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DISSERTATION

Emotion and Anticipation Processing Bias in Manic and Depressive Patients – three Functional Magnetic Resonance Imaging (fMRI) Studies

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Abstract

Anticipation of upcoming events is an important skill allowing individuals to develop adaptive responses for their homeostasis and survival in a changing environment. In several psychiatric diseases this adaptive mechanism is impaired leading to well-known symptoms, like excessive worry and pessimistic views on future. Although this is an established model for clinicians dealing with such patients, the neural correlates of this mechanism have only been discovered recently, using brain imaging methods. In this dissertation three functional magnetic resonance imaging studies, using different paradigms that are known to elicit certain emotions or anticipation of emotions, are presented. We studied the brain activation patterns in manic and depressive patients as they anticipated and perceived emotional salient pictures, as well as the anticipation of reward and punishment in form of monetary gain or loss in manic patients. Our results did not only yield various clinically relevant abnormal activations in brain regions including the amygdala, and the prefrontal cortex known to be involved in emotion processing, but also a correlation of these abnormalities with symptom severity. Further research is needed to understand the highly complex emotion processing mechanisms as well as the action of psychotropic medication on it.

Abstract

Die Erwartung herannahender Ereignisse ist eine wichtige Fähigkeit eines Individuums bei der Entwicklung adaptiver Reaktionen für seine Homöostase und das Überleben in einer veränderlichen Umwelt. In einigen psychiatrischen Erkrankungen ist dieser Anpassungsmechanismus beeinträchtigt, dieses führt zu bekannten Symptomen wie übermäßiger Besorgtheit und düsteren Zukunftsperspektiven. Obwohl dies ein etabliertes Modell für Kliniker ist, die mit solchen Patienten arbeiten, wurden die neuralen Korrelate dieses Mechanismus erst kürzlich durch den Einsatz moderner bildgebender Verfahren des Gehirns verstanden. In der vorliegenden Arbeit werden drei funktionelle Magentresonanztomographie Studien vorgestellt, die unterschiedliche Paradigmen nutzen, die bekannt sind, bestimmte Emotionen oder Erwartungen derselben hervorzurufen. Wir untersuchten die Aktivierungsmuster des Gehirns an manischen und depressiven Patienten, während sie emotionsgeladene Bilder erwarteten und wahrnahmen sowie bei manischen Patienten die Erwartung von Belohnung und Bestrafung in Form von Geldgewinn und Verlust. Unsere Ergebnisse beschrieben nicht nur verschiedene klinisch relevante Abnormalitäten in Hirnregionen wie der Amygdala und dem präfrontalen

Kortex, die bekanntermaßen an der Verarbeitung von Emotionen beteiligt sind, sondern auch die Korrelation dieser Normabweichungen mit der Schwere der Symptomatik. Weitere Untersuchungen sind notwendig, um die hochkomplexen emotionsverarbeitenden Mechanismen sowie die Wirkung psychotroper Medikation auf sie zu verstehen.

1. Introduction

Depression is classified by the World Health Organization (WHO) as a global public health concern. Although lifetime prevalence varies between countries, it is estimated to be between 8% and 12% worldwide (1). Unlike depression, which is observed almost twice more often in women than men, bipolar disorder effects both genders equally and show a similar prevalence and incidence worldwide (2). A lifetime prevalence of 3% in the general population makes it the sixth leading cause of disability worldwide and the most expensive mental health care diagnosis (3).

While depression is characterized by low mood as the cardinal symptom, a manic episode is the defining feature of bipolar disorder (4), which is characterized by an elevated mood state. Accompanying symptoms like increased energy levels, self-esteem, impulsivity and engagement in pleasurable and high-risk behaviors are commonly observed. Depending on the presence of a psychosis and the need for psychiatric hospitalization, as well as the maintenance of social functions of the individual, a milder form of a manic episode is generally defined as hypomania (5). Taking the pattern of manic, hypomanic and depressive episodes into consideration, scientists have described distinct subtypes of bipolar disorder i.e. bipolar spectrum disorders.

Modern brain imaging methods, especially functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have opened up a new era in understanding the underlying mechanisms of depression and bipolar disorder. These methods not only gave scientists the possibility to determine brain regions according to their functionality, but also led to a better understanding of dysfunctions in most psychiatric conditions.

Functional Magnetic Resonance Imaging (fMRI) is based on the measurement of cerebral blood flow changes coupled to neuronal activity (6). It is only 20 years old and relies on two basic theories; the hemodynamic response and the BOLD (blood-oxygen-level-dependent) signal. Neurons do not store internal reserves of glucose and oxygen, which are essential for their

function. Therefore an increase in neuronal activity requires more glucose and oxygen to be rapidly delivered via the blood stream. This is called the hemodynamic response, i.e. blood providing glucose and oxygen to active neurons at a faster rate compared to inactive neurons. The second theory is the different magnetic susceptibility of oxygenated and deoxygenated hemoglobin. Hemoglobin without bounded oxygen molecules, i.e. deoxyhemoglobin, is paramagnetic because of the high spin state of the heme iron. In contrast, oxygen-bound hemoglobin, i.e. oxyhemoglobin, has low spin and is diamagnetic. The hemodynamic response results in a surplus of oxyhemoglobin localized in the active area, leading to a measureable change in the ratio of oxy - to deoxyhemoglobin. This provides a localizable marker of activity for MRI, the so-called BOLD signal (7, 8, 9, 10).

fMRI studies in Affective Neuroscience –the study of the neural mechanisms of emotion processing– have demonstrated which brain circuits are involved in different stages of emotion processing. An important recent finding of these studies is the separation of perception of emotions from their anticipation. Although partly overlapping, distinct brain regions were shown to be involved in anticipation and perception of different emotions (11, 12). Depending on the stimulus type (visual, tactile, nociceptive and reward stimuli) different brain regions are activated as one is anticipating an emotion or exposed to the emotion per se. The perception and the processing in healthy subjects depend on various factors like the personal attitude and the magnitude of the stimulus. Alterations of this stage of emotion processing in different psychiatric diseases are intensively studied and gradually better understood. On the contrary, the anticipation of upcoming emotions and events has only recently become a focus of interest and research.

Earliest studies about emotion processing based on observations of changes in patients with lesions in certain brain areas. Until some decades ago, limbic system was thought to be the only brain region involved in emotion processing. By the application of modern brain imaging methods, researchers have not only found out the involvement of different regions, but also they precisely detected several crucial brain regions, which were activated during the anticipation of emotional stimuli. For healthy individuals these regions consist prominently of the prefrontal cortex (PFC), anterior cingulate cortex (ACC) and amygdala, as well as the cerebellum and occipital, i.e. the visual cortex (13). Another aspect of these studies was to investigate the brains reward system, which brought novel approaches to addiction disorders. Healthy individuals activate the Nucleus Accumbens, linked to the Ventral Tegmental Area (VTA) via mesolimbic path, as response to natural rewards such as food, sex and social interactions. This could also be

successfully demonstrated in fMRI studies as response to monetary gain (14,15). Another interesting finding of these studies was to demonstrate a hemispheric localization according to the valence of the anticipated emotion, the so-called 'valence lateralization hypothesis'. In other words, the expectancy of unpleasant emotional stimulus tends to be intensively processed on right PFC and vice versa. Although not well established like language processing and opposed with more recent findings (16, 17), a more complex hemispheric organization possibly depending on the stage of the anticipation (immediate perception of threat accompanied with fear or awaiting a stressful event in the near future) seems to be more plausible (18).

More than 50 years ago, Aaron Beck proposed his cognitive model of depression, which put biased thoughts, emotion processing, attention, memory and rumination as well as dysfunctional attitudes and schemas in the focus of the pathology of depressive disorder (19). This innovative model led to the establishment of cognitive behavioral therapy (CBT), which is the most commonly used technique in modern psychotherapy. Although, the effectiveness of CBT in various psychiatric disorders has consistently been shown in many studies (20), the neural correlates of it were demonstrated only recently by the help of fMRI. There are discrepancies between findings, making an interpretation rather complicated, but still there is a general consensus that patients with major depressive disorder (MDD) tend to show an enhanced activation in ventromedial PFC and ventral ACC, as well as a reduced activation in dorsomedial PFC and dorsal ACC (21, 22). This distinct pattern of activation is a very important finding, since studies in healthy subjects had already shown ventral and dorsal parts of PFC and ACC to be involved in different stages of emotion processing. Ventromedial PFC, ventral ACC and amygdala are thought to be part of an emotion sensitive network, getting activated as a response to exposure to emotionally salient stimuli (23), whereas dorsal parts of PFC and ACC have been associated with regulation of emotion related responses (24).

Biased anticipation of emotions plays a central role in generalized anxiety disorder (GAD), panic disorder as well as in social phobia. GAD patients struggle with "worst case scenarios" that might happen in future, and can be hardly distracted from that. Social phobia and panic disorder patients avoid situations or places, which -according to their anticipation- can trigger their symptoms, although most of them never being confronted with the feared situation. Due to its aforementioned clinical relevance, studies so far focused more on the processing of negative stimulus anticipation in healthy individuals demonstrating consistently the involvement of the ACC, amygdala and thalamus, but also on structures such as the insula and cerebellum (25).

The latter being especially important in understanding the emotional disturbances and personality changes seen in Cerebellar Cognitive Affective Syndrome (CCAS).The correlation of brain activation with certain personality traits like novelty seeking and mood states as well as the effect of very basic psychotherapeutic interventions served a better conceptualization of these findings (26). Studies examining the effects of pharmaceutical treatments (27) or recreational drugs deepened the understanding of these neural circuits.

Because of practical limitations, functional imaging studies of patients during a manic or hypomanic phase are rather limited. Pioneering work in this field demonstrated a bias in form of an increased responsiveness to anticipatory cues, signaling future rewards and reduced responsiveness to aversive anticipatory cues (28). This can be plausibly linked to well-known clinical symptoms like pleasure seeking, hypersexual behavior, abnormal goal pursuit and loss of normal social inhibitions (29, 30). fMRI studies with manic patients focused mostly on affect recognition. Increased activation of amygdala and attenuated activation of OFC is a commonly observed pattern in these patients, which suggests a general arousal state and a global cortico-lymbic (i.e. PFC and amygdala) functional disconnection. This understandably may lead to emotional and affective dysregulation as well as a failure in behavior modulation with regard to feedback from environment.

An important issue of this research field is the discrepant results, which at a first glance can be quite contradictory. Technical differences like the variability of imaging methods and task designs but also patient characteristics like disease history and medication status lead to an unequivocal interpretation of the findings. The functional heterogeneity of investigated regions and the high complexity of emotion processing contributes to the aforementioned problem. Studies like ours dealing with different stages and aspects of emotion processing, using paradigms, which are designed to focus on isolated tasks are needed to improve the preciseness of future research.

2. Objectives:

The following three studies aim to make a contribution to the current understanding of emotional processing in patients with manic and depressive episodes. Our main objective was to study the possible alterations of emotion and anticipation progressing in manic and hypomanic phase of bipolar disorder and depressive phase of major depressive disorder. Investigating the role and possible malfunctions of cortical and limbic systems compared to healthy subjects, as well as

within-group comparisons were designed to describe trait and state dependent alterations. Our hypotheses were based on the existing knowledge about the functional neuroanatomy of central nervous system, previous fMRI studies and the clinical manifestations of the diseases. Specific questions addressed to each study can be summarized as follows.

Study 1: What is the function of the amygdala in the perception of emotional valence in manic patients? Do demonstrated structural changes of amygdala have also relevance in functional changes leading to a mood congruent processing bias? Is there a correlation between self-reported emotional valence and intensity or clinical manifestation severity and the relevant amygdala activation?

Study 2: How does the brain's reward system function in manic patients? What are the differences to healthy subjects in anticipation of monetary gain or loss? Are these alterations persistent or reversible with symptom regression?

Study 3: Which brain circuits are involved in the processing of emotional anticipation in depressed patients? What are the differences compared to healthy subjects? Is there a correlation between the valence of the anticipated emotion or clinical manifestation and the observed activation?

3. Methodology

3.1. Study design

Study 1:10 patients with bipolar disorder were scanned during a manic episode (meeting the DSM IV criteria for a manic episode) during their hospitalization. Subjects passively viewed photographs taken from the International Affective Picture System (IAPS) while being scanned. Following the fMRI session they rated the presented pictures on emotional valence and intensity (arousal). Symptom severity was assessed using the Young Mania Rating Scale (YMRS).Comparisons were made with a group of healthy subjects (n=10) who were matched in relevant variables (age, gender, smoking habits, verbal IQ and hand preference) to the patient group. Healthy control subjects had no axis I or II disorder according to the Structured Clinical Interview for DSM IV (SCID1-2). Matching variables and recruitment procedures for healthy subject group were applied in all three studies. Patients were recruited from the inpatient and outpatient center of the Department of Psychiatry and Psychotherapy, Charite -

Universitätsmedizin Berlin, Campus Mitte. Healthy control participants were recruited from the local community through advertisement. All three studies were approved by the ethics committee of the Charite´ - Universitätsmedizin Berlin and all subjects gave a written informed consent.

Study 2: 16 manic patients meeting the DSM IV criteria for a manic episode were recruited. Seven patients were rescanned after remission. The subjects completed a Monetary Incentive Delay Task (MID) known to activate brains reward system (15). The antipsychotic medications of patients were converted to chlorpromazine dose equivalents in order to make a comparison of effect of medication possible. The control group consisted of 26 subjects.

Study 3: 19 unipolar depressive patients were scanned in medication free status (minimum three months) together with healthy subjects (n=19). The patients all met the criteria for an unipolar depression according to DSM IV using SCID, excluding any other psychiatric diseases or substance abuse other than nicotine. The symptom severity was assessed using the Hamilton Rating Scale for Depression (HAM-D), at the time of scanning patients having a minimum score of 15 points. All subjects were scanned as they passively viewed pictures taken from IAPS.

3.2 fMRI paradigms

Emotion processing paradigm

In the first and the third study, we used pictures chosen from the International Affective Picture System (IAPS), which is a database of pictures used to elicit a range of emotions (31). In the first study we investigated the BOLD signal as the subjects viewed 36 pictures in each category, randomly distributed in two runs i.e. perceived positive negative or neutral stimuli. In the third study a cue appeared prior to each picture, followed by a fixation cross. The anticipation phase consisted of the cue and the following fixation cross, in which the BOLD signal activation was investigated. In half of the trials the cue indicated the emotional valence of the upcoming picture (positive, negative, neutral), in the other half being just a meaningless letter combination.

Reward processing paradigm

The second study used a monetary incentive delay task to investigate the anticipation of potential monetary gain, loss or no consequences. Anticipatory cues were defined as follows: circle = gain, square = loss and triangle = neutral. The number of horizontal lines (one, two or three lines) in the gain or loss anticipation cues, indicated the magnitude of gain or loss i.e. 0.10, 0.60

and 3.00 EUR respectively. The subjects could either win or prevent loosing the indicated amount of money depending on their performance in response to a white square (target cue) appearing shortly on the screen. After the button press a feedback screen showed to the subjects their win or loss for the current trial, as well as their total balance. Subjects performed two sessions of 72 trials each and received the amount of money of their better performed session.

3.3. fMRI data acquisition and statistical analysis

All MRI scans were performed on a 1.5-T scanner (Magnetom VISION SiemensVR) equipped with a standard circularly polarized 4-channel head coil using gradient echo-echo planar imaging (EPI) sequence using the following common parameters: repetition time (TR): 2,3s., echo time (TE): 40ms., matrix 64X64, flip angle 90°.

The acquired data was initially corrected for differences in slice time acquisition, followed by realignment of the first volume, spatial normalization to the standard EPI template of the Montreal Neurological Institute (MNI template) and smoothing with a 8mm full width at half maximum Gaussian Kernel. The preprocessed data was analyzed with General Linear Model (GLM) using a parametric modulation approach as implemented in SPM (Statistical Parametric Mapping, SPM2 for the first study and SPM5 for the other studies) for condition and subject effects. Parametric designs provide information about the correlation between a stimulus (or more) and the following BOLD response.

Study 1: Second level random effects analysis, was analyzed with t-tests. We applied a Small Volume Correction (SVC; $p<0.05$) in our a-priori regions of interest in both amygdalae. Statistical parametric maps for both regions of interest for different contrasts were estimated. A mood coefficient was generated by subtracting irritable mood subscores from euphoric mood sub scores of YMRS. Single subject parameter estimates were correlated with this mood coefficient of each subject in order to test a correlation between YMRS scores and BOLD signals.

Study 2: In order to investigate the effect of valence, magnitude and their interaction (expected value) on BOLD signal, independent of cue processing, one cue onset regressor and three parametric regressors were defined. This parametric approach allows including all cue conditions in one (onset) regressor and studying the effects of valence, magnitude and expected value independent of each other. The feedback period was modeled as a regressor of no interest. The parametric, cue onset and no interest regressors were convolved with a hemodynamic response

function (hrf) provided by SPM5. Parametric regressors were used to create individual SPM maps for the defined factors, which then went through a second-level random effect analysis with the help of t-test. For our regions of interest (ventral striatum, medial prefrontal and orbitofrontal cortex) we used $p < 0.001$, uncorrected and voxel size (k=5) as threshold. The data of remitted patients were in the same manner compared with healthy controls. Effect of psychotropic medication was investigated in two ways. First manic patients taking (n=10) and not taking (n=5) medication were compared as two groups. Second analysis required converting all antipsychotic medication doses to their chlorpromazine equivalent and correlation analysis with parameter estimates.

Study 3: As in the previous studies using SPM, nine conditions according to valence and phase (anticipation, perception) were defined and second level random effect analysis were done using two sample t- tests ($p < 0.001$, uncorrected, $k > 10$ voxels). Parametrical maps were estimated for relevant contrasts. Beck Depression Inventory (BDI) scores were correlated with BOLD signals for different contrasts using the Pearson's linear correlation coefficients.

4. Results

Study 1

Behavioral Results

Manic patients had higher valence ratings for positive [$F(1,16) = 11.1$, $p = 0.005$] and neutral [$F(1,16) = 6.3$, $p = 0.024$] pictures but not for negative stimuli compared to controls [$F(1,16) = 0.4$, n.s.]. There were no other significant differences observed in reaction times (the subjects were instructed to confirm having seen the picture with a button press), or emotional intensity ratings between the two groups.

fMRI results

The comparison analyses in the group comparison manic > healthy and in the contrast positive > negative stimulus revealed a significant activation in the left amygdala resulting from a larger signal increase during exposure to positive pictures but not any other effect. Furthermore this activation in the left amygdala during positive picture perception was correlated with YMRS scores i.e. with euphoric mood coefficients.

Study 2

Behavioral results

Reaction times for the button press revealed no significant differences between expected value (F=1,4, n.s.) group (F=0,3, n.s.) or their interaction (F=1,6, n.s.) showing a similar attentional load between groups and conditions.

fMRI results

The BOLD signals associated with the magnitude of the incentive cue revealed no differences of activation. Both groups showed activations in expected brain regions, i.e. manic patients did not show a disturbance in activating reward related circuitry. Comparison of valence revealed an activation difference in right posterior cingulate adjacent to cuneus (BA 30, peaking at [x = 21, y = -66, z = 3]; T = 3.83) in healthy subjects, but not in manic patients. The BOLD signals associated with the expected value (i.e. magnitude – by – valence interaction) in left lateral OFC showed for manic patients stronger responses to increasing gain cues and weaker responses to increasing loss cues. The differentiation tended to normalize with remission and was not related to psychotropic medication.

Study 3

Behavioral results

The depressed patient group had longer reaction times for negative pictures (M= 1,20 s., S.D.= 0,28s. compared to control subjects (M=1,00s.,S.D.=0,30s., t=2.03, p=0.05)and higher intensity ratings (M = 4,89, S.D. = 1,32) also compared with healthy controls (M = 4,04 S.D. = 1,61) for negative pictures.

fMRI results

The comparison analyses in healthy subjects > depressive patients showed in both conditions (i.e. anticipation of positive and negative pictures) activation differences. In the first condition left lateral PFC (BA 44, $p < 0.05$) and in the latter right OFC (BA 47, $p < 0.001$ uncorrected) were significantly activated in healthy subjects but not in patients. There was a negative correlation between the depression severity and aforementioned activations. The BOLD signals acquired during the perception of the pictures in these regions were not different between the

groups, suggesting a specific activation of these brain regions during anticipation but not perception of the stimulus.

5. Discussion

The presented studies investigate the perception and anticipation of different emotional conditions in manic and depressed patients. The first and the second study investigated patients in a manic phase, the third study dealt with medication-free depressive patients.

Current models of bipolar disorder suggest a dysfunction of a cortico - limbic circuitry leading to disruptions of mood and affect modulation. The amygdala is suggested to play a modulating role in this circuitry by evaluating the affective input and regulating complex socioemotional outputs. The first study revealed an increased activation of left amygdala with positive but not negative stimuli. This finding is supported by the behavioral ratings showing that manic patients had higher valence ratings for positive and neutral pictures compared to healthy controls but not for negative pictures. The lack of activation for negative stimuli might be seen at first glance as contradictory to some earlier findings (32). However, our paradigm did not specifically include fearful stimuli in the negative emotion condition, which was the case in earlier studies and this may explain our divergent results. Furthermore, the behavioral ratings showed no differences in arousal ratings, making it likely that the detected activation in the left amygdala is specific to the perception of positive valence. Our paradigm has first the advantage that is easy to understand and perform (which is critical for manic patients who often show attentional deficits), and second, that it is largely independent of additional cognitive processes (in relation to the social stimuli), especially executive functions, which have been found to be impaired in mania (33). Sustained attention of patients to the stimuli during the scanning was confirmed by no reaction time differences between groups. A crucial and novel finding of the first study is the positive correlation of symptom severity and the left amygdala activation, which is a strong evidence for a mood congruent bias of emotion processing in manic patients. If amygdala hyperactivation is per se the main pathology, or if it is a compensatory reaction to a failure in cortico-limbic circuitry remains to be answered by future studies.

The second study investigated reward and punishment anticipation in manic patients based on monetary gain or loss. In healthy subjects lateral OFC is activated with increasing loss anticipation, during evaluation and possibly reversal of a behavior, encoding new expectations about punishment. Increasing number of studies conducted in healthy individuals as well as

primates delineate that the activity in the medial part of the OFC is related to monitoring, learning, and memory of the reward value of reinforcement. Activity in the lateral OFC is related to the evaluation of punishment, which may lead to a change in ongoing behavior(34, 35). Subjects with greater volume in this area have been found to score higher on Machiavellian personality traits (36) and activity in this region has generally been connected with Machiavellian thinking (37). Our study design allowed us to separately investigate the effect of valence (gain or loss), magnitude (0.10, 0.60, 3.00 EUR) and their interaction (i.e. expected value). In contrast to other studies applying MID task in various psychiatric diseases (schizophrenia, alcohol addiction, depression, ADHD), manic patients in our study showed increasing activation in ventral striatum with increasing magnitude of incentive cues, and that like healthy subjects regardless of the valence of the cue.

During loss expectation, manic patients showed decreasing lateral OFC responses with increasing loss magnitude, i.e., an activation pattern opposite to that found in healthy individuals. Furthermore, activation of OFC during gain expectation, in manic patients increased with magnitude, which is also the opposite of the activation pattern seen in healthy subjects. This altered activation pattern of lateral OFC can be an explanation of impaired evaluation and modulation of behaviour in manic patients. Taking into consideration the regular activation in ventralstriatum -which was not significantly different than healthy subjects- this finding leads us more to a disruption of integration of expected magnitude and valence i.e. expected value, in lateral OFC. This is a key finding in accordance with previous studies (38) showing a disruption of decision-making and unrealistic outcome expectation in manic patients, extending the current knowledge to an altered representation of expected value in lateral OFC rather than a malfunction of ventral striatum.

Although the sample size was modest (n=7), manic patients who were rescanned after remission showed normalization in their activation pattern. There are studies providing similar evidence, supporting the alterations to be specific to manic state (39) as well as contrary evidence, supporting abnormal OFC responses also in euthymic state (40). This controversial situation is likely to depend on the highly complex functional organization of subregions of the OFC and the applied task i.e. paradigm. In both studies the sample size was relatively small, as it is the case in most imaging studies due to understandable practical difficulties of scanning manic patients. The most important limitation of both studies was that, scanned patients received psychotropic medication at the time of recruitment. Although antipsychotics and mood stabilizers are shown to weaken the BOLD response (41) we still observed in the first study stronger activation in left

amygdala, which makes it unlikely that our results are due to unspecific medication effects. Additionally seven rescanned patients in the second study were at the time of second scanning still receiving medication and showed a normalization of their activation. That allows us to postulate a negligible effect of medication, which is also supported by a recent review showing that the neuroimaging results in bipolar disorder are not significantly affected by medication (42, 43). Still though, confounding effect of medication can only be excluded in future studies with first episode manic patients, if possible without any medication in their history.

The medication effect could be excluded in our third study, since we recruited medication free patients with a depressive episode. Our hypothesis predicted weakened responses to positive and enhanced responses to negative anticipation in the PFC based on the existing research, which suggests a negative bias of emotion processing in depressed patients. Confirming our hypothesis, depressed patients indeed showed attenuated activation during expectancy of positive stimuli in left lateral PFC compared to healthy subjects. The observed activation in this region in healthy subjects confirms the existing data showing the role of left inferior frontal gyrus in positive expectancy of pictorial stimuli (13). Attenuated activation of depressed patients can also be explained by reduced appetitive motivation. Contrasting to our hypothesis depressed patients did not show enhanced but weakened BOLD responses in right lateral OFC during negative stimuli anticipation. This attenuation was correlated with depressive symptom severity and was observed during the anticipation but not the perception of the stimuli.

The activation of this region during negative expectancy in healthy subjects is confirmative of previous findings (44), but the lack of activation in depressed patients is a novel finding. Emotion context insensitivity theory (ECI) is a relatively new but rapidly emerging concept, which delivers a plausible explanation to our finding. The ECI theory derived from the discrepancies of positive attenuation and negative potentiation theories of depression. It can be seen as a new dimension to both aforementioned approaches, with its anthropological roots. According to this theory depression has a function to bias an organism against action, as a response to aversive situations like famine. Regression and withdrawal from motivated activity cause non-responsiveness both to positive and negative stimuli, but help the organism to survive (45). Our results also suggest a context insensitive (both to negative and positive stimuli) attenuation of emotional anticipation in medication free depressed patients.

Conclusions

All three presented studies (second study being the first research to use MID task in manic patients) demonstrate various important results. The role of amygdala hyperactivation might be an explanation for clinical symptoms during mania, such as mood and affect dysregulation. Future research is needed to determine if this is a cause or a consequence of another dysfunction in emotion processing. Likewise the highly complex functional network of orbitofrontal cortex requires to be further investigated, preferably in medication free first episode manic patients. Understanding the neural basis and related clinical symptoms have made a so-called tailor made treatment of depressive disorders possible. Our research does not only support the development of a similar approach in mania, but also provides evidence to newly developed theories like ECI in depression.

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Eidesstattliche Versicherung

„Ich, Ali Umut Dalanay, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: "Emotion and Anticipation Processing Bias in Manic and Depressive Patients - three Functional Magnetic Resonance Imaging (fMRI) Studies" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum 18.12.2014 _____ Unterschrift

<u>Anteilserklärung an den erfolgten Publikationen</u>

Ali Umut Dalanay hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Bermpohl, F*.& Dalanay, U*. & Kahnt, T. & Sajonz, B. & Heimann, H. & Ricken, R. & Stoy, M &.Hägele, C. & Schlagenhauf, F. & Adli, M.& Wrase, J. & Ströhle, A & Heinz, A.& Bauer, M.. " A preliminary study of increased amygdala activation to positive affective stimuli in mania" Bipolar Disorders, (2009, 1/11), pp. 70-75
*These authors contributes equally to the study

Durchführung alle MRI Messungen der Patienten sowie den gesunden Probanden, Vorbereitung der Daten, Durchführung der Verhaltenstests, SPM Analyse der erhobenen Daten, Verfassung der Publikation.

Publikation 2: Bermpohl, F. & Kahnt, T. & Dalanay, U. & Hägele, C. & Sajonz, B. & Wegner, T. & Stoy, M. & Adli, M. & Krüger, S. & Wrase, J. Ströhle, A. Bauer M, & Heinz, A., "Altered Representation of Expected Value in the Orbitofrontal Cortex in Mania" Human Brain Mapping (2010 / 31), pp.958-969

Alle MRI Messungen der Patienten sowie den gesunden Probanden, Vorbereitung der Daten, Durchführung der Verhaltenstests, SPM Analyse der erhobenen Daten, Verfassung der Publikation.

Publikation 3: Feeser, M. & Schlagenhauf, F. & Sterzer P. & Park, S. & Stoy, M. & Gutwinski, S. & Dalanay, U.& Kienast, T. & Bauer, M. & Heinz, A. & Ströhle, A. & Bermpohl, F. " Context insensitivity during positive and negative emotional expectancy in depression assessed with functional magnetic resonance imaging" Psychiatry Research : Neuroimaging (2013 / 212), pp.28-35

Teilnahme an MRI Messungen der Patienten sowie gesunden Probanden, Vorbereitung der erhobenen Daten, SPM Analyse der erhobenen Daten, Teilnahme an Verfassung der Publikation

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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1) A preliminary study of increased amygdala activation to positive affective stimuli in mania.

Bermpohl F1, Dalanay U, Kahnt T, Sajonz B, Heimann H, Ricken R, Stoy M, Hägele C, Schlagenhauf F, Adli M, Wrase J, Ströhle A, Heinz A, Bauer M.

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2) Altered representation of expected value in the orbitofrontal cortex in mania.

Bermpohl F1, Kahnt T, Dalanay U, Hägele C, Sajonz B, Wegner T, Stoy M, Adli M, Krüger S, Wrase J, Ströhle A, Bauer M, Heinz A.

Hum Brain Mapp. 2010 Jul;31(7):958-69.

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3) Context insensitivity during positive and negative emotional expectancy in depression assessed with functional magnetic resonance imaging.

Feeser M1, Schlagenhauf F, Sterzer P, Park S, Stoy M, Gutwinski S, Dalanay U, Kienast T, Bauer M, Heinz A, Ströhle A, Bermpohl F.

Psychiatry Res. 2013 Apr 30;212(1):28-35.

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Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

Complete list of publications

1) Bermpohl, F*. & Dalanay, U*. & Kahnt, T. & Sajonz, B. & Heimann, H. & Ricken, R. & Stoy, M &.Hägele, C. & Schlagenhauf, F. & Adli, M.& Wrase, J. & Ströhle, A & Heinz, A.& Bauer, M.. "A preliminary study of increased amygdala activation to positive affective stimuli in mania" Bipolar Disorders, (2009, 1/11), pp. 70-75 (IF: 4.888)
*These authors contributed egually to the study

2) Bermpohl, F. & Kahnt, T. & Dalanay, U. & Hägele, C. & Sajonz, B. & Wegner, T. & Stoy, M. & Adli, M. & Krüger, S. & Wrase, J. Ströhle, A. Bauer M, & Heinz, A., "Altered Representation of Expected Value in the Orbitofrontal Cortex in Mania" Human Brain Mapping (2010 / 31), pp.958-969 (IF: 6.924)

3) Feeser, M. & Schlagenhauf, F. & Sterzer P. & Park, S. & Stoy, M. & Gutwinski, S. & Dalanay, U.& Kienast, T. & Bauer, M. & Heinz, A. & Ströhle, A. & Bermpohl, F. " Context insensitivity during positive and negative emotional expectancy in depression assessed with functional magnetic resonance imaging" Psychiatry Research : Neuroimaging (2013 / 212), pp.28-35 (IF: 2.831)