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Research paper

Affective responses across psychiatric disorders—A dimensional approach

Claudia Hägele[a,*], Eva Friedel[a], Florian Schlagenhauf[a,b], Philipp Sterzer[a,c], Anne Beck[a], Felix Bermpohl[a,c], Meline Stoy[a], Dada Held-Poschardt[a], André Wittmann[a], Andreas Ströhle[a,c], Andreas Heinz[a,c]

[a] Department of Psychiatry and Psychotherapy, Charité–Universitätsmedizin, Campus Mitte, Berlin, Germany
[b] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[c] Berlin School of Mind and Brain, Germany

HIGHLIGHTS

- We assessed emotion processing across nosological boundaries mental disorders.
- Pleasant stimuli activated the ventromedial prefrontal cortex across all subjects.
- Aversive stimuli activated the left amygdala across all subjects.
- We did not find significant group differences or a clear dimensional correlate.

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ABSTRACT

Studying psychiatric disorders across nosological boundaries aims at a better understanding of mental disorders by identifying comprehensive signatures of core symptoms. Here, we studied neurobiological correlates of emotion processing in several major psychiatric disorders. We assessed differences between diagnostic groups, and investigated whether there is a psychopathological correlate of emotion processing that transcends disorder categories. 135 patient with psychiatric disorders (alcohol dependence, n = 29; schizophrenia, n = 37; major depressive disorder (MDD), n = 25; acute manic episode of bipolar disorder, n = 12; panic disorder, n = 12, attention deficit/hyperactivity disorder (ADHD), n = 20) and healthy controls (n = 40) underwent an functional magnetic resonance imaging (fMRI) experiment with affectively positive, aversive and neutral pictures from the International Affective Picture System (IAPS). Between-group differences were assessed with full-factorial ANOVAs, with age, gender and smoking habits as covariates. Self-ratings of depressed mood and anxiety were correlated with activation clusters showing significant stimulus-evoked fMRI activation. Furthermore, we examined functional connectivity with the amygdala as seed region during the processing of aversive pictures. During the presentation of pleasant stimuli, we observed across all subjects significant activation of the ventromedial prefrontal cortex (vmPFC), bilateral middle temporal gyrus and right precuneus, while a significant activation of the left amygdala and the bilateral middle temporal gyrus was found during the presentation of aversive stimuli. We did neither find any significant interaction with diagnostic group, nor any correlation with depression and anxiety scores at the activated clusters or with amygdala connectivity. Positive and aversive IAPS-stimuli were consistently processed in limbic and prefrontal brain areas, irrespective of diagnostic category. A dimensional correlate of these neural activation patterns was not found.

Abbreviations: ANOVA, analysis of variance; ADHD, attention deficit/hyperactivity disorder; BDI, Beck Depression Inventory; BOLD, blood oxygen level-dependent; BA, Brodman area; FWE, family-wise error; fMRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; MDD, major depressive disorder; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; PPI, psychophysiological interaction; RDoC, Research Domain Criteria; ROI, region of interest; STAI, State-Trait Anxiety Inventory; SCID, Structured Clinical Interview for DSM-IV disorders; vlPFC, ventro-lateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VS, ventral striatum.

* Corresponding author at: Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charitéplatz 1, D-10117 Berlin, Germany.
E-mail address: claudia.haegele@charite.de (C. Hägele).

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1. Introduction

A dimensional approach in psychiatry was suggested e.g. by the Research Domain Criteria (RDoC) project [20,43] aiming at a better understanding and treatment of psychiatric disorders by investigating neurobiological signatures across nosological boundaries [44,74]. Clinical categories such as schizophrenia or major depressive disorder lack distinct biological trait markers [5,6,48] and diagnoses rely on a pattern of symptoms [38,74,93]. Therefore, the separation of disorders into dimensional components – comparable to the approach in somatic disorders [39,88] – and studying these single dimensions, e.g. hallucinations or anhedonia which are relevant in schizophrenia as well as affective disorders, can link distinct brain (dys)function with certain symptom dimensions, thus facilitating a better understanding of neural substrates of these symptoms (exemplary, for review on schizophrenia, see Goghari et al., 2010 [32]). Furthermore, single mechanisms of these disorders such as reward learning transcend diagnostic categories and are found in varying degrees of severity in many psychiatric disorders [20,39,72,75]. A *transdiagnostic* study of a particular dimension (e.g. learning from reinforcement or emotion processing) may further enhance the understanding of the underlying mechanisms [17,43,72]. On the other hand, a pure neurobiological perspective of single symptoms could be too distant from the clinical phenomena physicians and patients have to deal with on a daily basis, and it might be possible that some of the dimensions have different nuances and neurobiological correlates that mirror existing diagnostic categories [50]. A combination of diagnostic categorical and dimensional approaches might therefore be most promising in order to identify neurobiological signatures of core symptoms within and across psychiatric disorders.

In accordance with these hypotheses, two recent studies by Bebko et al. and our own group observed that reward processing is impaired in a cluster of disorders – with distinct differences between these disorders – and dimensionally correlates with mood states in adolescents and adults across nosological boundaries [11,33]. In addition, Bebko et al. also observed that patterns of resting state connectivity correlate with affective dimensions such as mania and depression [10]. Resting state connectivity provides information of neural networks free of specific challenges such as cognitive tasks [10]. With respect to task-specific activations, it was observed that blunted activation of the ventral striatum (VS) elicited by reward anticipation was associated with depressive mood (but not anxiety) across nosological boundaries [33]. Anxiety may be closer related to emotion processing in the limbic system, most prominently the amygdala, and its serotonergic modulation [22,36,42,70]. Therefore, processing of affectively aversive stimuli and its underlying neurobiological mechanisms might be another dimension worth studying within and across disease categories.

Emotion processing has been studied thoroughly; and the regions consistently and strongly associated with positive and negative emotion processing are the amygdala, the hippocampus and parahippocampus, the VS, the ventrolateral prefrontal cortex (vlPFC) and ventromedial PFC (vmPFC), the insula and the orbitofrontal cortex (OFC) [16,65,68,71,78,89]. The amygdala appears to play a central role in emotion processing [15,60,64], and this was reported to be the case for positive as well as aversive emotional cues [63,78,92]. Many studies have used emotional valenced facial stimuli to compare processing of different emotional states, and taken together, found activation of the same brain regions (e.g. the amygdala, the gyrus fusiforme) during different emotional states, though intensities may have varied (meta-analysis of 105 studies [28]). Only a few studies compared positive and negative emotional states using the pictures from the International Affective Picture System (IAPS) [49]. IAPS pictures might elicit smaller responses and recruit a smaller network than faces, but have been found to activate the same regions [16,37,78].

When comparing processing of affective pictures in adults between psychiatric disorders and healthy controls, activation elicited by positive and aversive pictures seemed to be affected differently (for corresponding table, please see supplement):

In one of two fMRI studies on *alcohol dependence*, patients showed more activation to aversive than to positive cues, and more activation to aversive cues than controls, and an overall stronger activation in the amygdala [30]. In the other study on alcohol dependence [41], patients also showed more activation of the PFC (Brodman area (BA) 10) during the presentation of aversive pictures compared to healthy controls; surprisingly, they also showed more activation to positive stimuli in the anterior cingulate cortex, BA 10 and VS, which appeared to be a resilience marker and correlated with better treatment outcome.

The four functional magnetic resonance imaging (fMRI) studies comparing positive and aversive picture processing between patients with *schizophrenia* and healthy controls (including two positron emission tomography (PET) studies) found patterns of hypo- as well as hyperactivation in patients, most prominently, but not restricted to the amygdala [57,58,82,83].

In patients with *major depressive disorder* (*MDD)* or *dysthymia*, four of five fMRI studies found an increased activation during the presentation of aversive pictures in patients compared to controls in the amygdala and further limbic and prefrontal areas [2,69,73,91]. One study found an attenuated response of the BA 10 in patients [27].

Two fMRI studies assessed processing of IAPS pictures in euthymic [77] and manic patients [13] with *bipolar disorder*. In acute mania, patients showed stronger activation during the presentation of positive pictures in the amygdala [13], whereas euthymic patients (and their healthy siblings) showed stronger activation in the left insula when processing aversive pictures [77].

In the only fMRI study in patients with untreated *Attention deficit/hyperactivity disorder* (*ADHD)*, patients showed an attenuated response to aversive as well as positive pictures in the subgenual cingulate and the VS [76].

So far, there was no fMRI study on patients with *panic disorder* using the IAPS-task.

Very few studies have used the IAPS pictures during emotion induction tasks (excluding studies using IAPS-pictures during cognitive tasks e.g. in working memory) to assess functional connectivity, and these studies only report using aversive pictures: In patients with *MDD*, two studies found decreased cortico-limbic correlation [2] and decreased amygdala-insula/medial PFC correlation in adolescents [59], respectively. Additionally, Friedel et al. [27] reported a genotype-depending increase of BA10-amygdala coupling in healthy controls, whereas patients with MDD showed a reverse pattern. A study on patients with bipolar disorder [18] compared manic and depressive episodes of these longitudinally: During a manic episode, the right amygdala was positively correlated with the left inferior frontal gyrus, whereas it was positively correlated with the right insula during a depressive episode. In schizophrenia, a reduced negative correlation between amygdala and PFC was reported [3].

Taken together, most studies using the IAPS-task to compare emotion processing in psychiatric disorders with healthy controls found elevated limbic and prefrontal blood oxygen level-dependent (BOLD) responses in patients, mainly during negative emotion processing, and attenuated amygdala-prefrontal connectivity. To the best of our knowledge, no fMRI-study so far compared different disorders directly. Our own group had studied emotion processing in patients with alcohol dependence, schizophrenia, MDD, acute manic episode in bipolar disorder, ADHD [13,27,41,57,73,76] and panic disorder (unpublished data),