Effects of cognitive-behavioral therapy on neural processing of agoraphobia-specific stimuli in panic disorder and agoraphobia

Supplement

	patients with panic disorder and agoraphobia (included in pre-post-analysis) (*n*=51)	patients with panic disorder and agoraphobia (not included in pre-post-anlyses)* (*n*=21)	Group Differences	
			Chi² / *T*	*p*
female (*n*)	34	8	.15	.70
left-handed (*n*)	4	3	.70	.40
smokers (*n*)	25	8	.72	.40
education (*n*)				
13 years	26	6	3.40	.18
10 years	21	11		
9-10 years	4	4		
age (*M*/*SD*)	36.4 / 11.1	37.7 / 11.9	.51	.61
HAM-A T1 (*M*/*SD*)	23.7 / 5.4	23.6 / 4.5	-.17	.87
Mobility Inventory T1 (*M*/*SD*)	2.7 / 0.8	2.9 / 0.7	.85	.4

* due to bad data quality (n=10), dropping out during CBT treatment (n=1) or being randomized in wait-list patient group (n=10)
M = mean; *SD* = standard deviation; education: reported are years at school; HAM-A = Hamilton Anxiety Rating Scale

Supplement Table 1 (Sociodemographical data of included vs. not-included patients)

Supplement Figure 1 (Design of the Westphal-Paradigm)

anxiety ratings picture category	patients (*n*=47)		healthy controls (*n*=48)		patients vs. healthy controls (*t* / *p* / *d*)	
agoraphobia-specific (*M*/*SD*)						
T1	2.8 / 0.9		1.2 / 0.4		**-11.41 /<.001**	**/ 2.7**
T2	2.0 / 0.8		1.2 / 0.4		**-5.78 /<.001**	**/ 1.6**
T1-T2	0.9 / 0.8		-0.03 / 0.3		**-7.35 /<.001**	**/ 2.0**
(*t*/*p*/*d*)	**7.43 /<.001**	**/ 1.1**	-0.8 / .44	/ 0.04		
neutral (*M*/*SD*)						
T1	1.2 / 0.3		1.1 / 0.3		**-2.08 /.04**	**/ 1.3**
T2	1.1 / 0.3		1.1 / 0.4		0.18 /.86	/ 0.1
T1-T2	0.1 / 0.4		-0.1 / 0.3		**-2.32 /.02**	**/ 1.4**
(*t*/*p*/*d*)	1.89 /.07	/ 1.3	-1.34 /.19	/ 0.2		
agoraphobia-specific vs. neutral (*M*/*SD*)						
T1	1.6 / 0.8		0.1 / 0.2			
(*t*/*p*/*d*)	**13.64 /<.001**	**/ 2.7**	**4.30 /<.001**	**/ 0.9**		
T2	0.9 / 0.7		0.1 / 0.2			
(*t*/*p*/*d*)	**8.29 /<.001**	**/ 1.9**	**3.31 /.002**	**/ 0.6**		
T1-T2	0.8 / 0.8		0.03 / 0.3			
(*t*/*p*/*d*)	**6.47 /<.001**	**/ 1.6**	0.77 / .44	/ 0.3		

(4 patients and 3 healthy controls refused to give their ratings)
M = mean and *SD* = standard deviation of anxiety ratings; *d* = Cohen´s d = $(M_1-M_2)/SD_{pooled}$
T1=before CBT/waiting periode; T2=after CBT/waiting period
T1-T2=Difference of values from before CBT/waiting time and after

Supplement Table 2 (Picture ratings)

Anticipation Phase (agoraphobia-specific cues vs. neutral cues)

Group Differences

Hyperactivations in Patients > Controls T1

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Superior Frontal Gyrus	6	L	-18	5	70	2,4	.009
Frontal Lobe	Superior Frontal Gyrus	8	R	33	38	52	2,37	.01
Frontal Lobe	Inferior Frontal Gyrus	45	R	60	41	4	2,93	.002
Frontal Lobe	Middle Frontal Gyrus	9	R	60	26	37	2,34	.01
Anterior Lobe	Culmen		R	15	-55	-8	2,59	.006
Temporal Lobe	Superior Temporal Gyrus	38	R	57	20	-23	2	.02
Temporal Lobe	Superior Temporal Gyrus	22	L	-72	-43	19	2,46	.008
Temporal Lobe	Middle Temporal Gyrus	21	R	63	8	-26	2,63	.005
Limbic Lobe	Cingulate Gyrus	23	L	-9	-16	31	4,32	<.001
Occipital Lobe	Cuneus	17	L	-15	-94	1	2,66	.005
Occipital Lobe	Cuneus	17	R	9	-82	7	1,92	.03
Occipital Lobe	Lingual Gyrus	18	R	15	-73	4	1,7	.05
Posterior Lobe	Declive	-	L	0	-64	-14	2,26	.01
Sub-lobar	Putamen	-	R	15	8	-8	4,42	<.001
Sub-lobar	Insula	13	L	-48	-22	22	3,22	.001

Hyperactivations in Patients > Controls T2

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Middle Frontal Gyrus	9	R	27	38	34	5,16	<.001
Parietal Lobe	Postcentral Gyrus	3	L	-33	-34	46	4,98	<.001
Parietal Lobe	Superior Parietal Lobule	7	L	-21	-61	58	4,87	<.001

Hyperactivations in Controls > Patients T1

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Occipital Lobe	Inferior Occipital Gyrus	18	L	-45	-94	-8	2,72	.004
Occipital Lobe	Cuneus	18	R	3	-103	16	2,21	.014
Occipital Lobe	Lingual Gyrus	18	L	-9	-103	-14	1,97	.014

Hyperactivations in Controls > Patients T2

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Sub-lobar	Caudate		R	15	-34	22	2,7	.004
Limbic Lobe	Cingulate Gyrus	24	R	9	-10	25	2,68	.004
Limbic Lobe	Cingulate Gyrus	24	L	-6	2	25	2,2	.015

Picture Phase (agoraphobia-specific pictures vs. neutral pictures)

Group Differences

Hyperactivations in Patients > Controls T1

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Inferior Frontal Gyrus	46	L	-60	35	13	2,13	0,018
Frontal Lobe	Inferior Frontal Gyrus	47	R	33	17	-11	1,99	.024
Frontal Lobe	Middle Frontal Gyrus	46	L	-48	35	25	2,23	.014
Frontal Lobe	Middle Frontal Gyrus	46	R	36	29	19	3,44	<.001
Frontal Lobe	Middle Frontal Gyrus	9	R	33	17	25	1,67	.048
Frontal Lobe	Medial Frontal Gyrus	8	R	9	26	40	2,98	.002
Frontal Lobe	Precentral Gyrus	6	L	-39	-1	34	2,44	.008
Frontal Lobe	Precentral Gyrus	6	R	66	2	25	1,93	.028
Parietal Lobe	Inferior Parietal Lobule	40	L	-60	-52	52	2,25	.013
Temporal Lobe	Inferior Frontal Gyrus	21	L	-57	-7	-11	2,32	.011
Temporal Lobe	Inferior Frontal Gyrus	13	R	30	8	-13	3,03	.002
Temporal Lobe	Fusiform Gyrus	37	R	30	-37	-14	2,76	.003
Temporal Lobe	Middle Temporal Gyrus	21	L	-66	-1	-20	2,74	.004
Limbic Lobe	Cingulate Gyrus	23	L	0	-13	28	1,97	.025
Limbic Lobe	Parahippocampal Gyrus	19	L	-18	-49	-5	2,28	.012
Occipital Lobe	Superior Occipital Gyrus	19	L	-30	-79	25	2,01	.023
Midbrain	Red Nucleus	-	L	-3	-22	-14	4,69	<.001
Midbrain	Substania Nigra	-	R	6	-13	-11	4,66	<.001
Sub-lobar	Hypothalamus	-	L	-9	-4	-2	2,67	.004
Sub-lobar	Putamen	-	R	18	5	-5	3,56	<.001
Sub-lobar	Caudate	-	R	12	-7	22	2,42	.009

Hyperactivations in Patients > Controls T2

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Parietal Lobe	Precuneus	7	R	21	-52	46	1,72	0,044
Temporal Lobe	Hippocampus	-	R	27	-40	4	2,89	0,002
Limbic Lobe	Parahippocampal Gyrus	-	L	-24	-43	4	2,29	0,012
Occipital Lobe	Middle Occicital Gyrus	19	R	60	-67	-5	1,97	0,025
Brainstem	Pons	-	R	6	-34	-23	2,28	0,012

Hyperactivations in Controls > Patients T1

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Inferior Frontal Gyrus	45	L	-57	26	13	2,54	0,006
Frontal Lobe	Inferior Frontal Gyrus	45	R	57	35	1	2	0,024
Frontal Lobe	Inferior Frontal Gyrus	46	R	57	44	4	2,09	0,019
Frontal Lobe	Superior Frontal Gyrus	10	L	-33	62	-2	2,05	0,021
Frontal Lobe	Superior Frontal Gyrus	6	L	-9	17	58	2,03	0,022
Frontal Lobe	Superior Frontal Gyrus	6	R	6	23	58	2,09	0,019
Frontal Lobe	Superior Frontal Gyrus	8	L	-18	32	49	1,92	0,028
Frontal Lobe	Superior Frontal Gyrus	9	L	-27	53	34	1,84	0,034
Frontal Lobe	Medial Frontal Gyrus	6	L	-12	8	55	1,71	0,045
Frontal Lobe	Subcallosal Gyrus	34	R	12	5	-11	1,91	0,029
Parietal Lobe	Precuneus	7	L	-9	-61	49	2,15	0,017
Parietal Lobe	Precuneus	7	R	12	-40	52	1,69	0,046
Temporal Lobe	Superior Temporal Gyrus	39	L	-45	-52	13	2,63	0,005
Limbic Lobe	Anterior Cingulate	24	L	-3	32	16	2,07	0,020
Limbic Lobe	Cingulate Gyrus	31	L	-3	-55	28	1,94	0,034
Limbic Lobe	Anterior Cingulate	32	R	12	23	22	1,77	0,039
Limbic Lobe	Amygdala	-	R	18	-7	-14	1,7	0,045
Occipital Lobe	Middle Occipital Gyrus	19	L	-36	-88	19	2,69	0,004
Occipital Lobe	Cuneus	18	L	-18	-85	22	2,05	0,021
Occipital Lobe	Cuneus	17	R	18	-94	-2	1,7	0,045
Posterior Lobe	Declive	-	L	-15	-67	-11	1,73	0,042
Sub-lobar	Insula	13	L	-39	11	7	1,93	0,028
Sub-lobar	Insula	13	R	48	-40	19	2,08	0,020
Sub-lobar	Lateral Globus Pallidus	-	L	-24	-16	-2	2,03	0,022
Sub-lobar	Putamen	-	L	-15	11	-5	1,98	0,025
Brainstem	Pons	-	L	-6	-19	-23	3,6	0,000

Hyperactivations in Controls > Patients T2

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Inferior Frontal Gyrus	46	L	-51	29	16	1,69	0,046
Frontal Lobe	Superior Frontal Gyrus	10	R	30	59	4	1,67	0,048
Frontal Lobe	Middle Frontal Gyrus	46	R	45	44	28	2,46	0,008
Frontal Lobe	Middle Frontal Gyrus	9	L	-39	47	28	2,12	0,018
Frontal Lobe	Precentral Gyrus	6	L	-27	-13	55	2,01	0,023
Frontal Lobe	Precentral Gyrus	6	R	18	-16	67	1,66	0,049
Anterior Lobe	Culmen	-	R	27	-40	-23	2,31	0,012
Parietal Lobe	Precuneus	7	R	18	-73	52	1,69	0,046
Temporal Lobe	Inferior Temporal Gyrus	20	L	-45	-22	-29	4,43	0,000
Occipital Lobe	Cuneus	-	L	-12	-100	4	1,86	0,032
Posterior Lobe	Declive	-	L	-6	-79	-14	5,52	0,000
Sub-lobar	Thalamus	-	R	3	-13	1	4,66	0,000
Sub-lobar	Insula	13	L	-36	-10	16	2,16	0,016

Changes over Time

Change over time in Patients > Controls T1 > T2

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Middle Frontal Gyrus	46	R	36	29	19	3,57	<.001
Frontal Lobe	Medial Frontal Gyrus	8	R	9	29	40	2,4	.009
Frontal Lobe	Precentral Gyrus	6	L	-39	-4	28	2,27	.013
Frontal Lobe	Inferior Frontal Gyrus	46	L	-57	35	13	2	.023
Frontal Lobe	Inferior Frontal Gyrus	45	L	-60	14	19	2,12	.018
Parietal Lobe	Inferior Parietal Lobule	7	R	45	-70	52	2,39	.009
Temporal Lobe	Fusiform Gyrus	37	R	30	-37	-14	2,65	.005
Limbic Lobe	Parahippocampal Gyrus	19	L	-18	-49	-5	2,5	.007
Limbic Lobe	Parahippocampal Gyrus	30	L	-12	-43	4	2,03	.022
Limbic Lobe	Parahippocampal Gyrus	36	R	42	-31	-11	1,81	.036
Limbic Lobe	Cingulate Gyrus	24	R	3	-10	28	2,42	.009
Occipital Lobe	Superior Occicital Gyrus	19	L	-33	-82	28	2,14	.017
Midbrain	Red Nucleus	-	R	3	-16	-14	3,97	<.001
Sub-lobar	Hypothalamus	-	L	-9	-4	-5	2,55	.006
Sub-lobar	Putamen	-	R	18	5	-5	3,16	.001
Sub-lobar	Caudate	-	R	9	-7	22	2,4	.009

Change over time in Patients > Controls T2 > T1

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Inferior Frontal Gyrus	45	R	60	17	19	2,11	.019
Frontal Lobe	Inferior Frontal Gyrus	9	R	69	17	22	1,74	.042
Frontal Lobe	Precentral Gyrus	6	L	-51	-4	7	3,99	<.001
Frontal Lobe	Superior Frontal Gyrus	10	L	-27	53	-2	3,27	<.001
Frontal Lobe	Superior Frontal Gyrus	11	L	-18	59	-11	2,22	.014
Frontal Lobe	Superior Frontal Gyrus	8	L	-36	32	55	2,35	.010
Frontal Lobe	Superior Frontal Gyrus	10	R	33	59	-2	3,46	<.001
Frontal Lobe	Superior Frontal Gyrus	8	R	27	38	52	2,44	.008
Frontal Lobe	Middle Frontal Gyrus	11	L	-24	41	-11	2,29	.012
Frontal Lobe	Middle Frontal Gyrus	8	L	-42	35	49	2,49	.007
Frontal Lobe	Middle Frontal Gyrus	6	R	18	-10	61	2,73	.004
Frontal Lobe	Middle Frontal Gyrus	8	R	33	23	46	2,56	.006
Frontal Lobe	Medial Frontal Gyrus	9	L	-18	22	28	2,57	.006
Frontal Lobe	Medial Frontal Gyrus	6	L	-9	-7	58	3,16	.001
Parietal Lobe	Superior Parietal Lobule	7	L	-27	-64	64	3,08	.001
Parietal Lobe	Postcentral Gyrus	1	L	-69	-25	40	2,06	.021
Parietal Lobe	Postcentral Gyrus	5	R	12	-46	64	2,12	.018
Temporal Lobe	Inferior Temporal Gyrus	37	R	63	-58	-8	3,43	<.001
Temporal Lobe	Superior Temporal Gyrus	38	L	-45	8	-26	4,53	<.001
Temporal Lobe	Superior Temporal Gyrus	38	R	48	5	-20	2,66	.004
Temporal Lobe	Superior Temporal Gyrus	22	L	-45	-37	4	3,72	<.001
Temporal Lobe	Superior Temporal Gyrus	22	R	69	-58	22	3,51	<.001
Temporal Lobe	Middle Temporal Gyrus	37	L	-54	-61	4	3,71	<.001
Temporal Lobe	Middle Temporal Gyrus	21	R	72	-4	1	3,98	<.001
Temporal Lobe	Transverse Temporal Gyrus	42	R	63	-13	10	2,13	.018
Temporal Lobe	Sub-Gyral	20	R	36	-13	-17	2,97	.003
Limbic Lobe	Cingulate Gyrus	32	L	-15	17	34	2,73	.004
Limbic Lobe	Amygdala	-	L	-24	-1	-23	2,46	.008
Limbic Lobe	Parahippocampal Gyrus	34	L	-12	-13	-26	2,4	.009
Limbic Lobe	Parahippocampal Gyrus	34	R	9	-1	-20	2,1	.019
Occipital Lobe	Inferior Occicital Gyrus	18	R	39	-94	-8	2,06	.021
Occipital Lobe	Middle Occicital Gyrus	18	R	24	-106	7	2,72	.004
Occipital Lobe	Cuneus	19	R	6	-100	31	2,71	.004
Occipital Lobe	Cuneus	17	R	21	-85	7	2,05	.021
Occipital Lobe	Lingual Gyrus	19	R	24	-61	1	2,68	.004
Posterior Lobe	Declive	-	L	-9	-67	-11	2,3	.012
Posterior Lobe	Declive	-	R	36	-70	-17	2,7	0,004
Sub-lobar	Caudate	-	L	-18	26	4	3,25	.001
Sub-lobar	Claustrum			24	26	4	3,45	<.001
Sub-lobar	Insula	13	L	-39	14	13	2,57	.006
Sub-lobar	Thalamus		L	0	-16	10	2,33	.012

Change over time in Patients > Controls T1 > T2

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Inferior Frontal Gyrus	9	R	48	17	22	2,39	0,009
Frontal Lobe	Inferior Frontal Gyrus	13	L	-27	14	11	1,69	0,046
Frontal Lobe	Inferior Frontal Gyrus	11	R	15	29	-20	1,66	0,048
Frontal Lobe	Middle Frontal Gyrus	9	L	-39	38	37	3,08	0,001
Frontal Lobe	Middle Frontal Gyrus	9	R	48	8	34	2,07	0,020
Frontal Lobe	Middle Frontal Gyrus	8	R	27	20	46	1,78	0,038
Frontal Lobe	Medial Frontal Gyrus	6	L	-3	-1	52	2,47	0,009
Frontal Lobe	Precentral Gyrus	6	L	-45	-3	43	2,11	0,018
Frontal Lobe	Orbital Gyrus	47	R	18	26	-23	1,85	0,033
Parietal Lobe	Superior Parietal Lobule	7	L	-27	-67	52	2,87	0,002
Parietal Lobe	Postcentral Gyrus	5	L	-30	-43	58	1,99	0,024
Parietal Lobe	Supramarginal Gyrus	40	L	-54	-37	37	1,79	0,038
Temporal Lobe	Inferior Temporal Gyrus	20	L	-45	-22	-29	3,95	0,000
Temporal Lobe	Superior Temporal Gyrus	38	R	42	17	-23	3,6	0,000
Temporal Lobe	Angular Gyrus	39	L	-42	-73	31	2,02	0,023
Limbic Lobe	Uncus	28	R	24	5	-20	3,64	0,000
Limbic Lobe	Cingulate Gyrus	31	R	6	-28	40	2,06	0,021
Occipital Lobe	Cuneus	18	R	3	-91	13	3,58	0,000
Anterior Lobe	Culmen	-	L	-42	-40	-23	2,23	0,014
Anterior Lobe	Culmen	-	R	15	-37	-11	1,87	0,032
Posterior Lobe	Declive	-	L	-12	-82	-17	3,92	773755

Change over time in Patients > Controls T2 > T1

Lobe	Cerebral structure	BA	HS	x	y	z	T	p_{corr}
Frontal Lobe	Superior Frontal Gyrus	8	L	-18	32	49	1,96	0,026
Occipital Lobe	Superior Occicital Gyrus	19	L	-36	-82	22	1,7	0,045
Brainstem	Pons	-	R	9	-34	-23	2,46	0,008

x,y,z = MNI-Coordinates, y(uncor) = uncorrected p(.05, .0) = left hemisphere, (+) = right hemisphere, T1 = before CBT/waiting time, T2 = after CBT/waiting time

Supplement Table 3 (Whole brain corrected results)