



Segregated neural representation of psychological and somatic-vegetative symptoms in severe major depression

Alexander Heinzl^{a,1}, Simone Grimm^{b,1}, Johannes Beck^b, Daniel Schuepbach^b, Daniel Hell^b, Peter Boesiger^c, Heinz Boeker^b, Georg Northoff^{b,d,*}

^a Department of Nuclear Medicine, University of Duesseldorf, Germany

^b Department of Psychiatry, University of Zurich, Switzerland

^c Institute of Biomedical Engineering, ETH and University of Zurich, Switzerland

^d Department of Psychiatry, University of Magdeburg, Germany

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ABSTRACT

Objective: The Beck Depression Inventory (BDI) is probably the most widely used depression scale. It has been suggested that it contains a two-factor structure measuring cognitive-affective (i.e. psychological) and somatic-vegetative depressive symptoms. In this study we aim to evaluate these factors by probing for their neural correlates. **Methods:** Neural responses evoked by emotional perception, relative to an emotional judgment task, were measured using functional magnetic resonance imaging (fMRI) in 20 medication-free patients with severe MDD. Psychological and somatic-vegetative symptoms were evaluated with the BDI. **Results:** Psychological symptoms correlated with signal changes in the dorsomedial and right ventrolateral prefrontal cortex, while somatic-vegetative symptoms correlated with signal changes in the pre-genual anterior cingulate cortex. **Conclusions:** These preliminary findings demonstrate segregated neural representation of psychological and somatic-vegetative symptoms of MDD in different cortical regions. Thus, our results indicate that the two-factor structure of the BDI is related to distinct neural correlates.

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The Beck Depression Inventory (BDI) [2] is probably the most widely used depression scale [40]. It consists of 21 items on how the patient has been feeling resulting in a total score which allows assessing the severity of depressive symptoms. Due to criticisms on the original version from 1961 the scale has been revised several times [4,3]. Our results are based on the German version of the BDI-II [26].

It has been suggested that the BDI contains a two-factor structure measuring cognitive-affective (i.e. psychological) and somatic-vegetative (e.g. loss of appetite) depressive symptoms [41,46,44,39]. However, this view is not undisputed (see, e.g. [1,11,45]).

These factors are also clinically important because they may contribute to a better categorization of the depression subtype and thus lead to a more appropriate treatment. One way to further evaluate the two factors is to look for segregate neural represen-

tations of the cognitive-affective factor on one hand and for the somatic-vegetative factor on the other hand.

Recent functional imaging studies using emotional stimuli identified a complex network of brain regions involved in the pathophysiology of MDD [14]. Moreover, functional imaging studies found that the global severity of MDD assessed by the total score of the BDI is related to altered neural processing [12,18,24]. However, it remains unclear if the observed altered neural activation may be related to distinct symptoms of MDD as assessed by the BDI-II.

Mayberg and co-workers developed a model of impaired functional activity. They proposed that cognitive symptoms of depression are related to altered neural activity in a dorsal compartment consisting of the medial frontal cortex, the dorsolateral prefrontal cortex, posterior cingulate and parietal cortices. In contrast, somatic-vegetative symptoms are involved in altered neural activity in a ventral compartment including the perigenual anterior cingulate, ventral insula, hypothalamus and rostral inferior frontal regions [28,31,29].

Based on these findings we hypothesised a differential correlation of cognitive-affective and vegetative-somatic symptoms of MDD. On an exploratory basis we aimed to probe if the cognitive-affective symptoms are related to the dorsal compartment and the somatic-vegetative symptoms are related to the ventral compartment.

Abbreviations: PV, picture viewing; PJ, picture judgment; DMPFC, dorsomedial prefrontal cortex; PACC, pre-genual anterior cingulate cortex; rVLPFC, right ventrolateral prefrontal cortex.

* Corresponding author at: Department of Psychiatry, University of Magdeburg, Leipzig Strasse 44, 39120 Magdeburg, Germany. Tel.: +49 391 6714234.

E-mail address: georg.northoff@medizin.uni-magdeburg.de (G. Northoff).

¹ These authors contributed equally to the paper.

To that end, 20 medication-free depressed patients with an acute MDD episode performed an emotional task during fMRI applying visual emotional stimuli. The resulting changes in fMRI BOLD signal were correlated with the results of the psychological and somatic-vegetative factor of the BDI.

Twenty medication-free depressed patients (11 women, 9 men; age: 40.7 years; range: 25–62 years) with an acute severe major depressive episode (DSM IV, APA 1994) were recruited from the Inpatient Department of Psychiatry at the University of Zurich (Switzerland). Inclusion criterion was a score of at least 24 on the 21-item Hamilton Rating Scale for Depression (HDRS) (12) (means \pm S.D.: 33.12 ± 7.13). We selected a HDRS score of at least 24 as an inclusion criterion in order to ensure the investigation of a rather homogeneous group of severely depressed patients. The 21-item version was used since it is part of the standardized psychopathological screening at the Psychiatric University Hospital Zurich. Exclusion criteria were any neurological/medical disorder and any psychiatric disorder other than MDD. Patients had been free of psychotropic medication for at least 1 week prior to scanning (9.1 ± 7.98 days; means \pm S.D.). Three of the depressed subjects had never taken anti-depressants. One patient had to be excluded from the sample due to structural abnormalities in the 3D T1-weighted anatomical scan. This resulted in usable fMRI data on 19 subjects with depression. Patients showed the following characteristics (means \pm S.D.): number of episodes: 1.8 ± 2.2 ; duration of current episode: 15.83 weeks \pm 16.24; duration of illness: 6.6 years \pm 8.1. All patients completed the German version of the BDI [26] (means \pm S.D.: 29.94 ± 4.93) from which the psychological (means \pm S.D.: 18.81 ± 4.81) and somatic subscores (means \pm S.D.: 16.06 ± 3.45) were extracted. This was done by using a two-factor solution (psychological subscore, somatic-vegetative subscore) as proposed by [39].

In addition to the BDI we used the HDRS for the evaluation of the patients. The HDRS consists of a clinical rating scale whereas the BDI-II is a self-report instrument. Thus, their combined use allows evaluating the patients from self-reported and clinically rated perspectives increasing the confidence in the accuracy of the assessment [25,43].

After a detailed explanation of the study design and any potential risks, all subjects gave their written informed consent. The study was approved by the Institutional Review Board of the University of Zurich/Switzerland. The same sample has been used in previous studies by Grimm et al. [18,19].

Reaction times and judgments (positive/negative rating) were analysed in a multivariate ANOVA.

A total of 158 positive or negative pictures from the International Affective Picture System (IAPS) [8] were presented in each case for 4 s. In half of the trials subjects had to view the pictures (PV) and in the other half to judge (PJ) them. PV and PJ pictures were matched for emotional valence and intensity.

After the presentation of each picture, a resting period followed, where a fixation cross was presented for 6–8 s (6.0, 6.5, 7.0, 7.5, and 8.0 s). This allowed the subjects to recover from emotional stimulation and, in addition, served as a baseline condition to distinguish between positive and negative BOLD responses [42].

Reaction times were measured differently for the PJ and the PV condition. During PJ the subjects were instructed to press the button under their right index finger in the case of positive judgment and to press the button under their left index finger in the case of negative judgment. During PV the subjects were instructed to randomly press a button as quickly as possible with their left or right index finger without making any judgment.

During fMRI, the pictures were projected automatically via a forward projection system onto a translucent screen placed at the foot of the scanner [20].

The aim of this paper was to focus on emotional experience in MDD patients. In order to address emotional experience during the fMRI measurement the subjects were explicitly requested only to passively view and not to judge the pictures during the PV condition. However, due to the presentation time of 4 s it is unlikely that we were able to completely exclude any kind of judgment. We purposely used a rather long presentation time to allow strong emotional experience of the stimuli. It has to be noted that such a presentation time does not serve to look specifically for subliminal implicit processing. The presentation time would need to be shorter.

To minimize the confounding influence of cognitive processing, such as judgment, we subtracted the emotional judgment condition (PJ) from the passive picture viewing condition (PV). It seems likely that this subtraction also eliminated implicit processing therefore the resulting activation maps should be solely related to explicit perceptual emotional processing.

The same sample has also been used in a previous study Grimm et al. [18] which had focused on emotional judgment.

fMRI measurements were performed on a Philips Intera 3T whole-body MR unit. In order to reduce possible susceptibility artifacts functional time series were acquired with sensitivity encoded single-shot echo-planar sequence (SENSE-sshEPI) [37]. SENSE compared to conventional EPI has been shown to reduce susceptibility-related image distortion and signal dropout [38]. The following acquisition parameters were used in the fMRI protocol: TE (echo time)=35 ms, FOV (field of view)=22 cm, acquisition matrix=80 \times 80, interpolated to 128 \times 128, voxel size: 2.75 mm \times 2.75 mm \times 4 mm, SENSE acceleration factor $R=2.0$. Using a midsagittal scout image, 32 contiguous axial slices were placed along the AC-PC plane covering the entire brain (TR=3000 ms, $\theta=82^\circ$). The first three acquisitions were discarded due to T1 saturation effects. A 3D T1-weighted anatomical scan was obtained for structural reference.

Image processing and statistical analyses were carried out using MATLAB 6.5.1 and SPM2 (<http://www.fil.ion.ucl.ac.uk>). The images were corrected for differences in slice acquisition time, realigned to the first volume, corrected for motion artifacts, mean adjusted by proportional scaling, re-sliced and normalized into standard stereotactic space, and smoothed using a 8 mm full-width-at-half-maximum Gaussian kernel.

The time series were high pass filtered to eliminate low frequency drifts (cut-off 128 s). We analyzed our data using the summary statistic approach in which subject-specific activations were estimated at the first level and then passed to a second, between-subject, level for regression on the BDI scores. The first level analysis used a conventional linear convolution model [16]. The design matrix included regressors encoding PV, PJ and baseline. Moreover, for each experimental run, the six parameters obtained in the realignment procedure were included as covariates of no interest in the design matrix. After the first level models were estimated, we summarized subject-specific activations using contrasts testing for activation in PV that was greater than PJ. These contrasts were then passed to a second-level analysis, where we regressed the contrasts or activations on the two BDI scores. We tested for the effects of either BDI score in regions showing a main effect of activation (tested with a one-sample t -test).

Under the null hypothesis, this provides an orthogonal constraint on the search for correlations between activations and BDI scores over subjects. We report our SPMs thresholded at point 0.005 uncorrected (and $k>10$). However, the results we discuss survived a small volume or regional correction using a sphere centered on maxima of the activation contrast above. To quantify the effect sizes in terms of activation differences, we plotted the BDI predictor variables and contrast or activa-

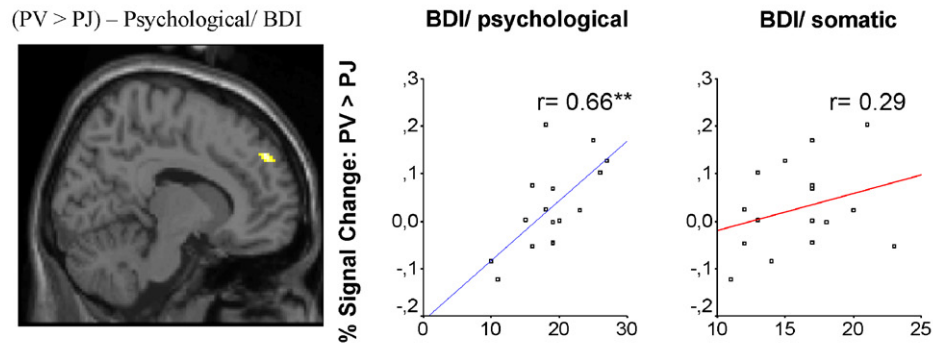
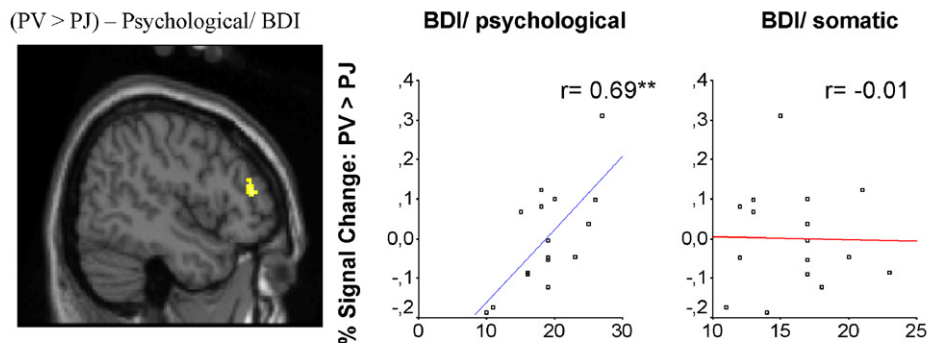
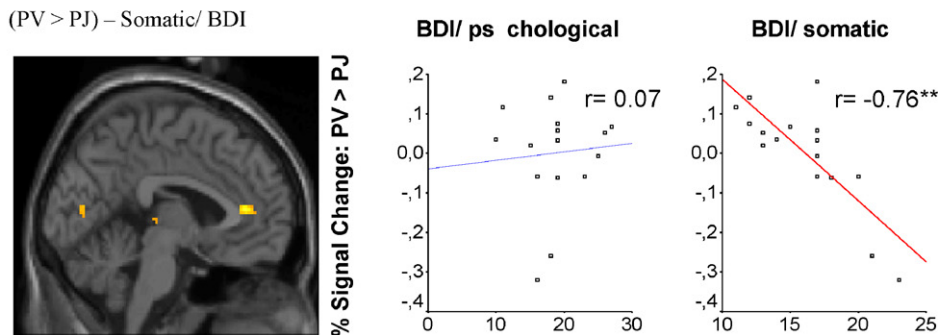
(a) Positive correlation of psychological symptoms (blue curve) with the DMPFC**(b) Positive correlation of psychological symptoms (blue curve) with the rVLPFC****(c) Negative correlation of somatic symptoms (red curve) with the PACC**

Fig. 1. Correlation of psychological and somatic-vegetative BDI subscores with signal changes during PV > PJ in MDD. The images show the maximum intensity projections of correlating clusters with BDI subscores during PV > PJ and statistical parametric (T) maps overlaid on a single subject's normalized brain ($p < 0.005$; uncorrected; $k > 10$). The sagittal view represents the right hemisphere in all images. Scatter plots show psychological and somatic-vegetative BDI subscores on x-axis and signal percent changes on y-axis, the latter extracted for individual correlation maps shown in images for the group. **** is used to indicate the significance of the correlation coefficient r . (a) Positive correlation of psychological symptoms (blue curve) with the DMPFC. *Left panel* shows correlation in the DMPFC with coordinates [12, 50, 38; $z = 3.54$]. *Right panel* shows correlation curves for the relationship of DMPFC % signal change and psychological/somatic-vegetative BDI subscores ($**p < 0.01$). (b) Positive correlation of psychological symptoms (blue curve) with the rVLPFC. *Left panel* shows correlation in the rVLPFC with coordinates [48, 42, 14; $z = 3.19$]. *Right panel* shows correlation curves for the relationship of rVLPFC % signal change and psychological/somatic-vegetative BDI subscores ($**p < 0.01$). (c) Negative correlation of somatic symptoms (red curve) with the PACC. *Left panel* shows correlation in the PACC is shown with coordinates [-4, 38, 10; $z = 3.50$]. *Right panel* shows correlation curves for the relationship of PACC % signal change and psychological/somatic-vegetative BDI subscores ($**p < 0.01$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

tion responses at the maxima of the ensuing SPMs (see Fig. 1, right panel). Moreover, percent signal changes for the different conditions were extracted for each subject separately using Marsbar (<http://www.sourceforge.net/projects/marsbar>). Percent signal changes were extracted into a scatter plot and correlated with BDI psychological and somatic subscores using Pearson correlation analysis (see Fig. 1, left panel). We did not perform a similar analysis with the subscales of the HDRS.

The results of the above-described analyses represent correlations of BDI subscores with general emotional processing containing the whole range of emotional valence. In order to test if these results may be related to specific valence-processing (i.e. negative or positive) we calculated four additional contrasts. We divided the stimuli according to their valence into two groups and calculated correlations for the PV > PJ contrast of each valence with BDI psychological and somatic subscores using simple regres-

sion analysis. Based on the results from correlations with general emotional processing we conducted a ROI-analysis using a sphere centered on the local maxima of the rVLPFC, DMPFC and pACC. We only report significant activations.

The MDD patients showed longer reaction times for PJ than for PV ($T = -2.57$; $d.f. = 1060$, $p = 0.010$).

We found a positive correlation of psychological symptoms with signal changes in the DMPFC and the right VLPFC (see Fig. 1a and b for exact coordinates, images and curves). Moreover, there is a negative correlation between the somatic-vegetative symptom components with signal changes in the pre-genual anterior cingulate cortex (PACC) (and a small spot in the medial occipital cortex) (see Fig. 1c for exact coordinates, curves and image).

The valence-specific analyses showed the following correlations: the somatic-vegetative symptoms correlated with negative emotional processing in the PACC ($x = -6$, $y = 42$, $z = 4$, $Z = 3.02$) and the psychological symptoms correlated with negative emotional processing in the rVLPFC ($x = 48$, $y = 40$, $z = 12$, $Z = 3.19$).

Our study demonstrates association of psychological and somatic-vegetative symptoms with neural activity in different cortical regions during emotion perception in medication-free severe MDD patients on an exploratory basis. The psychological symptom component was associated with neural activity in the DMPFC and the right VLPFC. The greater signal changes in the DMPFC and the right VLPFC during emotion perception, the stronger psychological symptoms were present in MDD patients. Our findings are in accordance with recent studies showing abnormalities in these regions in MDD in both resting state and emotion perception [12,24,5,7,32]. They extend these results by demonstrating association of the DMPFC and the right VLPFC with a specific symptom component, i.e. psychological symptoms rather than somatic-vegetative symptoms.

In contrast, somatic-vegetative symptoms were associated with neural activity in the PACC. The smaller signal changes in the PACC during emotion perception, the stronger somatic-vegetative symptoms were present in MDD patients. Neural activity in the PACC has often been shown to be abnormal in MDD during both resting state and emotion perception [29,36]. Our results complement these observations by associating PACC activity specifically with somatic-vegetative symptoms. Furthermore, negative correlation of neural activity in the PACC with somatic-vegetative symptoms contrast with positive correlation of psychological symptoms with neural activity in DMPFC and right VLPFC. Thus psychological and somatic-vegetative symptoms could not only be distinguished by different correlating regions but also by the direction of their correlation. Such opposite correlation patterns in relation with distinct symptom types are well in accordance with the limbic-cortical dysregulation model of MDD that postulates inverse neural activity in ventral and dorsal prefrontal cortical regions [29,36]. However, the limbic-cortical dysregulation model also involves subcortical and limbic structures. We did not find a correlation for these regions.

It has been shown that the subgenual part of the anterior cingulate plays a central role in depression [9,27,30,17]. Moreover, since this region has strong connections with the lateral hypothalamus it is considered the most important region within the frontal cortex for regulating autonomic function [33]. Given these observations one may expect to find a correlation between the somatic scores of the BDI and neural activity in the subgenual anterior cingulate. However, the anterior cingulate cortex has been involved in attentional and cognitive processes that regulate emotion such as, e.g. assessing the salience of emotional and motivational information [6]. In contrast, our experimental paradigm focuses on the experiential component of emotions aiming to avoid confounds by cognitive components (see above). Thus, the elimination of cognitive components from the paradigm may explain our lack of findings in the subgenual anterior cingulate.

Several studies indicated valence-specific abnormalities in major depression (see, e.g. [13]). Therefore, it may be questioned if the correlations with the neural signal changes in the DMPFC, the rVLPFC, and the PACC may be valence-specific as well or rather related to general emotional processing. Concerning the PACC, we found that negative emotional processing showed a specific correlation with somatic-vegetative symptoms. This is in accordance with the results of [13] who found strong response to negative stimuli in the same region. Moreover, previous studies have demonstrated that activity in the VLPFC is correlated with the degree of negative thinking in MDD patients [24,12]. This is in accordance with our observation of a correlation between psychological symptoms with negative emotional processing in the VLPFC. Therefore, one may speculate that the VLPFC and the PACC show valence-specific correlations with the BDI subscores whereas the correlation of the DMPFC might be related to general emotional processing.

There are some methodological issues that have to be considered.

It has to be noted that the investigated sample consisted of a rather homogeneous group of severely depressed patients resulting in a limited variance of scores on psychological and somatic BDI dimensions. This might have led to smaller effects in the correlational analysis. Therefore, it cannot be excluded that a wider range of severity of symptoms might have revealed correlations with other cortical or subcortical areas.

Furthermore, it has to be acknowledged that the investigated group of depressed patients consisted of a convenience sample that may not be representative for the larger population of MDD patients. Therefore, it cannot be excluded that the results are confounded by a sampling bias.

Moreover, we did not perform a confirmatory analysis to justify the use of the two-factor solution of the BDI-II. For such a study a much higher sample size, using different kinds of statistics, is needed (see, e.g. [46]). In contrast, the aim of our study was to probe on an exploratory basis if the two-factor solution may be related to distinct neural correlates. For functional imaging studies investigating the neural correlates of behavioral measures a sample size of 19 patients is broadly accepted [14,10].

We did not explore the correlations with other factor solutions of the BDI-II (see, e.g. [41,45]). Thus, we cannot exclude that different solutions of the BDI-II may show equal or stronger correlations with the neural activations during emotional processing.

In order to achieve a high level of sensitivity for detection we set the level of significance for the covariate maps at $k > 10$ voxels and $p < 0.005$. It has to be noted that our results are uncorrected for multiple comparisons. This is in accordance to other studies in the field of affective neuroscience [21,34,35]. However, the high level of sensitivity implies an increased risk of false-positive results. Therefore, our results are presented as preliminary findings.

We employed an 8 mm full-width-at-half-maximum Gaussian kernel to enhance the sensitivity and to reduce the effects of anatomical discrepancies as important features in multisubject fMRI studies of higher cognitive functions [15,22].

A possible confounding parameter in fMRI studies is the signal drift. However, in contrast to blocked designs, event-related designs are known to be less sensitive to the possible influence of signal drift [23].

In order to focus on emotional experience we used PJ as a control condition to PV. It has to be noted that PJ does not represent a typical control condition, such as, e.g. the often applied fixation cross. Due to the explicit cognitive task, PJ may contain stronger activations than PV. Therefore, it is not possible to decide if the observed differences between the two conditions represent activation of PV or deactivation of PJ.

Since this paper focuses on emotional experience in MDD patients, we only investigated the correlations of the contrast

PV > PJ. However, it would be of interest to examine correlations with other contrasts.

In summary, our results provide preliminary evidence for segregated representation of psychological and somatic-vegetative symptoms in different cortical regions during emotion perception in medication-free patients with severe MDD. This does not only complement recent imaging studies and the limbic–cortical dysregulation model of MDD in psychopathological respect but also emphasizes the importance of employing a symptom-dimension-based approach in future clinical and neuroscientific examination of MDD.

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References

- [1] R.C. Arnau, M.W. Meagher, M.P. Norris, R. Bramson, Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients, *Health Psychol.* 20 (2001) 112–119.
- [2] A.T. Beck, A systematic investigation of depression, *Compr. Psychiatry* 2 (1961) 163–170.
- [3] A.T. Beck, R.A. Steer, G.K. Brown, Beck Depression Inventory, second edition manual, The Psychological Corporation, San Antonio, TX, 1996.
- [4] A.T. Beck, R.A. Steer, M.G. Garbin, Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation, *Clin. Psychol. Rev.* 8 (1988) 77–100.
- [5] A.L. Brody, M.W. Barsom, R.G. Bota, S. Saxena, Prefrontal-subcortical and limbic circuit mediation of major depressive disorder, *Semin. Clin. Neuropsychiatry* 6 (2001) 102–112.
- [6] G. Bush, P. Luu, M.I. Posner, Cognitive and emotional influences in anterior cingulate cortex, *Trends Cogn. Sci.* 4 (2000) 215–222.
- [7] T. Canli, H. Sivers, M.E. Thomason, S. Whitfield-Gabrieli, J.D. Gabrieli, I.H. Gotlib, Brain activation to emotional words in depressed vs healthy subjects, *Neuroreport* 15 (2004) 2585–2588.
- [8] Center for the Study of Emotion and Attention, International Affective Picture System, University of California Gainesville, Florida, 1999 (Ref Type: Audiovisual Material).
- [9] R.J. Davidson, D. Pizzagalli, J.B. Nitschke, K. Putnam, Depression: perspectives from affective neuroscience, *Annu. Rev. Psychol.* 53 (2002) 545–574.
- [10] J.E. Desmond, G.H. Glover, Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses, *J. Neurosci. Methods* 118 (2002) 115–128.
- [11] M. Dum, J. Pickren, L.C. Sobell, M.B. Sobell, Comparing the BDI-II and the PHQ-9 with outpatient substance abusers, *Addict. Behav.* 33 (2008) 381–387.
- [12] R.T. Dunn, T.A. Kimbrell, T.A. Ketter, M.A. Frye, M.W. Willis, D.A. Luckenbaugh, R.M. Post, Principal components of the Beck Depression Inventory and regional cerebral metabolism in unipolar and bipolar depression, *Biol. Psychiatry* 51 (2002) 387–399.
- [13] R. Elliott, J.S. Rubinsztein, B.J. Sahakian, R.J. Dolan, The neural basis of mood-congruent processing biases in depression, *Arch. Gen. Psychiatry* 59 (2002) 597–604.
- [14] P.B. Fitzgerald, A.R. Laird, J. Maller, Z.J. Daskalakis, A meta-analytic study of changes in brain activation in depression, *Hum. Brain Mapp.* 29 (2008) 683–695.
- [15] P. Fransson, K.D. Merboldt, K.M. Petersson, M. Ingvar, J. Frahm, On the effects of spatial filtering—a comparative fMRI study of episodic memory encoding at high and low resolution, *Neuroimage* 16 (2002) 977–984.
- [16] K.J. Friston, A.P. Holmes, J.B. Poline, P.J. Grasby, S.C. Williams, R.S. Frackowiak, R. Turner, Analysis of fMRI time-series revisited, *Neuroimage* 2 (1995) 45–53.
- [17] I.H. Gotlib, H. Sivers, J.D. Gabrieli, S. Whitfield-Gabrieli, P. Goldin, K.L. Minor, T. Canli, Subgenual anterior cingulate activation to valenced emotional stimuli in major depression, *Neuroreport* 16 (2005) 1731–1734.
- [18] S. Grimm, J. Beck, D. Schuepbach, D. Hell, P. Boesiger, F. Bermpohl, L. Niehaus, H. Boeker, G. Northoff, Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder, *Biol. Psychiatry* 63 (2008) 369–376.
- [19] S. Grimm, P. Boesiger, J. Beck, D. Schuepbach, F. Bermpohl, M. Walter, J. Ernst, D. Hell, H. Boeker, G. Northoff, Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects, *Neuropsychopharmacology* (2008).
- [20] S. Grimm, C.F. Schmidt, F. Bermpohl, A. Heinz, Y. Dahlem, M. Wyss, D. Hell, P. Boesiger, H. Boeker, G. Northoff, Segregated neural representation of distinct emotion dimensions in the prefrontal cortex—an fMRI study, *Neuroimage* 30 (2006) 325–340.
- [21] U. Herwig, T. Baumgartner, T. Kaffenberger, A. Bruhl, M. Kottlow, U. Schreier-Gasser, B. Abler, L. Jancke, M. Rufer, Modulation of anticipatory emotion and perception processing by cognitive control, *Neuroimage* 37 (2007) 652–662.
- [22] J.B. Hopfinger, C. Buchel, A.P. Holmes, K.J. Friston, A study of analysis parameters that influence the sensitivity of event-related fMRI analyses, *Neuroimage* 11 (2000) 326–333.
- [23] A.M. Kang, R.T. Constable, J.C. Gore, S. Avrutin, An event-related fMRI study of implicit phrase-level syntactic and semantic processing, *Neuroimage* 10 (1999) 555–561.
- [24] P.A. Keedwell, C. Andrew, S.C. Williams, M.J. Brammer, M.L. Phillips, The neural correlates of anhedonia in major depressive disorder, *Biol. Psychiatry* 58 (2005) 843–853.
- [25] P.C. Kendall, S.D. Hollon, A.T. Beck, C.L. Hammen, R.E. Ingram, Issues and recommendations regarding use of the Beck Depression Inventory, *Cogn. Ther. Res.* 11 (1987) 289–299.
- [26] C. Kuhner, C. Burger, F. Keller, M. Hautzinger, Reliability and validity of the Revised Beck Depression Inventory (BDI-II). Results from German samples, *Nervenarzt* 78 (2007) 651–656.
- [27] M. Liotti, H.S. Mayberg, S.K. Brannan, S. McGinnis, P. Jerabek, P.T. Fox, Differential limbic–cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders, *Biol. Psychiatry* 48 (2000) 30–42.
- [28] H.S. Mayberg, Limbic–cortical dysregulation: a proposed model of depression, *J. Neuropsychiatry Clin. Neurosci.* 9 (1997) 471–481.
- [29] H.S. Mayberg, Modulating dysfunctional limbic–cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment, *Br. Med. Bull.* 65 (2003) 193–207.
- [30] H.S. Mayberg, S.K. Brannan, J.L. Tekell, J.A. Silva, R.K. Mahurin, S. McGinnis, P.A. Jerabek, Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response, *Biol. Psychiatry* 48 (2000) 830–843.
- [31] H.S. Mayberg, M. Liotti, S.K. Brannan, S. McGinnis, R.K. Mahurin, P.A. Jerabek, J.A. Silva, J.L. Tekell, C.C. Martin, J.L. Lancaster, P.T. Fox, Reciprocal limbic–cortical function and negative mood: converging PET findings in depression and normal sadness, *Am. J. Psychiatry* 156 (1999) 675–682.
- [32] M.S. Milak, R.V. Parsey, J. Keilp, M.A. Oquendo, K.M. Malone, J.J. Mann, Neuroanatomic correlates of psychopathologic components of major depressive disorder, *Arch. Gen. Psychiatry* 62 (2005) 397–408.
- [33] D. Ongur, X. An, J.L. Price, Prefrontal cortical projections to the hypothalamus in macaque monkeys, *J. Comp. Neurol.* 401 (1998) 480–505.
- [34] K.L. Phan, D.A. Fitzgerald, P.J. Nathan, G.J. Moore, T.W. Uehde, M.E. Tancer, Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study, *Biol. Psychiatry* 57 (2005) 210–219.
- [35] E.A. Phelps, K.J. O'Connor, J.C. Gatenby, J.C. Gore, C. Grillon, M. Davis, Activation of the left amygdala to a cognitive representation of fear, *Nat. Neurosci.* 4 (2001) 437–441.
- [36] M.L. Phillips, W.C. Drevets, S.L. Rauch, R. Lane, Neurobiology of emotion perception II: implications for major psychiatric disorders, *Biol. Psychiatry* 54 (2003) 515–528.
- [37] K.P. Pruessmann, M. Weiger, M.B. Scheidegger, P. Boesiger, SENSE: sensitivity encoding for fast MRI, *Magn. Reson. Med.* 42 (1999) 952–962.
- [38] C.F. Schmidt, N. Degonda, R. Luechinger, K. Henke, P. Boesiger, Sensitivity-encoded (SENSE) echo planar fMRI at 3T in the medial temporal lobe, *Neuroimage* 25 (2005) 625–641.
- [39] C.K. Schotte, M. Maes, R. Cluydts, D.D. De, P. Cosyns, Construct validity of the Beck Depression Inventory in a depressive population, *J. Affect. Disord.* 46 (1997) 115–125.
- [40] A.B. Shafer, Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung, *J. Clin. Psychol.* 62 (2006) 123–146.
- [41] R.J. Siebert, F.H. Walkey, L. Turner-Stokes, An examination of the factor structure of the Beck Depression Inventory-II in a neurorehabilitation inpatient sample, *J. Int. Neuropsychol. Soc.* 15 (2009) 142–147.
- [42] C.E. Stark, L.R. Squire, When zero is not zero: the problem of ambiguous baseline conditions in fMRI, *Proc. Natl. Acad. Sci. U.S.A.* 98 (2001) 12760–12766.
- [43] R.A. Steer, A.T. Beck, J.H. Riskind, G. Brown, Relationships between the Beck Depression Inventory and the Hamilton Psychiatric Rating Scale for Depression in depressed outpatients, *J. Psychopathol. Behav. Assess.* 9 (1987) 327–339.
- [44] E.A. Storch, J.W. Roberti, D.A. Roth, Factor structure, concurrent validity, and internal consistency of the Beck Depression Inventory-Second Edition in a sample of college students, *Depress. Anxiety* 19 (2004) 187–189.
- [45] S. Vanheule, M. Desmet, H. Groenvynck, Y. Rosseel, J. Fontaine, The factor structure of the Beck Depression Inventory-II: an evaluation, *Assessment* 15 (2008) 177–187.
- [46] M.A. Whisman, J.E. Perez, W. Ramel, Factor structure of the Beck Depression Inventory-Second Edition (BDI-II) in a student sample, *J. Clin. Psychol.* 56 (2000) 545–551.