Title:

Individual and problem-related stimuli activate limbic structures in depression: an fMRI study

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Abstract

Background: According to the model of cortico-limbic dysregulation, major depression is characterized by hypoactivity in prefrontal areas and hyperactiviy in limbic-paralimbic regions. Results so far have been inconsistent, though, and stimuli applied were rather unspecific to depression. This study explored brain activity in patients with depression while processing individualized and clinically-derived stimuli.

Method: Eighteen unmedicated patients with recurrent major depressive disorder and 17 never-depressed control subjects received standardized clinical interviews to condense formulations that essentially describe their dysfunctional interpersonal relations. This material was thereafter presented to subjects during functional magnetic resonance imaging (fMRI) assessment.

Results: For both, patients with depression and controls, increased activation in anterior cingulate cortex, fusiform gyrus and occipital lobe was observed when viewing individualized stimuli. Relative to control subjects, patients with depression showed increased activity in limbic-paralimbic and subcortical regions (e.g. amygdala and basal ganglia) but no signal decrease in prefrontal regions.

Conclusions: This study provided first evidence that individualized stimuli produced in a highly standardized and clinical fashion can activate regions associated with self-referential and emotional processing in both groups and limbic-paralimbic and subcortical structures in individuals with depression.

Introduction

Major depression is a common and severe disease, with a lifetime prevalence around 15% (1). Neuroimaging methods may help to identify structural and functional abnormalities correlated with depression and may thus provide novel insights into to the role of brain-behaviour relationships and its psychopathology. The aim is to optimize treatment strategies by basing them on objective measures of brain function in the future (2, 3). Although at present we are far from that ideal at an individual level, the past decade has seen substantial progress in the search for neurobiological correlates of depression. Integrating diverse empirical findings, the model of cortico-limbic dysregulation proposed by Helen Mayberg (2) has gained some prominence. The basic assumption is that depression is associated with hypoactivity in prefrontal areas and hyperactivity in limbic-paralimbic regions. Prefrontal abnormalities might be responsible for the cognitive deficits in depression (4, 5), and limbic hyperactivity might underlie abnormal emotional processing (6). Although not consistently reported in all studies (7), hypoactive prefrontal regions are thought to be a central feature of depression (8).

For patients with depression, hyperactivity has been reported in the medial and inferior frontal cortex and basal ganglia (caudate or putamen) during induction of negative affect (9). An important limbic structure associated with hyperactivity in depression is the amygdala (10, 11). Studies showing amygdala hyper-responsivity to emotional stimuli have typically used faces (e.g.12, 13) or emotional pictures (e.g.14, 15). This activation is thought to be part of an automatic and sustained brain response to negative stimuli, possibly reflecting a bias for negative events in depression (16). Nevertheless, there are studies showing no specific amygdala activity in patients with depression when exposed to negative stimuli (17, 18), and findings in the amygdala are said to be quite variable (3). One possible reason for this inconsistency could lie in the nature of the stimulus material applied. Although often used in basic emotion research, emotional faces or pictures are rather unspecific, heterogeneous stimuli. They have only a limited relation to clinical features

of depression and are of little personal relevance to the patients. Literature reviews and meta-analyses on amygdala function have shown that this region's reactivity is not confined to fear-related stimuli but rather sensitive to a vast variety of emotional stimuli, including positive and negative emotions (19-21). At a more general level, the amygdala is supposed to be involved in the processing of biologically relevant and salient stimuli (22). It has also been associated with the processing of rewards and losses (23, 24). Importantly, studies using specific and personally relevant emotional words found clear amygdala activation in subjects with depression (16, 25). Whereas these studies represent an important step forward in the definition of the role of the amygdala in depression, the use of single words of personal relevance is still not a clinically-derived way of relating individual psychopathology to brain function.

The aim of this study, hence, is to expose patients with depression to individually tailored stimuli that specifically activate their psychological mechanisms of depression (26). To this end, patients and control participants viewed sentences derived from their individual clinical interview conducted according to the system of Operationalized Psychodynamic Diagnosis (OPD) (27). The chosen sentences essentially describe the participants' dysfunctional interpersonal relations with the aim to expose them to their core problems while measuring brain activity. A control task, presenting arousing, negative but unspecific situations (related to traffic stress), was also introduced.

Since this is the first study to use such personalized stimuli in depression, whole-brain analyses were conducted to check for any area being active when subjects were confronted with their problematic relations in particular. Specifically, the following hypotheses were put forward:

(I) When confronted with their specific dysfunctional interpersonal relations as opposed to unspecific negative stimuli, patients as well as control participants should show more activity in areas that are important for emotional processing, conflict monitoring, and self-referential processing (mostly cortical structures of the midline).

(II) A relative hyperactivity in limbic-paralimbic (e.g. amygdala) and subcortical regions (e.g. basal ganglia)

and hypoactivity in prefontal regions was expected when patients are confronted with their interpersonal problems as opposed to the control task and the brain activity of healthy controls.

Methods and Materials

Participants

Eighteen unmedicated patients with recurrent major depressive disorder and seventeen healthy control participants took part in the study (demographics in table 1). Patients were recruited from the outpatient departments of one psychotherapeutic institute and diagnosed by two trained clinicians using the Structured Clinical Interviews I and II for DMS-IV Diagnosis (German version; (28)). They reported between 1 and 15 depressive episodes (M[SD] = 5.6[5.5]) and their age at first occurrence of depression was between 8 and 40 years (M[SD] = 19.3[8.2]). Ten patients were diagnosed with co-morbid anxiety disorders. Exclusion criteria were other psychiatric conditions as main diagnosis, substance abuse, significant medical or neurological conditions, or eye problems. Control participants were recruited from the community, matched for age, sex and education, and had no history of previous depressive episodes or other psychiatric conditions (SCID). All participants were right-handed. In both groups, depression severity and general psychological symptoms were assessed using the Beck Depression Inventory (BDI,(29)) and the revised Symptom Check List (SCL-90-R, (30)), respectively. All participants gave written informed consent after complete description of the study and prior to their inclusion. The study protocol was approved by the ethical committee of the University of Ulm.

Stimuli

Most patients with depression have dysfunctional interpersonal relations as a main feature of their disorder. To assemble individualized and personally relevant stimuli that relate to depressive symptoms, an OPD interview (Operationalized Psychodynamic Diagnosis) (27) was conducted with each patient and each control participant. OPD is a multiaxial, clinically proven system to assess psychopathology on several levels (31). Going beyond pure description of symptoms (Axis V), it includes experience of illness (Axis I),

dysfunctional interpersonal relations (Axis II), conflicts (Axis III) and psychological structure (Axis IV). Details can be found in the manual of the OPD Task-Force (27). Although OPD is at its core a psychodynamic approach, dysfunctional relations (Axis II) are considered by most therapeutic schools to be important in the development and maintenance of depression, e.g. Interpersonal Psychotherapy (32), Cognitive Behavior Analysis System of Psychotherapy (33). The OPD interviews were conducted by a trained clinician (HeK), videotaped, and rated independently by 2-3 expert raters (OPD-Trainers) who were blind to the status of the interviewees (patient or control). They rated the interviews on all five axes but for the purpose of our stimulus production only OPD Axis II (dysfunctional interpersonal relations) was relevant. Although not suffering from depression, control participants also experienced dysfunctional relations which cause distress and are perceived as "weak spots". It is the strength of the OPD Axis II to assess personally relevant material that relates to individual depressive symptoms for patients but also describes interpersonal problems in otherwise healthy persons. The basic structure of the OPD relationship axis depicts the circular or transactional character of human interaction (interchange of subjective experience and response to the environment). The construction of the OPD instrument is achieved from the following two perspectives: (1) How does the patient experience herself/himself in relationships? (2) How does the patient experience the behavior of others? Thirty-two items (e.g. "to back out of contact", "doing too much for others" or "self-incrimination") help to define the variety of behaviors seen in relationships. From this systematic and item-based relationship diagnosis four sentences were identified representing the central topics of the dysfunctional relationship theme of each person (e.g. "You wish to be accepted by others.", "Therefore you do a lot for them.", "That is often too close for them, so they retreat.", "Then you feel empty and lonesome."). These individual sentences served as stimuli during the fMRI-session (OPD condition). Word count and semantic structure of the stimulus sentences (i.e. distribution of the thirty-two items assigned) did not differ between patients and controls (average word count of the four sentences, Controls: 31 words, Patients: 33 words, T- Test between groups, $T(33) = 1.1$; n.s.).

The control condition was termed “traffic” and comprised four sentences, which generally described stressful traffic situations (“The other driver makes a mistake.”, “You are very upset about this.”, "You react to the other driver.", "But he reacts inadequately."). Prior to testing, participants were asked to remember a recent and stressful situation they experienced in traffic. They were instructed to mentally engage in that situation when reading the “traffic” sentences. The rationale behind this control condition was to induce negative emotions and recall autobiographical memories with a personally relevant situation including human interactions, but without engaging in specific depression-related, clinically relevant material.

In order to separate the two conditions (OPD and traffic), and let subjects calm down after emotionally demanding sentences, “relaxation” sentences were inserted between conditions. Those sentences instructed participants to relax. See figure 1 for an overview of all types of sentences.

Whereas the OPD sentences were derived individually for each person, “relaxation” and “traffic” were the same sentences across all subjects. OPD sentences were slightly but significantly longer (M[SD] = 49.8[9.1] characters) than “traffic” sentences (43.5 characters, $p<.001$). There was, however, no significant difference in length between the OPD sentences for patients and controls.

fMRI Tasks

Stimuli (sentences) were presented on a projector while subjects were lying in the scanner. The four sentences of a condition (OPD, traffic, relaxation) were presented for 7.5 seconds each, resulting in 30 second blocks. During the OPD block participants were asked to mentally engage in situations with significant others, as described by the OPD sentences. They received no instruction to regulate their emotions, but should let spontaneous thoughts, emotions and memories come to mind. “Traffic” and “relaxation” conditions also comprised four sentences with each lasting 7.5 seconds. The instructions were to mentally engage either in the traffic situation or to relax. In total, we presented 12 “relaxation”, 6 “traffic” and 6 “OPD” blocks. Blocks were separated by a 5-seconds fixation cross. The entire experiment lasted approximately 15 minutes (see figure 1).

Procedure

Four to six weeks prior to fMRI assessment, participants were interviewed (SCID I+II, OPD), and filled out questionnaires (Beck Depression Inventory [BDI], Symptom-Check-List [SCL-90-R]) and informed consent forms. At the beginning of the fMRI session, subjects were briefed, saw their individual OPD sentences prior to actual scanning and were asked, whether the sentences fit and could cause them to think about their problematic relations. To control for state affectivity, all participants filled out the Positive and Negative Affect Schedule (PANAS; (34)) before entering the scanner. After scanning, a second PANAS and a questionnaire were filled out, assessing on a 7-point Likert scale the extent to which the OPD sentences were correct and caused emotional arousal.

Image Acquisition

MRI data were recorded (DW and PE) using a 3-T SIEMENS Magnetom Allegra head scanner (Siemens, Erlangen, Germany), equipped with a standard quadrature head coil. Subjects were positioned on a scanner couch in a slightly dimmed fMRI chamber, they wore foam earplugs to reduce scanner noise. An experienced psychotherapist (ST or HeK) assisted the setup procedure and spoke to the patients prior to and after the experiment and between the scanning sessions. To reduce anxiety levels, data acquisition started with anatomical images for app. 15 minutes (3D high resolution T1-weighted isotropic volume, MPRAGE-sequence (MPRAGE = Magnetization Prepared Rapid Gradient Echo; (35)); TR = 2.3s, FOV = 256 × 256 × 176 mm, TE = 4.38ms, TI = 900ms, flip angle = 8°, 1 mm isovoxel, total acquisition time 14.45 min). After that, the therapist talked to the patient via the scanner intercom to assure that the patient was able to participate in the experiment.

Functional scans were performed using a single shot echo planar imaging sequence (EPI). A total of 365 T2*-weighted whole brain volumes were acquired (EPI-sequence; TR 2500 ms, TE 30 ms, flip angle 90º, FOV 192 mm, matrix 64 x 64, 44 slices, slice thickness 3 mm, interleaved acquisition order, standard

AC-PC- Orientation, 2 dummy scans prior to data acquisition, total acquisition time: 15.18 min). To reduce head movement and ambient noise, the subject's head was placed into an appropriate pillow and foam rubber.

FMRI data analysis

Data were analyzed and visualized using Brain Voyager QX 1.10 (Brain Innovation, Maastricht, Netherlands) and SPSS 13.0. Preprocessing: Functional data were slice-time corrected, motion parameters were estimated, and motion was corrected relative to the first volume of the run (trilinear/sinc interpolation). To remove low frequency drifts, data were high-pass filtered (3 cycles, three sine waves fall within the extent of the data). Structural and functional data were transformed into the standard space of Talairach and Tournoux (36). Talairach data points were labelled using Talairach Daemon (37). The design matrix was modeled using the two gamma hemodynamic response function. To accommodate residual anatomical differences across subjects and to improve signal-to-noise ratio, functional data were smoothed using an 8 mm full width at half maximum (FWHM) isotropic Gaussian Kernel.

Statistics: Group data were analyzed using random effects analyses in the GLM framework based on z-transformed functional data. An ANOVA, including the within-subject factor CONDITION (OPD sentences vs. traffic sentences) and between-subject factor GROUP (patient vs. control) was performed to identify differences in hemodynamic response. Separate brain maps were generated for the main effect CONDITION and GROUP and for the interaction CONDITION x GROUP. The main effect of CONDITON is displayed as a t statistic, which yields the same results as the F statistics, but allows to color-code the direction of changes. Motion-correction parameters (z-transformed, linear trends removed) were included in the GLM-Model.

Maps are shown with a threshold of $p < 0.001$. Correction for multiple comparisons for the within-factor CONDITION was based on False Discovery Rate (FDR) (38, 39). However, literature suggests differences between controls and patients in relatively small cortical and subcortical regions (9), but FDR is very strict if

there are small active areas. Thus, the between-factor GROUP and the interaction are reported on $p < .001$ (uncorrected). In addition, for all reported comparisons, Type I error was reduced based on cluster size threshold estimation (40, 41) with an estimated cluster size threshold of 16 voxels. Active voxels are displayed in native resolution without interpolation and plotted on the Talairach-transformed “Colin27-brain” (42).

Results

Behavioral Data

Table 1 shows behavioral data for patients and controls. As expected, patients had significantly higher depression scores (BDI, table 1 and figure 2) and general symptoms (GSI-scale of the SCL 90-R). Patients and control participants judged the OPD sentences to be adequate descriptions of their dysfunctional interpersonal relations. After the fMRI session, all participants reported that the OPD sentences caused emotional arousal in the scanner. There were no significant differences between groups in terms of adequacy or arousal induced by the OPD sentences (table 1 and figure 3). Patients with depression had significantly higher negative affect before and after scanning (table 1). However, there were no significant differences between pre- and post-fMRI affectivity across all subjects. PANAS ratings in both groups were comparable to normative data obtained from a large group of healthy subjects under stress-free conditions (34).

Neuroimaging Results

Main effect of *GROUP*

The main effect GROUP did not reveal any differences in the BOLD signal between controls and patients ($p < .001$) in cortical areas. However, there was one significant cluster in the brainstem with stronger signal for controls, comprising the pons with a cluster size of 84 mm^3.

Main effect of *CONDITION*

The main effect CONDITION, displayed as a t-contrast, identified regions with a stronger signal for OPD relative to traffic sentences. These regions were located in the occipital cortex, in the superior parietal lobe, the superior frontal gyrus, in the anterior cingulate cortex, and in the medial frontal gyrus. Conversely, a stronger signal for Traffic relative to OPD sentences was observed in a cluster including parts of the superior

and middle frontal gyrus. See table 2 and figure 4. Figure 5 shows individual beta values in the ACC for the contrast OPD relative to traffic sentences.

Interaction *GROUP X CONDITION*

A significant group by condition interaction was found in a variety of regions, including the inferior frontal gyrus, the postcentral gyrus, the amygdala, the precentral and middle frontal gyrus, and the basal ganglia. In general, the activation pattern can be described as a signal increase for patients when confronted with OPD relative to Traffic sentences. In contrast, controls show a signal decrease for this comparison (See figure 6). Table 3 provides additional data regarding the anatomical locations, cluster sizes, Brodmann areas and the Talairach coordinate for the center of mass of each cluster.

Discussion

This study compared brain activation of patients with depression to those of matched healthy control participants. A main feature of this experiment is the use of individually tailored, yet highly standardized stimuli with regard to length and display time. Although individualized stimuli have already been used in neuroimaging studies with PTSD patients (e.g. script-driven imagery; 43), a control condition with emotionally arousing, personally relevant but not disease-specific content (traffic) has not been included in comparable experimental designs so far.

Across both groups, individualized sentences describing dysfunctional interpersonal relations led to activity in the anterior cingulate, fusiform gyrus and large portions of the occipital lobe. Thus, our new paradigm yielded plausible activations in areas related to emotional processing, perspective-taking, mentalizing and self-referential processes. When confronted with these interpersonal stimuli, patients with depression, when compared to healthy controls, displayed increased activity in limbic-paralimbic and subcortical structures including the amygdala, but did not show a corresponding signal decrease in the prefrontal cortex. Thus our results partially confirmed the model of cortico-limbic dysregulation (2).

Bilateral ACC, which forms part of the cortical midline structures, was more active during the personally relevant OPD condition. Generally, cortical midline structures have been associated with the processing of self-referential stimuli (44, 45). Hence, consistent activation of these areas points to the self-relevance of the OPD condition. Interestingly, in another study the medial frontal gyrus was active in patients with depression and controls when judging self-relevant attributes (46). The anterior cingulate cortex is also involved in emotional processing in general (20), and is supposed to play a key role when attending to subjective emotional responses (47). Importantly, the area of our ACC activation lies in the affective division of the anterior cingulate (48). This could reflect the higher emotional load of the OPD condition as opposed to the traffic condition.

There are several explanations for the more consistent activation in bilateral visual cortex in the OPD condition. First, the OPD sentences are of enhanced personal relevance and, therefore, have a high potential to trigger vivid mental images. Increased mental images are also thought to underlie the greater activity of visual areas for concrete relative to abstract words (e.g. 49). Furthermore, in a meta-analysis almost half of the studies comparing emotional with neutral conditions showed enhanced activity in visual cortex (20). This is believed to reflect emotional arousal acting upon visual areas to enhance perception of salient stimuli (20). For instance, the fusiform gyrus, an area active in our study, shows enhanced activity upon visual stimuli (faces) depicting danger (50). Although both conditions, traffic and OPD, can be regarded as emotional, the salience and emotional load of relation sentences was higher.

Although not in the primary focus, it is interesting to notice that the few areas selectively active when mentally engaging in stressful traffic situations, are located in the superior and middle frontal gyrus (BA 6). This part of Broadman area 6 is a region with supplementary motor functions (51) . We speculate here, that visualising oneself in a traffic situation engages supplementary motor systems.

It is of note, that amygdala activation which has been obtained only inconsistently with non-individualized emotional stimuli in previous studies (3, 9-11), was very robust in our task. Two previous studies have used stimuli of personal relevance (words) and have also found amygdala activation in subjects with depression (16, 25). Critical word stimuli were generated by participants who were asked to find words that “best represent what [they] think about when [they] are upset, down, or depressed” (16, p. 697). The sentence materials used in the present study likely describe problematic interpersonal relations (which are an important factor in depression) even more adequately than single words and hence involve the amygdala. We speculate here that enhanced amygdala activity in subjects with depression reflects their higher emotional involvement in problematic relations.

In line with our results in the amygdala, putamen and caudate nucleus were also active in patients when engaging in the relation situations. According to a recent meta-analysis, the basal ganglia have consistently

displayed increased activity in depression after induction of negative affect (9). This is not surprising, since the basal ganglia have rich interconnections with limbic structures (including the amygdala) and prefrontal areas, and form part of many cortico-subcortical loops engaged in reward and punishment, affect and motivation (23, 52, 53). In line with this, the basal ganglia are increasingly discussed as a target location in the context of deep brain stimulation for the treatment of depression (52, 54).

Among the other areas selectively active in patients with depression, some have also been reported in a recent meta-analysis, such as the inferior and middle frontal gyrus and the inferior parietal lobule (9). However, the exact role of these areas in the psychopathology of depression is largely unknown at this point.

Importantly, we found no differential activity in the dorsolateral prefrontal cortex (DLPFC), which has often been reported to be hypoactive in depression. Decreased DLPFC activity is supposed to reflect cognitive deficits (2), and in particular may be related to decreased drive. As the current task used personalized stimuli with high significance for the patients, this might have counteracted any signal decrease in this structure. In fact, our task is optimized to tap emotional processes in the handling of clinically-derived stimuli and does not aim to reveal cognitive aspects of depression in particular. Indeed, results for the DLPFC in depression have been quite heterogeneous (3, 7, 55, 56). One reason for this could be that the extent of cognitive deficits varies greatly between patients with depression in general (57). Other measures of our patient group not reported here (e.g. mentalisation, psychological capacities) clearly speak for a sample with little cognitive impairments, supporting the lack of DLPFC signal decrease. Interestingly, according to a meta-analysis, the least consistency of DLPFC activation has been found in emotional activation studies and better evidence of frontal hypoactivity could only be achieved in resting or treatment studies, both applying predominantly PET or SPECT techniques to measure the resting brain (6).

Altogether, the present study describes clear differences between patients with depression and non-depressed control participants using personalized stimuli in a highly standardized fashion. Activity in anterior cingulate cortex when confronted with problematic interpersonal sentences suggests that our novel experimental design

engaged both groups of participants in self-referential processing. The stronger signal in amygdala and basal ganglia found for OPD sentences in patients indicates particular involvement of those structures in the handling of clinically-derived material. These results set the stage for a second part of our study: Patients currently undergo intensive psychotherapy and will be retested to assess whether this treatment is a) accompanied by changes in psychometric measures of depression and b) results in a different pattern of brain activations in response to individualized stimuli.

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Tables

Table 1:

Measure			Control	Patient	significant difference
Demographics					
N		total	17	18	
Gender		women : men	14 : 3	14 : 4	
Age		Mean (SD)	38 yrs (11.6)	39.8 yrs (12.8)	t (33) = .67; n.s.
		Range	22 - 64	20 - 64	
Education		Secondary school level I	4	7	
		Secondary school diploma	11	7	
		University	2	4	
Diagnostics					
BDI		Mean (SD)	2.2 (2.5)	24.8 (9.3)	t = - 9.68; p<.001
		Range	0 - 9	10 - 40	
SCL-90-R, GSI,		Mean (SD)	.2 (.1)	1.4 (.6)	t = - 6.52; p<.001
		Range	0 - .4	.2 – 2.5	
Post Scan rating of adequacy of relation sentences (0-7)		Mean (SD)	5.9 (.7)	5.8 (.9)	t = .20; n.s.
		Range	5 - 7	4 - 7	
Post Scan rating of emotional arousal caused by relation sentences (0-7)		Mean (SD)	4.8 (.7)	5.1 (1.0)	t = - 1.16; n.s.
		Range	4 - 7	3 – 7	
PANAS	Pre Scan Positive Affect	Mean	30.0 (5.7)	25.9 (6.5)	t = 1.89; n.s.
		Range	18 - 39	14 - 37	
	Pre Scan Negative Affect	Mean	11.7 (1.5)	16.8 (4.4)	t = - 4.37; p<.001
		Range	10 - 15	10 - 29	
	Post Scan Positive Affect	Mean	27.9 (7.2)	25.5 (7.7)	t = .92; n.s.
		Range	14 - 41	12 - 37	
	Post Scan Negative Affect	Mean	10.7 (1.3)	15.3 (6.1)	t = - 2.97; p<.01
		Range	10 - 15	10 - 29	

1 Table 2:

2

Main Region	Cluster size	X	Y	Z	Side	Regions	BA	Number of Voxels
OPD>Traffic								
occipital	79785	-4	-73	0	R	Cerebellum		3773
						Cuneus	18,17,30,23,7	3190
						Lingual Gyrus	18,19,17	3160
						Posterior Cingulate	30,31,23	864
						Precuneus	31,23	800
						Fusiform Gyrus	19,37	551
						Middle Occipital Gyrus	18,19	416
						Parahippocampal Gyrus	19,30	248
					L	Cerebellum		7160
						Lingual Gyrus	18,19,17	2195
						Middle Occipital Gyrus	18	1266
						Cuneus	18,17,30,23,19	1201
						Fusiform Gyrus	19,18,37	902
						Posterior Cingulate	30,31,23	795
						Inferior Occipital Gyrus	18,19,17	567
						Precuneus	31,23	257
						Parahippocampal Gyrus	19,30,37,18	178
SPL	621	31	-48	52	R	Superior Parietal Lobule	7	90
						Precuneus	7	77
						Inferior Parietal Lobule	40	28
SFG	540	21	38	48	R	Superior Frontal Gyrus	8	223
MFG/ACC	4752	-2	40	1	R	Medial Frontal Gyrus	10	263
						Anterior Cingulate	32,24,10	251
					L	Anterior Cingulate	32,24	862
						Medial Frontal Gyrus	10,11	291
Traffic>OPD								
SFG/MFG	2133	-21	3	58	L	Superior Frontal Gyrus	6	186
						Middle Frontal Gyrus	6	166
						Medial Frontal Gyrus	6	21

1 Table 3:

2

MainRegion	Cluster size	X	Y	Z	Side	Regions	BA	Number of Voxels
IFG	702	51	14	2	R	Inferior Frontal Gyrus	45,47	116
						Precentral Gyrus	44	36
						Superior Temporal Gyrus	22	19
Amyg	432	23	-3	-17	R	Amygdala		342
MFG	540	21	-3	51	R	Medial Frontal Gyrus	6	72
R_Put	2592	16	18	-7	R	Putamen		353
						Caudate Head		272
						Lateral Globus Pallidus		27
						Inferior Frontal Gyrus	47	24
						Middle Frontal Gyrus	11	21
L_Put	2538	-15	17	-8	L	Putamen		465
						Caudate Head		209
						Subcallosal Gyrus	34,47	52
						Inferior Frontal Gyrus	47	37
Prec.G./MFG	837	-33	-7	47	L	Precentral Gyrus	6	216
						Middle Frontal Gyrus	6	206
Postc.G.	432	-40	-29	44	L	Postcentral Gyrus	2,40	103
						Inferior Parietal Lobule	40	90

Table legends

Table 1: Participant demographics and behavioral data. Abbreviations: PANAS = Positive and Negative Affect Schedule, BDI = Beck Depression Inventory, SCL-90, GSI = Symptom Check List, Global Severity Index.

Table 2: Areas which are significant for the Main Effect CONDITION; $p < .001$, FDR, cluster-threshold 16 Voxel. X,Y, Z values indicate center of gravity of the cluster in Talairach-space. BA = Areas according to Brodmann. Number of voxels gives the number of active voxels in this specific region and/or in this Brodmann area. Abbreviations in column “Main regions” correspond to column “Regions”.

Table 3: Areas which are significant for the interaction CONDITION x GROUP; $p < .001$, clusterthreshold 16 Voxel. X,Y, Z values indicate center of gravity for the cluster in Talairach-space. BA = Areas according to Brodmann. Number of voxels gives the number of active voxels in this specific region and/or in this Brodmann area. Abbreviations in column “Main regions” correspond to column “Regions”.
See also figure 6 .

Figure legends

Figure 1: Experimental design. One block consisted of four sentences describing an OPD-derived relation (OPD condition) or traffic situation. Both conditions were separated by four screens prompting to relax. Prior to each condition, there was a fixation cross. Each block was repeated six times. Subjects were required to mentally engage in the different conditions. See text for further details. OPD = Operationalized Psychodynamic Diagnosis

Figure 2: BDI (Beck Depression Inventory) scores for all subjects and group data. Error bars show +/- 1 SE.

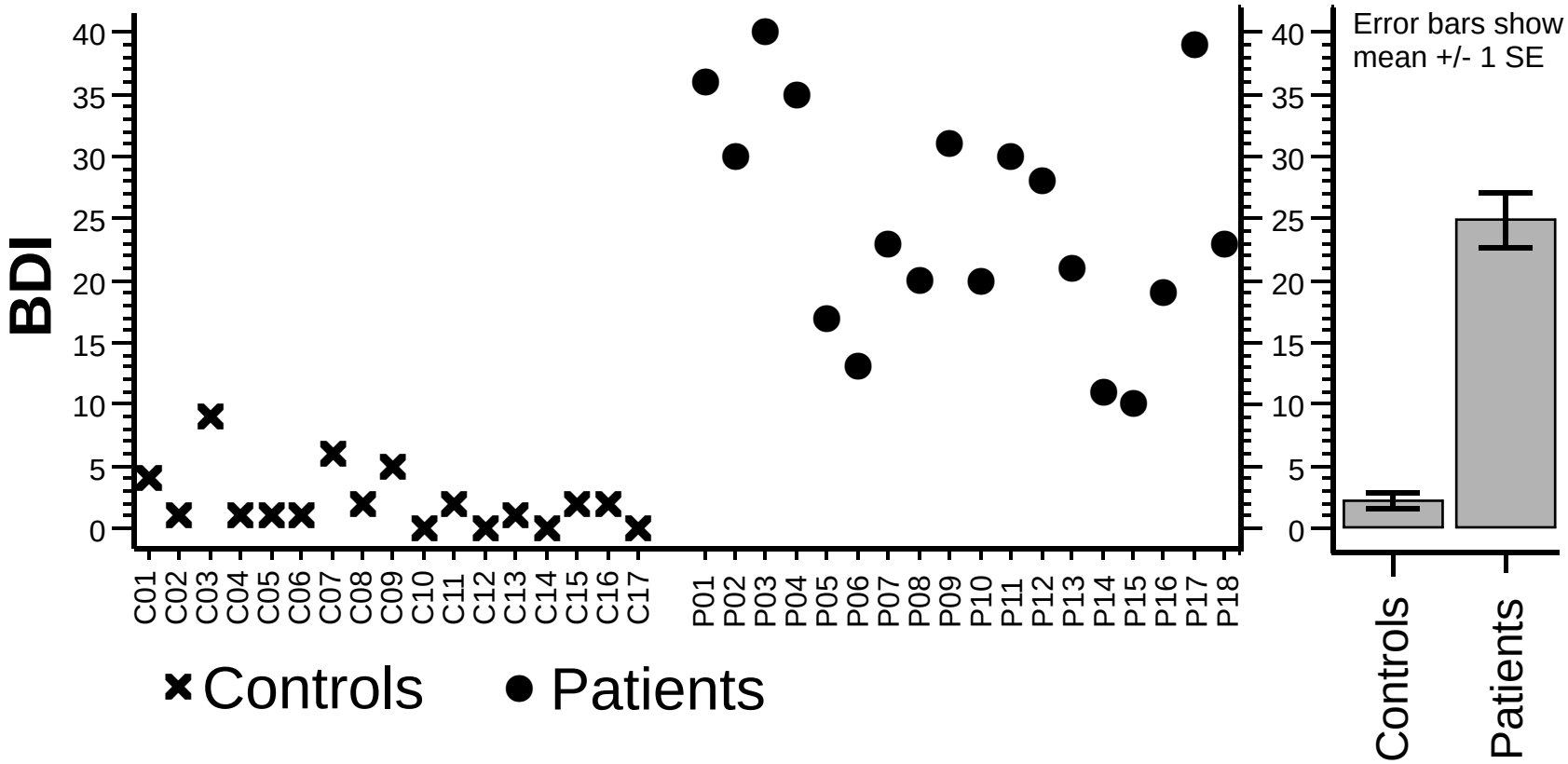
Figure 3: Scales display whether the OPD sentences were adequate for the participant (upper part) and whether participants where emotionally aroused by the OPD sentences. Values are given on individual level (left) and on group level (right)

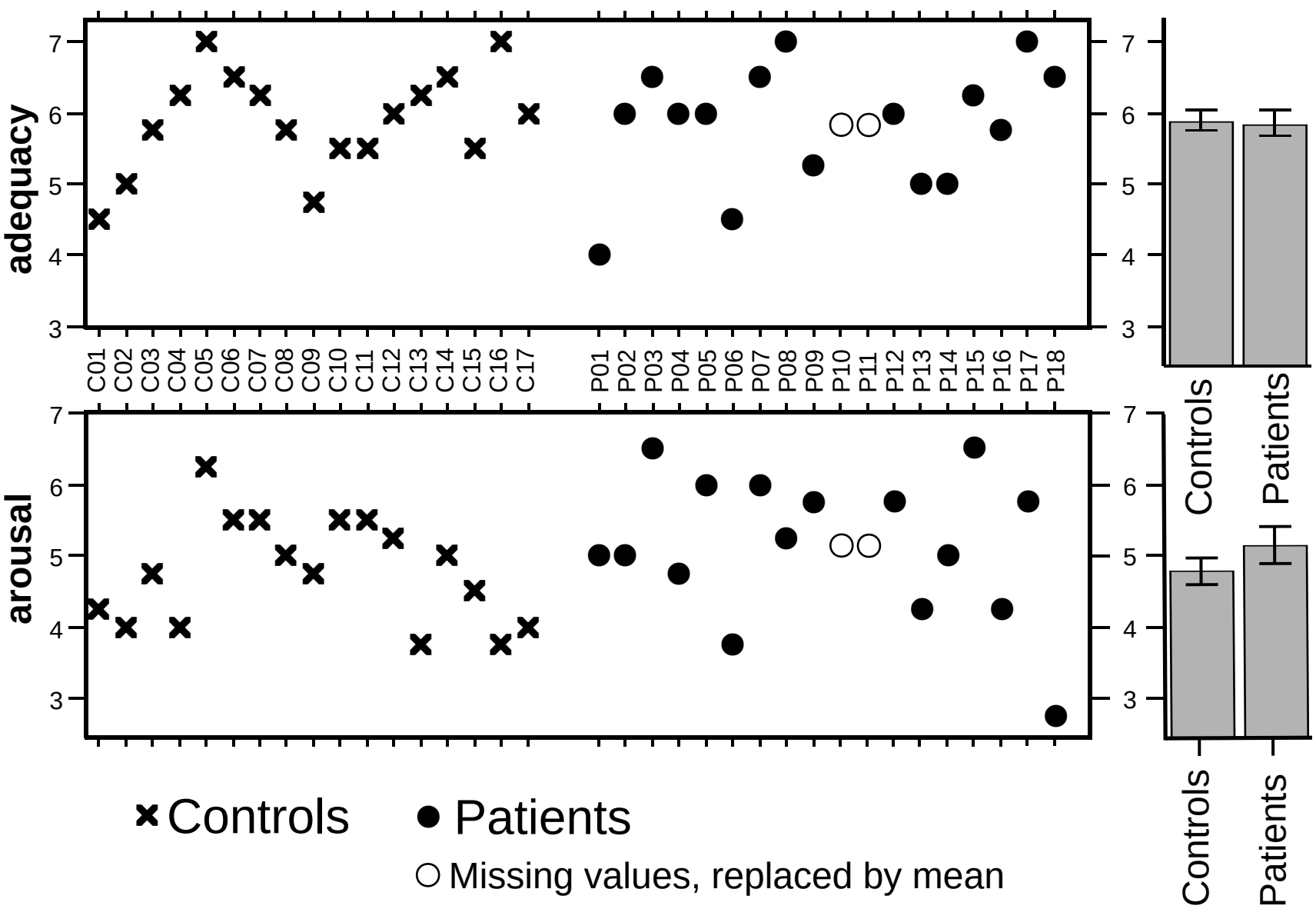
Figure 4: Main effect of *CONDITION*. Left side: t-maps, $p < .001$, FDR, cluster threshold 16 Voxel. Right side: Beta plots for regions with significant main effect, orange-yellow-scale: OPD > Traffic, Blue Scale: Traffic > OPD. Abbreviations as in table 2.

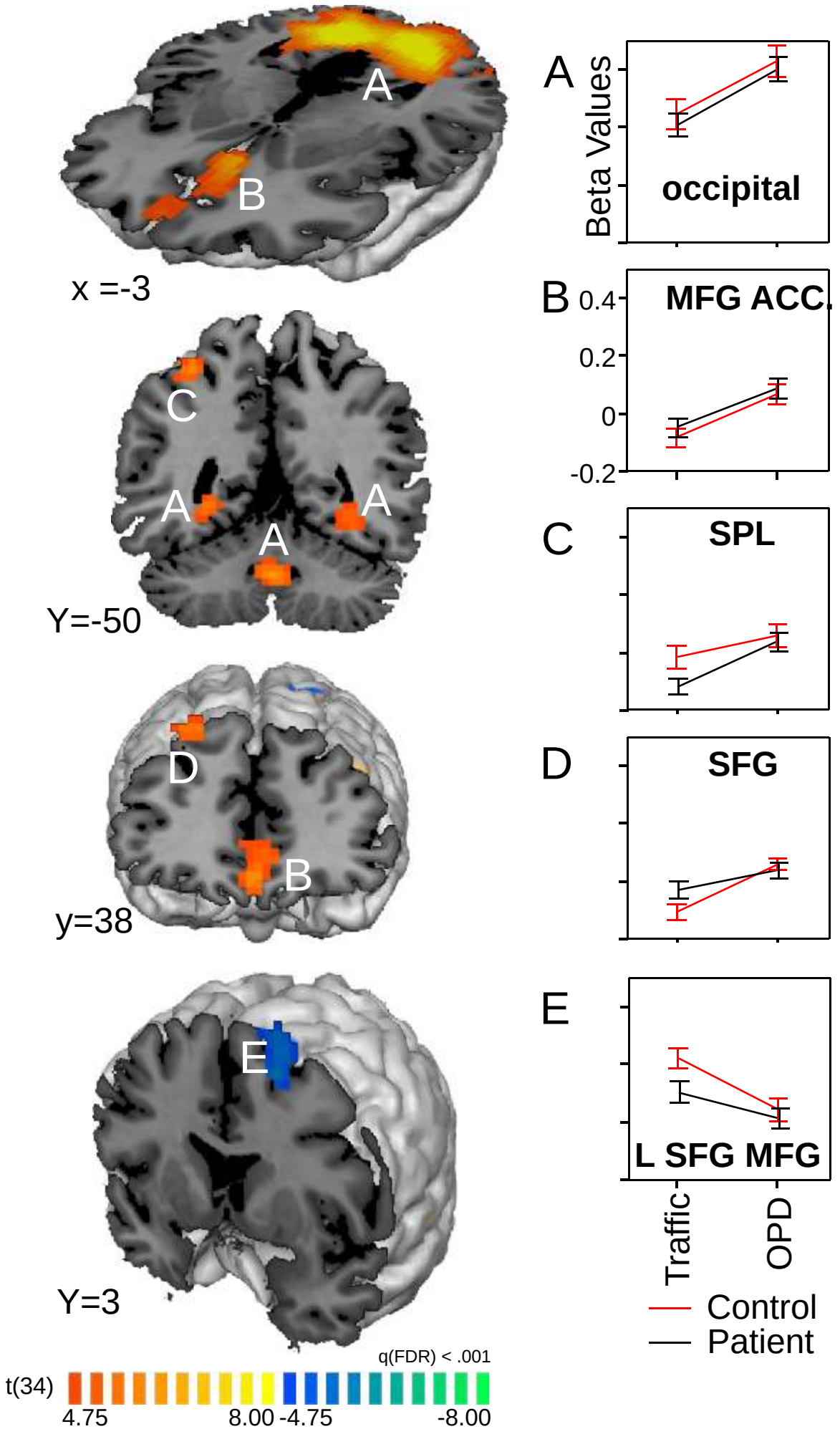
Figure 5: Beta values, plotted for the traffic and the OPD condition, separately for each subject.

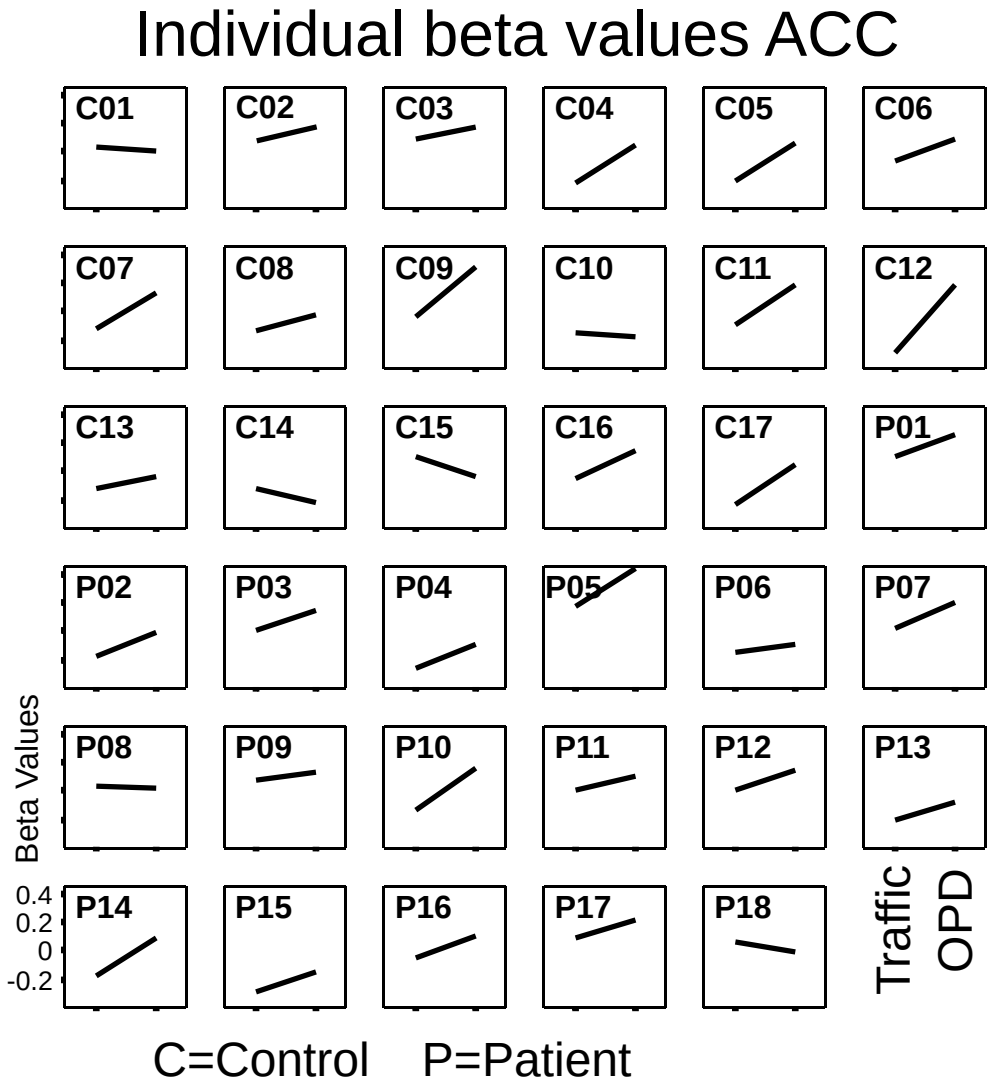
Figure 6: Interaction effect *CONDITION* x GROUP, $p < .001$, cluster threshold 16 Voxel. Brain slices depict coronar view of the active clusters. Right site: Interaction plots for active clusters, based on beta values for OPD and traffic sentences. Abbreviations as in table 3.

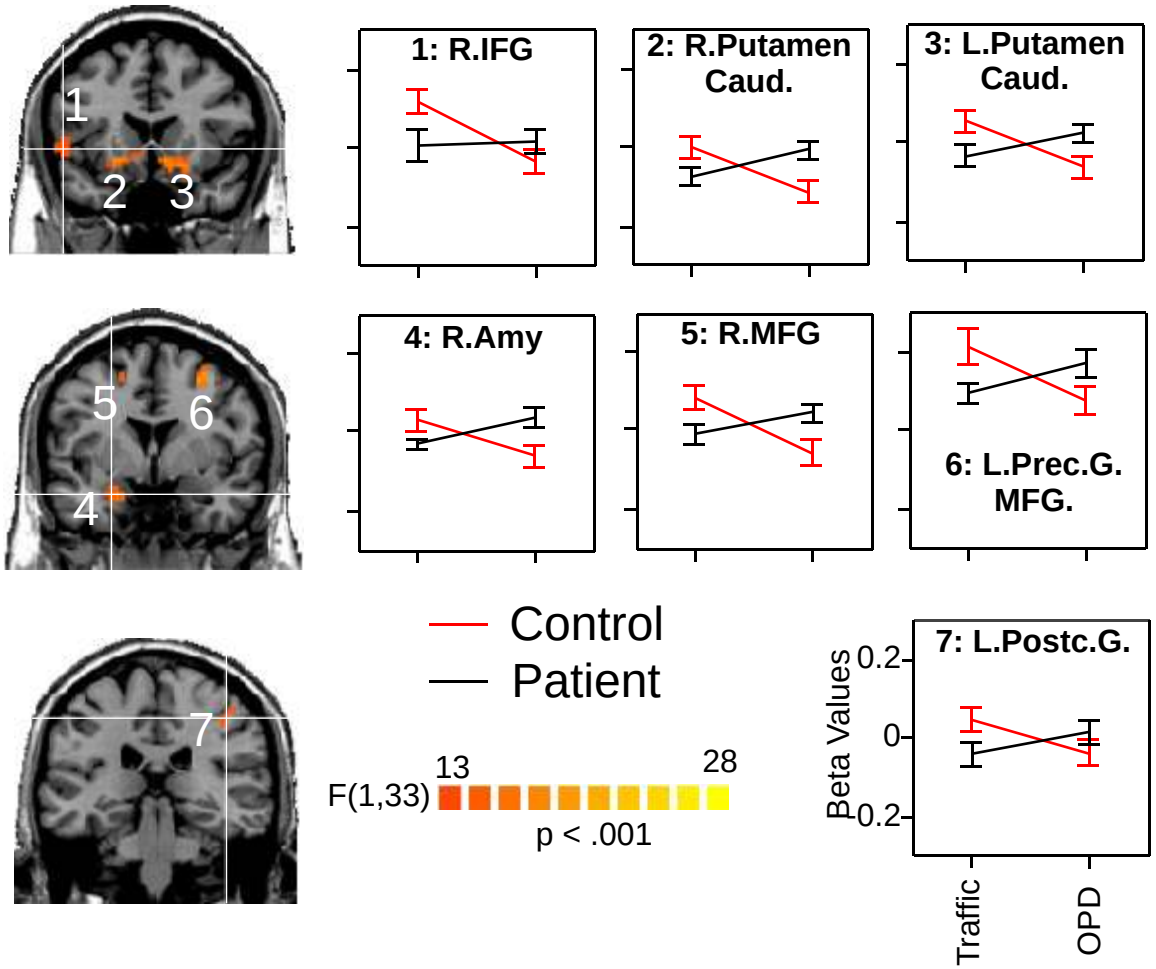

7.5 sec
7.5 sec
7.5 sec
7.5 sec
Think of your safe place
Please try to relax
Try to get the head clean
and try to think about nothing.
You wish to be accepted by others
Therefore you do a lot for them.
That is often too close for them, so they retreat
Then you feel empty and lonesome
Think of your safe place
Please try to relax
Try to get the head clean
and try to think about nothing.
the other driver makes a mistake
you are very upset about this
you react to the other driver,
but he reacts inadequately.
Relax
OPD
Relax
Traffic


BDI
40
35
30
25
20
15
10
5
0
C01
C02
C03
C04
C05
C06
C07
C08
C09
C10
C11
C12
C13
C14
C15
C16
C17
P01
P02
P03
P04
P05
P06
P07
P08
P09
P10
P11
P12
P13
P14
P15
P16
P17
P18
Controls
Patients
Error bars show
mean +/- 1 SE
Controls
Patients


adequacy
arousal
7
6
5
4
3
C01 C02 C03 C04 C05 C06 C07 C08 C09 C10 C11 C12 C13 C14 C15 C16 C17
P01 P02 P03 P04 P05 P06 P07 P08 P09 P10 P11 P12 P13 P14 P15 P16 P17 P18
Controls
Patients
Controls
Patients
Controls
Patients
Missing values, replaced by mean


A
B
x =-3
C
A
A
A
Y=-50
D
B
y=38
E
Y=3
q(FDR) < .001
t(34)
4.75
8.00
-4.75
-8.00
A
Beta Values
occipital
B
0.4
0.2
0
-0.2
MFG ACC.
C
SPL
D
SFG
E
L SFG MFG
Traffic
OPD
Control
Patient


Individual beta values ACC
C01
C02
C03
C04
C05
C06
C07
C08
C09
C10
C11
C12
C13
C14
C15
C16
C17
P01
P02
P03
P04
P05
P06
P07
P08
P09
P10
P11
P12
P13
P14
P15
P16
P17
P18
Beta Values
0.4
0.2
0
-0.2
Traffic
OPD
C=Control P=Patient


1
2
3
1: R.IFG
2: R.Putamen Caud.
3: L.Putamen Caud.
5
6
4
4: R.Amy
5: R.MFG
6: L.Prec.G. MFG.
7
Control
Patient
13
28
F(1,33)
p < .001
7: L.Postc.G.
Beta Values
0.2
0
0.2
Traffic
OPD