des
synaptisch freigesetzten
terminalen Serotonins
(primärer akustischer Kortex)

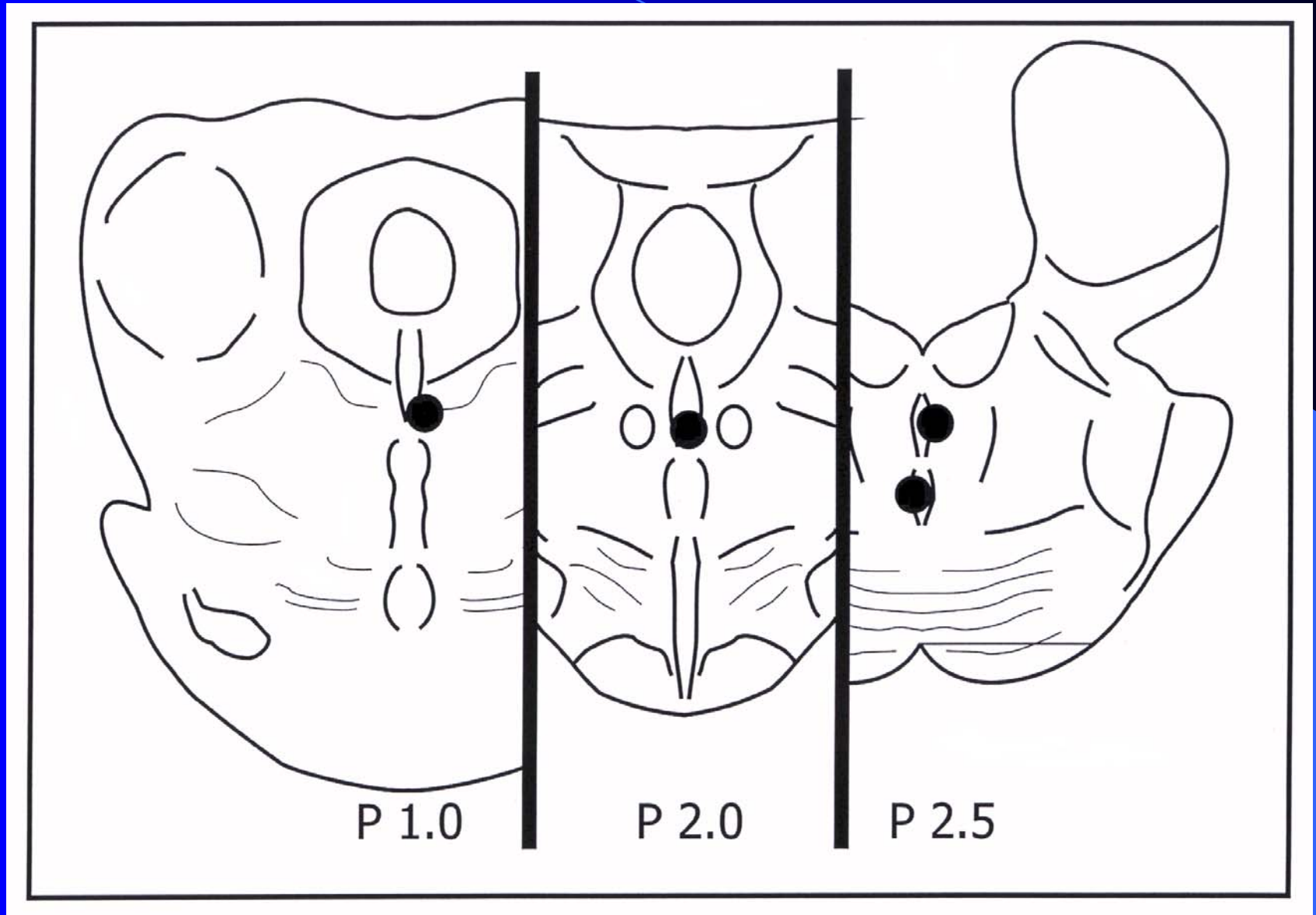


Juckel et al. 1996, 1997, 1999,
Hegerl und Juckel 1993

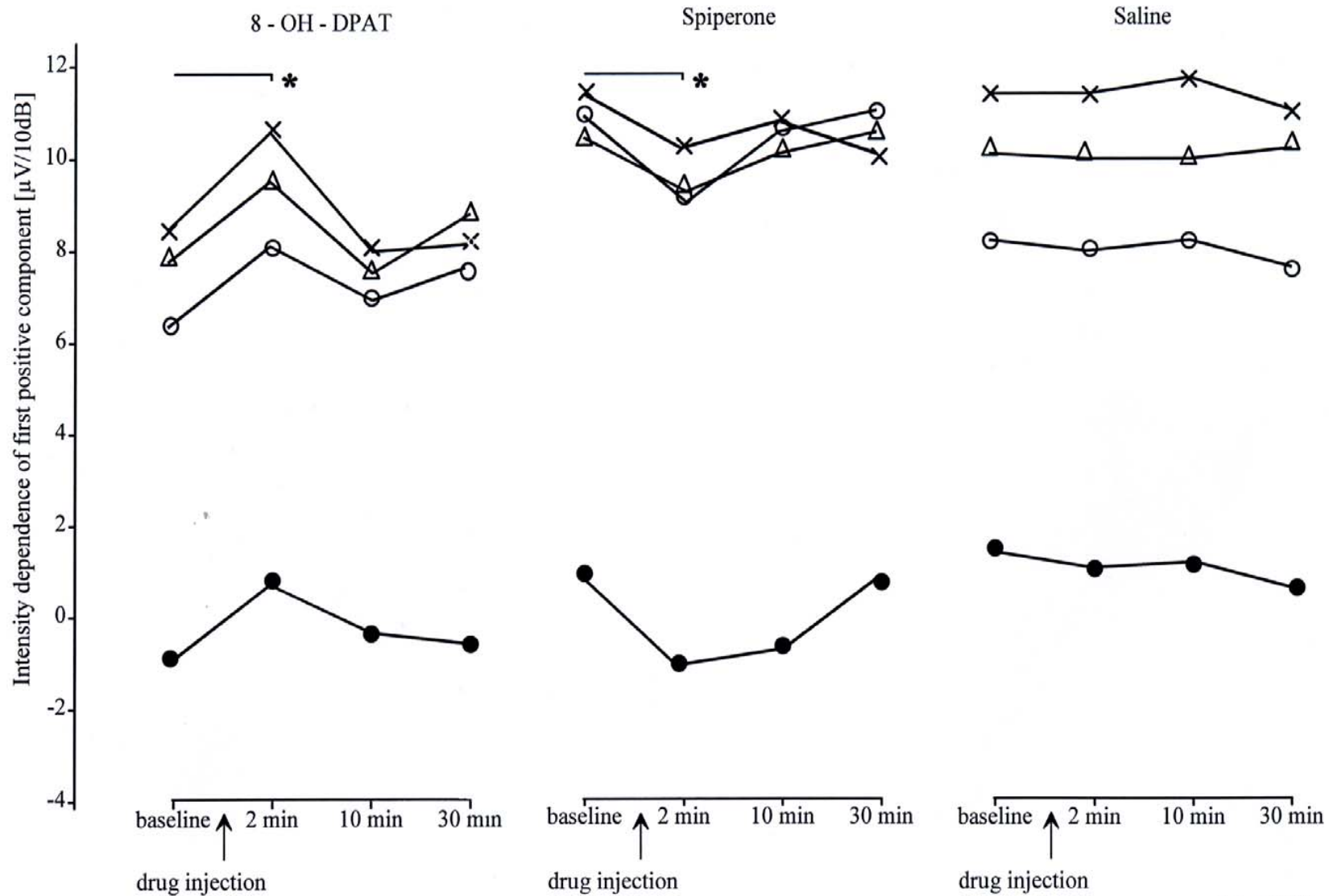
Tiermodell der LAAEP



Injektion von 8-OH-DPAT und Spiperon lokal in den Raphe dorsalis (Juckel et al. 1999)

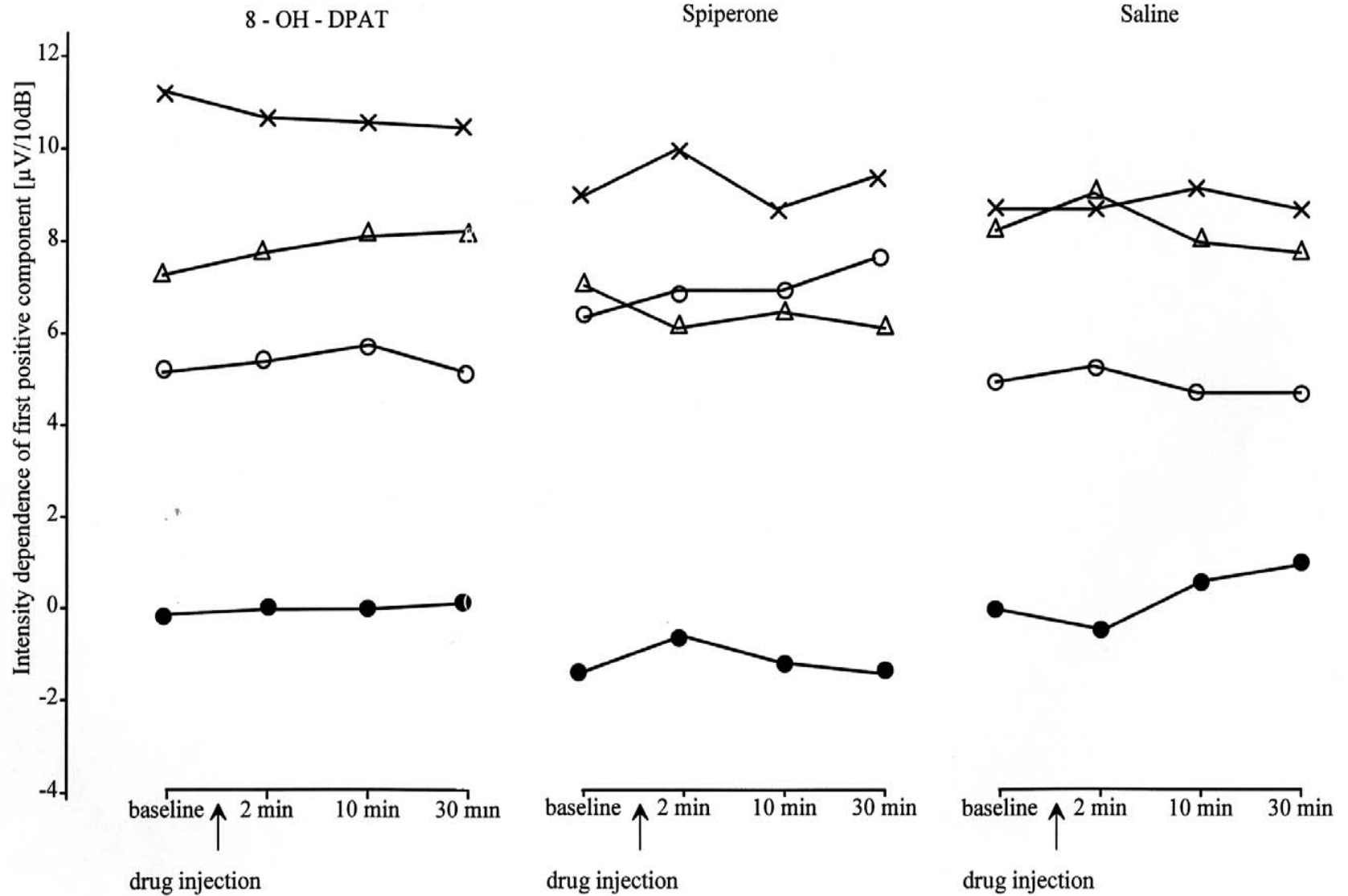


PRIMARY AUDITORY CORTEX

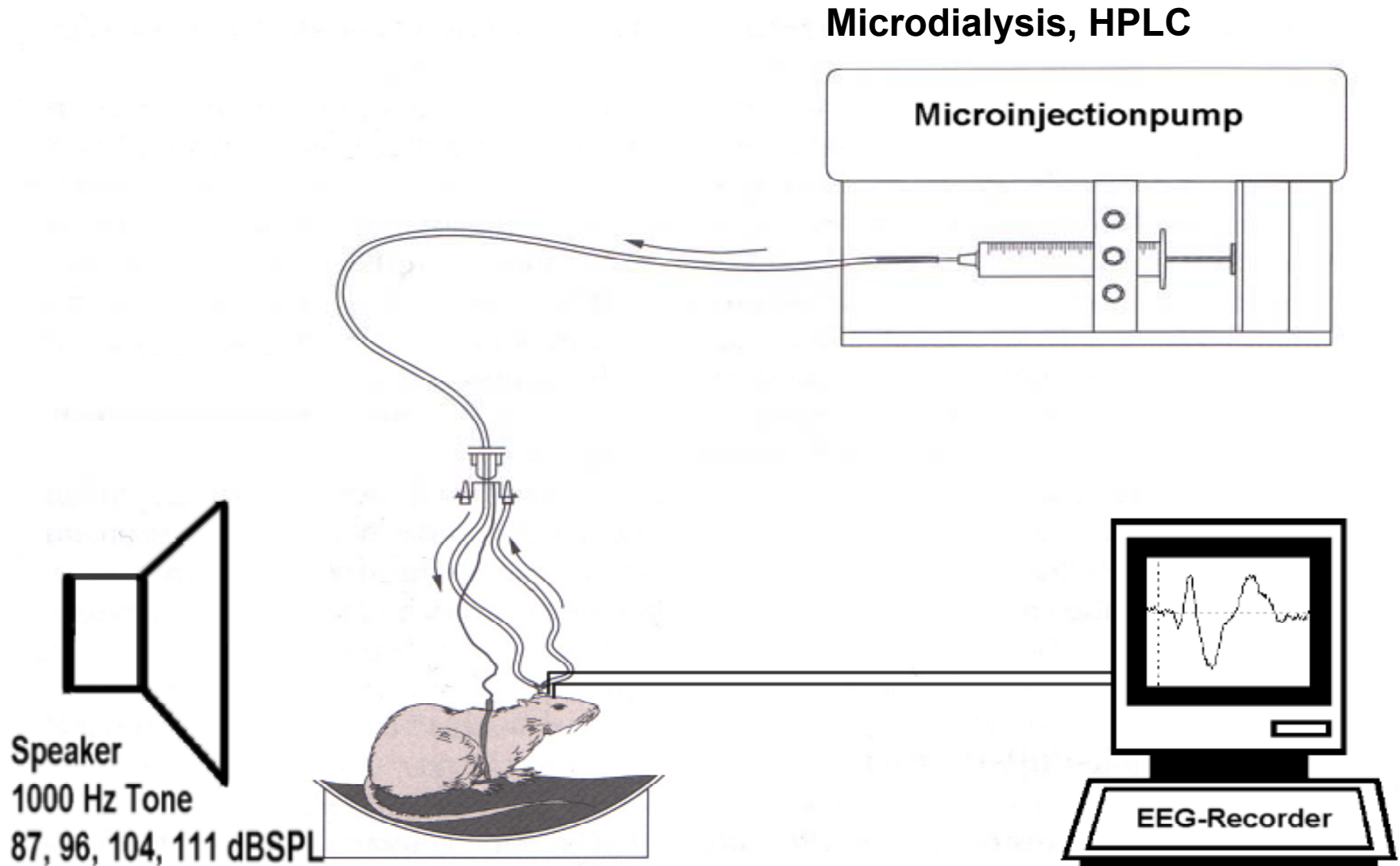


* $p < 0.05$

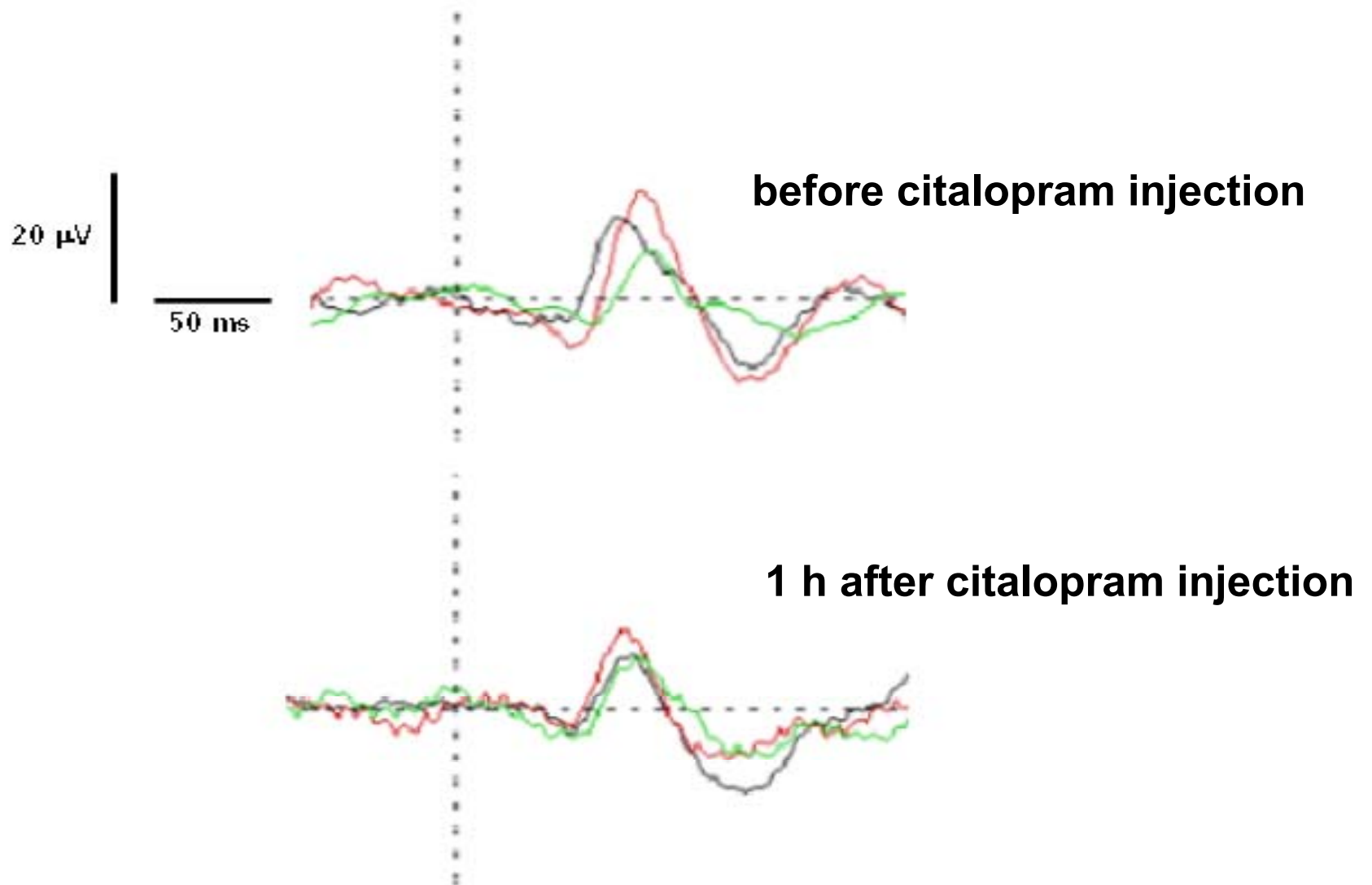
SECONDARY AUDITORY CORTEX



Simultane Messung von LAAEP und Serotonin-Spiegel im primären akustischen Kortex der Ratte



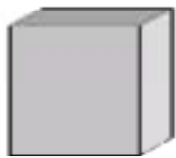
AEP vor und nach Injektion des SSRI Citalopram



Serotonin-Spiegel und LAAEP im primären akustischen Kortex

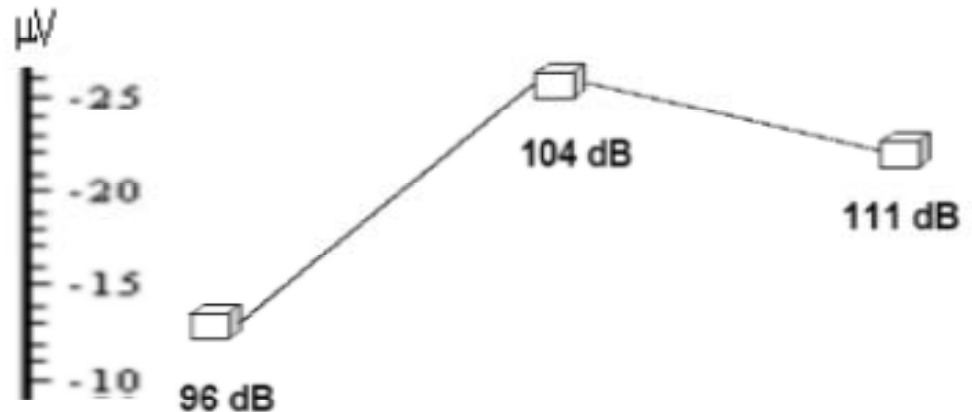
Serotonin level

0,308 pg/ μ l



5 HT

before
SSRI

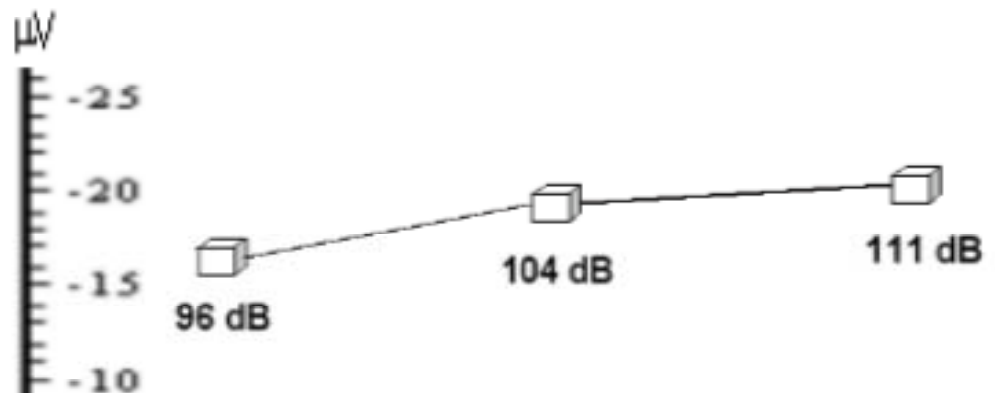


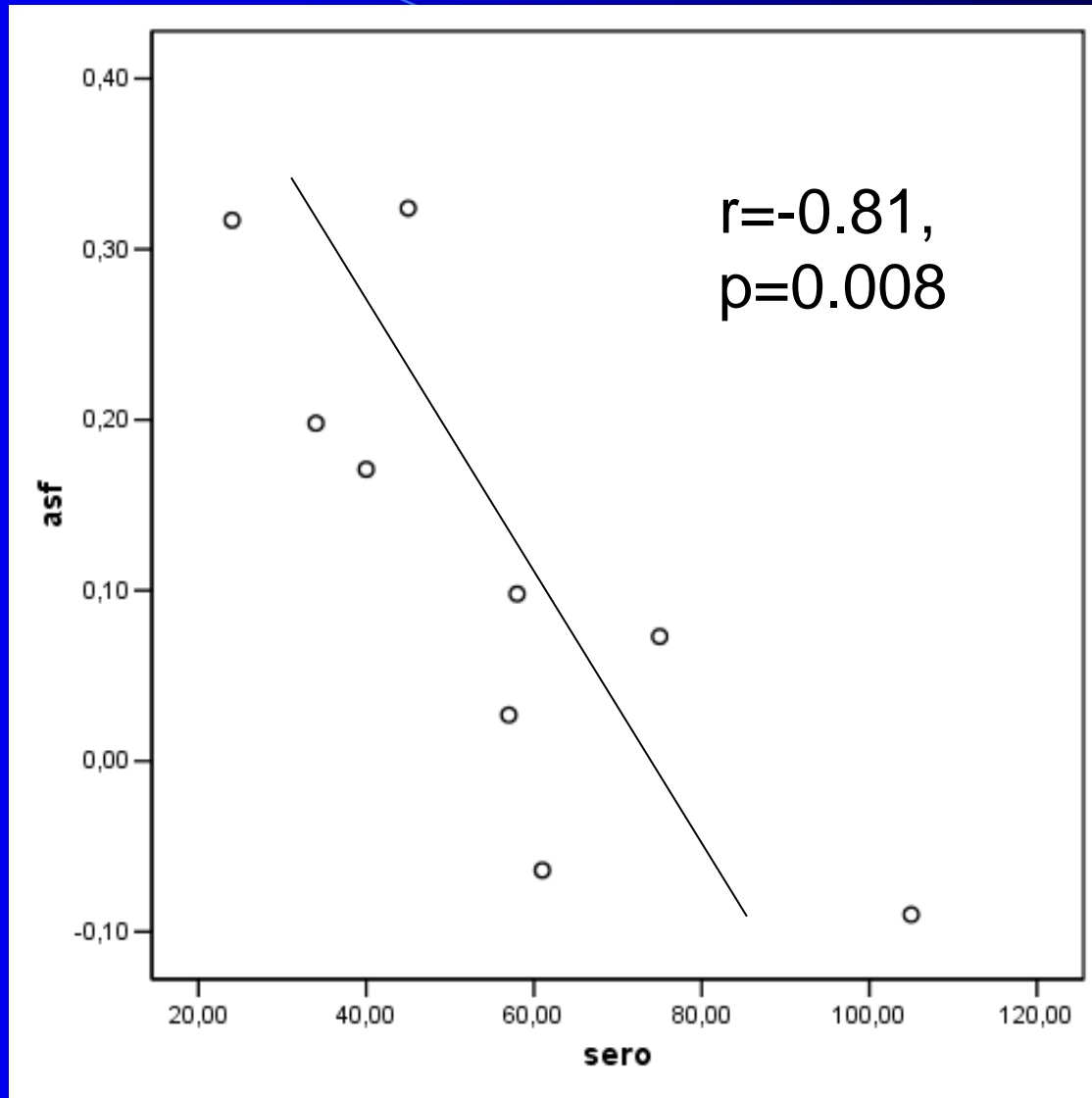
0,609 pg/ μ l



5 HT

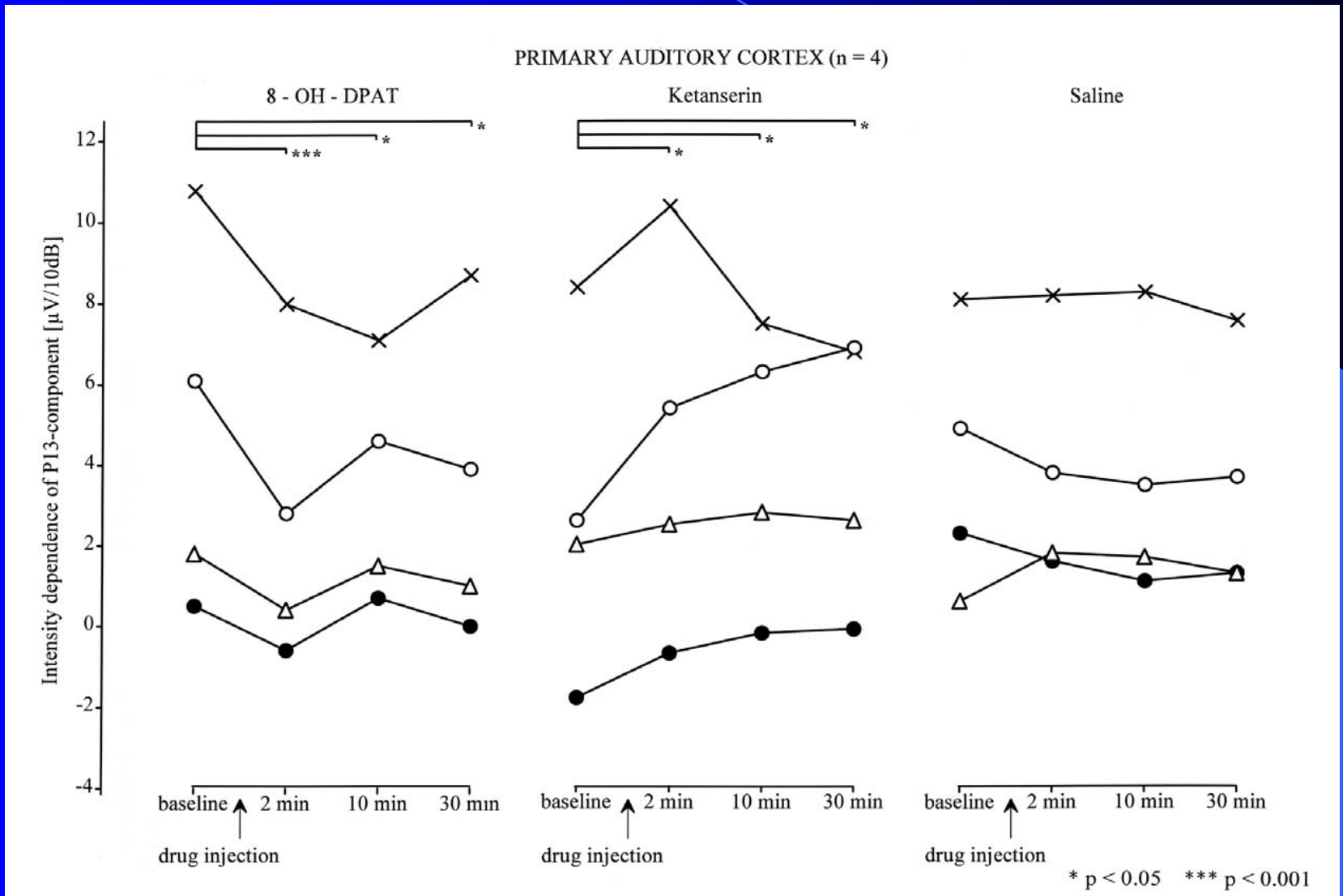
1 h after
injection
of SSRI



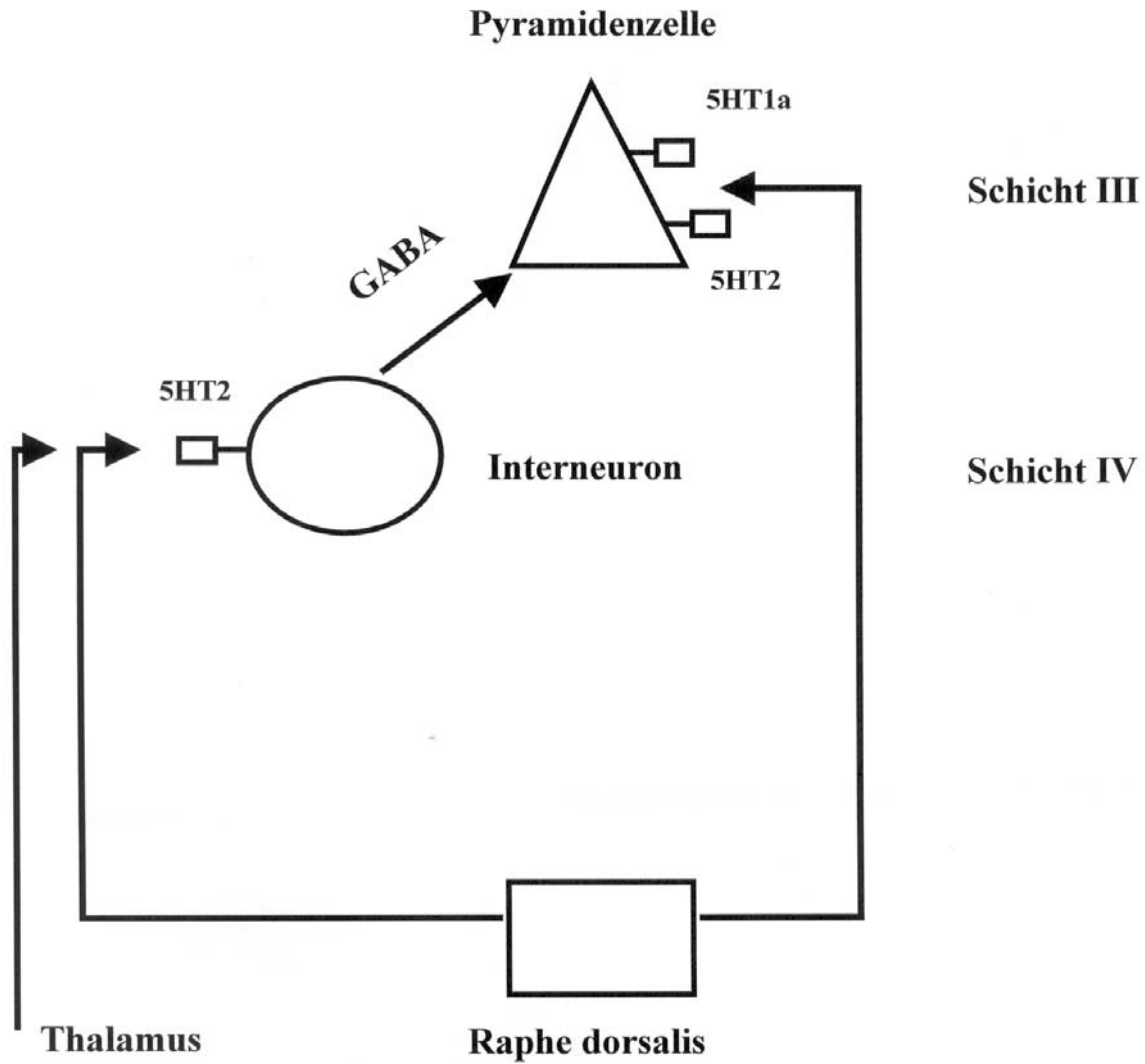


Wutzler et al. 2008

Wirkung von 5-HT_{1A}-Agonisten (8-OH-DPAT) und 5-HT₂-Antagonisten (Ketanserin) auf LAAEP (Juckel et al. 1997)



Lautstärkeabhängigkeit



LAAEP bei 185 gesunden Probanden

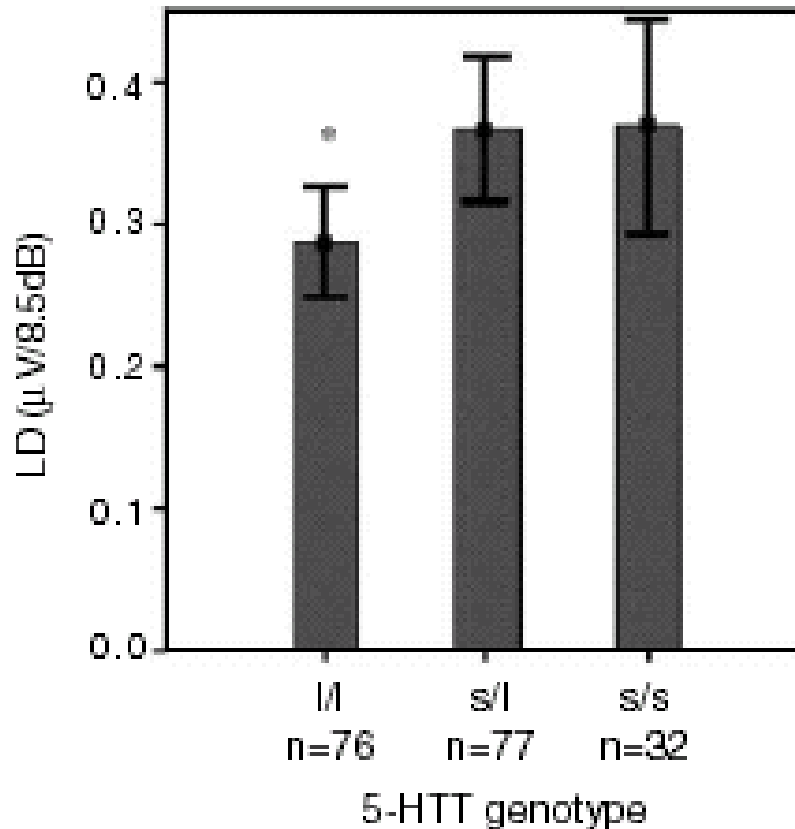


Figure 1 Mean values and standard error of mean of the LD for three genotypes. The l/l homozygous group has a significant weaker LD as compared to the s/l group (* $p = 0.022$).

$$F_{(2,182)} = 4.172, p = 0.017$$



Hensch und Strobel-Arbeiten: LDAEP erhöht bei I/I

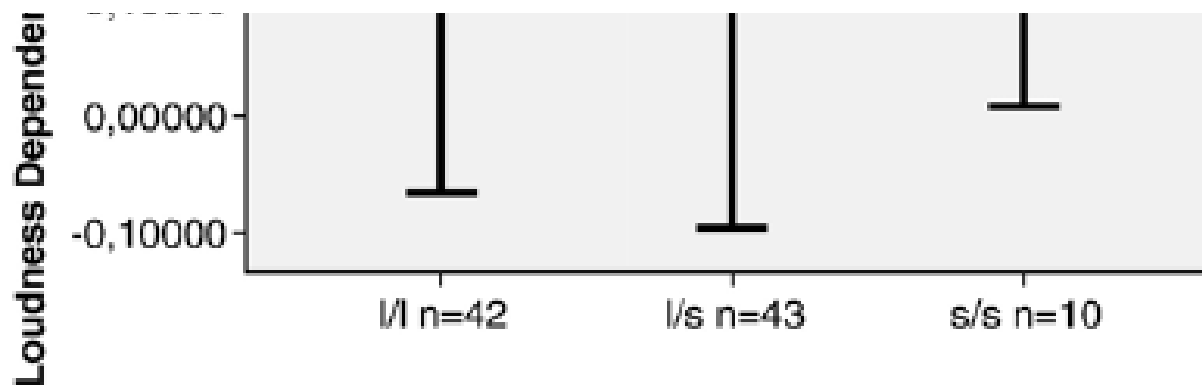
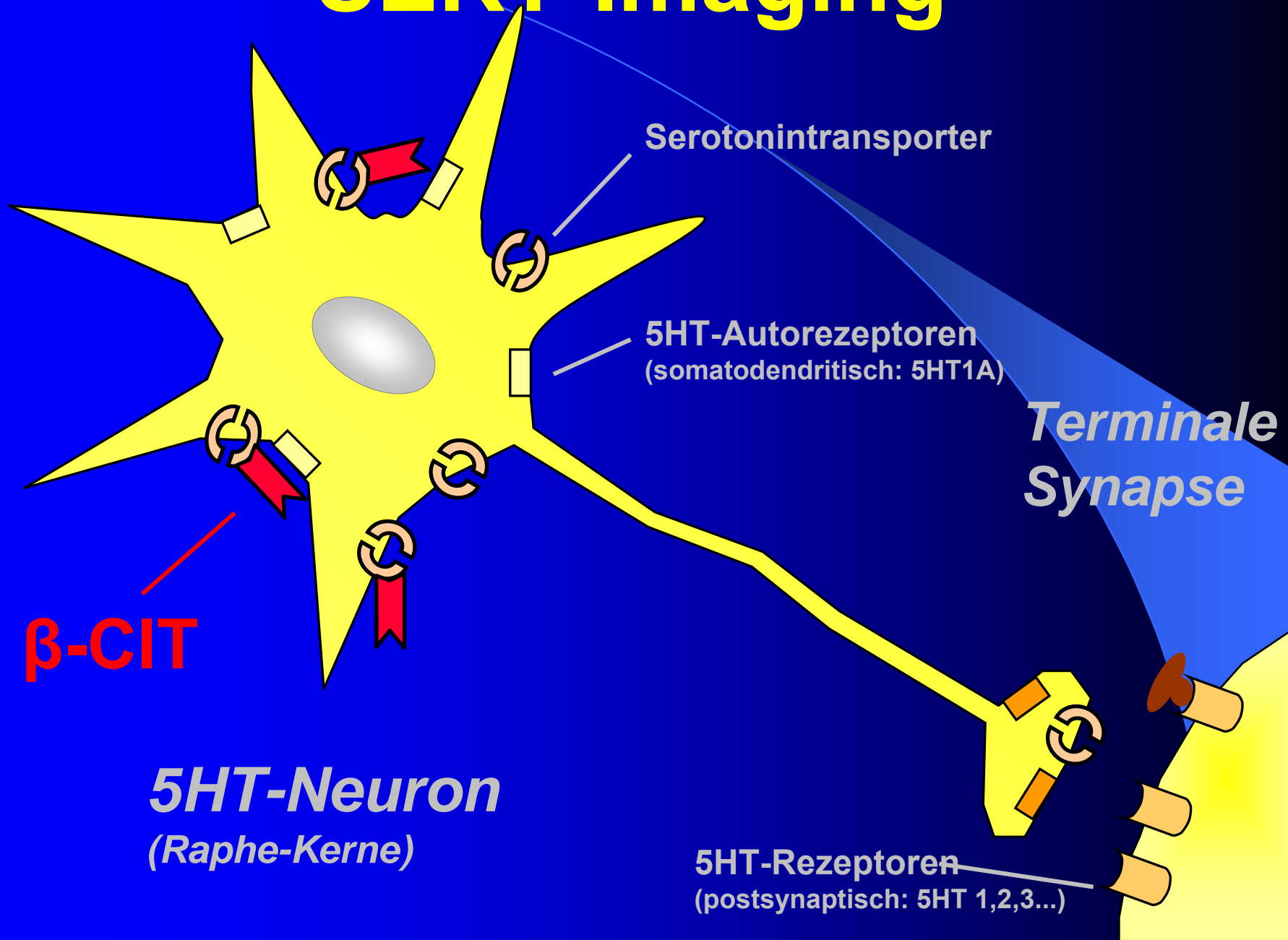


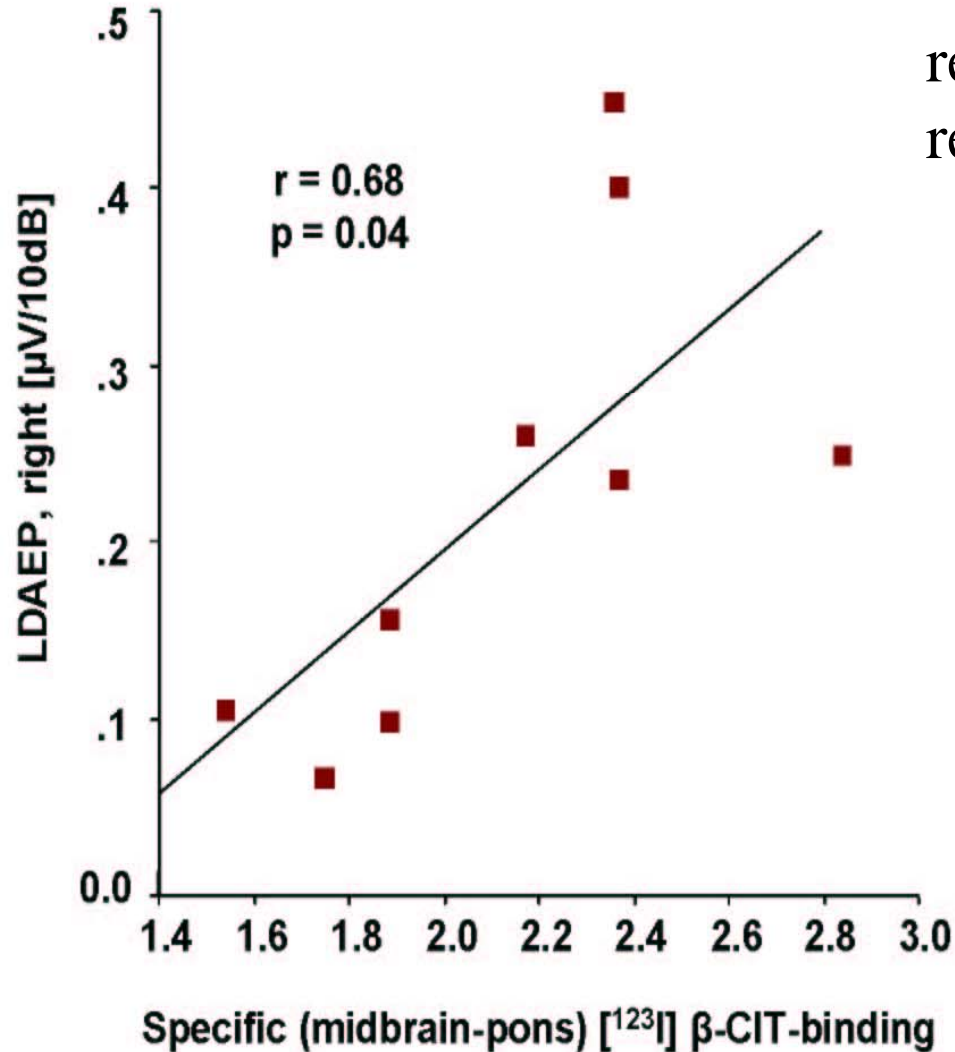
Fig. 2. Mean values and standard deviations of loudness dependence (LD) for the three genotypes of the polymorphism in the promoter region of the 5-hydroxytryptamine transporter (*5-HTT*) gene (*rs4795541* Ins/Del).

SERT-Imaging



Combination of AEP and SPECT in Patients with OCD

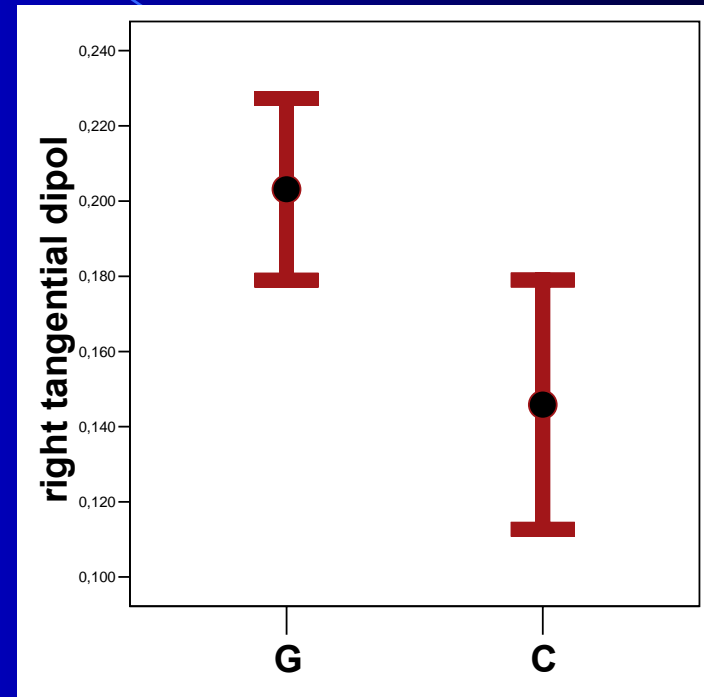
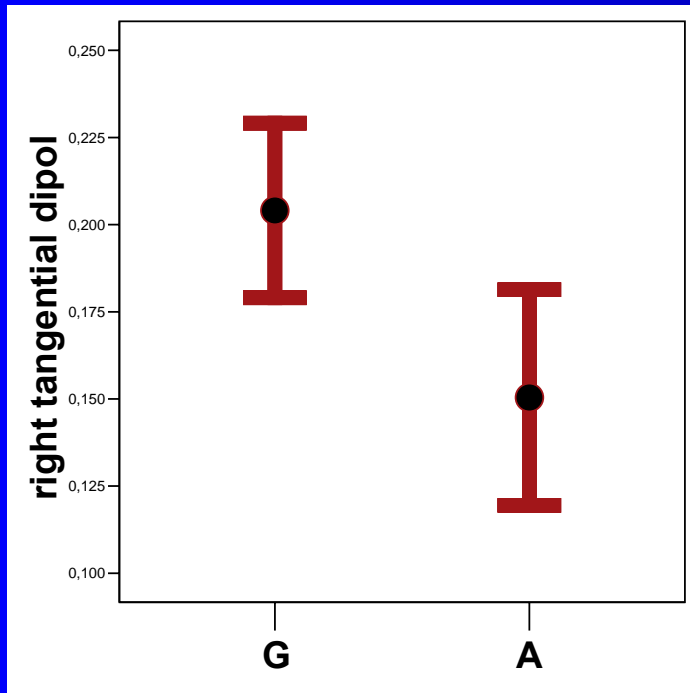
Correlation of LDAEP and SERT-availability as assessed by β -CIT and SPECT



release marker and
reuptake marker

Pogarell et al. 2004

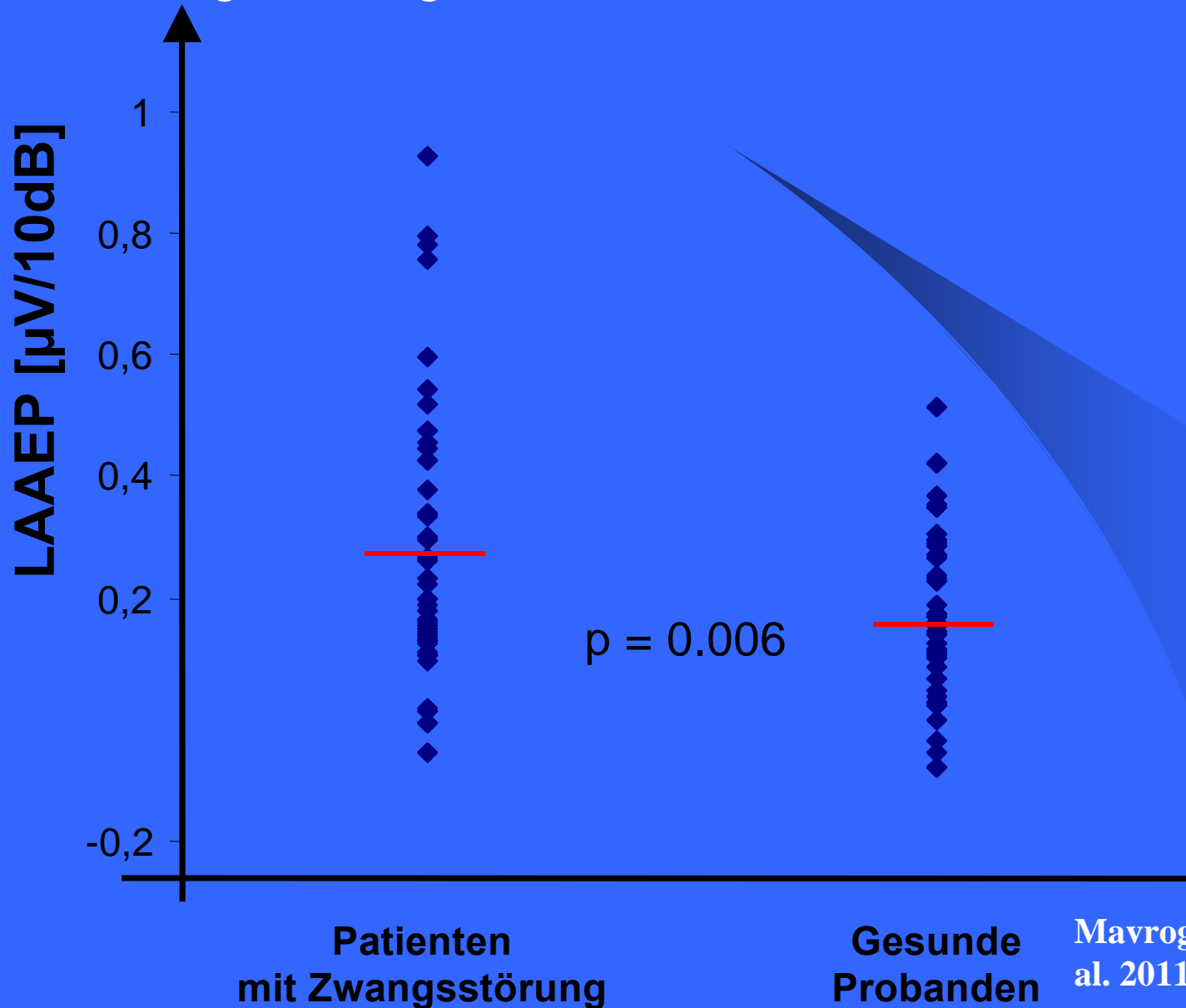
5-HT1B-Rezeptor Polymorphismen: SNPs (rs1213368 and rs6296)



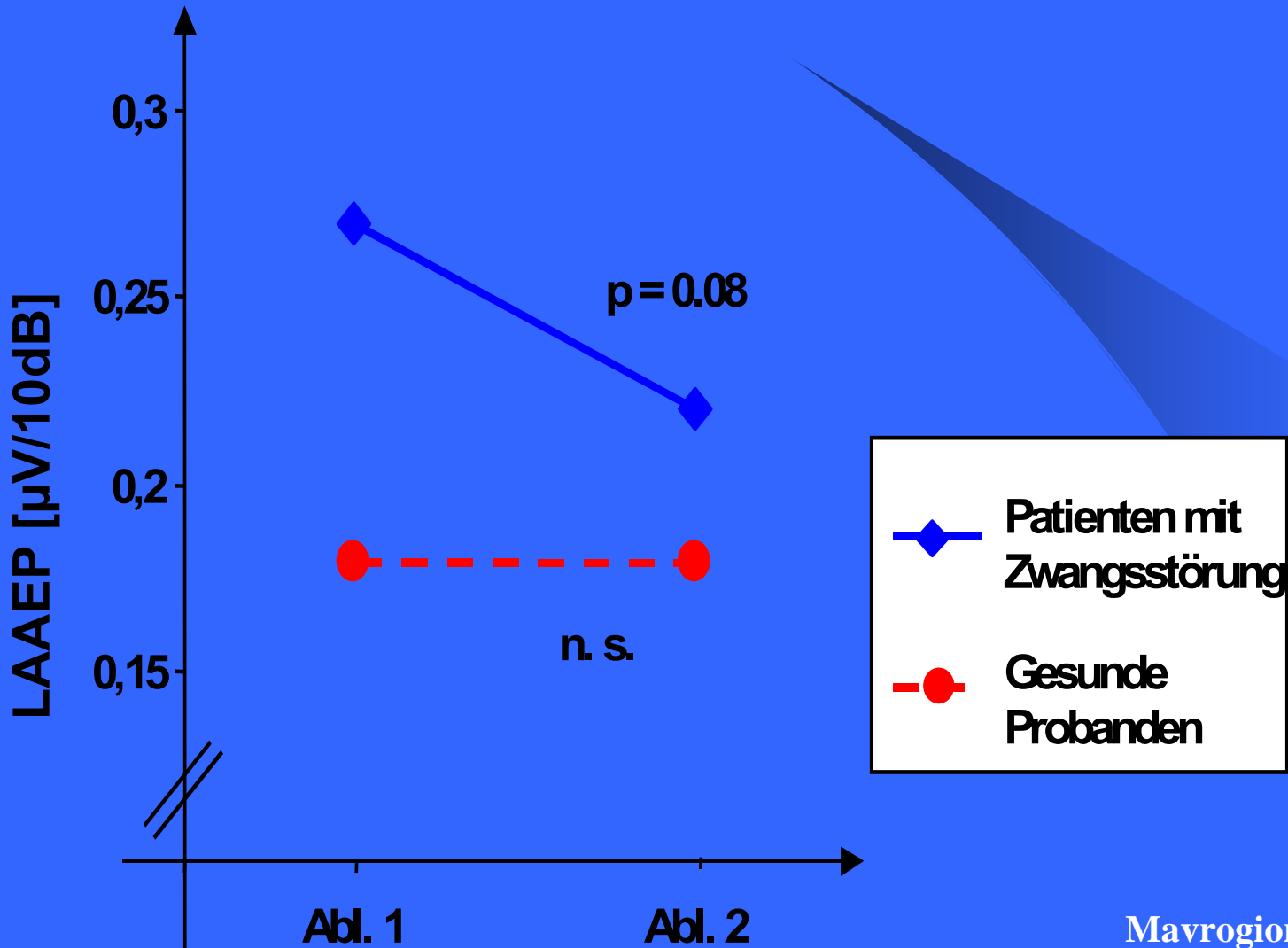
Haplotype Score=3.05, $p=0.002$

Juckel et al. 2008

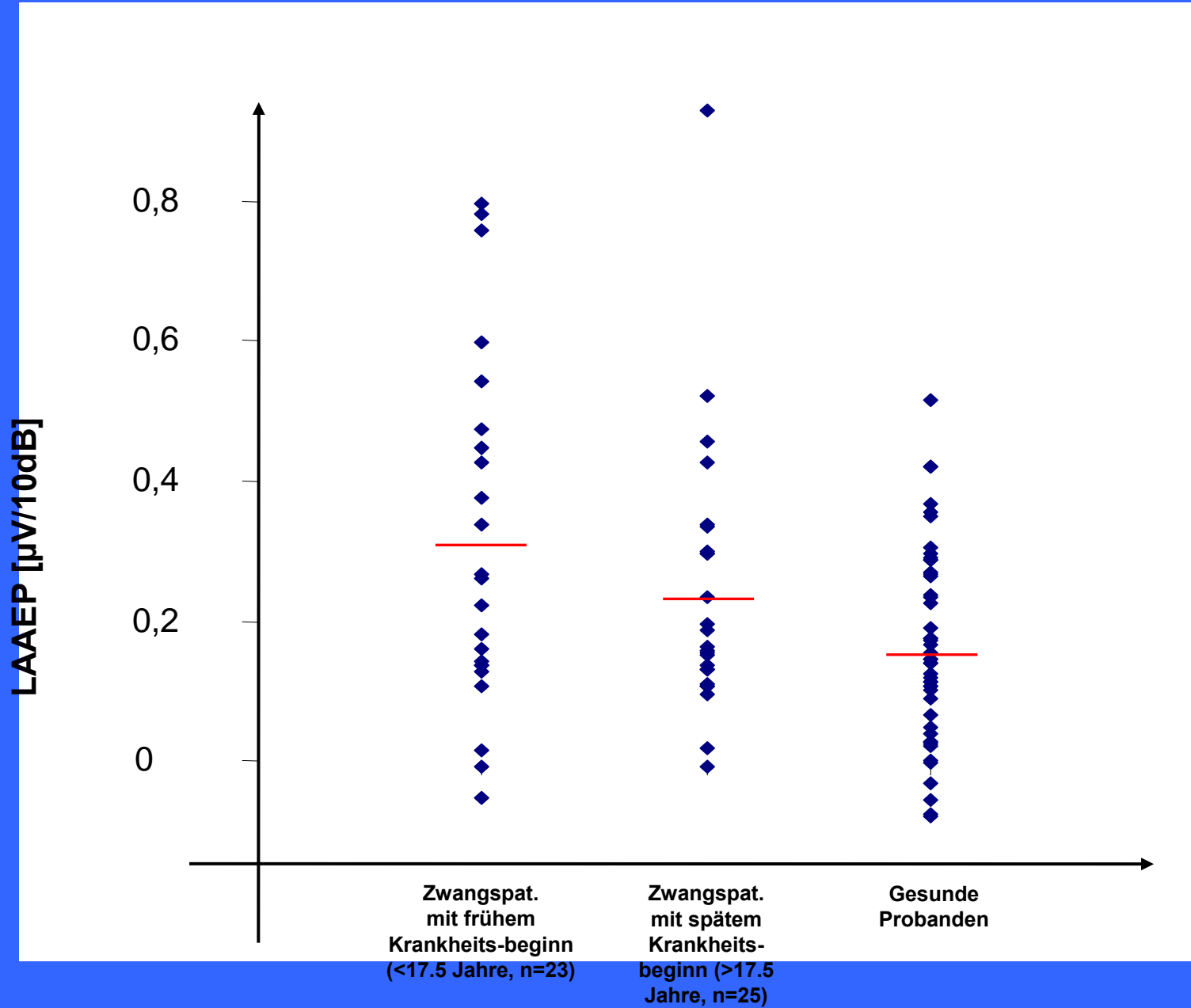
LAAEP des primären akustischen Kortex bei Patienten mit Zwangsstörung



Zwangspatienten (n=31) vor und nach einer 10-wöchigen Behandlung mit dem SSRI Sertralin



Früher vs. später Krankheitsbeginn



BDNF - Serotonin

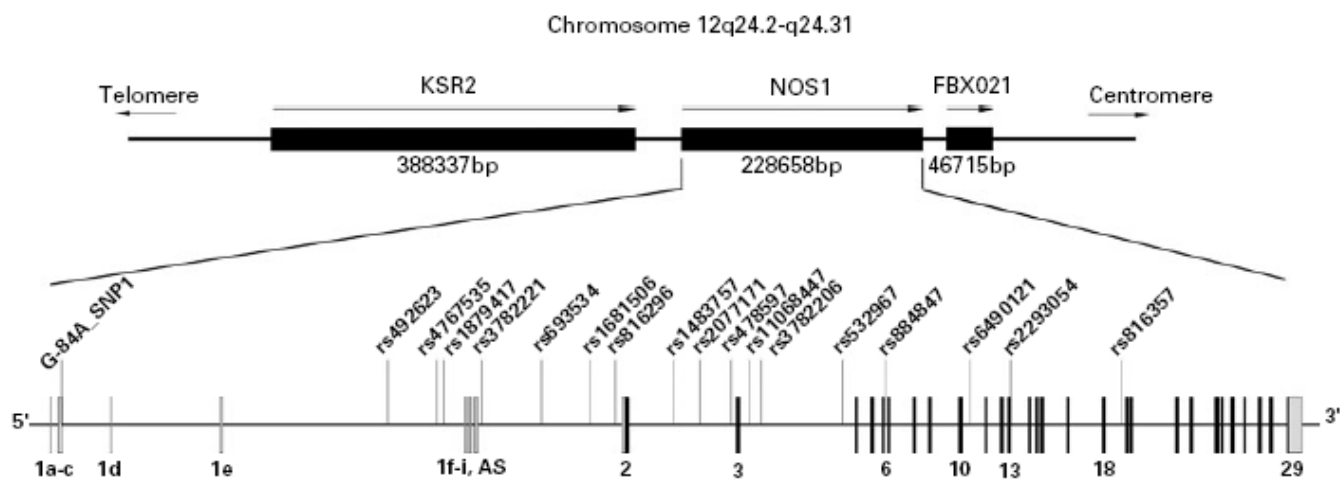
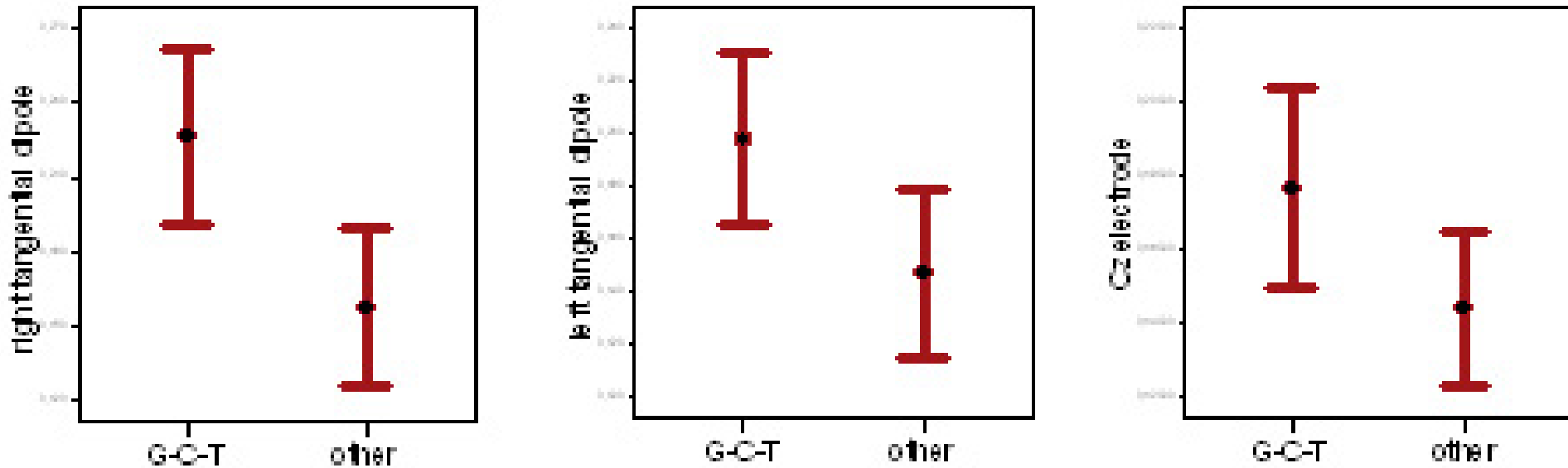


Figure 1. Overview of the NOS1 gene region, intron/exon structure and single nucleotide polymorphism sites.

**Low LDAEP
/NOS 1+
NOS3 Gen**

Juckel et al. 2009,
Kawohl et al. 2008

Inverse Beziehung zwischen LAAEP und Serotonin

Serotoninagonisten/-antagonisten: Zimelidin (SSRI), Sertralin (SSRI), Ecstasy, Fenfluramin, Zolmitriptan/Naratriptan, Lithium, Phenytoin, Alkohol, Nikotin, 8-OH-DPAT, Ketanserin, Clozapin, Olanzapin

Prädiktion: Fenfluramin, Fluvoxamin (SSRI), Fluoxetin (SSRI), Lithium, Schlafentzug, Buprion, Paroxetin, Citalopram (differentiell zu Reboxetin)

Genetik: Serotonintransporter (SLC6A4), Tryptophan-Hydroxylase (Intron-7)

Persönlichkeit: Sensation Seeking, Impulsivität, Novelty Seeking

Verhalten: Suizidalität, Schlaf, Angst, Schmerz, Aggression, Antisoziale Tendenzen, Serotonin-Syndrom

Erkrankungen: Depression, Somatisierungstörung, Borderline-Störung, Anorexia nervosa, Migräne, Schizophrenie, OCD

Chemie: 5-HIES im Liquor, 5-HIES im Serum, 5-HT im Vollblut, 5-HT im Serum, MAO in Thrombozyten

Klinische Anwendungsmöglichkeiten:

Prädiktion der z.B. Antidepressiva-Response

Monitoring von Suizidalität

UAW (z.B. Serotonin-Syndrom)

Früherkennung (z.B. Schizophrenie)

Clinical value of the prediction of therapeutic response to antidepressants

- Faster remission and reduction of time to suffer from depression for the patients (as well as for their relatives)
- Reduction of suicide risk
- Avoiding of unnecessary side effects caused by the not-effective antidepressant medication
- Reduction of lay-days
- Reduction of costs

Neurochemical subtypes of depressed patients

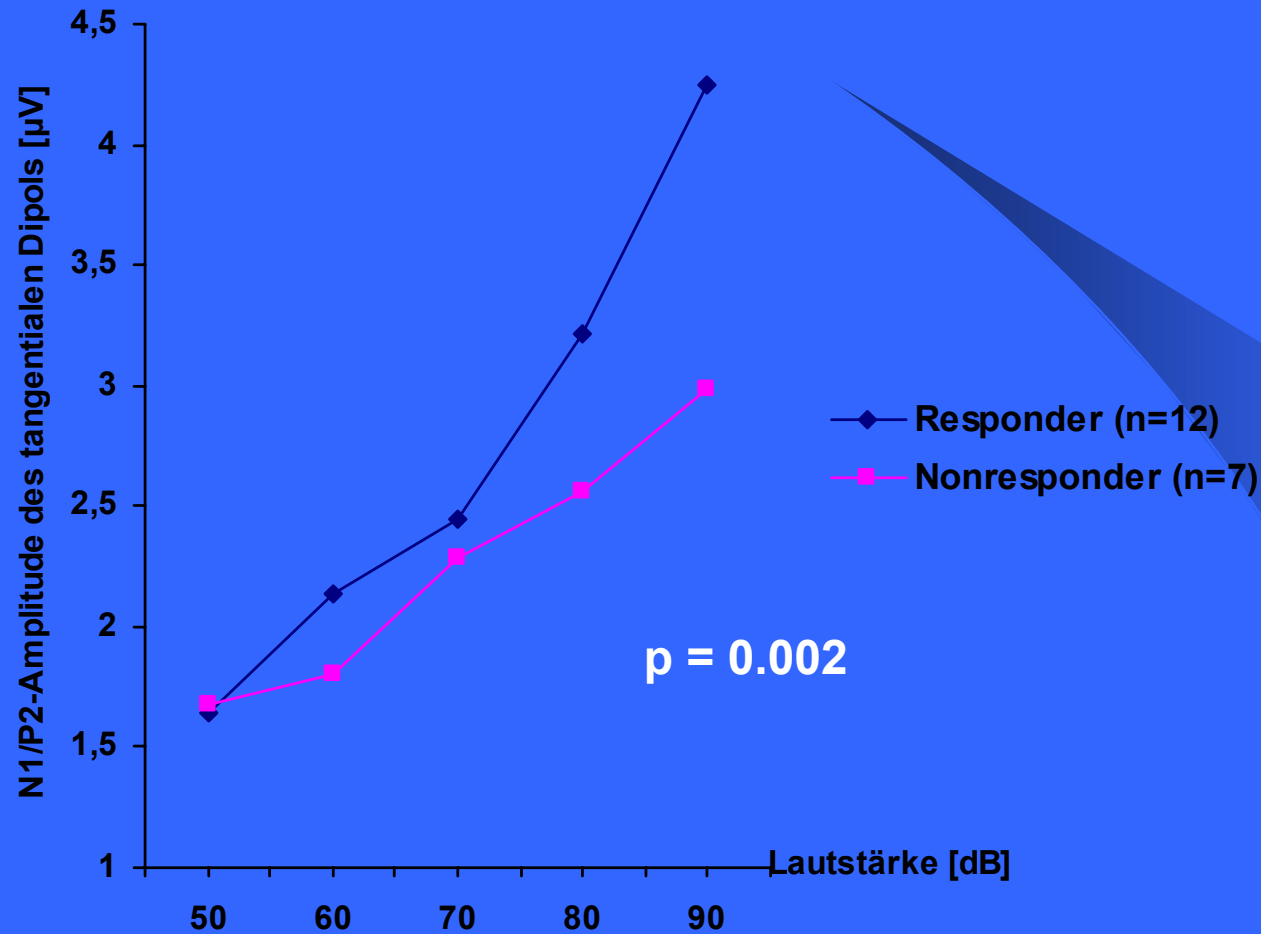
- Patients with a more serotonergic deficit and with better response to serotonin enhancing treatments (SSRIs: e.g. citalopram)
- Patients with a more noradrenergic deficit and with better response to norepinephrine enhancing treatments (NARIs: e.g. reboxetine)

Monoamine deficit hypothesis (Schildkraut, Schatzberg 1962...)

Previous studies of LDAEP as predictor of the therapeutic response to serotoninagonistic medication

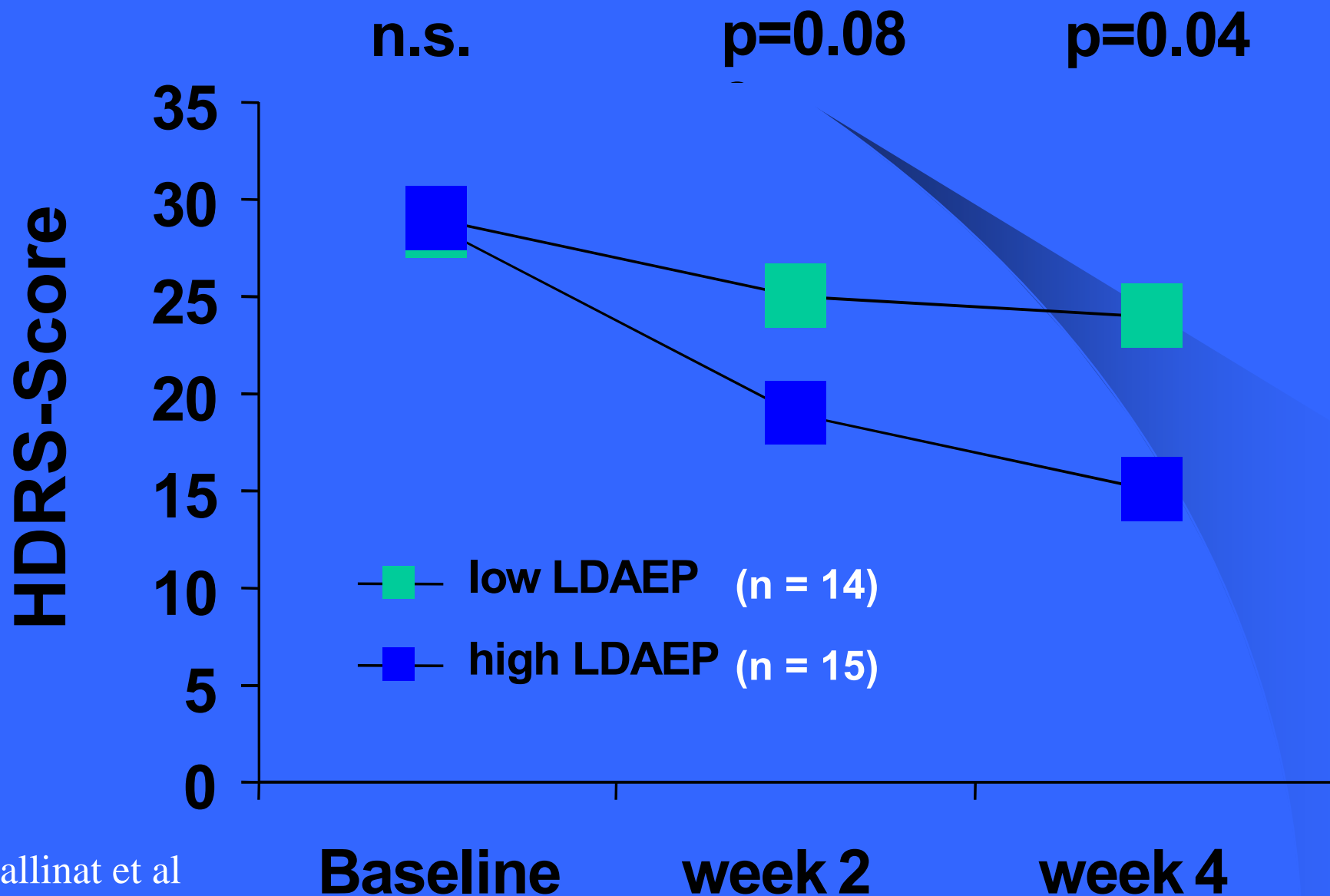
- ***Lithium***: Antidepressant and antimanic treatment (review: Hegerl und Herrmann 1990)
- ***Lithium***: Relapse prophylactic therapy (Hegerl et al. 1987, 1992, Juckel et al. 2004)
- ***Fenfluramine***: treatment of autistic children (Bruneau et al. 1989)
- ***Fluvoxamine***: Antidepressant treatment (Hegerl et al. 1991)
- ***Fluoxetine***: Antidepressant treatment (Paige et al. 1994)

Prediction: prophylactic treatment with lithium



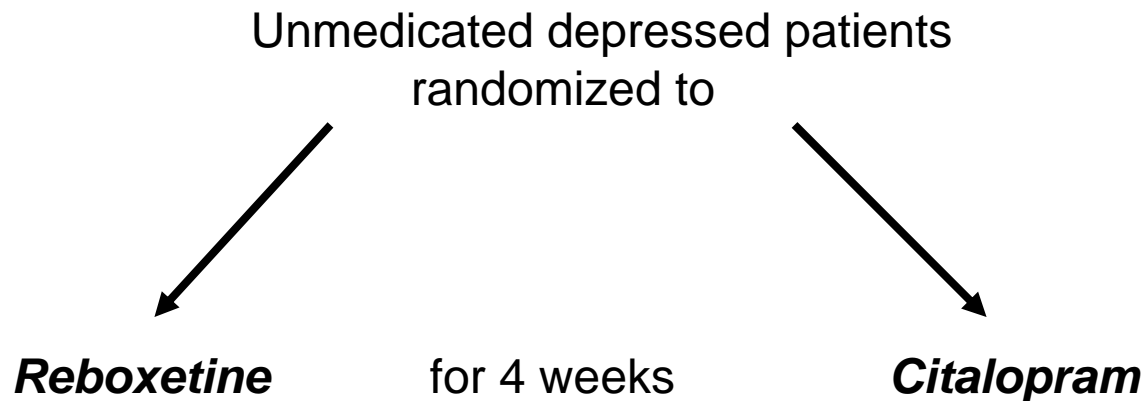
Juckel et al. 2004

Prediction: Antidepressive therapy with SSRI



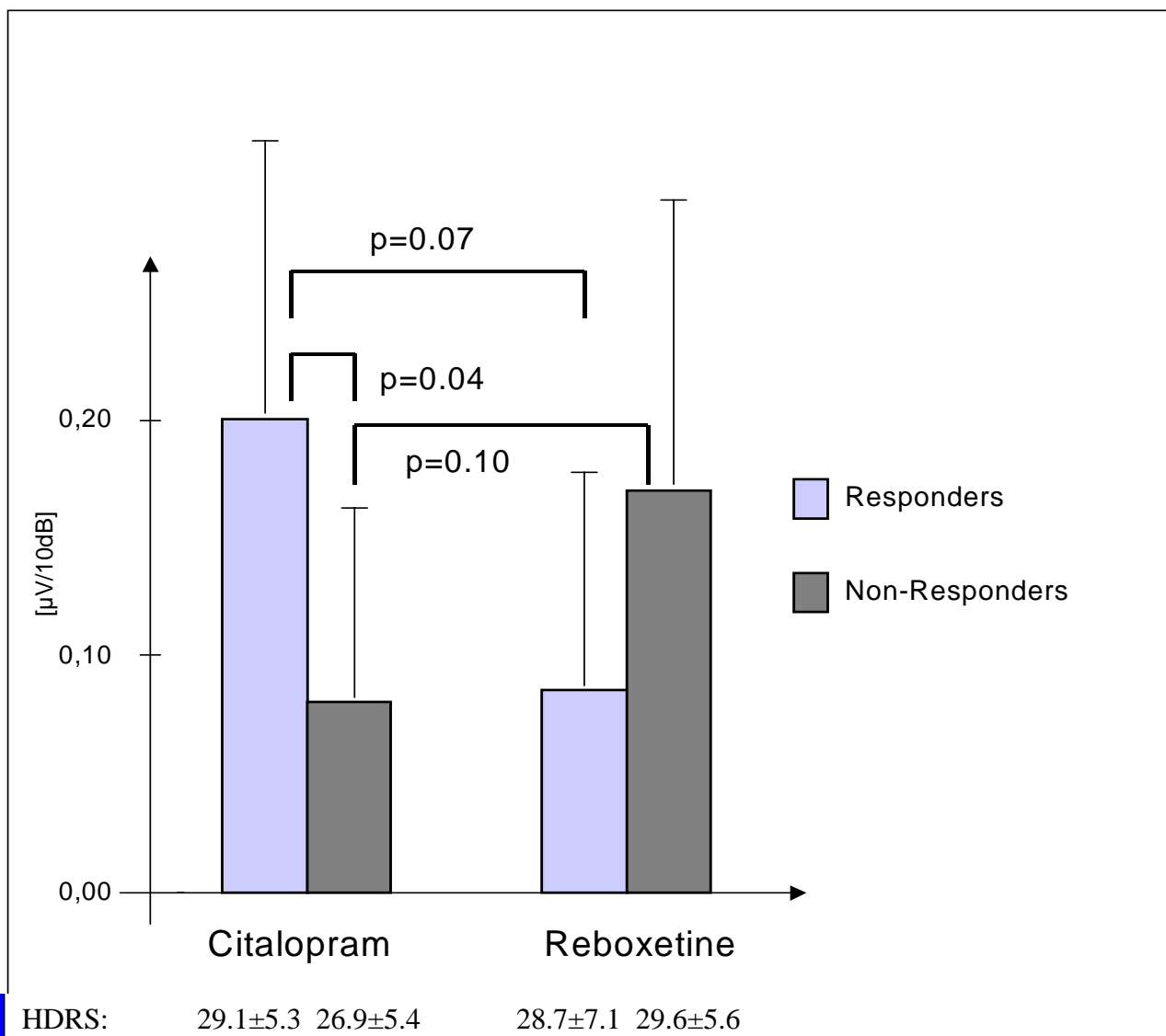
Reboxetine-Citalopram-Study

LDAEP at baseline



Treatment evaluation: HAMD, BRMS, MADRS, BDI

Differential prediction of the response to SSRI or NARIS



Sternbach´s criteria of serotonin syndrome

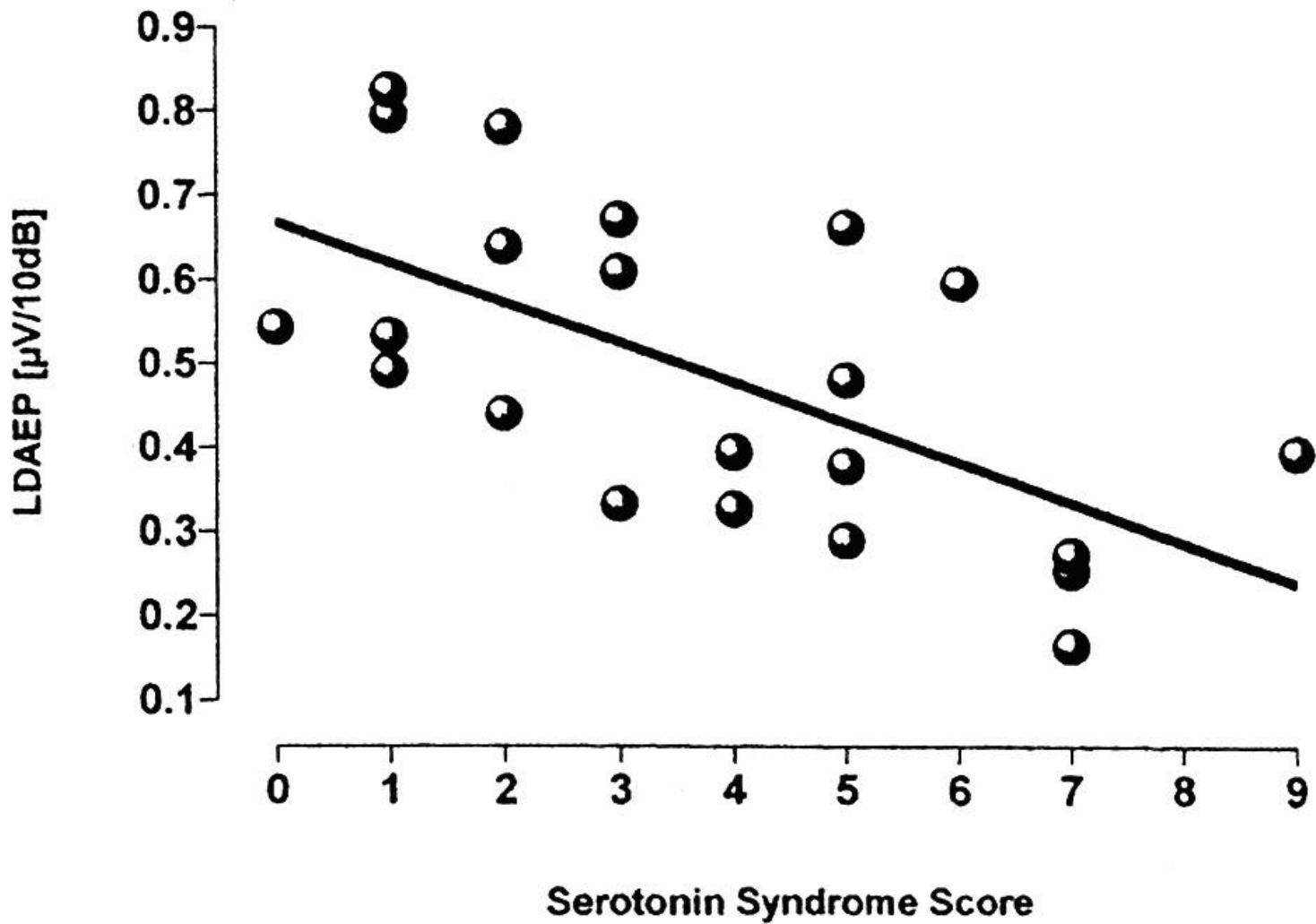
A) In Verbindung mit Zugabe oder Erhöhung einer serotonergen Substanz kommt s zum Auftreten von mindestens drei der folgenden Symptome:

- 1) Bewußtseinsstörungen (Verwirrtheit, Hypomanie)**
- 2) Agitiertheit**
- 3) Myoklonus**
- 4) Hyperreflexie**
- 5) Schwitzen**
- 6) Schüttelfrost**
- 7) Tremor**
- 8) Durchfall**
- 9) Koordinationsstörungen**
- 10) Fieber**

B) Andere Ursachen sind nicht gefunden worden

C) Dem Auftreten dieser Symptome ist weder der Beginn noch eine Erhöhung einer Medikation mit Neuroleptika vorausgegangen

Serotonin-Syndrome



Monitoring of suicidal behavior (risk / acute suicidality)

Tab. 1 History of suicide attempts and intensity dependence of auditory evoked dipole activity in alcoholics.

| | History of suicide attempts (n = 10) | No history of suicide attempts (n = 15) | t-test |
|---------------------------------|--------------------------------------|---|--------|
| Age (years) | 48.0 ± 10.3 | 44.1 ± 8.6 | n.s. |
| Depressed mood (Zungs' SDS) | 31.1 ± 7.1 | 28.6 ± 7.5 | n.s. |
| Anxiety (Zungs' SAS) | 30.9 ± 5.9 | 30.9 ± 4.5 | n.s. |
| Intensity dependence (µV/10 dB) | | | |
| - tangential dipole | 0.13 ± 0.05 | 0.19 ± 0.07 | 0.02 |
| - radial dipole | 0.06 ± 0.08 | 0.05 ± 0.05 | n.s. |

Tab. 4 History of suicide attempts and intensity dependence of AEP in patients with affective disorders.

| | History of suicide attempts (n = 7) | No history of suicide attempts (n = 6) | t-test |
|---------------------------------|--|--|--------|
| Age (years) | 46.4 ± 15.4 | 38.8 ± 9.7 | n.s. |
| Gender | 3 females 4 males | 4 females 2 males | |
| Diagnosis | 4 bipolar 1 unipolar 2 schizoaffective | 4 bipolar 2 unipolar | |
| Lithium | | | |
| - plasma level (mmol/l) | 0.57 ± 0.19 | 0.59 ± 0.32 | n.s. |
| - duration (months) | 10.1 ± 12.7 | 11.2 ± 8.1 | n.s. |
| Intensity dependence (µV/10 dB) | | | |
| - Cz | 0.7 ± 1.0 | 2.1 ± 1.6 | 0.03 |
| - C3 | 0.5 ± 0.7 | 1.4 ± 0.9 | 0.05 |
| - C4 | 0.7 ± 0.4 | 1.8 ± 0.9 | 0.01 |

Monitoring of acute suicidal behavior (risk / acute suicidality)

Tab. 2 History of suicide attempts and intensity dependence of AEP in depressed patients.

| | History of suicide attempts (n = 7) | No history of suicide attempts (n = 15) | t-test |
|---------------------------------|-------------------------------------|---|--------|
| Age (years) | 58.7 ± 8.3 | 62.1 ± 10.9 | n.s. |
| Gender | 5 females 2 males | 11 females 4 males | |
| Depressed mood (Hamilton) | 22.3 ± 2.6 | 21.1 ± 4.5 | n.s. |
| Intensity dependence (µV/10 dB) | | | |
| - Cz | 1.0 ± 0.8 | 1.9 ± 1.7 | n.s. |
| - C3 | 0.9 ± 0.5 | 1.2 ± 1.0 | n.s. |
| - C4 | 0.6 ± 0.4 | 1.2 ± 1.0 | 0.05 |

Tab. 3 Suicidality in depressed patients with weak (n = 11) and strong intensity dependence (n = 11).

| Patients with | Weak | Strong intensity dependence |
|--|------|-----------------------------|
| History of suicide attempts | 5 | 2 |
| Relatives with | | |
| - history of suicide attempts | 4 | 0 |
| - completed suicides | 2 | 1 |
| Acute suicidal ideas (Hamilton item 3) | 3 | 6 |

Serotonerge Dysfunktion bei der Schizophrenie

Erhöhte Neurotransmission (Meltzer 1989, Bennett 1998)

Post-mortem Befunde (Harrison 199)

Metabolite (5-HIAA) (Veelen und Kahn 1999)

Genetische Befunde (Eastwood et al. 2001)

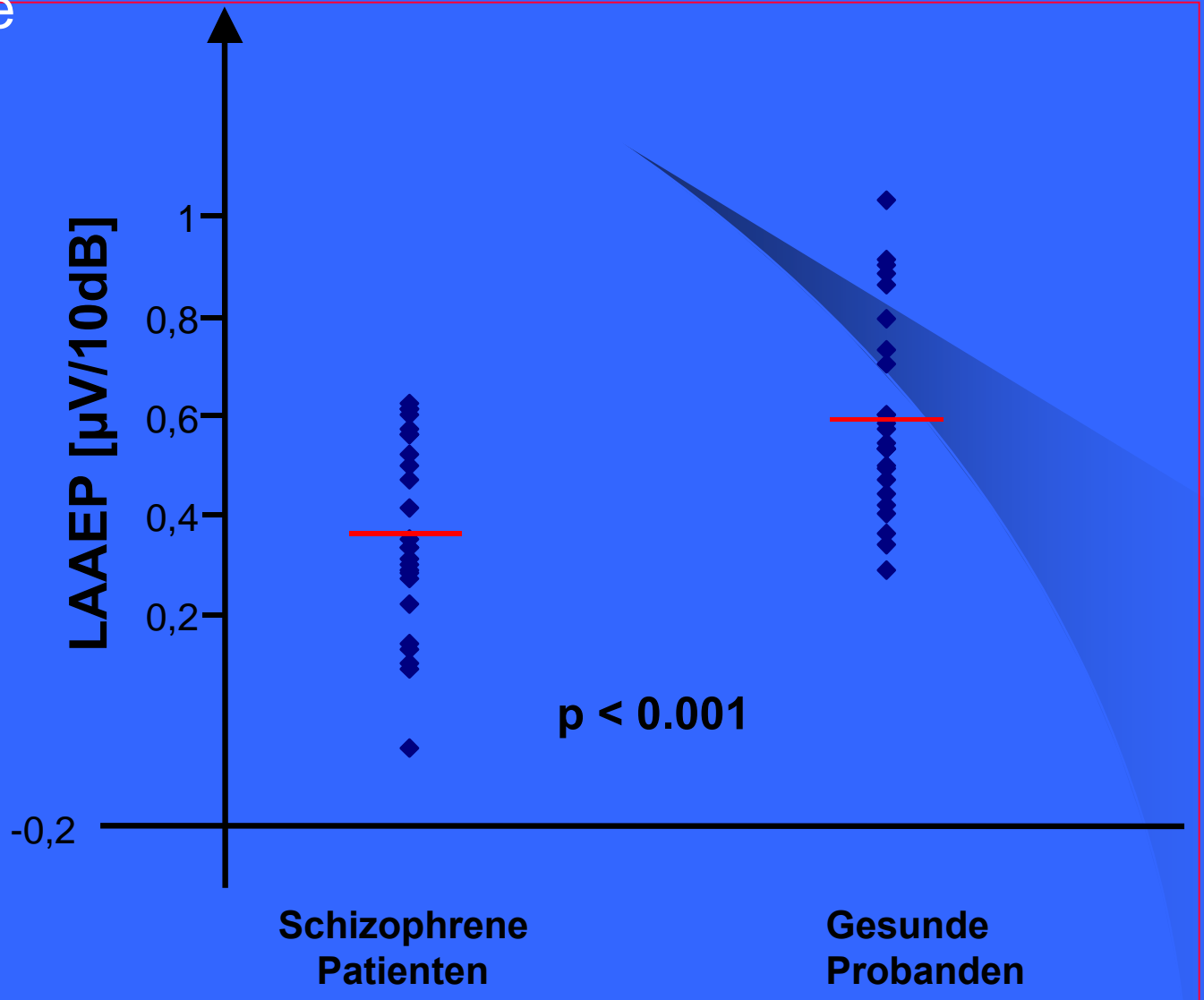
Bildgebung (Ngan et al. 2000)

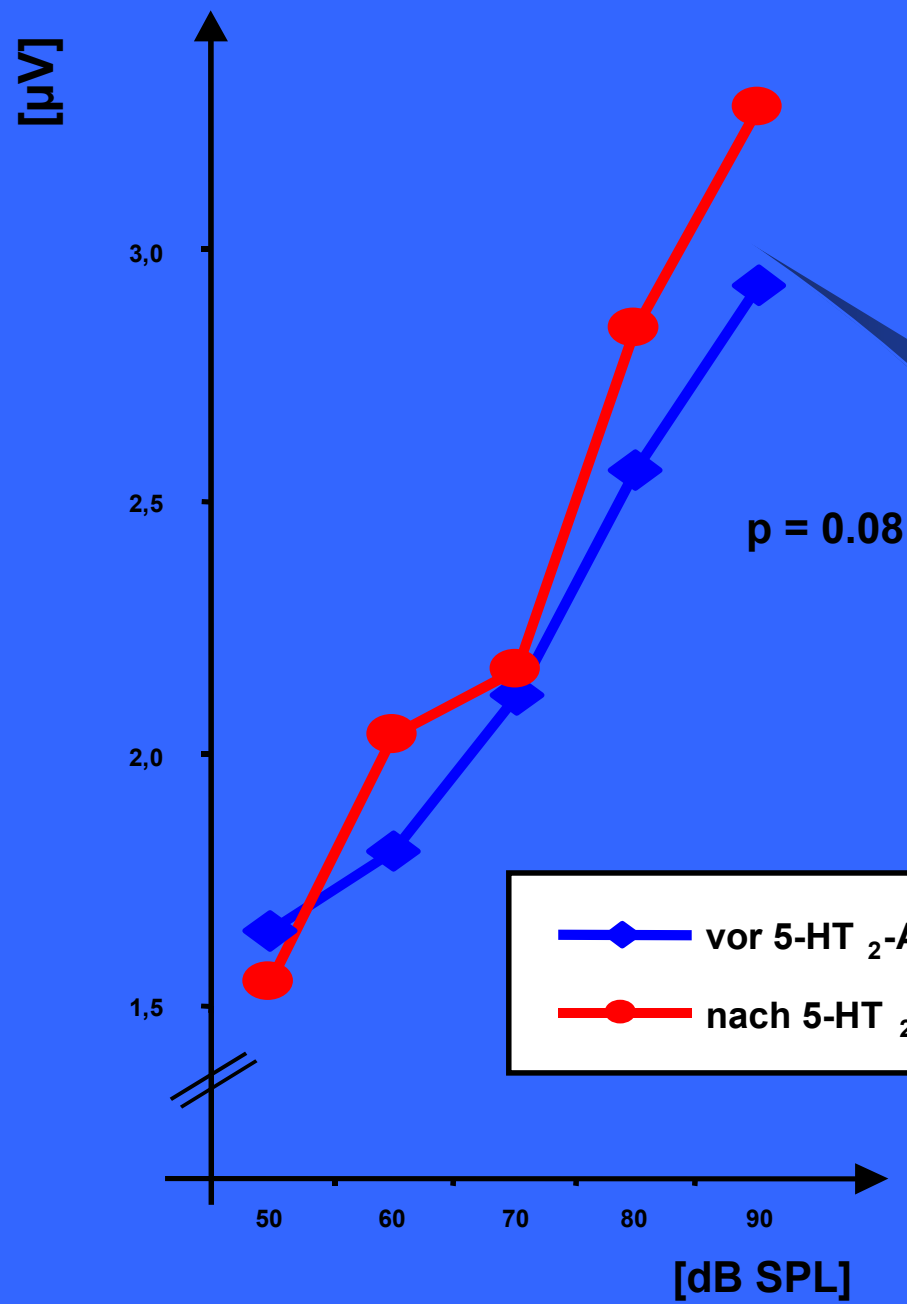
5-HT₂-Rezeptoren:

Stimulation (LSD etc.)

Blockade (Atypische Neuroleptika)

LAAEP des primären akustischen Kortex bei Patienten mit Schizophrenie



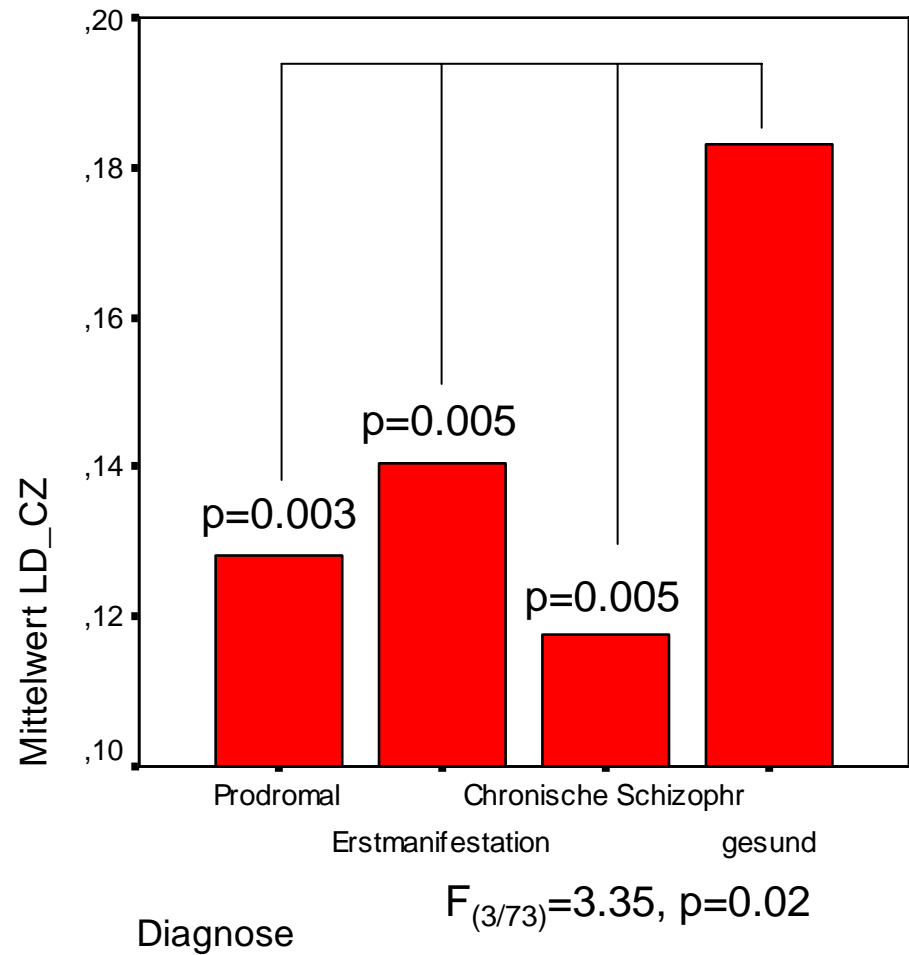


—◆— vor 5-HT₂-Antagonisten
—●— nach 5-HT₂-Antagonisten

p = 0.08

LAAEP bei Patienten im schizophrenen Prodromalzustand

Gudlowski et al. 2009



Akut depressive, stationäre Patienten (n=25)

- Unmediziert
- 21 unipolar, 4 bipolar
- 56.6 (29-78) Jahre
- 10 F, 15 M

Wie schaut es aus bei der bipolaren Störung, bzw. im bipolaren Prodrom ?

- EIP
- Lic
- AE LDAEP neg korr zu HDRS ($r=-0.43$; $p<0.05$)
und zu Serotonin im Vollblut (Änderungen x Änderungen
 $r=-0.69$; $p<0.01$)
- AE eeps
- Serotonin: im Vollblut, HPLC u. elektrochemischen Nachweis
- Psychopathologisches Rating: HAMD, AMDP, CGI, DS, BL, VAS

Ungeklärte Fragen zur Beziehung LDAEP – 5-HT-System

Erhöhter/erniedrigter Aktivitätszustand ?

Welche Rezeptoren ?

Welchen lokalen Veränderungen
(Projektionsbahnen, lokale Genexpression,
Zelltypen (z.B. GABAerge Interneurone)) ?

Zusammenfassung

LDAEP ist ein mittlerweile tier- und humanexperimentell sowie genetisch gut validierter Indikator des Aktivitätszustandes des zentralen serotonergen Systems.

Es ist daher gerechtfertigt, diesen Indikator verstärkt in die klinische Praxis als neurobiologische Zusatzinformation einzuführen, z.B. zur Prädiktion der Antidepressiva-Response.

Die zellulären und molekularen Mechanismen der serotonergen Modulation der LDAEP müssen weiter untersucht werden.