Ulrich Frick (1)(2), Michael Landgrebe (2), Simone Hauser (2),
Göran Hajak (2), Peter Eichhammer (2)

(1) Univ. of Applied Sciences, Carinthia, Austria
(2) Psychiatric University Hospital, Regensburg, Germany

Investigation of the phenomenon of 'electromagnetic hypersensitivity' using an epidemiological study on 'electrosensitive' patients including the determination of clinical parameters

German Mobile Telecommunication Research Programme
International Workshop on Final Results of
Projects on Acute Health Effects
December 12-13, 2006

Bundesamt für Strahlenschutz

Rationale for the sample-design

This study aimed at analysing potential disposing factors for subjective electrosensibility.

Subjectively electrosensitives suffer from a variety of subjective symptoms at exposure levels which do not cause health related symptoms in most other people.

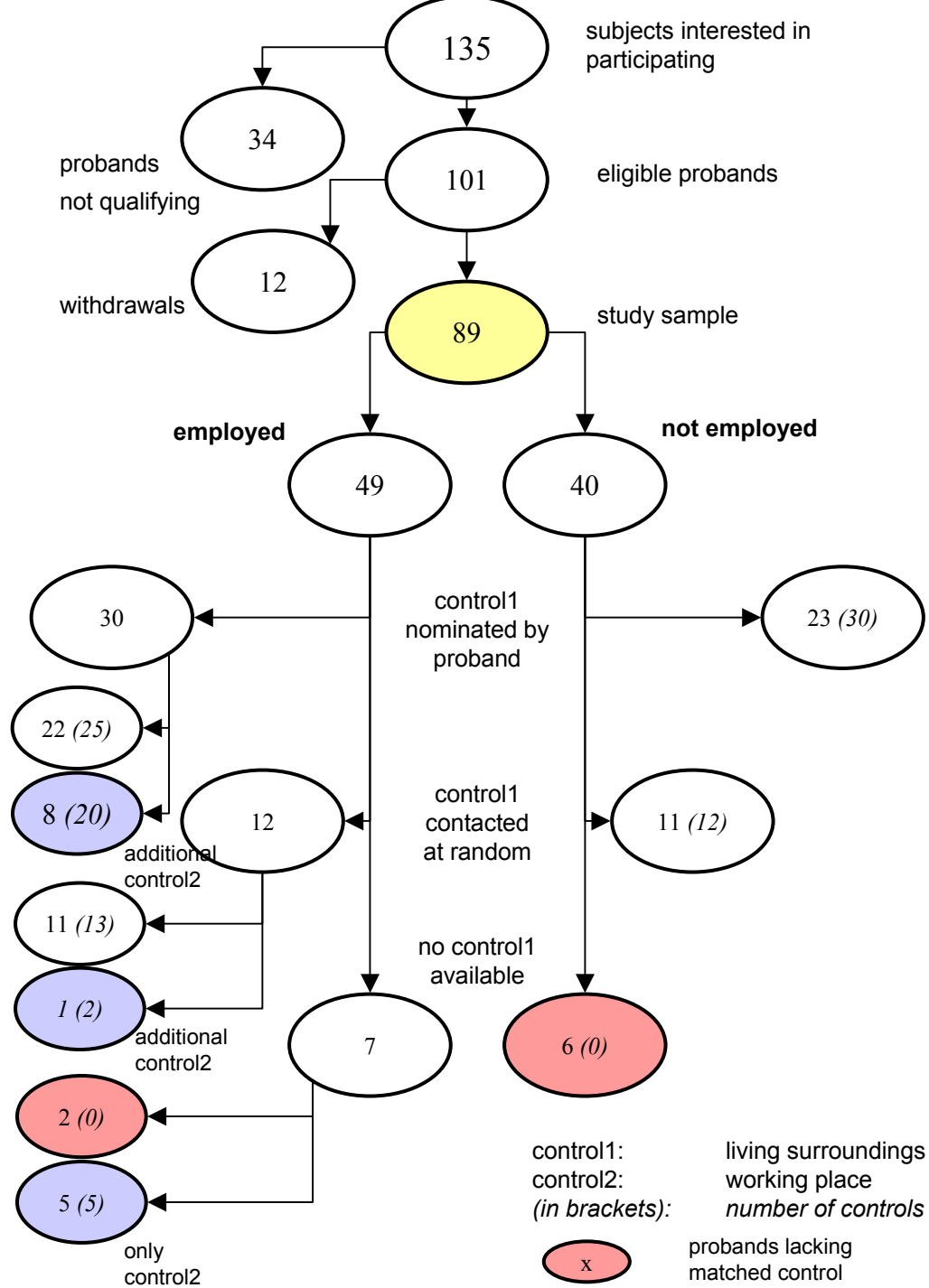
Thus, factors known to have an impact on symptom load, i.e.

- **age**
- **sex**

and conditions for every day exposure to EMFs, i.e.

- **place of residence**
- **working place/conditions**

have to be matched.



Enrollment to study:

n = 89 subjects with „electrosensibility“
n = 107 controls

controls matched for:
- **place of residence**
- **working place**
- **age**
- **sex**

no regular pattern of 1:m controls
⇒ **statistical analysis of independent samples (conservative!)**
⇒ **include sex/age into analysis**

Sample: descriptive data

Group	"Electrosensitives" (N=89)		Controls (N=107)		Significant Differences?	
	mean	SD	mean	SD	Statistic	p-value
Age	50.45	10,9	49.02	11,1		n.s.
Females	58.4%		62.6%			n.s.
Educational level	basic: 31.5%		basic: 42.1%		χ^2	0.322
	middle: 32.6%		middle: 26.2%			
	higher: 34.8%		higher: 31.8%			
	other: 1.1%					
Employment	full time: 37.1%		full time: 46.7%		χ^2	0.047
	part time: 18.0%		part time: 25.2%			
	not employed: 44.9%		not employed: 28.0%			

Sample: descriptive data (2)

Group	"Electrosensitives" (N=89)		Controls (N=107)		Significant Differences?	
Health Variable	**mean**	**SD**	**mean**	**SD**	**Statistic**	**p-value**
BMI	24.8	4.0	25.1	3.9	Mann-Whitney	n.s.
perceived health status	3.3	0.8	2.7	0.8	Mann-Whitney	$p < 0.001$
visits to physicians (last year)	18.6	16.0	9.4	10.5	T-Test	$p < 0.0001$
days sick leave (last year)	21.7	44.4	11.9	37.0	Mann-Whitney	$p = 0.013$
hospitalised last year?	18.0%		13.1%		Chi squared	n.s.
PSQI	9.1	3.2	6.6	2.4	Mann-Whitney	$p < 0.001$
WHO CIDI short form	**major depression**	23.6%	8.4%	Chi squared	$p = 0.0033$	
	gen. anxiety disorder	5.6%	0%	Fisher´s Exact Test	$p = 0.0181$	
SOMS	**somat. disorder**	10.1%	0%	Fisher´s Exact Test	$p < 0.001$	

Sample: descriptive data (3)

Group	"Electrosensitives" (N=89)		Controls (N=107)		Significant Differences?	
Use of electrical equipment ...	mean	SD (n)	mean	SD (n)	Statistic	p-value
... in own ...					Mann-Whitney	
sleeping room	2.0	2.4 (86)	2.7	1.9 (104)		p < 0.001
living room	4.9	2.8 (86)	5.3	3.0 (104)		n.s.
kitchen	6.5	2.5 (88)	6.8	2.0 (103)		n.s.
possession of mobile phone	64.0% (89)		71.7% (106)		Chi squared	p = 0.253
last invoice (Euros)	13.9	26.0 (89)	28.5	75.9 (103)	MWU	p = 0.069
EMF complaint score	47.5	21.0	15.6	15.0	MWU	p < 0.001
non smokers	52.8%		53.3%		Chi squared	n.s.
molestated by odeurs?	19.1%		13.1%		Chi squared	n.s.
molestated by noise?	37.1%		38.3%		Chi squared	n.s.

Procedures and Measurement

Intensity of EMF-related complaints (inclusion criterion)
(according to the Regensburg Inventory of EMF-related complaints: Frick et al., 2006)

- Perception of singular transcranial magnetic pulses
- Acting and resting motor thresholds (MEPs)
- Cortical excitability (paired pulse paradigm)

- Dysfunctional cognitions (questionnaire)

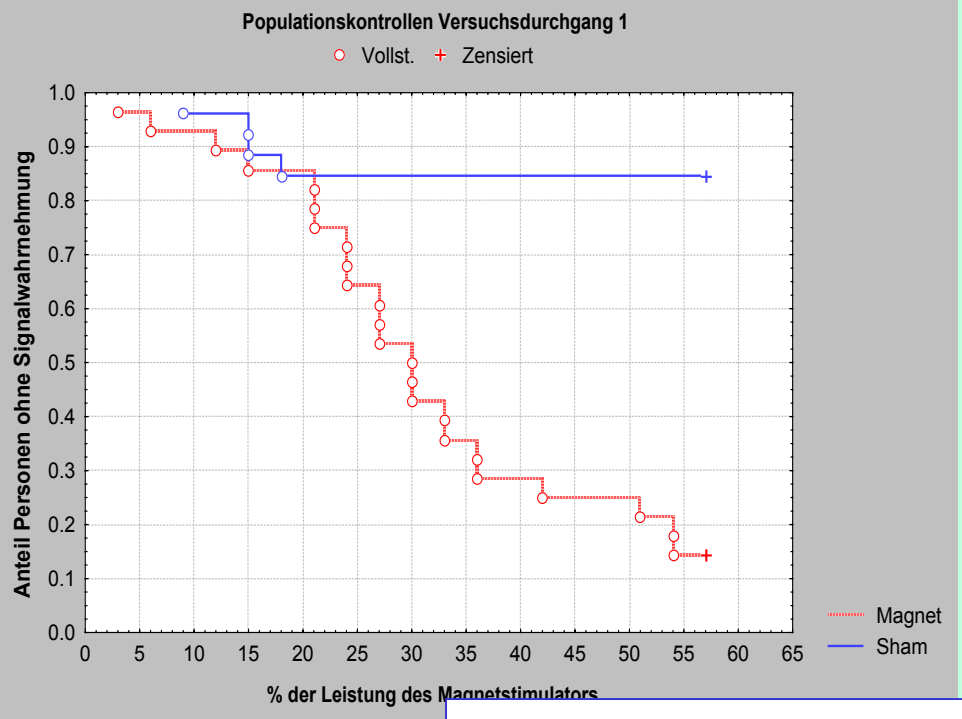
- Allostatic load
(HbA1c, Albumin, DHEA-S, Fibrinogen, TNF-α, Interleukin 6, Cystatin C)
- Alleles of two neurotransmitter genes
(serotonin transporter transmitter gene, dopamine d4 receptor polymorphism)

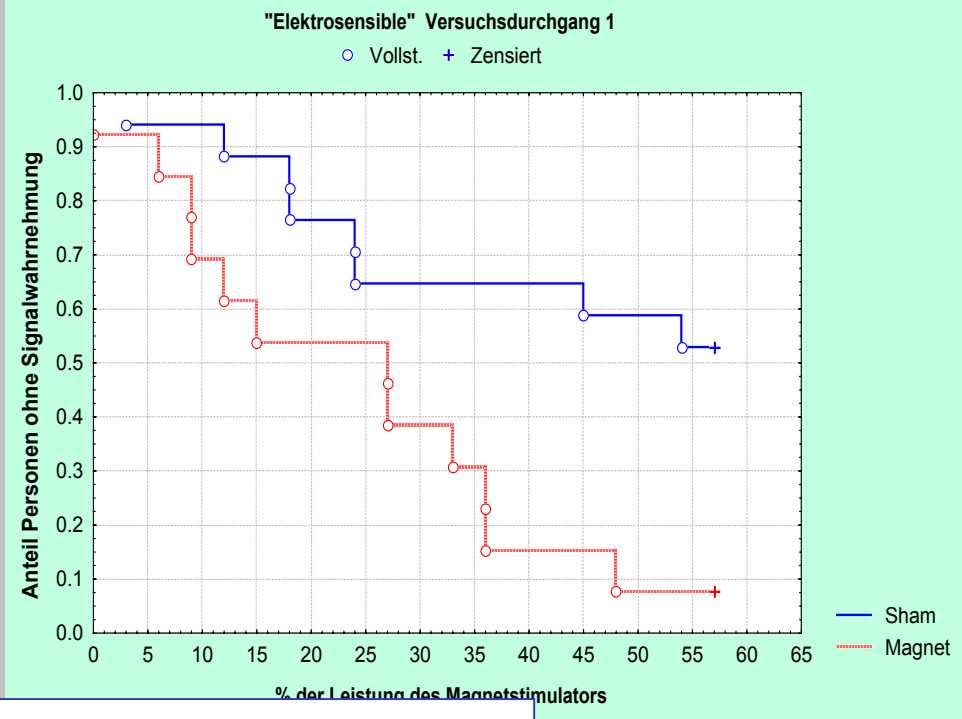
subsample: fMRI-paradigm

Singular transcranial magnetic pulses:
increasing intensity: 0 T to ~ 1.2 T (1.8 T max.)
Randomization: ABAB vs. BABA
subsequent measurement: motor threshold

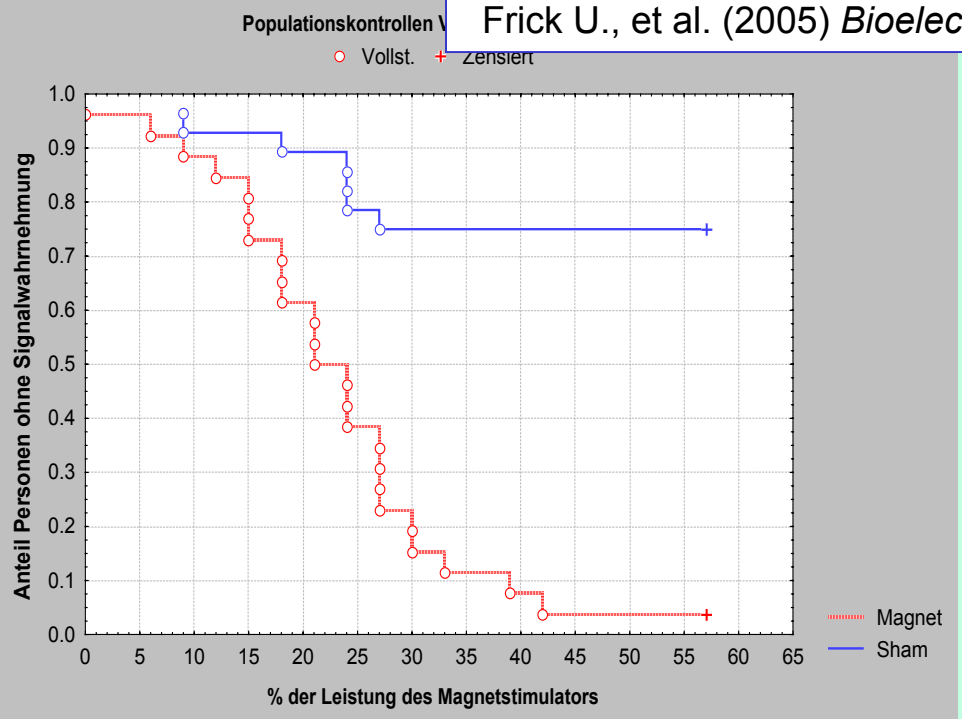
Equipment:
Magstim Super Rapid
Micromed ltd.
Sham-Coil
(2 x 70mm Placebo-Coil)

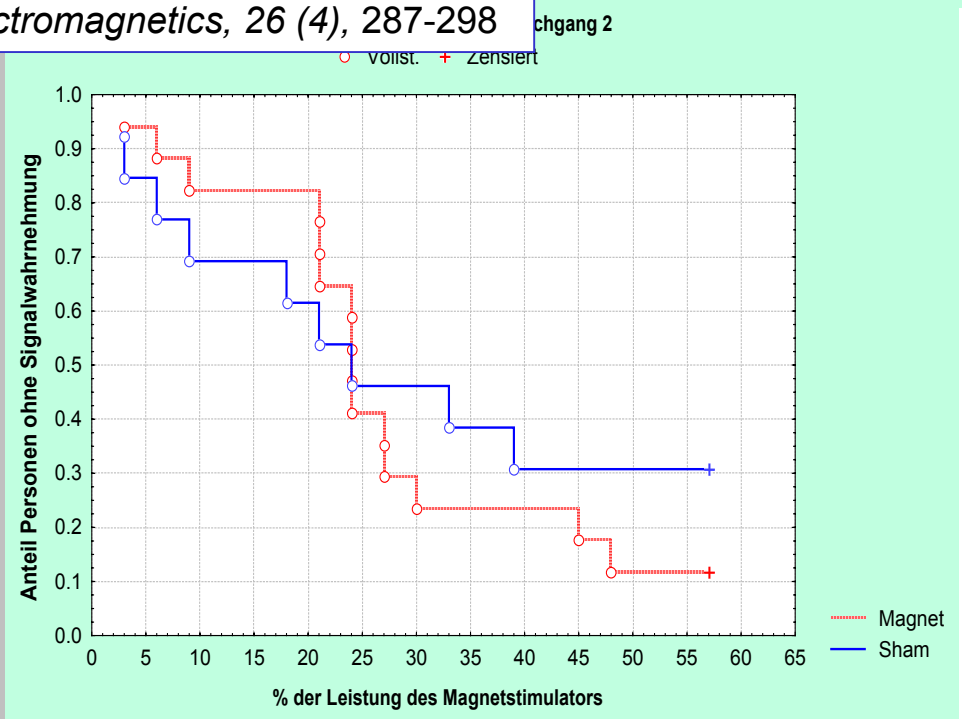
Feasibility study:
Double blind measurement of perception threshold



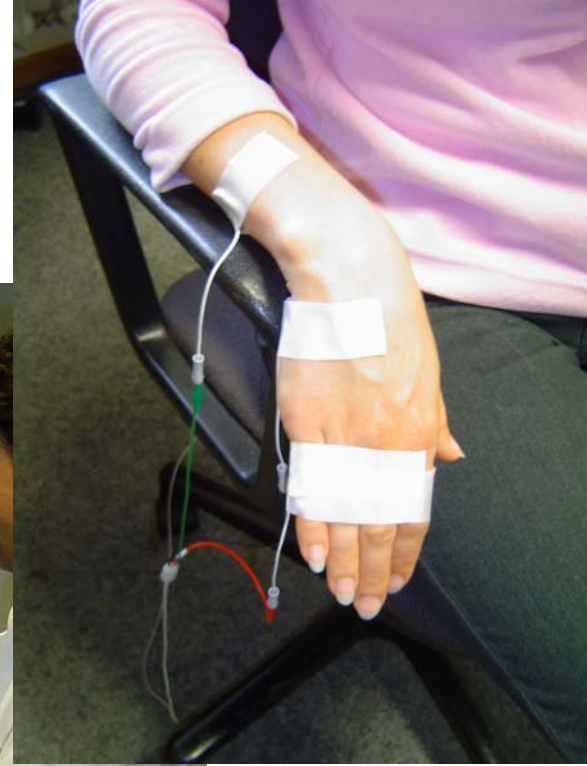


Frick U., et al. (2005) *Bioelectromagnetics, 26 (4),* 287-298



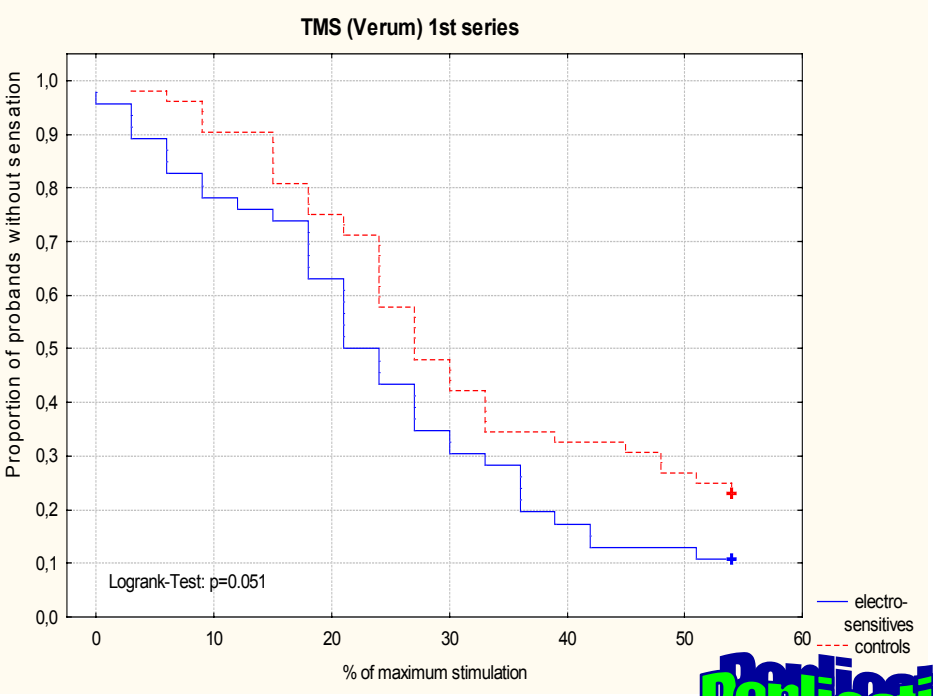


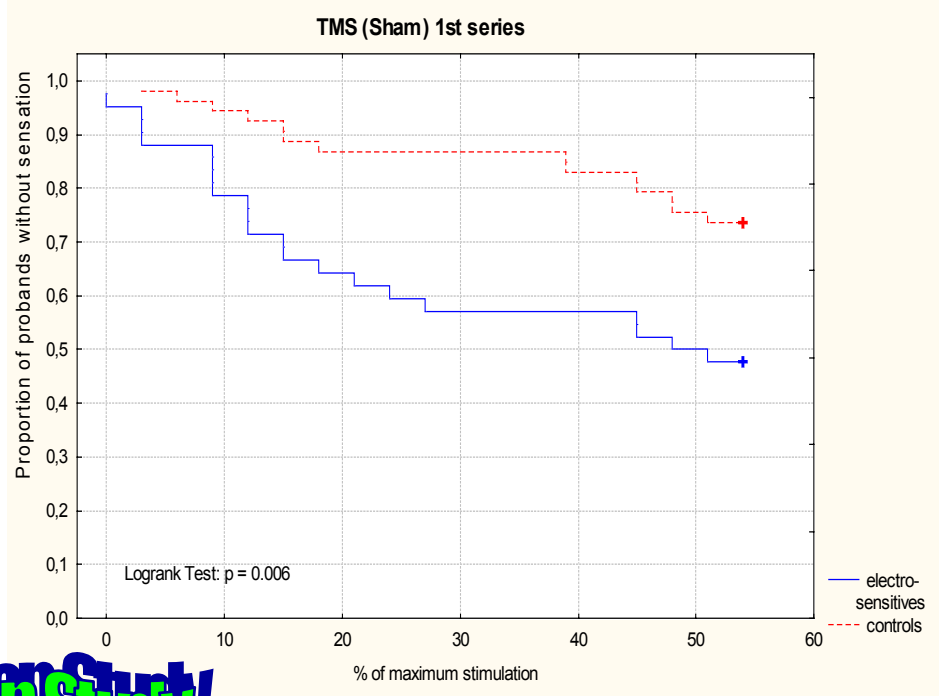
Singular transcranial magnetic pulses:
increasing intensity: 0 T to ~ 1.2 T (1.8 T max.)
Randomization: ABAB vs. BABA
subsequent measurement: motor threshold



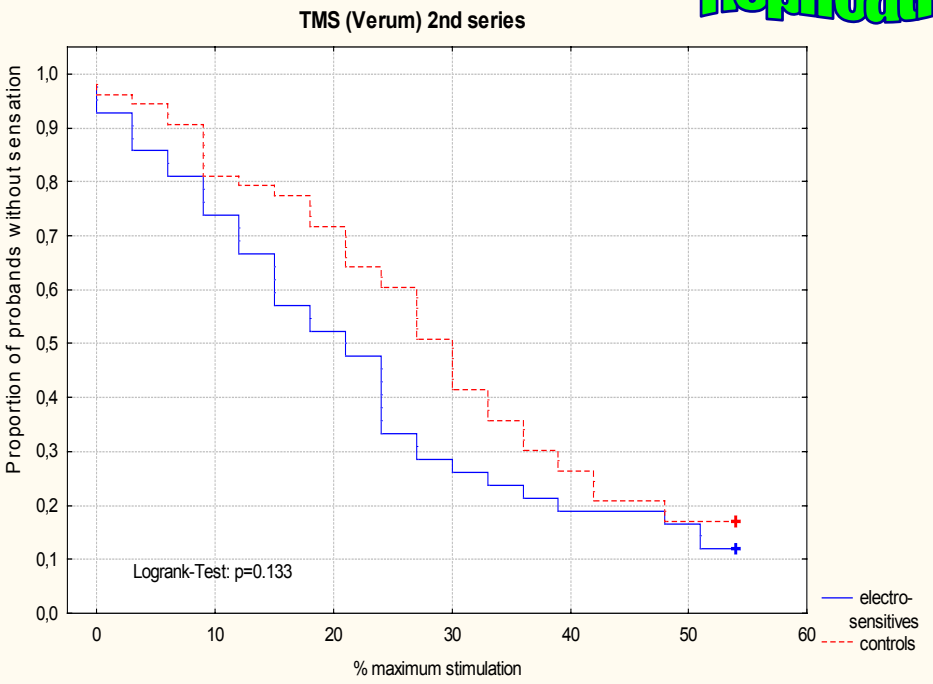
Equipment:
MagPro,
Firma
Medtronic A/S,
Dänemark

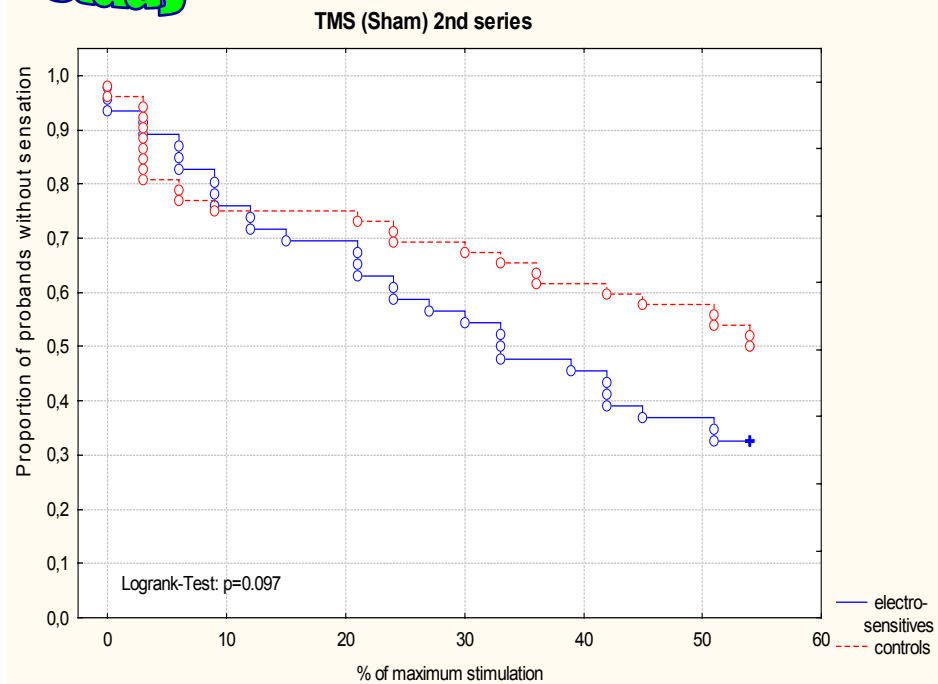
Replication study:
Single blind determination of perception threshold (observer also blinded)

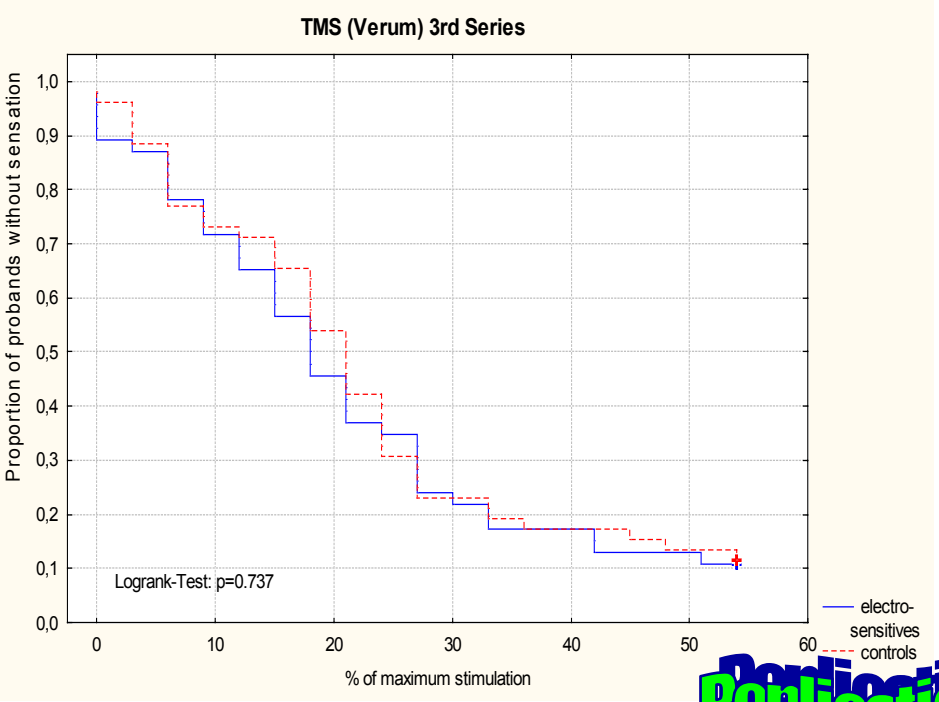


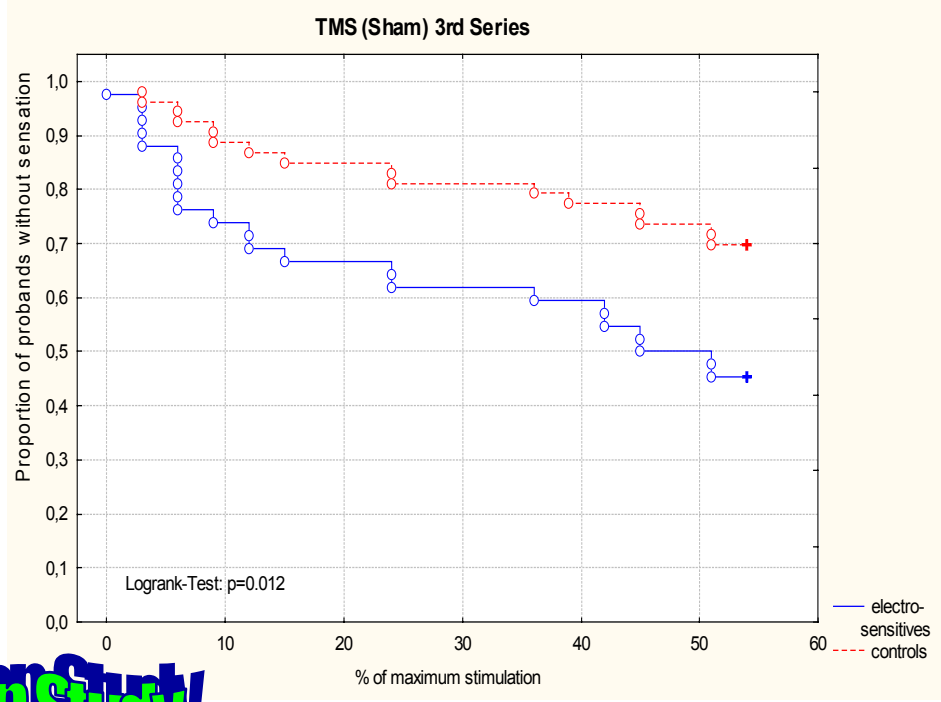


Replication Study

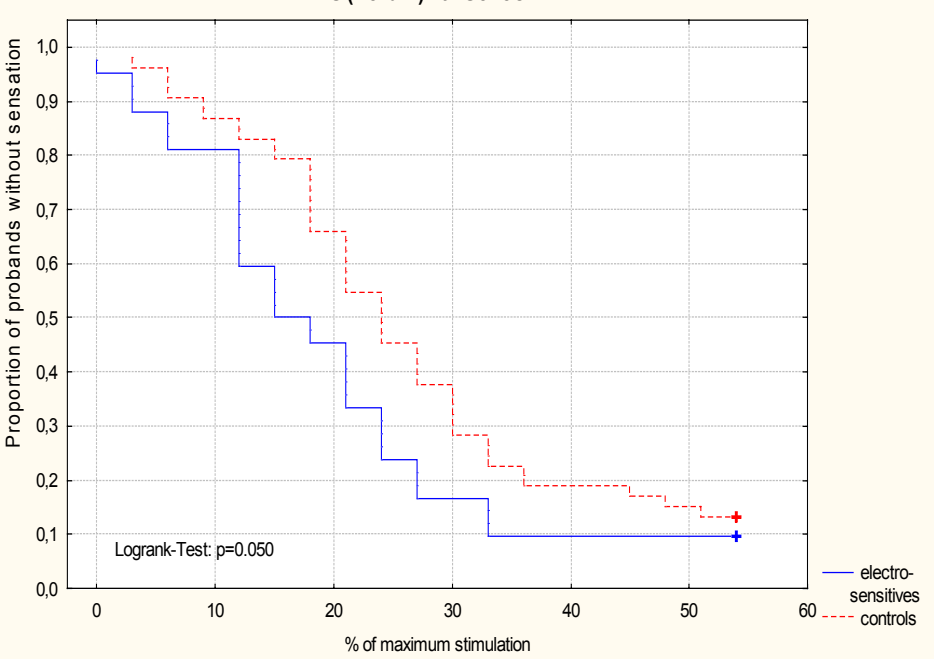


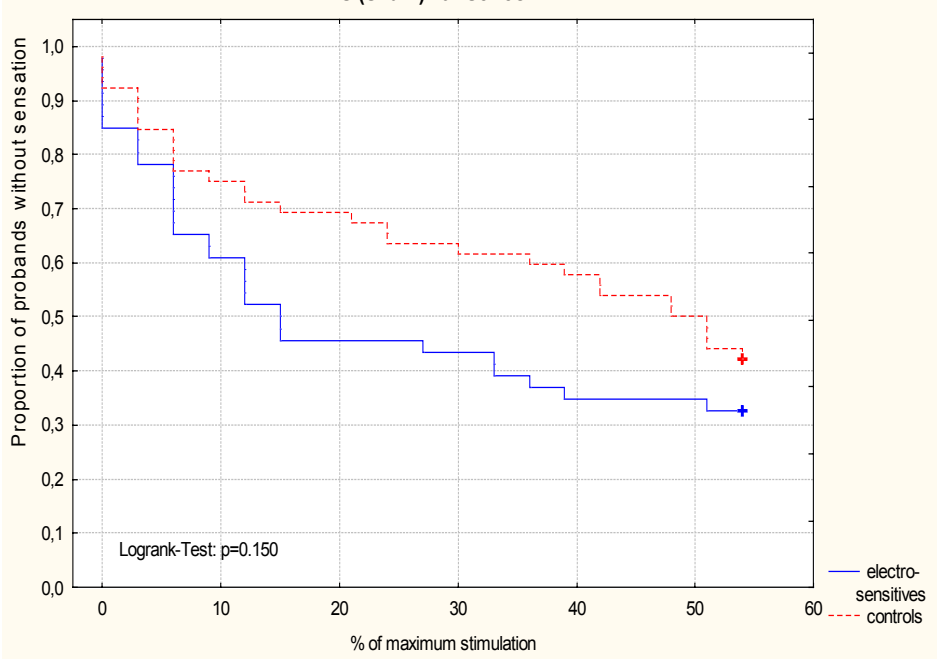






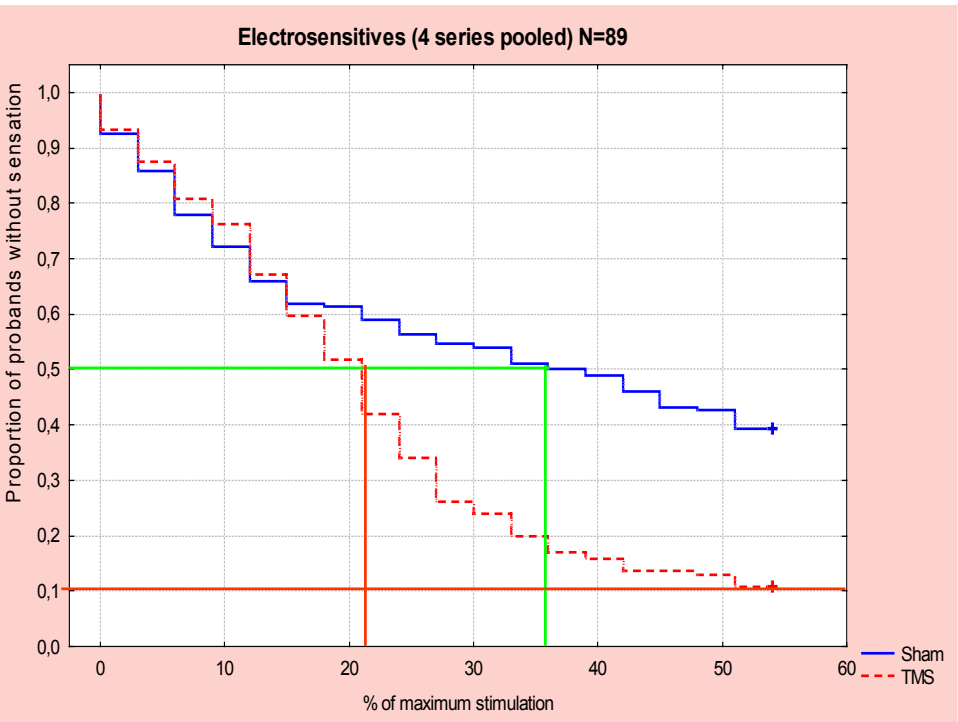
Replication Study

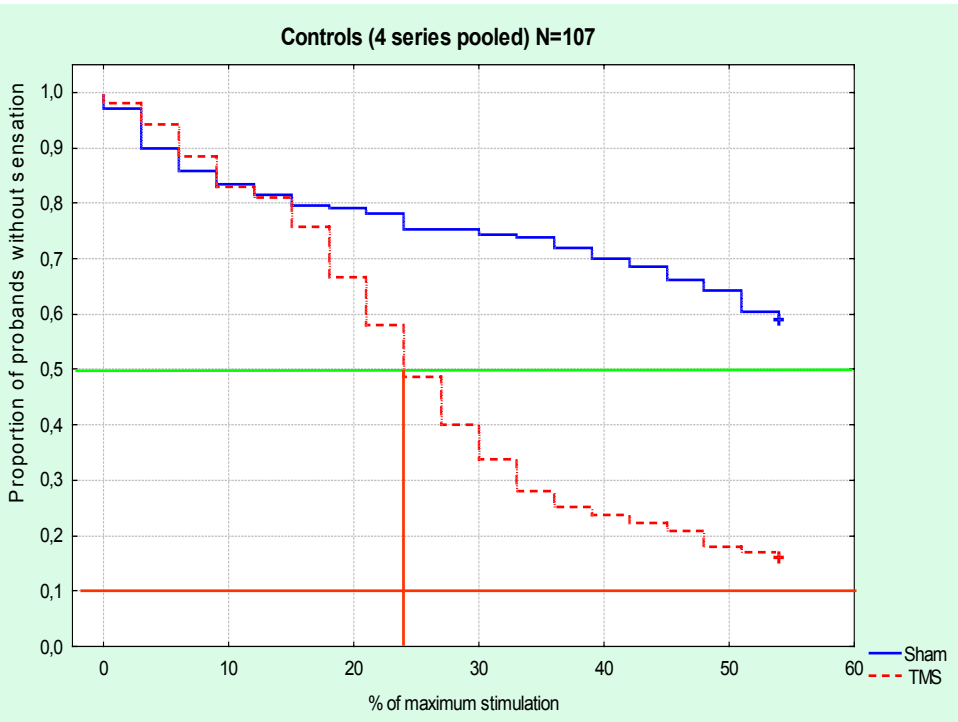




Descriptive results (pooled):

Distance of Sham stimulation curve (blue solid line)
to TMS curve (dotted red line)
is larger in controls. => better perceptual competence?





Major study endpoint: ability to discriminate TMS from sham exposure:
ability = $threshold_{sham}$ – $threshold_{TMS}$

Statistical analysis (1): perceptual competence

ANCOVA: Sex, sequence (VSVS), group (ES,controls), age
rep.Measurement: ability1, ability2 (learning effect)

The GLM Procedure

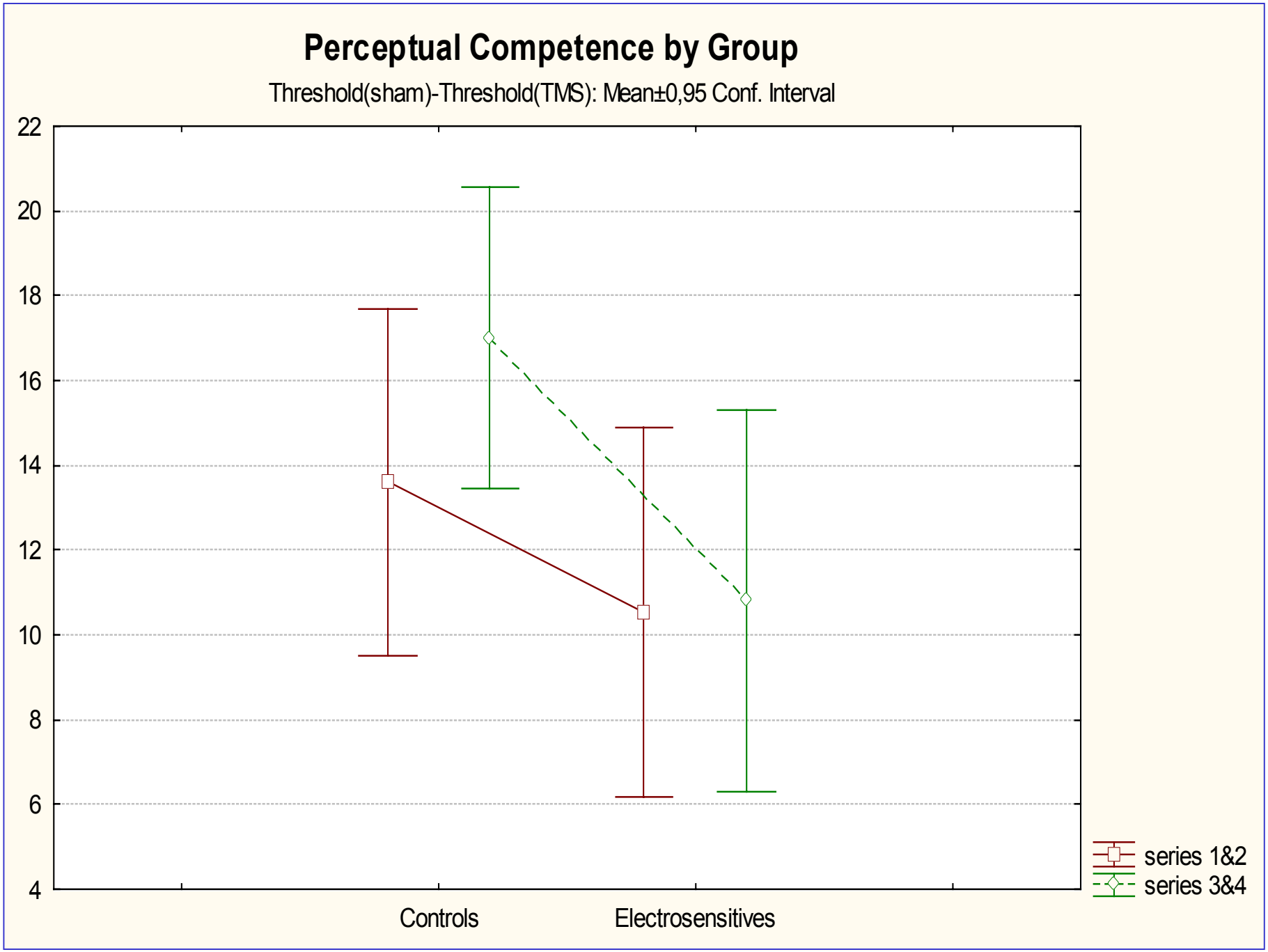
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

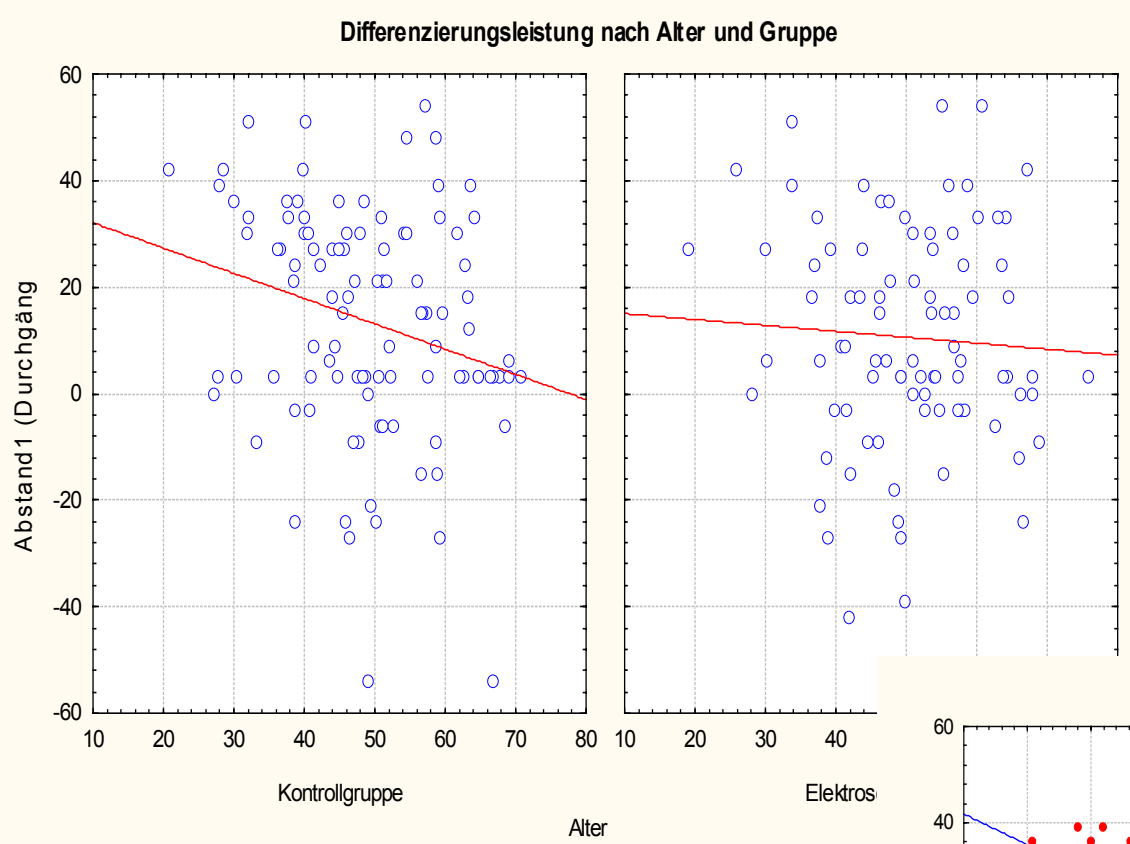
Source	DF	Type III SS	Mean Square	F Value	Pr > F
female	1	3568.76727	3568.76727	7.45	0.0070
group	1	3240.99648	3240.99648	6.77	0.0100
VSVS	1	6685.45970	6685.45970	13.95	0.0002
age	1	4430.66312	4430.66312	9.25	0.0027
age*group	1	2480.61222	2480.61222	5.18	0.0240
Error	186	89108.39007	479.07737		

Repeated Measures Analysis of Variance

Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
learning	1	22.87275	22.87275	0.09	0.7636
learning*female	1	4.18115	4.18115	0.02	0.8977
learning*group	1	469.80925	469.80925	1.86	0.1738
learning*VSVS	1	38.20197	38.20197	0.15	0.6975
learning*age	1	76.71158	76.71158	0.30	0.5818
learning*age*group	1	319.26840	319.26840	1.27	0.2618
Error(learning)	186	46877.10697	252.02746		


Perceptual Competence by Group
Threshold(sham)-Threshold(TMS): Mean±0,95 Conf. Interval
22
20
18
16
14
12
10
8
6
4
Controls
Electrosensitives
series 1&2
series 3&4



Confounding effect:

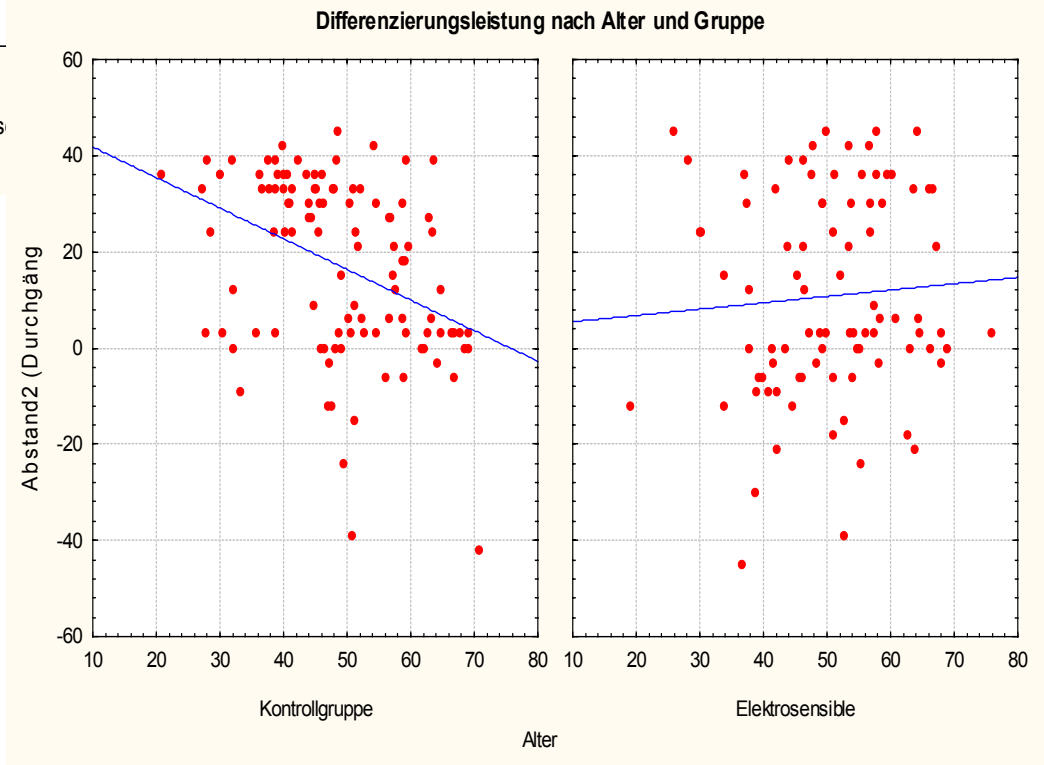
Age effect: The older, the more difficult is discriminating sham and TMS exposure.

Electrosensitives: with increasing age less diminuation of perceptual competence than controls

Major result:

After adjusting for age, sex, and experimental design (sequence) there is a clear difference between electrosensitives and controls:

Controls better discriminate TMS and sham exposure.



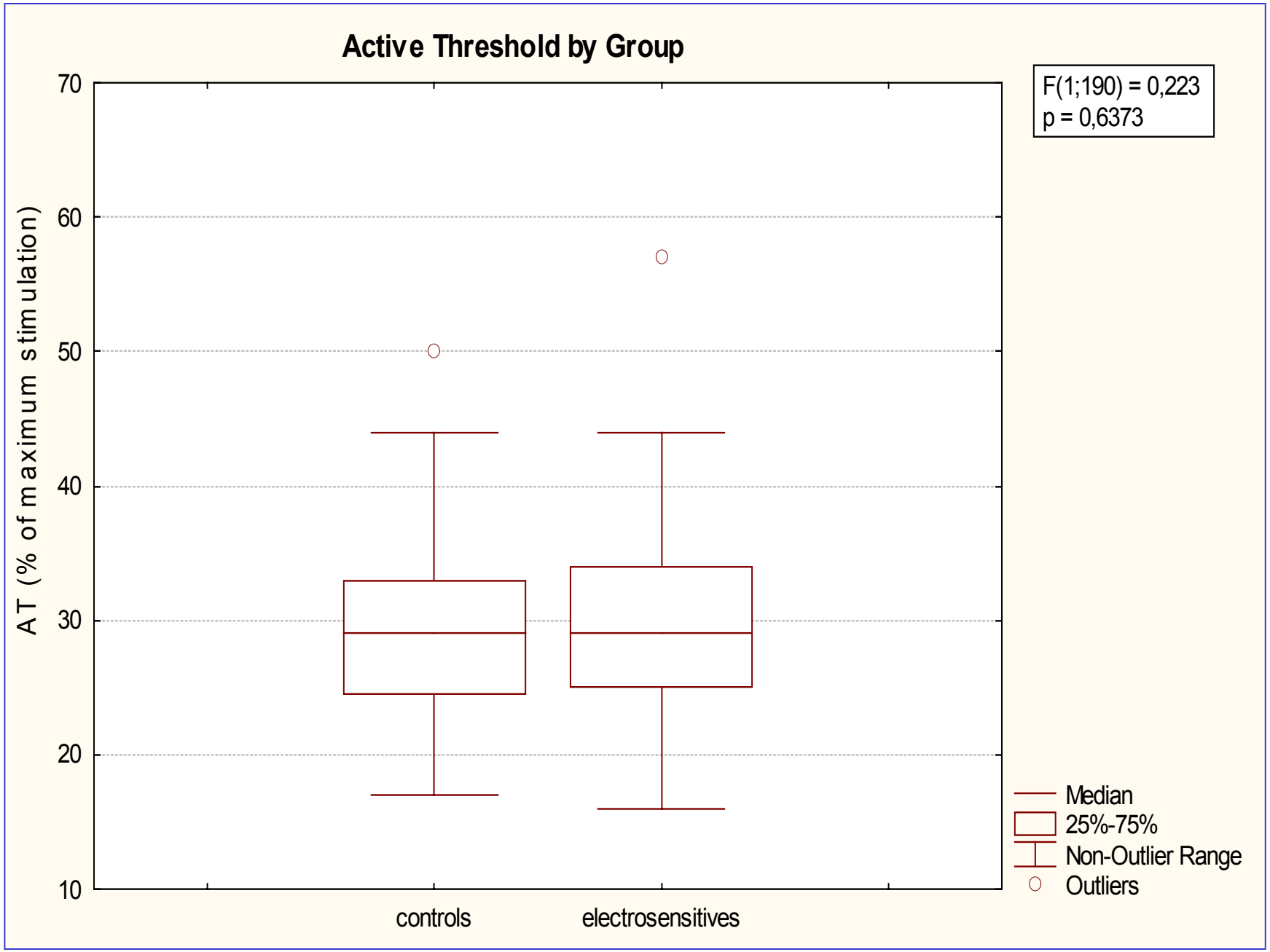
Results (2): Acting Motor Threshold

ANCOVA : **Sex, group (ES,controls), age**

Source	DF	Type III SS	Mean Square	F Value	Pr > F
female	1	221.2284343	221.2284343	4.82	0.0294
group	1	1.5163741	1.5163741	0.03	0.8560
age	1	200.3356585	200.3356585	4.36	0.0381
age*group	1	0.6381502	0.6381502	0.01	0.9063
group*female	1	6.2764370	6.2764370	0.14	0.7120
Error	186	8539.879303	45.913330		

Even after adjusting for sex and age electrosensitive probands do not display altered acting motor thresholds.

Female acting motor thresholds are slightly increased.
Age and acting motor threshold values correlate positively.

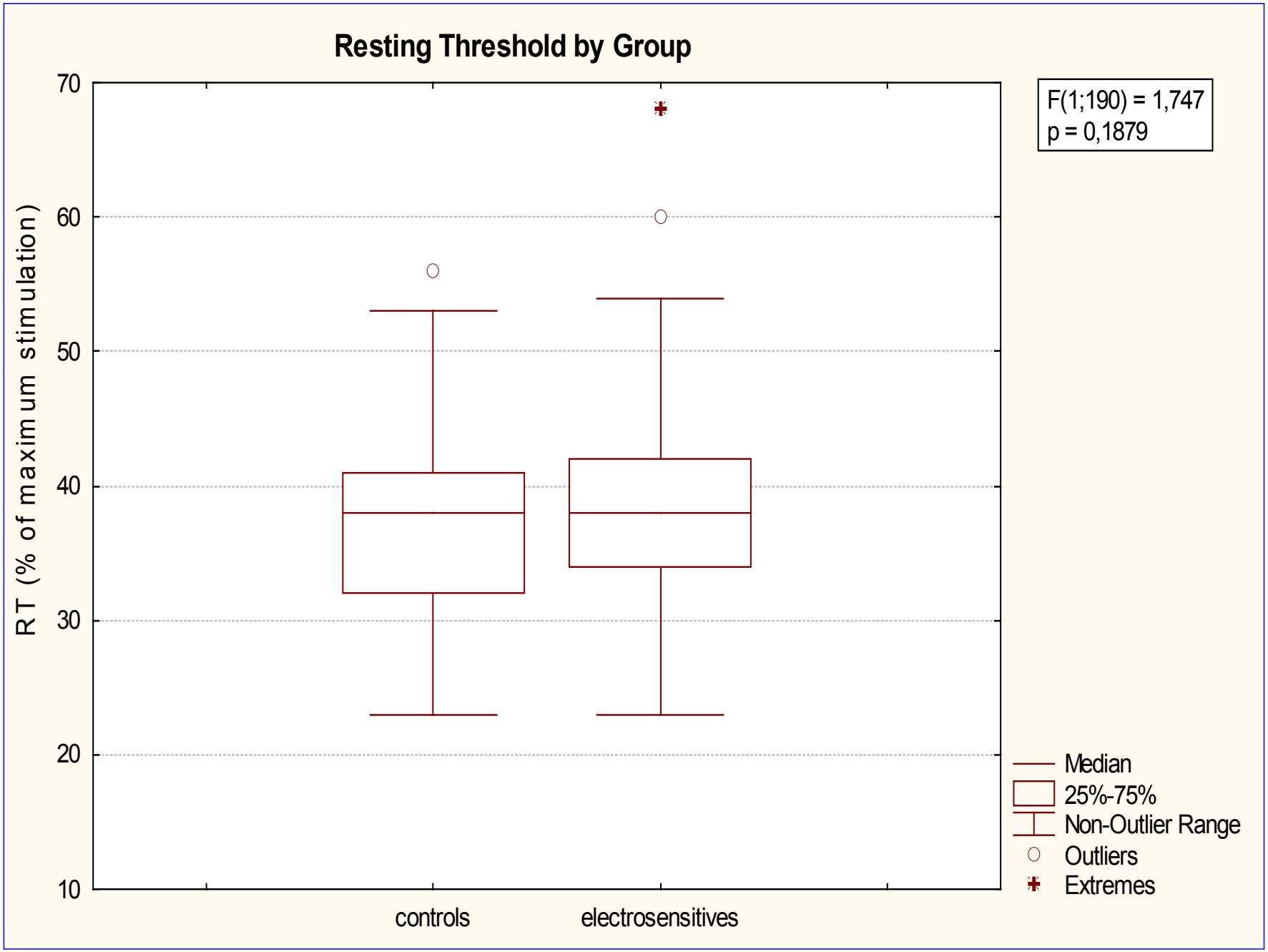

Active Threshold by Group
F(1;190) = 0,223
p = 0,6373
AT (% of maximum stimulation)
70
60
50
40
30
20
10
controls
electrosensitives
Median
25%-75%
Non-Outlier Range
Outliers

Results (3): Resting Motor Threshold

ANCOVA : **Sex, group (ES,controls), age**

Source	DF	Type III SS	Mean Square	F Value	Pr > F
female	1	53.4241574	53.4241574	0.91	0.3421
group	1	28.8423240	28.8423240	0.49	0.4849
age	1	203.1516084	203.1516084	3.45	0.0648
age*group	1	11.2982980	11.2982980	0.19	0.6619
group*female	1	12.1636107	12.1636107	0.21	0.6500
Error	186	10952.70154	58.88549		

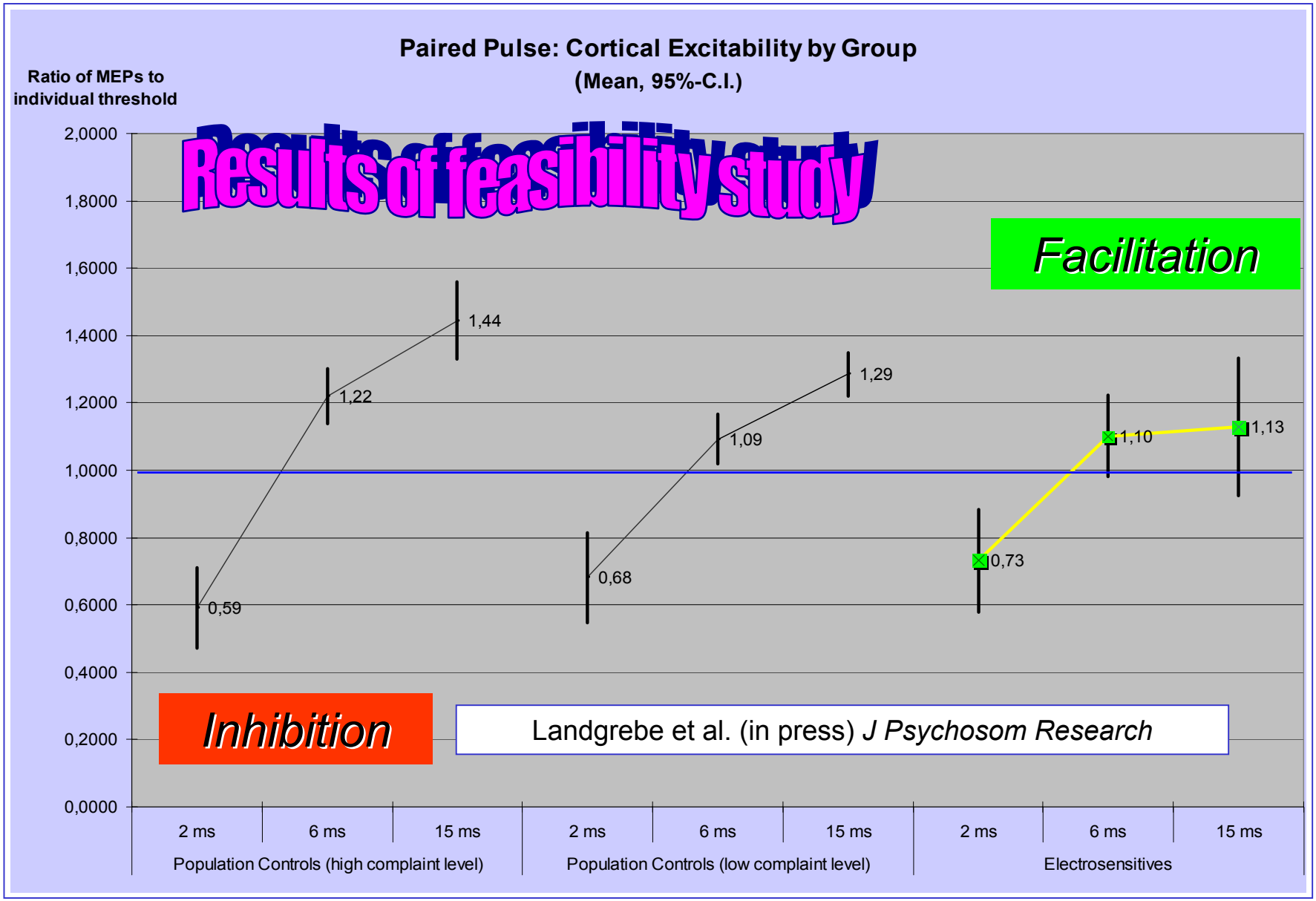
Even after adjusting for sex and age electrosensitive probands do not display altered resting motor thresholds.


Resting Threshold by Group
F(1;190) = 1,747
p = 0,1879
RT (% of maximum stimulation)
70
60
50
40
30
20
10
controls
electrosensitives
Median
25%-75%
Non-Outlier Range
Outliers
Extremes

Summary perception and motor thresholds:

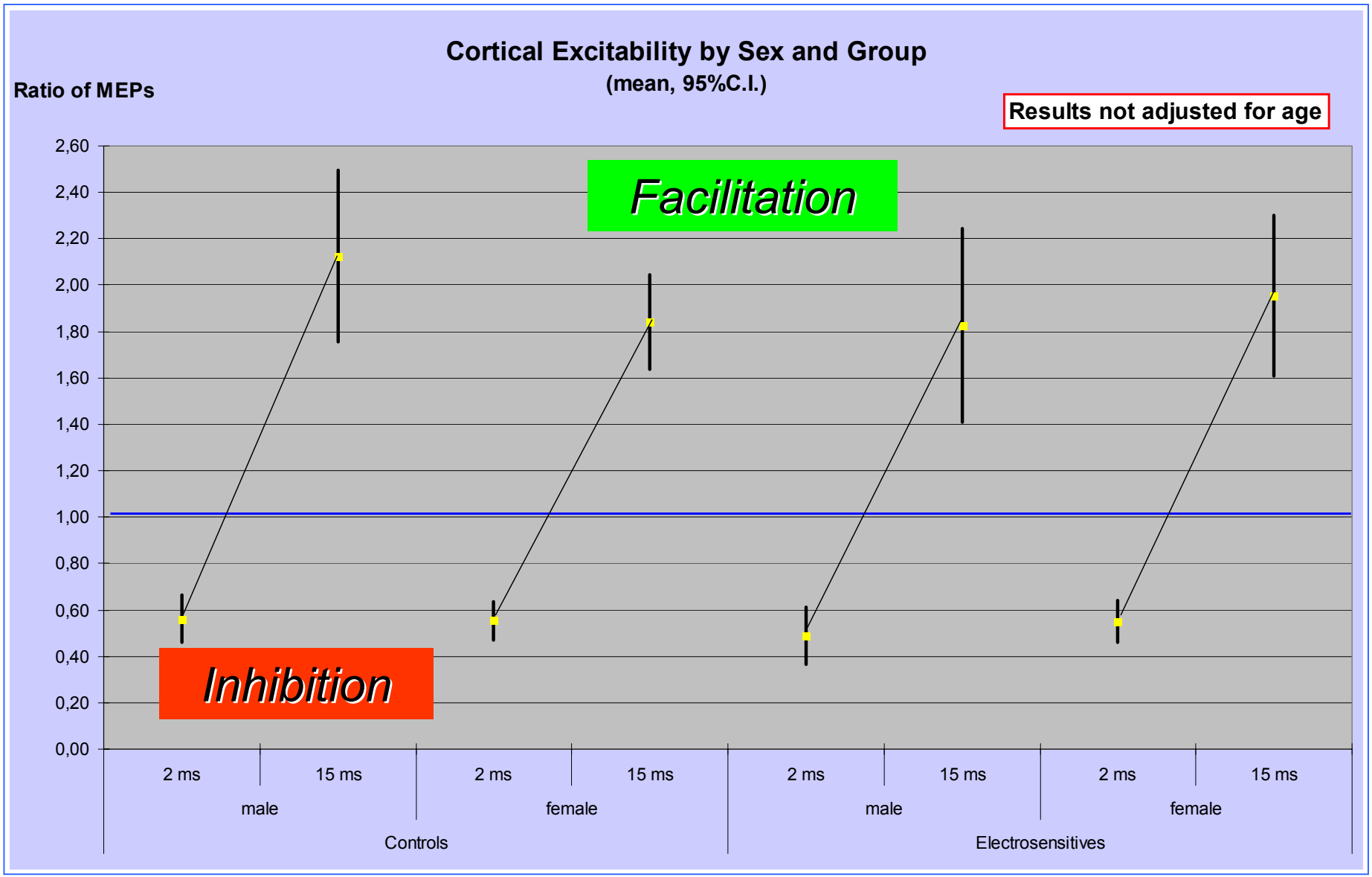
Subjectively electrosensitive people display a diminished ability to discriminate a sham from a magnetic pulse to their dorsolateral prefrontal cortex, while their perception threshold under verum stimulation is comparable to controls.

Their objectively measured acting and resting motor thresholds in transcranial magnetic stimulation do not differ from those of controls.



Feasibility study:

„Electrosensitives“: Diminished facilitation (ISI 15 ms)



Replication study:

„Elektrosensitives“: Differences not straightforward visible

Statistical analysis (4): Paired-Pulse MEPs

ANCOVA: Sex, group (ES,controls), age
Rep.Measurement: ISI2ms ISI15ms

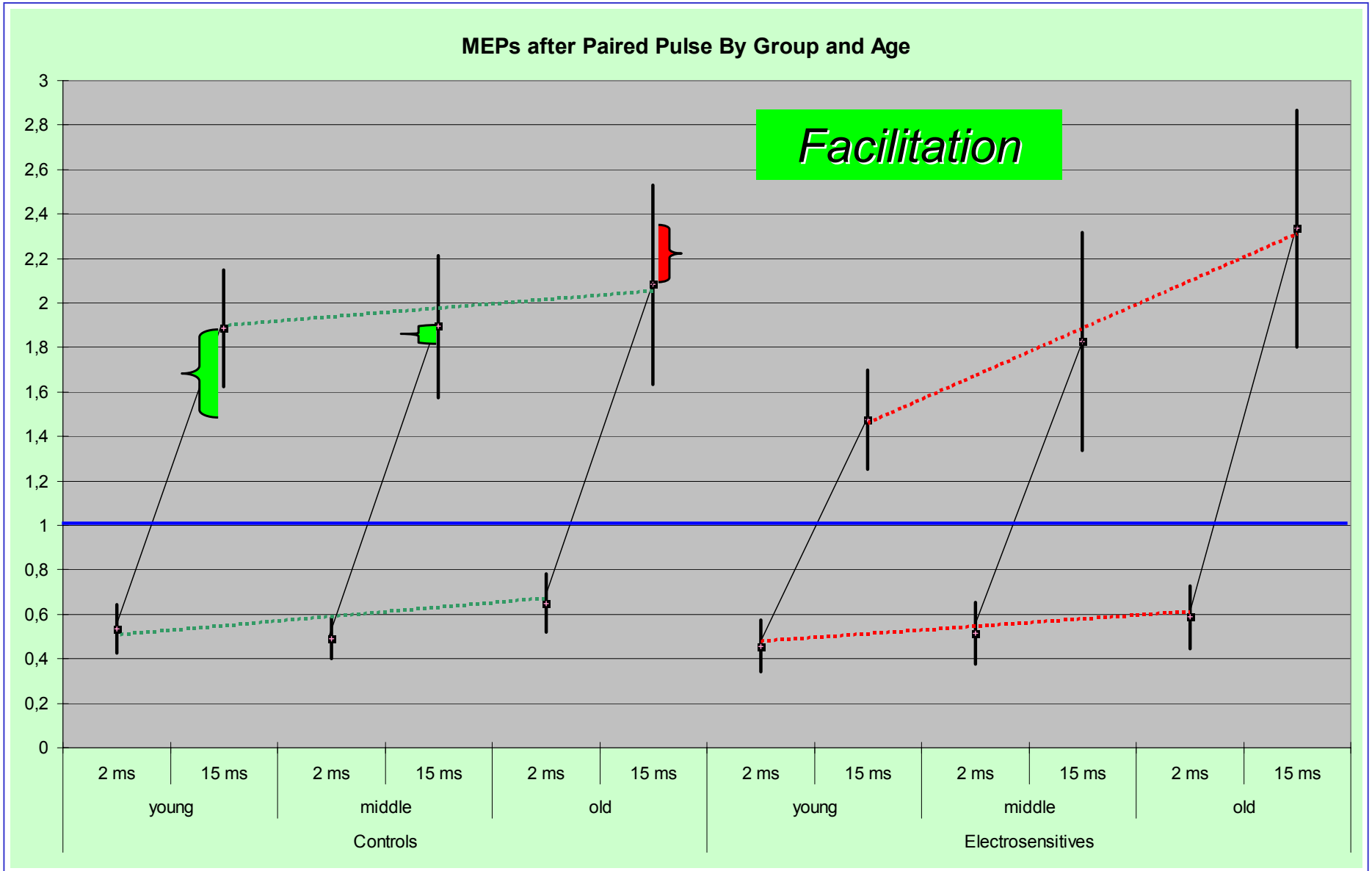
Source	DF	Type III SS	Mean Square	F Value	Pr > F
female	1	0.0377747	0.0377747	0.06	0.8143
group	1	3.3579724	3.3579724	4.92	0.0278
age	1	5.4149166	5.4149166	7.93	0.0054
age*group	1	2.8820325	2.8820325	4.22	0.0414
group*female	1	2.1034281	2.1034281	3.08	0.0809
Error	184	125.6777033	0.6830310		

Repeated Measures Analysis of Variance

Source	DF	Type III SS	Mean Square	F Value	Pr > F
gradient	1	1.2202083	1.2202083	1.92	0.1670
gradient*female	1	0.0212807	0.0212807	0.03	0.8548
gradient*group	1	2.7860726	2.7860726	4.39	0.0374
gradient*age	1	3.2254729	3.2254729	5.09	0.0253
gradient*age*group	1	2.6255420	2.6255420	4.14	0.0433
gradient*group*female	1	1.2236245	1.2236245	1.93	0.1664
Error(gradient)	184	116.6538890	0.6339885		

After adjusting for age effects
ES significantly differ from controls with respect to their facilitation.

Altered facilitation in ES: dependent on age



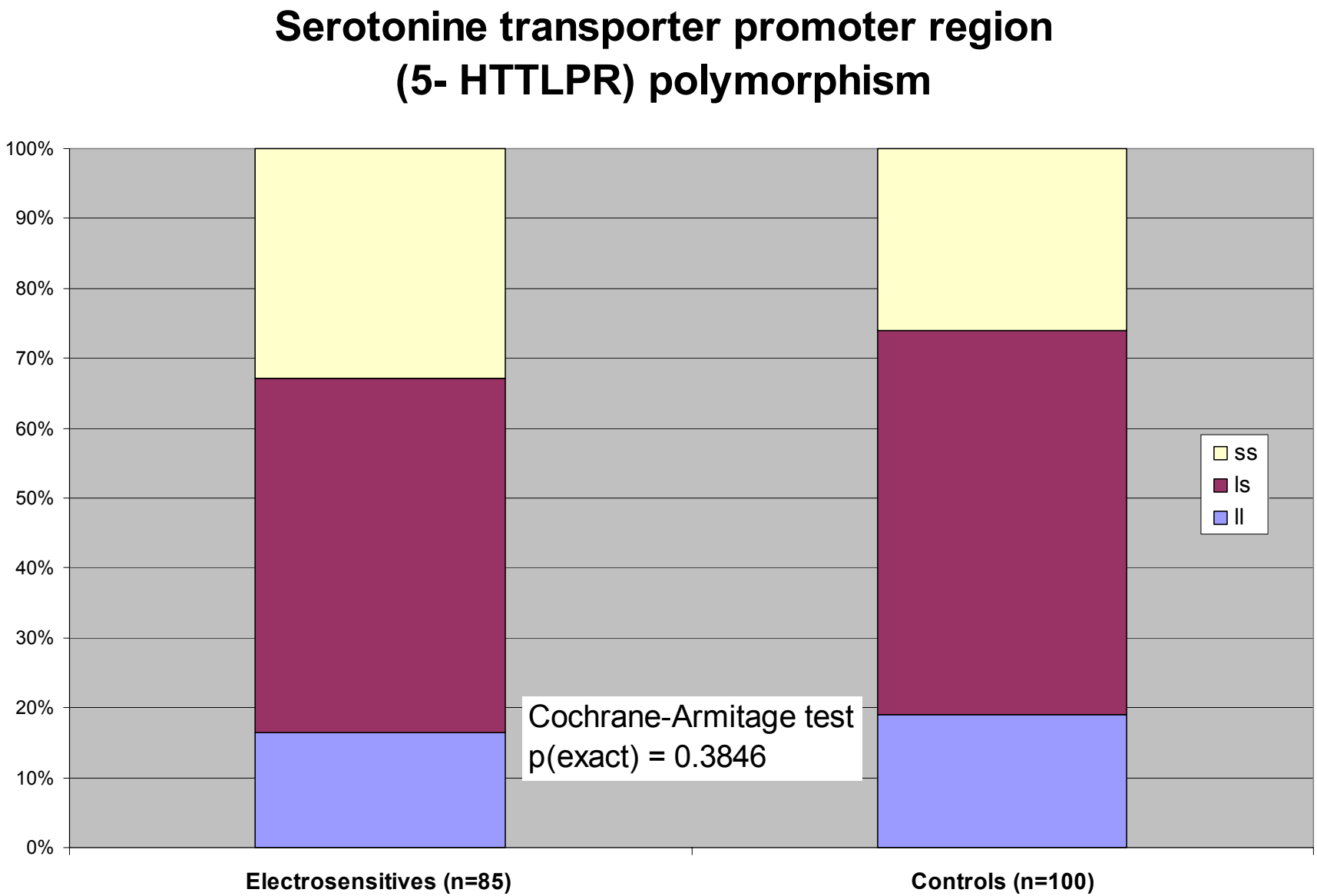
Summary cortical excitability

Subjectively electrosensitive people display an altered cortical excitability as measured by a paired-pulse paradigm and compared to controls.

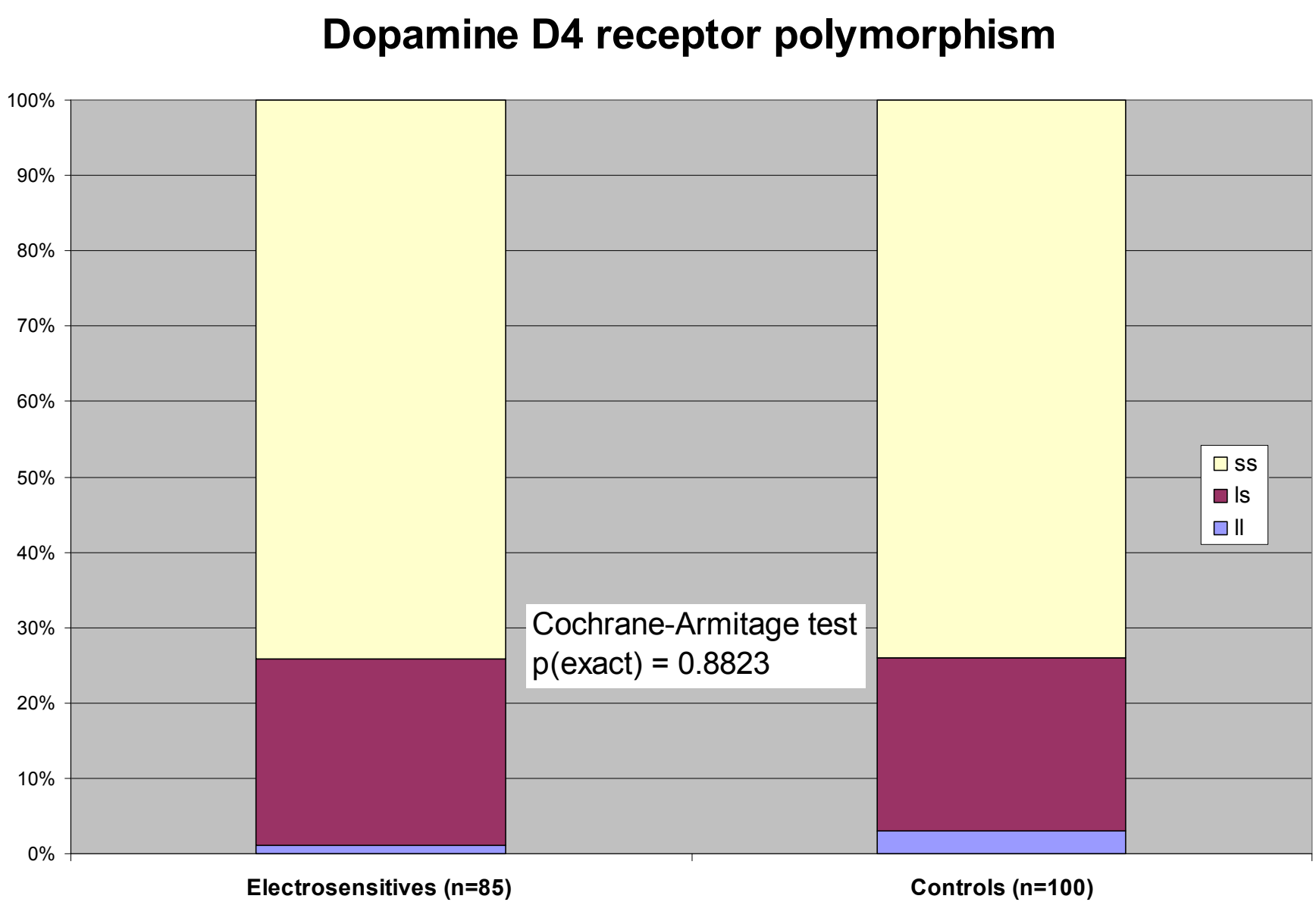
Depending on age their facilitation either is diminished (younger probands) or exaggerated (older probands).

While a prior feasibility study mainly had measured younger probands, results of this replication study are compatible with these earlier results.

Results (5): Serotonine transporter promoter gene



Results (6): Dopamine receptor polymorphism



Summary genetic predisposition

Subjectively electrosensitive people do not display an altered genetic predisposition with respect to

- **5-HTTLPR (serotonine transport promoter gene)**
- **D4 receptor polymorphism (dopamine receptor gene).**

Results (7): Allostatic Load

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	10.6299	10	0.3871
Score	9.9894	10	0.4414
Wald	8.8462	10	0.5468

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	2.6299	3.2925	0.6380	0.4244
age	1	-0.0116	0.0188	0.3804	0.5374
female	1	-0.0753	0.3720	0.0410	0.8396
bmi	1	-0.0177	0.0168	1.1043	0.2933
Albumin	1	-0.7893	0.5175	2.3258	0.1272
hba1c	1	0.6592	0.3956	2.7775	0.0956
Fibrinogen	1	0.00110	0.00390	0.0792	0.7784
DHEA_S	1	0.000127	0.000216	0.3486	0.5549
Cystatin_C	1	-2.0591	1.3717	2.2533	0.1333
interleukin6	1	-0.2905	0.2256	1.6577	0.1979
tumornekrose	1	0.0749	0.0699	1.1475	0.2841

Logistic regression on group membership

Summary Allostatic Load

Subjectively electrosensitive people do not display an altered allostatic load, even after adjusting for age and sex effects.

Results (8): Dysfunctional Cognitions

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	103.8170	7	<.0001
Score	79.9926	7	<.0001
Wald	47.9294	7	<.0001

Analysis of Maximum Likelihood Estimates

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	6.8595	1.3012	27.7921	<.0001
kogni_b	1	-0.7821	0.2331	11.2524	0.0008
kogni_h	1	0.6617	0.2351	7.9230	0.0049
kogni_n	1	0.4785	0.2269	4.4491	0.0349
rumi_a	1	-1.2076	0.2332	26.8157	<.0001
intol_c	1	-0.4710	0.2300	4.1924	0.0406
koerp_d	1	-0.8569	0.3133	7.4811	0.0062
Dauer_in_Minuten	1	-0.5190	0.1457	12.6880	0.0004

Logistic regression on group membership

Results Dysfunctional Cognitions

Empfindlich zu sein für EMF bedeutet (bedeutet für mich) dass....

... man anders als die andern ist .

... man eine besonders schwere Last zu tragen hat.

... man sich mehr schonen muss als die anderen.

Ich denke oft über (meine) ES nach.

Wenn ich plötzlich körperliche Beschwerden habe, warte ich erst mal ab, was daraus wird.

Ich vermeide grössere Anstrengungen, um meine Kräfte zu schonen.

Dauer: Minuten für die Beantwortung der 36 Items des Regensburger EMF-Beschwerdenbogens.

Items separate between ES and controls.

Indicators separating ES and controls

To be electrosensitive, for me has the implication that ...

... I'm different from others

... I'm sharing a big portion of burden

... I have to care for myself more intensively than others.

I'm reflecting quite a lot on (my) electrosensitivity.

Suffering from unexpected complaints, I usually observe them for a while before I react.

I avoid heavier duties to save my strength.

Duration of answering the 36 items of the Regensburg EMF-complaint list (in minutes).

Summary Dysfunctional Cognitions

Subjectively electrosensitive people display a higher level of rumination, intolerance towards complaints, and other cognitions that can explain maintenance of symptoms as a vicious cycle of exaggerated self attentiveness.

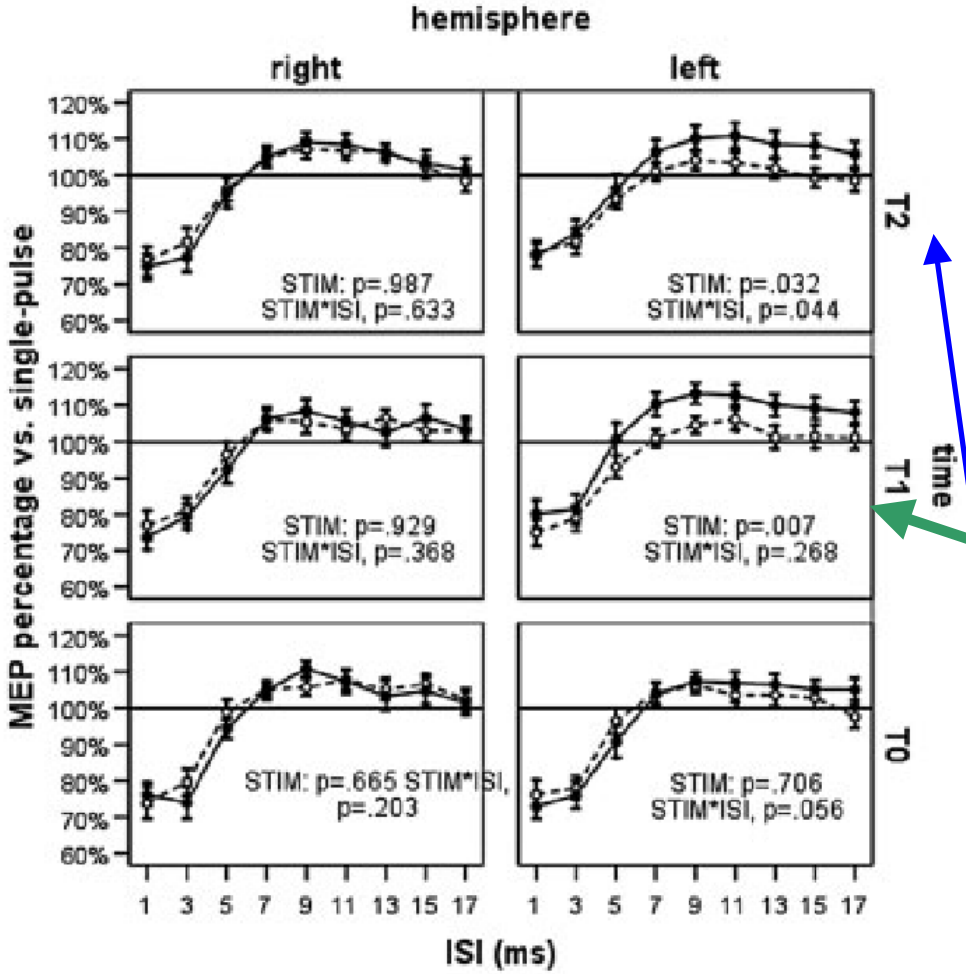


Fig 2. Inhibition-facilitation curves for each combination of the experimental design. Rows represent time (from bottom: baseline, soon after exposure, 1 hour after exposure). Columns represent hemisphere (right, left) and type of stimulation (continuous line indicates real; dashed line indicates sham). Error bars correspond to 95% confidence intervals after pooling subjects together. MEP = motor-evoked potential; ISI = interstimulus interval.

Altered facilitation in healthy subjects after GSM exposure

Ferreri et al., Ann Neurol 2006, 60, 188-96

Increased facilitation
in paired pulse paradigm
after 45‘ GSM-exposure
(double blind, placebo controlled),
lasting at least 1h.

=> Consequences for SES not yet understood.

Summary

Subjectively electrosensitive people (SES) display a diminished perceptual competence in separating a TMS from a sham stimulation.

Objectively measured motor thresholds are comparable.

The effect of altered cortical excitability of SES could be replicated, with age being a modifying condition on the direction of altered facilitation.

„Allostatic load“ as a marker of chronic stress could not be shown to differ between SES and controls.

Dysfunctional cognitions with specific content on EMF were more prevalent in SES.

For two neurotransmitter system receptor genes (5-HTTLPR , Dopamine D4), no differing allelic variants could be shown for SES.

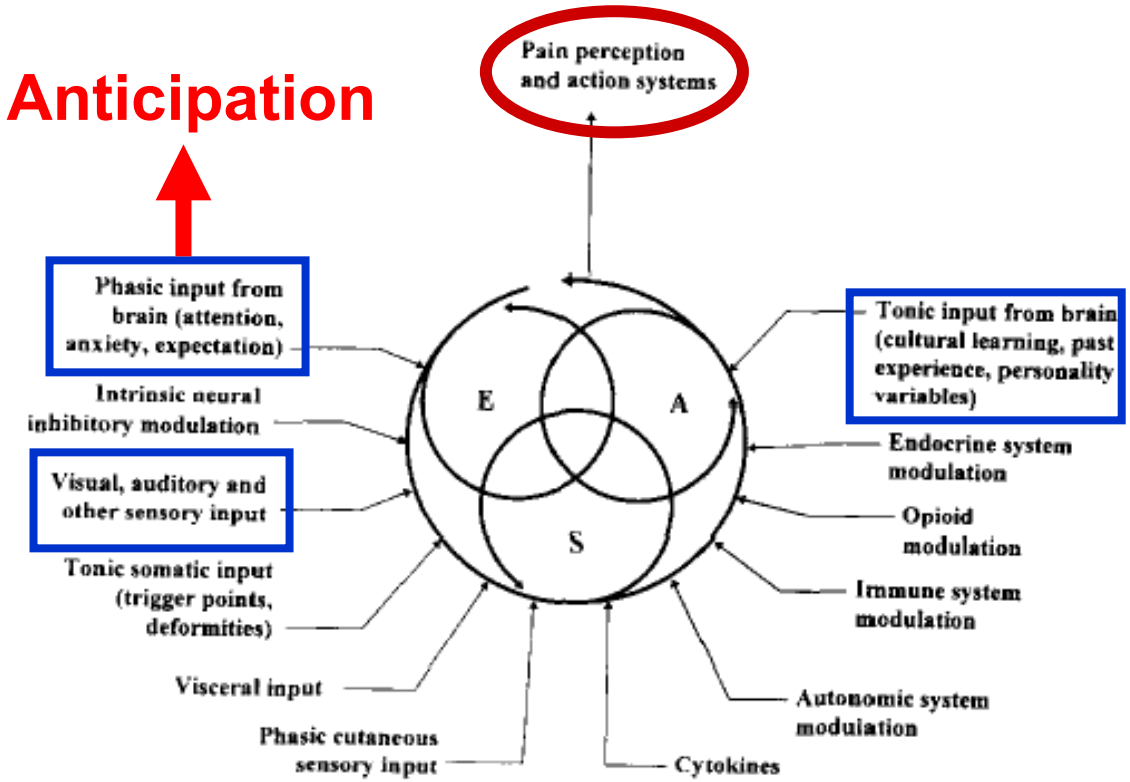
Altered cortical excitability recently was also observed as an effect of GSM exposure in young, healthy subjects.

Background and Rationale of fMRI sub-study

- Pathophysiology of subjective electrohypersensitivity is yet unknown
- Subjective electrosensitive patients (ES) suffer from a variety of unspecific health complaints
- Frequent condition (1-3%), high morbidity, reduced quality of life
- So far, no clear causal relationship between electromagnetic fields (EMF) exposure and health complaints could be established
- Higher cortical processes (e.g. anticipation) may play a role like in other functional somatic symptoms (e.g. chronic pain)

Background and Rationale

Chronic Pain

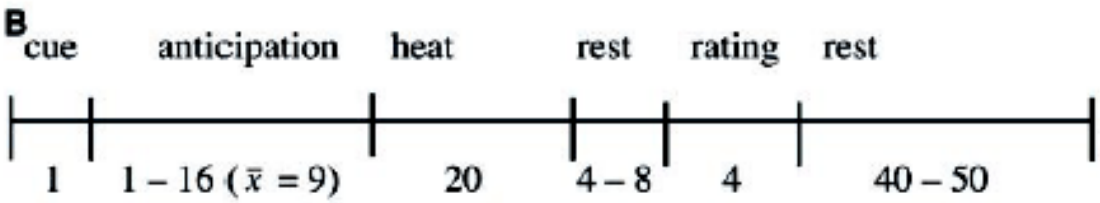


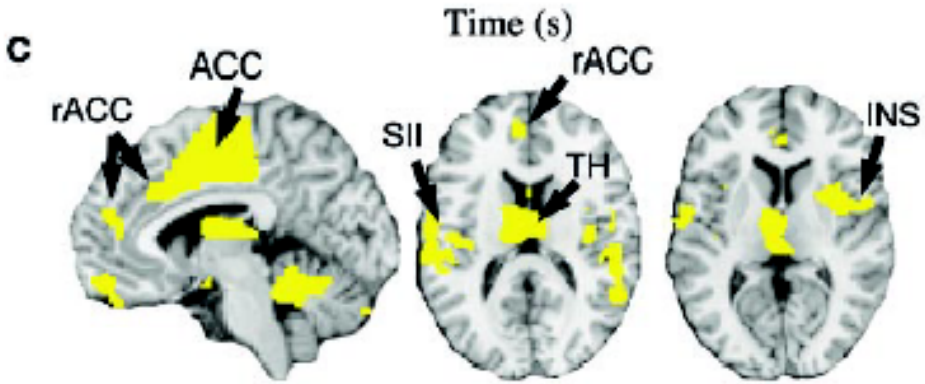
Pain Perception = Consequence of processing within pain neuromatrix

Melzack 1999, Pain Suppl. 6, S121-126

Background and Rationale

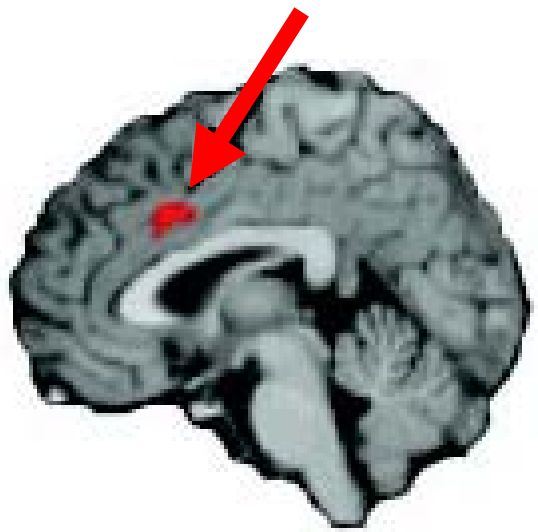
Chronic Pain - fMRI





Application of placebo analgetic creme

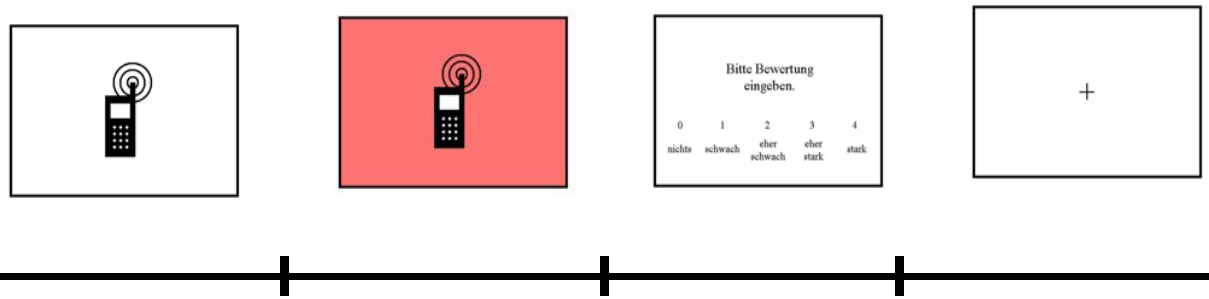
rACC activation



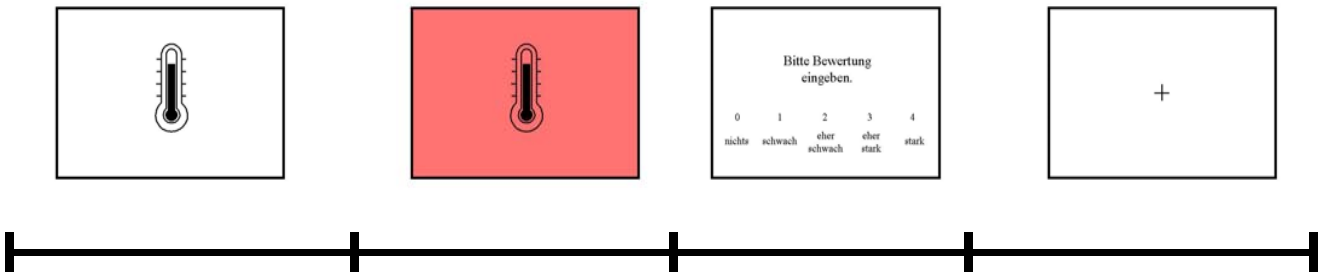
Wager et al. 2004, Science 303, 1162-67

Does anticipation play a role in subjective electrohyersensitivity?

fMRI-Design



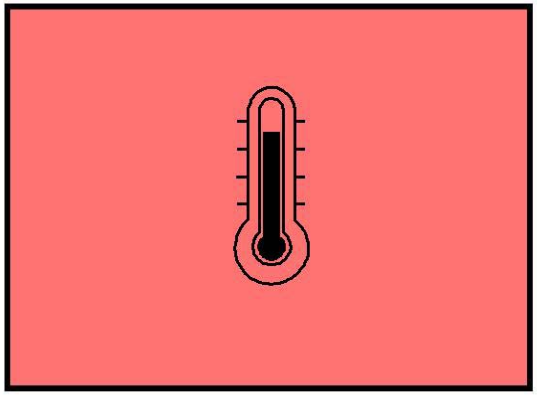
Cue/ Anticipation | Placebo EMF expousre / thermal stimuli | Intensitiy rating | Rest



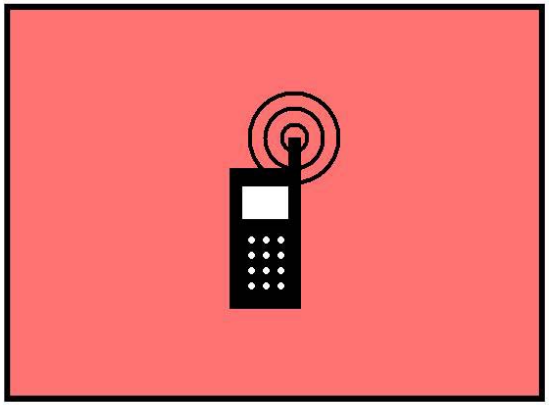
Duration [s]	2,4,6,8	12, 13.25,14.5	6	8,6,4,2	total: 24 s

Experiment time: 45 minutes

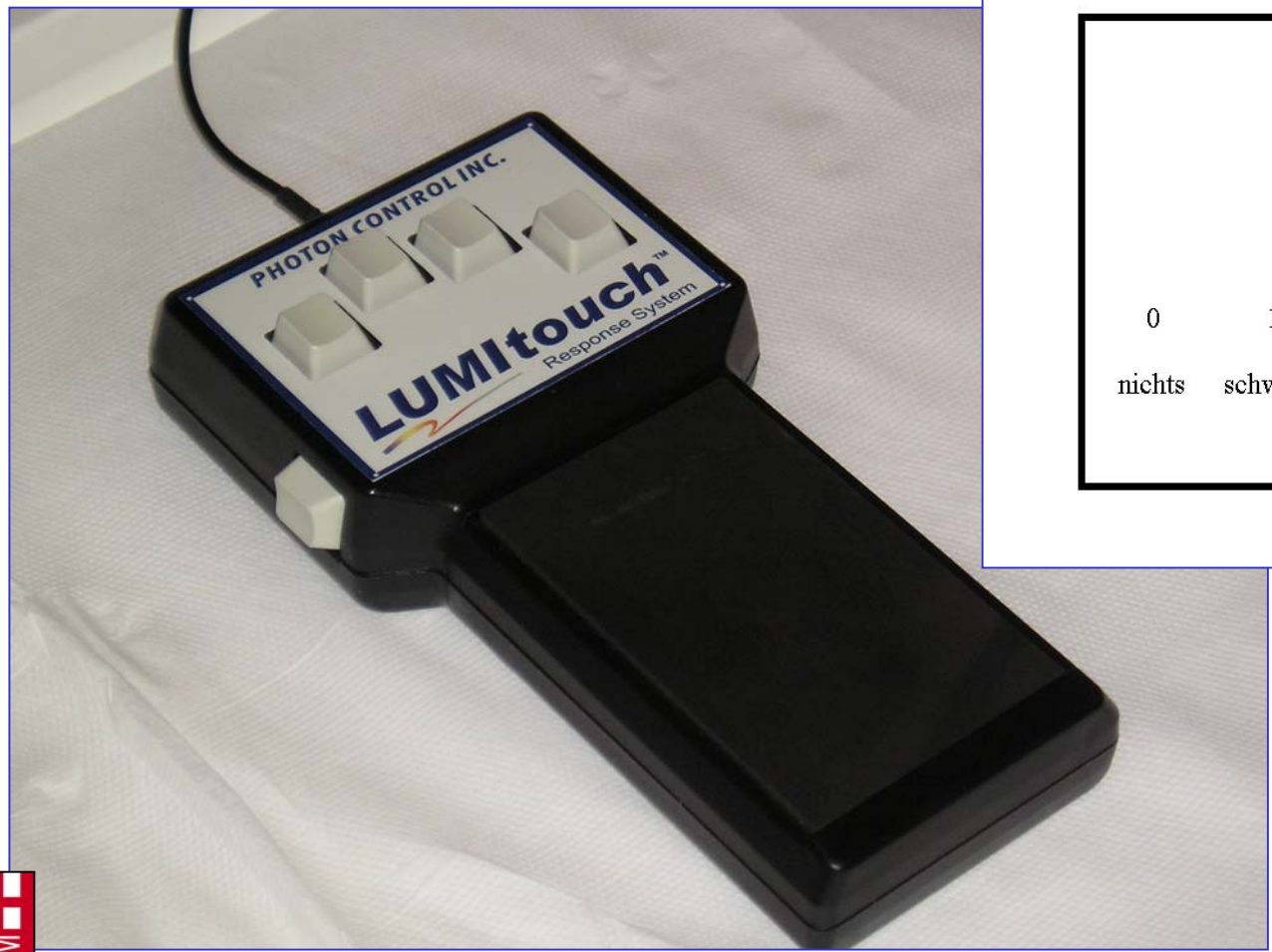
fMRI-Design: thermal stimulation



fMRI-Design: Placebo EMF exposure



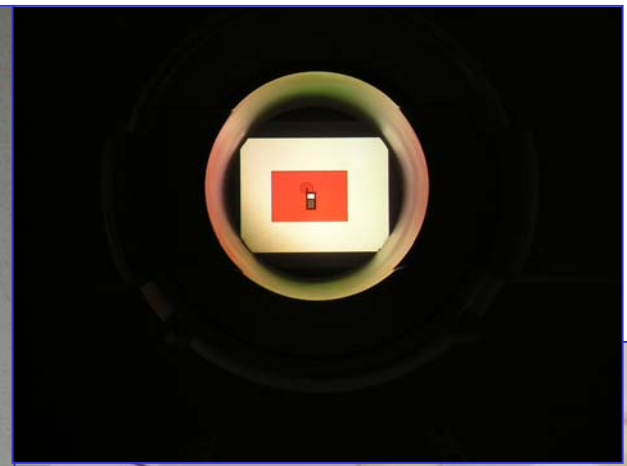
fMRI-Design: Intensity-Rating

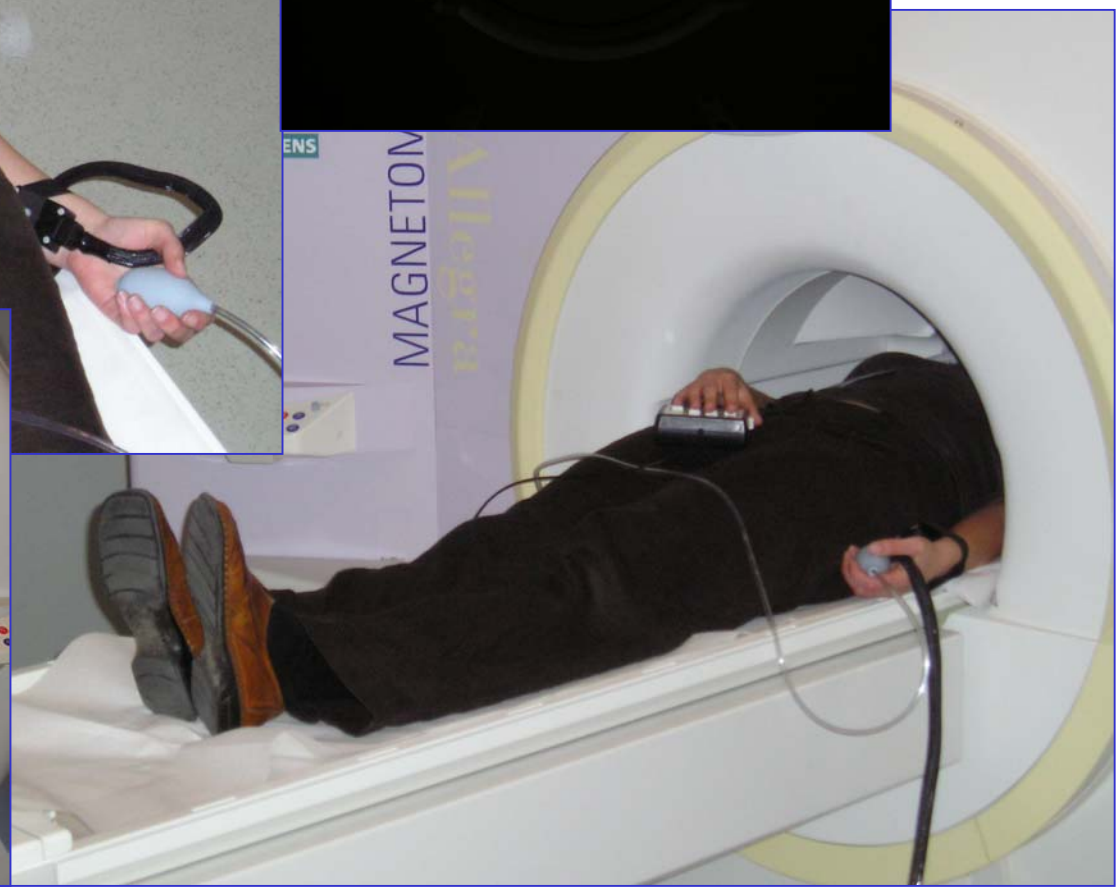


Bitte Bewertung eingeben.

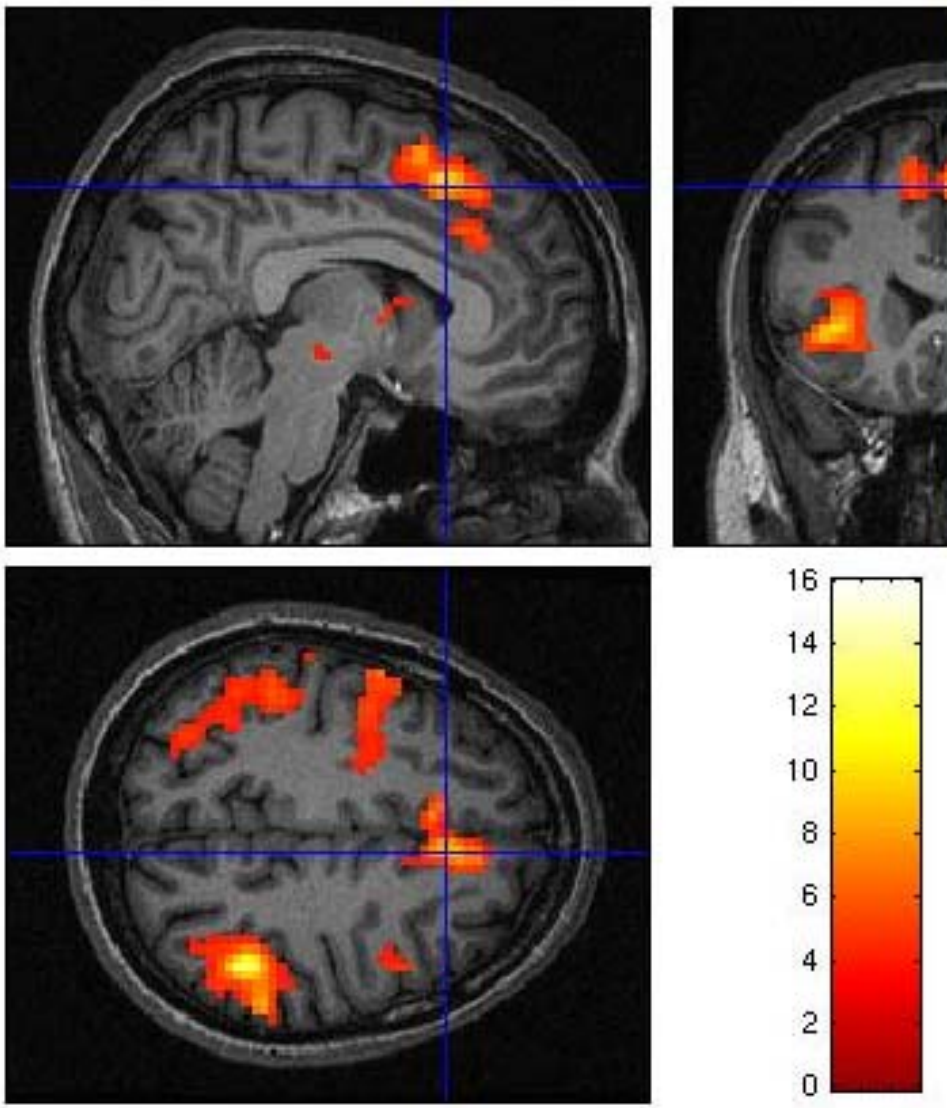
0	1	2	3	4
nichts	schwach	eher schwach	eher stark	stark

fMRI-Design: 3 tesla Siemens scanner





Analysis: „proof of principle“

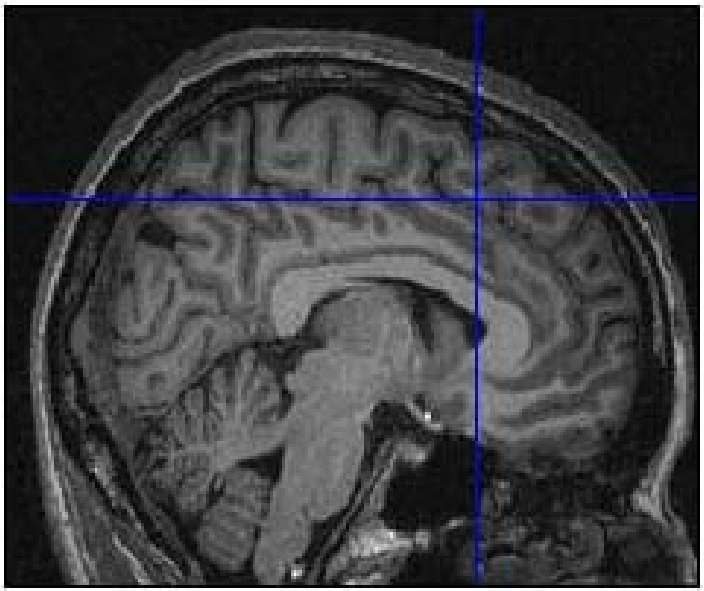


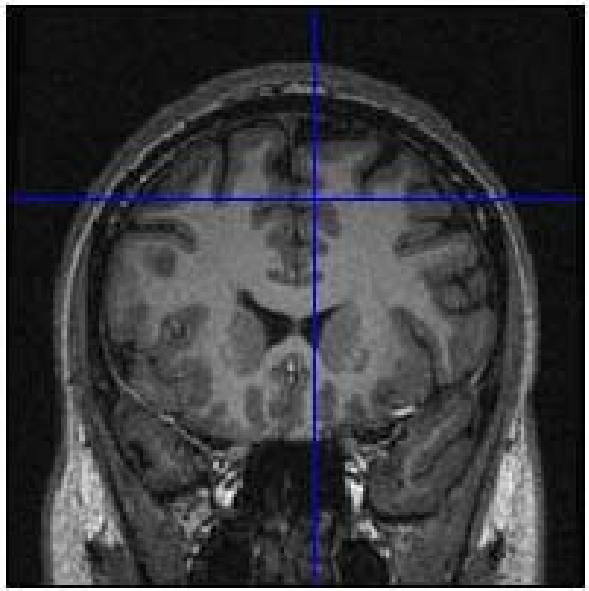
Behavioural effect:

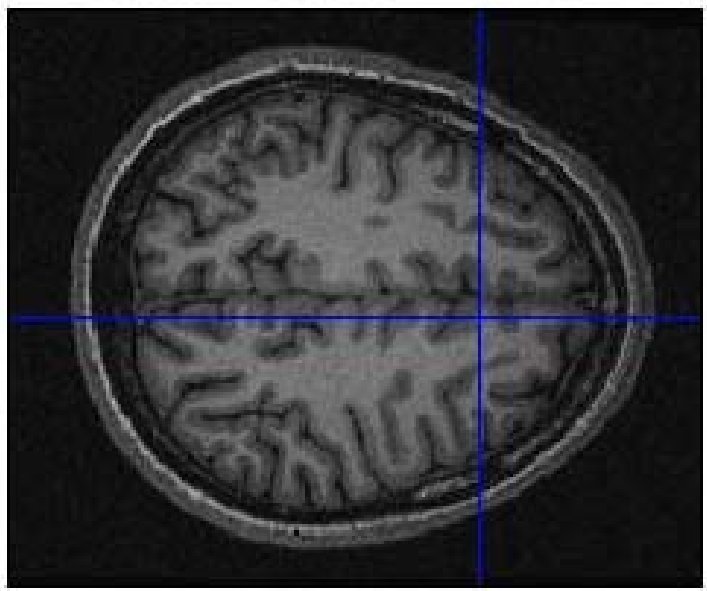
Heat experience

Thermal stimulation of the left lower arm leads to cortical activation in right primary somatosensory cortex

Analysis: Results





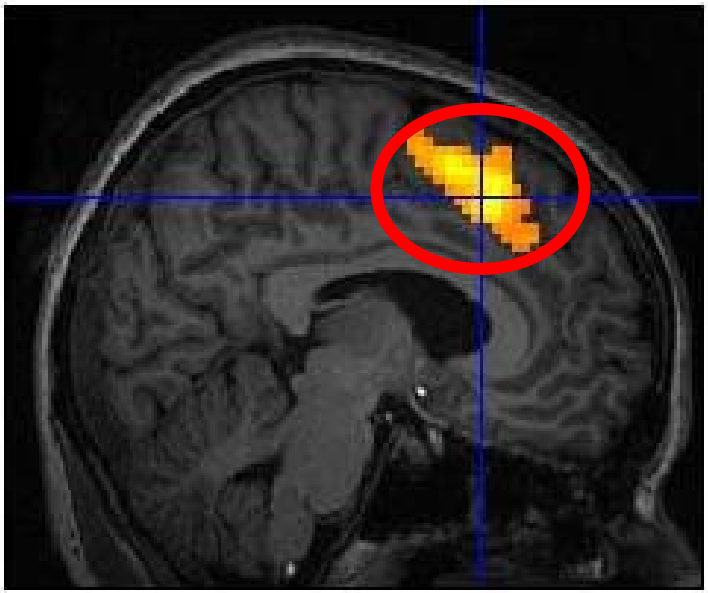


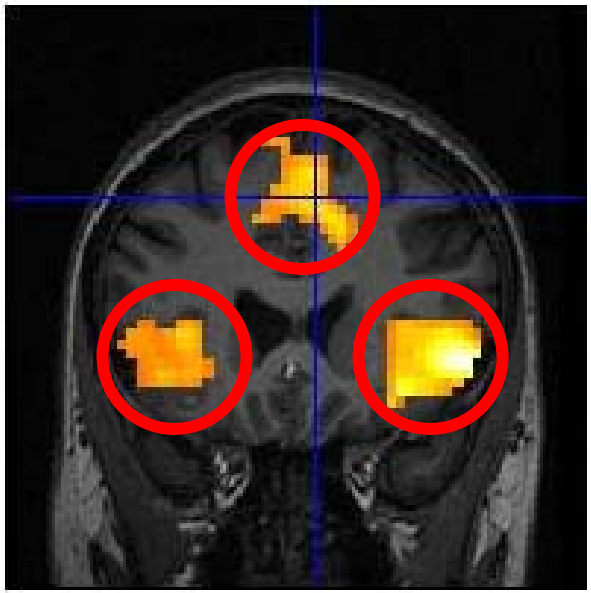
Behavioural effect:

No sensations

Cortical activation during placebo exposure to EMF in healthy controls (N=15):
No activation

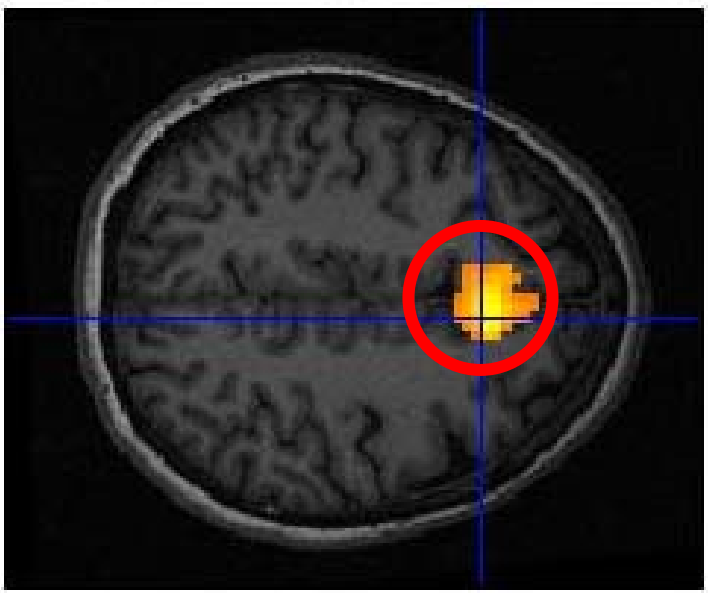
Analysis: Results

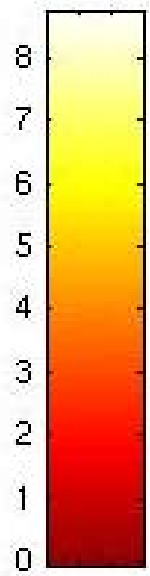




Behavioural effect:

Various sensations (e.g., prickling of the skin)





Cortical activation during placebo exposure to EMF in subjectively electrosensitives (N=15):
Activation of rACC and Insula

Conclusions

- functional magnetic resonance imaging is feasible in subjectively electrosensitive patients

- all patients and controls tolerated exposure to a 3 tesla magnetic field without side effects

- preliminary results point to a possible contribution of anticipation to symptom generation in subjectively electrosensitive patients

- cognitive behavioral therapy aiming at correcting dysfunctional cognitive strategies appears to be a promising approach to at least alleviate symptoms and improve quality of life

Final Question:

What are the physiological conditions of people in-sensitive to EMFs ?