Table S1 Epidemiological and psychometric data of the finally included subjects

	mean
N	16
sex (m/f)	4/12
age (SD)	28.4 (6.6)
SDS mean (SD)	28. 6 (6.3)
STAI mean (SD)	30.6 (7.9)
EPI-Neuroticism mean (SD)	6.7 (2.6)
EPI-Extraversion mean (SD)	14.1 (3.7)

SDS Self-Rating Depression Scale (Zung, 1965, German version: Zung, 2005)

STAI State Trait Anxiety Inventory (Spielberger *et al*, 1970, German version: Laux *et al*, 1981)

EPI Eysenck Personality Inventory (Eysenck and Eysenck, 1964, German version: Eggert, 1974)

Table S2 Presentation of the included sample and the existing data

Subject No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
PLC	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	A	A	A	B	C
CIT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A	B	C
RBX	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	A	A	A	B	C

+ available and included data; - missing data due to technical reasons (error of the scanner);

A = subject excluded from analysis due to excessive head movements in > 1 scan and less than 2 analyzable scans; B = subject excluded from study and analysis after detection of pathological T2 hyperintensities without clinical symptoms during the first scan; C = subject withdrew consent after second scan due to individual reasons, therefore completely excluded from analysis; PLC placebo, CIT citalopram, RBX reboxetine

Table S3 Characteristics of the used picture sets

Picture set nr.	1	2	3	statistics (1/2, 2/3, 1/3)
pleasure negative SD	2.87 0.88	2.91 1.04	2.69 0.79	ns (p = 0.89 / 0.44 / 0.49)
neutral SD	5.07 0.24	5.17 0.43	5.11 0.62	ns (p = 0.45 / 0.75 / 0.85)
positive SD	7.54 0.37	7.19 0.49	7.33 0.57	* p = 0.02 / ns (p= 0.39 / 0.18)
arousal negative SD	5.71 0.88	5.60 0.87	5.68 0.87	ns (p = 0.71 / 0.93 / 0.78)
neutral SD	2.97 0.61	3.30 0.92	3.11 0.88	ns (p = 0.26 / 0.58 / 0.62)
positive SD	4.84	4.98	4.81	ns (p = 0.59 / 0.59 / 0.92)
ng vs. ps	0.67 * (p < 0.01)	0.98 * (p < 0.05)	0.97 * (p < 0.01)	
pleasure – mean (neutral) negative SD	2.20 0.19	2.26 0.23	2.41 0.17	
positive SD	2.46	2.02	2.23	
ng vs. ps	0.81 ns (p = 0.21)	0.11 ns (p = 0.35)	0.12 ns (p = 0.41)	

Data from the original IAPS data set (Lang, 2005). Student's t-test between the used data sets. Last

row depicting the difference between positive/negative pictures and the mean of the neutral pictures

(i.e. the difference from neutral in both directions of valence). (ns not significant, ng negative, ps

positive). Numbers of the pictures are on request available from the authors. (annette.bruehl@puk.zh.ch)

Table S4 Emotional valence of the used pictures as rated by the included subject

Valence	PLC Mean/SD	CIT Mean/SD	RBX Mean/SD	PLC-CIT p	PLC-RBX p	CIT-RBX p
ng	2.8/ 1.44	2.9/ 1.34	2.7/ 1.38	0.600	0.55	0.24
nt	5.4/ 1.04	5.3/ 0.78	5.4/ 0.95	0.32	0.69	0.12
ps	7.2/ 1.26	7.1/ 1.26	7.3/ 1.41	0.17	0.45	0.10

Student's t-test between the treatment-conditions (plc Placebo, cit Citalopram, rbx Reboxetine, ng

negative, nt neutral, ps positive)

Table S5 ANOVA of the medication conditions on the conditions exp ng>exp nt and exp uk>exp nt, masked datasets (addition of the masks for the contrast exp ng > exp nt and exp uk > exp nt for each medication condition, each with p<0.00001)

p < 0.001 for CIT>PLC and RBX>PLC, p < 0.01 for RBX/CIT;

a) CIT > PLC	Brodmann area	tal x	tal y	tal z	n (voxel)	t max	p max
exp ng > exp nt							
Precentral gyrus R/DLPFC	6	51	-1	41	248	5.321	0.000108
Precentral gyrus R/DLPFC	6	45	-4	25	227	4.974	0.000204
Precentral gyrus L/DLPFC	6	-39	-10	52	602	6.018	0.000032
Middle FG R/DLPFC	6	27	-9	31	1229	8.185	0.000001
Middle FG R/DLPFC	8	25	23	46	563	5.381	0.000097
MFG R/MPFC	9	21	26	21	772	7.355	0.000004
MFG/ACC R	24	6	2	46	8039	10.404	0.000000
IFG L/VLPFC	45	-42	18	4	332	5.460	0.000084
IFG L/VLPFC	45	-52	29	7	1358	9.205	0.000000
Insula R	13	42	11	-5	205	5.482	0.000081
FFG R	37	43	-49	-8	4735	8.099	0.000001
FFG R	19	32	-60	-22	2375	9.086	0.000000
FFG L	37	-36	-58	-11	268	5.177	0.000140
middle occipital gyrus R	19	28	-82	16	380	5.209	0.000132
Lingual gyrus R	18	9	-64	-15	4102	9.086	0.000000
Lingual gyrus/FFG L	18	-16	-67	-20	2893	6.687	0.000010
Thalamus bilat.		1	-15	10	5820	7.457	0.000003
Caudate body L		-14	-14	21	2462	8.201	0.000001
Caudate body R		15	-16	23	3633	8.558	0.000001
Extended amygdala/BNST R		15	0	-8	282	6.854	0.000008
dorsal upper midbrain bilat.		2	-37	-1	5843	7.484	0.000003

exp uk > exp nt							
Caudate body R		18	-28	28	3446	8.527	0.000001
Caudate body L		-21	-20	22	968	5.205	0.000133
Inferior parietal lobule R	40	55	-49	40	295	6.048	0.000030

b) RBX > PLC	Brodmann area	tal x	tal y	tal z	n (voxel)	t max	p max
exp ng > exp nt							
MFG L/MPFC	8	0	29	40	1600	6.463	0.000031
Middle FG R/DLPFC	6	24	14	55	307	5.528	0.000130
Middle FG R/DLPFC	6	41	2	46	461	7.165	0.000011
Middle FG L/DLPFC	9	-51	8	34	165	5.037	0.000291
Precentral gyrus R/DLPFC	43	61	-10	16	169	5.307	0.000186
STG R	22	59	-37	19	461	7.137	0.000012
med. Thalamus		-3	-13	4	1261	7.455	0.000008
Caudate body L		-9	5	16	262	4.924	0.000351
exp uk > exp nt							
ACC L	32	-7	20	40	207	4.744	0.000477
Post. cingulate L	23	-2	-37	22	994	7.864	0.000004
Parieto-occipital sulcus R	7	24	-61	27	635	6.364	0.000036
STG R	22	63	-37	20	189	5.202	0.000221
Inferior occipital gyrus L	18	-36	-86	-14	358	5.417	0.000156

c) CIT > RBX	Brodmann area	tal x	tal y	tal z	n (voxel)	t max	p max
exp ng > exp nt							
Precentral gyrus R/DLPFC	6	27	-4	28	5311	8.001	0.000002
Precentral gyrus L	4	-36	-16	55	387	4.443	0.000663
Middle FG R/DLPFC	9	24	32	31	195	3.553	0.003538

Middle FG R/DLPFC –reaching to caudate body R	6	21	-7	54	1398	4.843	0.000321
Cingulate R	31	24	-40	33	221	4.426	0.000684
Cuneus R	18	15	-85	15	768	4.371	0.000757
FFG R	19	30	-67	-5	3135	5.019	0.000235
Lingual gyrus L	18	-3	-70	-20	437	3.678	0.002785
Dorsal upper midbrain bilat.		-3	-40	-5	671	6.120	0.000037
Caudate body L		-18	-13	25	625	3.915	0.001774
exp uk > exp nt							
caudate tail R		21	-28	25	165	4.450	0.000655

d) RBX > CIT	Brodmann area	tal x	tal y	tal z	n (voxel)	t max	p max
exp ng > exp nt							
Precentral gyrus R	6	49	2	52	141	5063	0.000217
Medial thalamus bilat.		0	-16	1	871	5.292	0.000146
exp uk > exp nt							
Cingulate R	31	24	-43	34	221	3.661	0.002876
Post. cingulate L	23	-9	-40	22	787	5.518	0.000099
Precuneus L	5	-6	-40	46	4025	4.279	0.000898
STG R	22	63	-34	7	883	4.782	0.000358
STG R	22	63	-46	19	547	5.185	0.000175
MTG L	37	-57	-67	8	1149	3.755	0.002406
Inferior occipital gyrus L	18	-36	-82	-11	1136	4.741	0.000386
FFG L	37	-42	-43	-9	220	3.634	0.003029
FFG L	19	-18	-61	-11	536	3.372	0.005000
PHG L	36	-27	-34	-11	702	4.192	0.001054
Caudate head R		9	8	4	616	4.460	0.000642
Medial thalamus bilat.		0	-16	1	203	3.567	0.003437

Abbreviations: R right, L left, DLPFC dorsolateral prefrontal cortex, MPFC medial prefrontal cortex, VLPFC ventrolateral prefrontal cortex, FG frontal gyrus, MFG medial frontal gyrus, IFG inferior frontal gyrus, ACC anterior cingulate cortex, STG superior temporal gyrus, MTG middle temporal gyrus FFG fusiform gyrus, PHG parahippocampal gyrus, post. posterior, med. medial, bilat. bilateral.

Table S6 Interaction (all expectation conditions) x medication (4x2-interaction each)

No masking, $p < 0.05$ for CIT/PLC and RBX/PLC, $p < 0.01$ for RBX/CIT;

a) CIT/PLC (p<0.05)	Brodmann area	tal x	tal y	tal z	n (voxel)	F max	p max
SFG R/MPFC	6	7	8	58	172	4.224	0.010681
MFG R/MPFC	6	3	2	61	243	3.820	0.016558
Middle FG R/DLPFC	6	27	-11	31	418	4.142	0.011664
IFG L/VLPFC	46	-48	28	10	410	9.440	0.000069
Inferior parietal lobule R	40	54	-49	49	367	4.715	0.006330
Caudate body R		14	-25	28	377	5.401	0.003100
Upper dorsal midbrain bilat.		-3	-34	-1	624	5.252	0.003615

b) RBX/PLC (p<0.05)	Brodmann area	tal x	tal y	tal z	n (voxel)	F max	p max
MFG L/MPFC	8	-3	29	40	158	3.571	0.023299
MFG L/MPFC	8	-9	17	46	319	4.323	0.010570
Precentral gyrus R/DLPFC	4	60	-11	24	260	3.897	0.016482
Precentral gyrus L/DLPFC	4	-31	-22	61	202	3.999	0.014814
Inferior parietal lobule R	40	51	-55	40	225	3.591	0.022790
Cingulate gyrus L	23	-3	-22	25	585	3.845	0.017418
Angular gyrus L	39	-36	-61	34	652	4.003	0.014751
Precuneus R	7	21	-61	31	2019	4.767	0.006721
Extended amygdala R		24	-13	-8	332	4.706	0.007148
Caudate body L		-3	8	16	139	4.402	0.009742

c) CIT/RBX (p<0.01)	Brodmann area	tal x	tal y	tal z	n (voxel)	F max	p max
Middle FG R/DLPFC	6	21	-7	55	1166	5.556	0.002840
Precentral gyrus R/DLPFC	43	60	-7	10	1105	6.464	0.001169
Precentral gyrus R/DLPFC	6	24	-4	31	1276	9.365	0.000086
Precentral gyrus L	4	-54	-15	33	2447	9.158	0.000103
Postcentral gyrus L	3	-39	-25	55	1349	6.173	0.001548
Insula R	13	39	-25	4	216	5.732	0.002384
Posterior insula R	13	27	-40	22	3909	8.041	0.000272
Superior temporal gyrus L	38	-42	5	-17	231	6.166	0.001558
Superior temporal gyrus L	22	-54	-16	1	5221	8.957	0.000122
Precuneus R	7	12	-58	52	485	6.481	0.001151
Precuneus L	7	-6	-52	46	302	4.993	0.005013
Precuneus L	7	-18	-55	46	634	6.683	0.000950
PHG/amygdalar complex L		-39	-13	-17	251	6.998	0.000706
Dorsal hippocampus R		33	-31	-5	370	6.549	0.001078
FFG R	19	33	-73	20	1746	6.288	0.001386
FFG R	19	14	-60	-6	4763	6.686	0.000947
FFG L	7	-30	-79	-25	599	6.622	0.001006
FFG L	19	-20	-64	-7	10582	9.154	0.000103
Lingual gyrus R	19	33	-67	1	11500	9.989	0.000051

Abbreviations: R right, L left, DLPFC dorsolateral prefrontal cortex, MPFC medial prefrontal cortex, VLPFC ventrolateral prefrontal cortex, FG frontal gyrus, SFG superior frontal gyrus, MFG medial frontal gyrus, IFG inferior frontal gyrus, ACC anterior cingulate cortex, STG superior temporal gyrus, MTG middle temporal gyrus FFG fusiform gyrus, PHG parahippocampal gyrus, post. posterior, med. medial, bilat. bilateral.

Supplementary data and discussion

Brain activation in the placebo condition

In order to assess the basis of the comparisons with the drug conditions, we performed a separate

explorative analysis of the placebo condition and compared this qualitatively and descriptively with

the results of a previous dataset of healthy subjects performing the same paradigm without medication

(Herwig *et al*, 2007). Whenever that dataset firstly had been performed with a different scanner (1.5T)

and a different scanning resolution, secondly had been analyzed based on another hemodynamic

response function (HRF, according to Boynton *et al*, 1996, not two-gamma according to Glover, 1999)

and third was not in the frame of a repeated measures crossover design and without placebo, we

considered a descriptive comparison to be informative. We analyzed the single contrasts exp ng > exp

nt and exp uk > exp nt in the PLC-treated scans (random effects analysis, using an explorative p<0.01)

and compared them, due to the mentioned methodological reasons, qualitatively and descriptively to

the results of Herwig *et al* (2007).

The contrast exp ng > exp nt in the subjects treated with placebo revealed activations (overview:

supplementary figure 2) in bilateral frontal regions (precentral gyrus, Brodmann area (BA) 6), bilateral

insula (BA 13), midbrain extending to the medial thalamus, the left bed nucleus of stria terminalis

(BNST) extending to the left caudate head, in temporo-occipital (BA 19) and left parietal regions (BA

7, 39) and in the left middle occipital gyrus (BA 19). Herwig *et al* (2007) found in this comparison

additional activations in the anterior cingulated cortex (ACC), the bilateral extended amygdalar and

parahippocampal region and the left striatum.

The contrast exp uk > exp nt revealed activations in bilateral frontal regions (superior frontal gyrus

bilaterally (BA 10, 8), right middle frontal gyrus as part of the dorsolateral prefrontal gyrus (BA 9),

left inferior frontal gyrus (BA 10)), in the left anterior insula (BA13), in bilateral temporal (BA 37)

and temporo-occipital (BA 19, 39) regions and in a left parietal area (BA 40) and in the precuneus

(BA 7). Herwig *et al* (2007) described in this contrast furthermore activations in the anterior cingulate

cortex, the bilateral extended amygdalar region and the BNST which were not present in the analysis

of the placebo datasets.

The analysis of the placebo treated subjects corresponded in the main regions with the previous published data (Herwig *et al*, 2007), although there are some differences: After PLC we found in both contrasts no activation in the ACC, the extended amygdala and the striatum. In the contrast euk > ent we likewise found no activation in the thalamic and midbrain region.

These differences could have a couple of reasons as in part also mentioned before:

1. The current study was done at a 3T scanner (General Electrics) compared to a 1.5T scanner (Siemens) in the previous study.

2. In the current study we used the more physiological two-parameter gamma hemodynamic response function (HRF, Glover, 1999), whereas in the previous study the HRF according to Boynton (Boynton *et al*, 1996) was used. For the comparison we used for this analysis of the placebo dataset the Boynton HRF as well, whereas the rest of the analysis was done with the two parametric gamma HRF.

3. An additional factor is the possible effect of habituation, as with respect to the pseudo-randomized crossover design in the placebo condition here only 1/3 of the subjects completed the task for the first time, in the previous study this was the case for all subjects. This could have lead to a reduced arousal (possibly resulting in the lack of amygdalar activation), a reduced novelty of the situation and the expectation (possibly resulting in a lack of cingulate cortex activation) and a reduction of cognitive effort required during the task (possibly resulting in a reduction of thalamic and cingulate activation).

Besides these differences in technical realization, analysis, and subjects, the activations in the placebo-treated subjects resemble in the main finding those of the previously published activations (Herwig *et al*, 2007). Notably, this was particularly the case for the regions reported in the context with the pharmacological modulation.

Comparable studies addressing the anticipation of stimuli with different specificity (emotionally negative, disgust, pain, shock) revealed similar, overlapping and in this way consistent results for the contrasts exp ng > exp nt within prefrontal, inferior frontal, insular, anterior cingulate, temporo-occipital and parietal regions as well as in subcortical regions including the extended amygdalar complex (Chua *et al*, 1999; Simmons *et al*, 2006; Ploghaus *et al*, 1999; Abler *et al*, 2007; Nitschke *et*

al, 2006; Jensen *et al*, 2003; Ueda *et al*, 2003). The pattern of activation in nt the current study is

consistent with these findings.

Supplementary figures
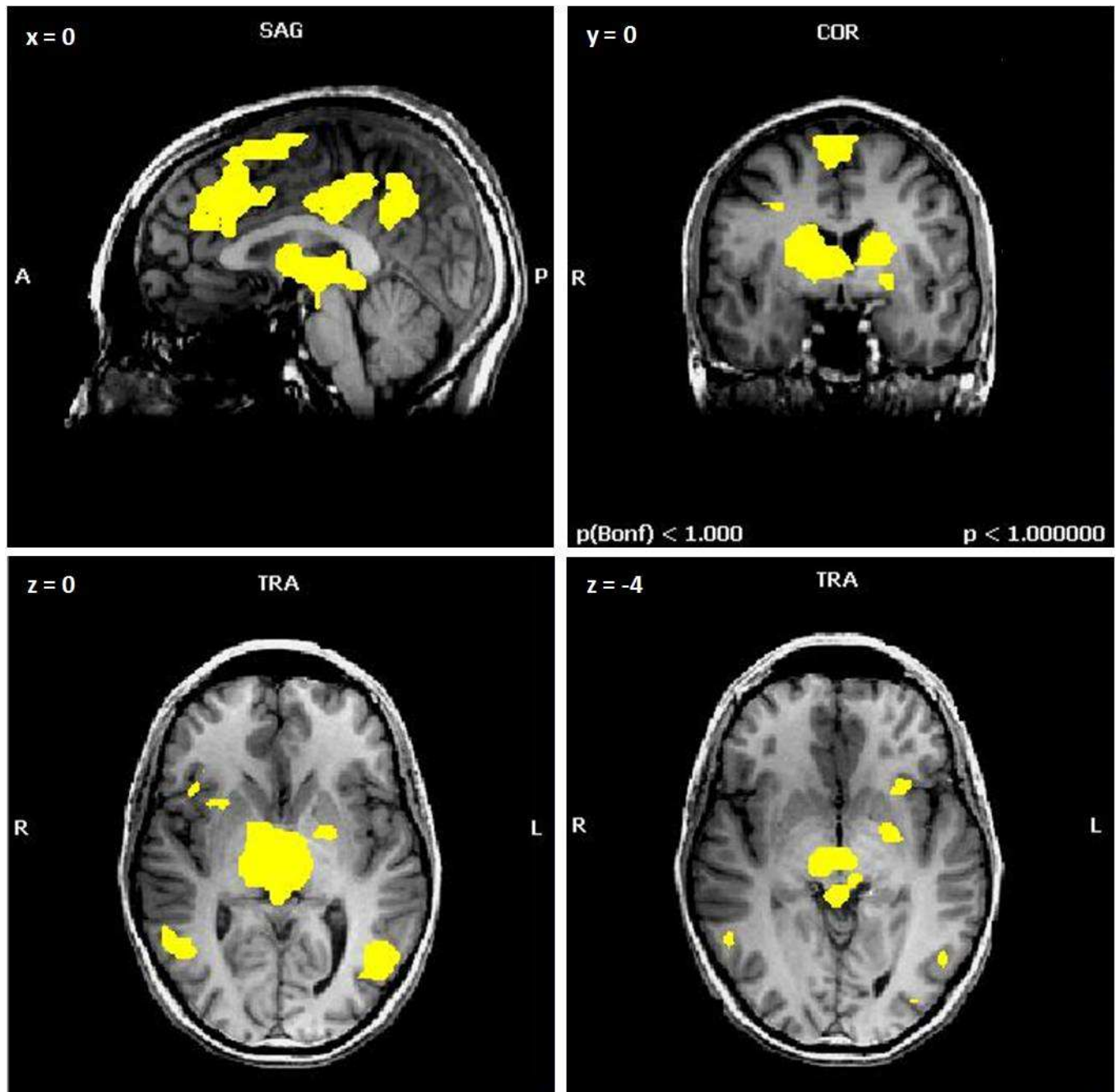
Supplementary figure S1: Representative overview of the used combined mask of the activations with

citalopram and reboxetine in the condition exp ng > exp nt & exp uk > exp nt (fixed effects analysis, p

< 0.001 uncorrected, Talairach coordinates x, y = 0, z = 0, -4), further existing areas not visible on the

chosen slices.
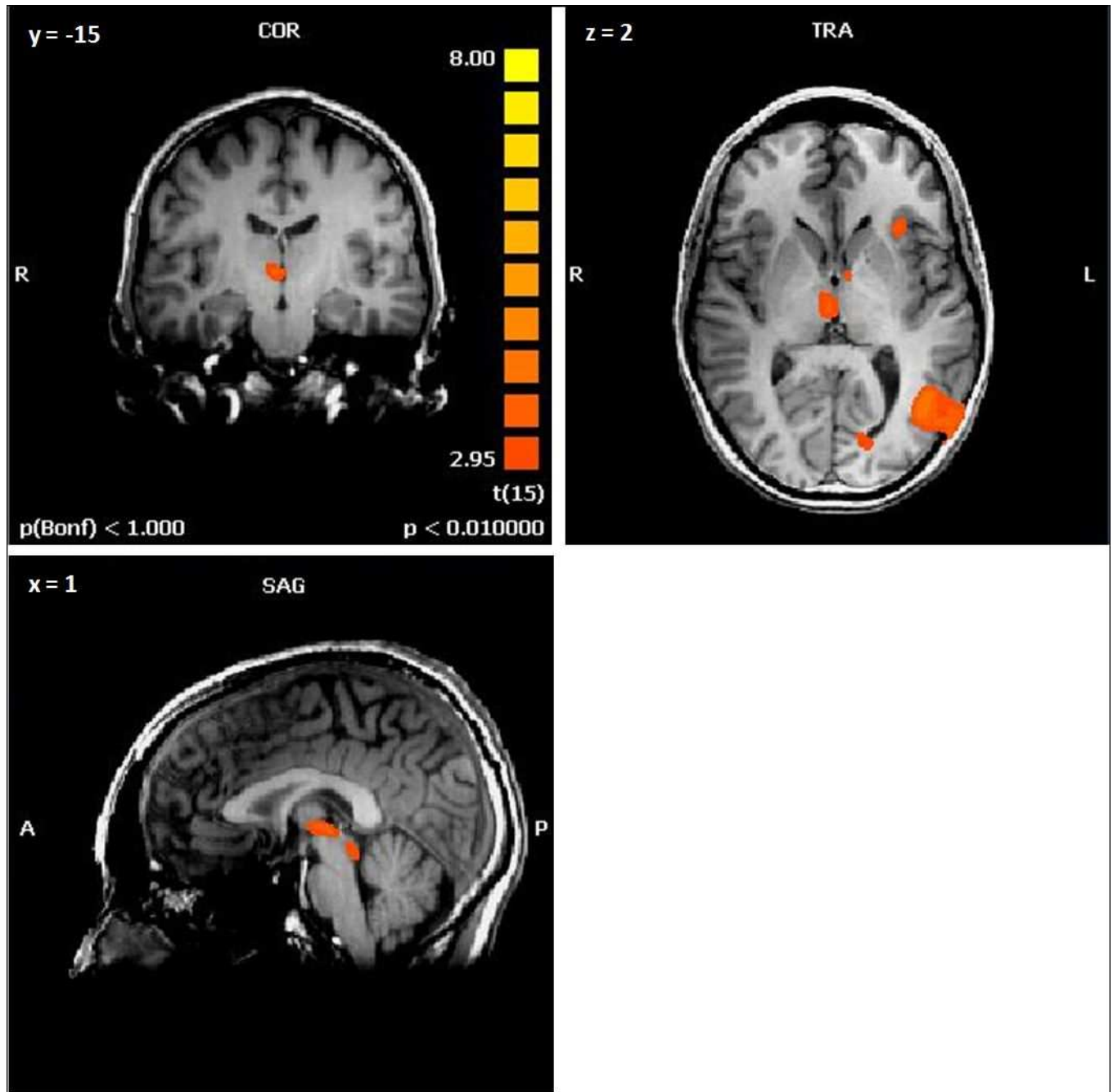
Supplementary figure S2: Exemplary overview of the activations in the placebo-condition in the contrast exp ng > exp nt (random effects analysis, p < 0.01, Talairach coordinates x = 2, y = -15, x = 1). Abbreviations: x, y, z Talairach coordinates, R right, L left, A anterior, P posterior, TRA transversal slice, COR coronal slice, SAG sagittal slice.

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