Aus der Klinik für Psychiatrie und Psychotherapie
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DISSERTATION

Limbic-cortical imbalance as intermediate phenotype of depression – investigation of a familial risk sample

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Abstract

Background: An established neurobiological model of negatively biased emotion processing in depression is the limbic-cortical imbalance model: limbic and ventral-prefrontal regions, including the amygdala, detecting threat and initiating automatic responses, are hyper-activated, while dorsal-cortical regions, controlling voluntary behavior, are hypo-activated; In addition, the functional connectivity (FC) of limbic areas with ventral prefrontal regions is increased, while it is decreased with dorsal-cortical regions. Findings of limbic-cortical imbalance in genetic risk for depression suggest that this pattern represents an intermediate phenotype (IP) and thus a potential target for preventive and therapeutic interventions. In this study, we examined an important criterion for an IP: its higher expression in non-affected relatives of patients with depression.

Methods: We examined 70 healthy first-degree relatives of patients with depression and 70 control subjects comparable for age, sex, years of education, and subclinical depressive measures. During an implicit emotion processing task, which required participants to match stimuli containing angry or fearful faces (emotion condition) or geometric shapes (control condition), brain activity and amygdala FC were assessed using functional magnetic resonance imaging (fMRI). The measures were assessed for effects of condition and group-by-condition interactions and examined for correlations with negative affectivity.

Results: The groups did not differ in brain activity. Amygdala FC was increased in relatives compared to controls with ventral prefrontal areas, while it was decreased with dorsal prefrontal regions. Stronger amygdala FC with the perigenual anterior cingulate cortex and the medial prefrontal gyrus were associated with lower negative affectivity. In relatives compared to controls, amygdala FC with ventral prefrontal areas was stronger context-modulated, while it was less strongly modulated in the dorsal prefrontal cortex.

Discussion: Altered brain activity could not be confirmed as an IP. Reduced amygdala FC with the dorsal prefrontal cortex might present a vulnerability marker, which might be compensated by increased amygdala-perigenual FC. Increased task-dependent modulations with ventral prefrontal regions and decreased modulations in dorsal prefrontal regions might facilitate an intensified automatic processing of negative emotional stimuli. The findings should be examined for reproducibility and complemented

by direct comparisons between risk, patient and control groups, prospective studies, and complementary measures of brain connectivity.
Conclusion: The validity criterion of an IP to be higher expressed in first-degree relatives could not be confirmed for an imbalance of limbic-cortical *activation*, but for an imbalance of limbic-cortical *connectivity*.

Zusammenfassung

Hintergrund: Eine etabliertes neurobiologisches Modell der Depression erklärt die Tendenz, negative emotionale Reize intensiver zu verarbeiten, anhand eines limbisch-kortikalen Ungleichgewichts: limbische und ventral-präfrontale Regionen, darunter die Amygdala, die Gefahr entdeckt und automatische Reaktionen initiiert, sind überaktiviert, während dorsal-kortikale Regionen, zuständig für die Handlungskontrolle, unteraktiviert sind; zudem sind limbische Areale mit ventral-kortikalen Regionen stärker, und mit dorsal-kortikalen Regionen schwächer funktionell verbunden. Befunde limbisch-kortikalen Ungleichgewichts bei genetischem Risiko für Depression legen nahe, dass dieses Muster einen *intermediären Phänotyp* (IP) darstellt, und somit einen wichtigen Ansatzpunkt für präventive und therapeutische Interventionen. In dieser Studie haben wir ein Validitätskriterium für einen IP untersucht: seine höhere Ausprägung bei nicht-depressiven Verwandten von Depressionspatienten.

Methoden: Es wurden 70 gesunde Verwandten ersten Grades von Depressionspatienten und 70 Kontrollpersonen untersucht, die in Alter, Geschlecht, Bildungsjahren, und subklinischen Depressivitätsmaßen vergleichbar waren. Während einer Aufgabe zur *impliziten Emotionsverarbeitung*, in der Probanden entweder wütende und ängstliche Gesichter (Emotionsbedingung) oder geometrische Formen (Kontrollbedingung) zuordneten, wurden mittels funktioneller Magnetresonanztomographie Gehirnaktivität und Amygdalakonnektivität (AK) ermittelt. Diese Maße wurden zwischen den Gruppen verglichen und auf Zusammenhänge mit negativer Affektivität untersucht.

Ergebnisse: Die Gruppen unterschieden sich nicht in der Gehirnaktivität. Die AK war in der Risikogruppe mit perigenual-präfrontalen Arealen erhöht und mit dorsal-kortikal-präfrontalen Regionen verringert. Eine höhere AK mit sowohl perigenualen als auch dorsal-präfrontalen Regionen ging mit geringerer negativer Affektivität einher. In der Risikogruppe war die AK mit ventral-präfrontalen Arealen stärker, mit dem dorsalen präfrontalen Kortex weniger stark durch den Aufgabenkontext moduliert.

Diskussion: Veränderte *Hirnaktivität* ließ sich nicht als IP bestätigen. Verringerte Amygdala-dorsale Konnektivität bei Verwandten lässt sich als Vulnerabilitätsmarker interpretieren, der durch erhöhte Amygdala-perigenuale Konnektivität kompensiert wird. Veränderte kontextabhängige AK in der Risikogruppe wird als intensivierte automatische Verarbeitung negativer emotionaler Reize diskutiert. Die Befunde sollten auf Reproduzierbarkeit untersucht und durch komplementäre Untersuchungen, z.B. direkte

Vergleiche zwischen Risiko-, Patienten- und Kontrollgruppen, prospektive Studien und alternative Konnektivitätsmaße ergänzt werden.

Fazit: Das hier geprüfte Validitätskriterium für einen IP konnte für ein Ungleichgewicht der limbisch-kortikalen *Aktivität* nicht bestätigt werden, wohl aber für eine Dysbalance der limbisch-kortikalen *Konnektivität*.

Introduction

Feeling sad. Not wanting or liking to do anything. Feeling out of energy. Having trouble sleeping or sleeping excessively without feeling rested. Losing appetite or eating boundlessly without feeling fed. Being restlessly agitated or heavily slowing down. Having trouble concentrating or to make the simplest decisions. Perceiving oneself as worthless or guilty. Being tired of life, wishing to be dead.

The burden of depression

Having at least four of these symptoms (if at least two of them are among the first three) for two weeks in a row is defined as a depressive episode[1] by the World Health Organization (WHO) in the International Classification of Diseases (ICD-10, World Health Organization, 1992). Its severity is scaled according to the number of present symptoms; a severe depressive episode is given with at least seven symptoms, including loss of self-esteem or ideas of guilt or worthlessness or suicidal thoughts, of which several are experienced as distressing. Severe depressive episodes can be accompanied by psychotic symptoms such as delusions, hallucinations, or stupor, that can impair social activities and that can put the affected person in danger of life.

In Germany, one in eight people suffers from major depressive disorder (MDD) at least once in their lifetime; in the USA it is one in six (Busch et al., 2013; Kessler et al., 2005). The global burden of disease due to depression has significantly increased by 46 percent in the past 30 years (GBD 2016 DALYs and HALE Collaborators, 2017) and is predicted by the WHO to become the leading cause of the disease burden in developed regions in 2020 (World Health Organization, 2002, p. 30). A serious problem is the limited efficacy of available treatment options. Only 30-40 percent of patients can obtain complete remission, while 30-50 percent do not respond to an antidepressant medication, and about 20 percent continue to suffer from depression for up to two years after its first onset (Trevino et al., 2014). For about 15 percent of patients, the disorder takes a chronic, *treatment-resistant* course, and one in thirteen patients with treatment-resistant depression commits suicide (Bergfeld et al., 2018; Bostwick and Pankratz, 2000; Reutfors et al., 2018).

[1] In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), loss of energy is listed only as a side symptom, and at least five symptoms (with at least one of them being depressed mood or loss of interest/pleasure) are required for a major depressive disorder (American Psychiatric Association, 2000).

The limbic-cortical imbalance model

To develop more effective interventions for depression, we need to refine our understanding of its pathogenesis. In order to do so systematically, it is helpful to subdivide its heterogeneous and complex clinical picture into dimensions of mental functioning, and to investigate those on biological, cognitive, and behavioral levels (Insel et al., 2010). A dimension that is normally distributed in the population and strongly pronounced in depression is *negative affectivity*, the disposition to experience unpleasant or painful emotional states such as "nervousness, tension, and worry, (…) anger, scorn, revulsion, guilt, self-dissatisfaction, a sense of rejection, and sadness" (Watson and Clark, 1984, p. 465). Negative affectivity goes along with negative *cognitive schemata* about the self and the environment (Beck, 1987), and is a risk factor for depression (Bernardini et al., 2017; Jeronimus et al., 2016). On the behavioral level, negative affectivity has been associated with the *negative emotional bias*, that is, a pronounced response towards negative emotional stimuli in psychological tasks that require attention, memory, and interpretation (Mathews and MacLeod, 2005). For example, in a forced-choice dot-probe task[2], participants with high negative affectivity responded faster to a stimulus presented on a threatening face than to one presented on a neutral face (Bradley et al., 1998).

A proposed neurobiological mechanism of negative affectivity is limbic-cortical-imbalance. It has been introduced as a "working model" by Helen Mayberg more than twenty years ago (1997, p. 471) and has since been one of the most widely studied and well-established theories of emotion processing in neuroscience. Using positron emission tomography (PET), a technique to visualize the blood flow that occurs in context of the neural metabolism, Mayberg had observed a dorsal-ventral imbalance in healthy participants who were induced with a sad mood state[3] as well as in depressed patients: blood flow was increased in ventral limbic and paralimbic regions (amygdala, hypothalamus, hippocampus, ventral insula, ventral prefrontal cortex and subgenual cingulate cortex), and decreased in dorsal limbic and neocortical areas (dorsal prefrontal cortex, dorsal and posterior cingulate cortex, and inferior parietal cortex). In a group of

[2] Participants were shown two photographs of faces on a screen, one with a threatening or happy expression, one with a neutral expression. A probe stimulus of two possible types (: or ..) was presented in the location of one of the faces, and the participants were required to indicate the type of probe as quickly as possible while avoiding mistakes.

[3] The sad mood states were provoked using autobiographical scripts of two recent sad personal experiences of the participants, which participants were instructed to recall during PET scanning (Mayberg et al., 1999).

successfully treated patients, these effects were reversed. Given that the dorsal regions were known to be involved in cognitive processes like attention, planning, and abstract reasoning (Dias et al., 1996), and that the ventral regions were known for their critical role in vegetative-automatic processes and their activation during negative mood states (Pardo et al., 1993), Mayberg concluded that negative mood states and insufficient emotion regulation in depression correspond to a disrupted integration of these ventral and dorsal areas. She further proposed that the perigenual anterior cingulate cortex (pgACC) plays a key role in this integration, as it is reciprocally connected to both sites and blood flow in this region predicted treatment response (Mayberg, 1997).

Since the introduction of the model, the majority of neuroimaging studies has been conducted with functional magnetic resonance imaging (fMRI), a technique that, compared to PET, is less expensive, does not rely on a radioactive isotope (which can be unsafe for the participant after repeated use), and has a higher spatial resolution. FMRI indirectly measures neuronal activation through the blood oxygenation level dependent (BOLD), a measure that is coupled to the metabolic activity in brain cells (Logothetis et al., 2001). The technique allows to identify the functional specialization of brain regions as well as their functional integration (Friston, 1994). The latter can be achieved through *functional connectivity* (FC), a measure of the statistical dependencies (most commonly the linear correlations) between the BOLD signal time series of distributed brain regions (Buckholtz and Meyer-Lindenberg, 2012).

Based on results of fMRI studies of brain activation and FC, the cortico-limbic imbalance model has been refined and extended (Disner et al., 2011). According to these extensions, as shown in Figure 1, the negative emotional bias in depression corresponds not only to a hyperactivation of ventral limbic regions (shown in red) and a simultaneous hypoactivation of dorsal cortical regions (shown in blue), but also to their altered FC: On the one hand, FC is increased (indicated by thicker arrows) between the thalamus, which provides visual input, the amygdala, responsible for salience detection and automatic response initiation[4] and the subgenual anterior cingulate cortex (sgACC), responsible autonomic emotional response manifestation (Drevets et al., 2008). On the other hand, FC is reduced (indicated by dotted arrows) between limbic and dorsal prefrontal

[4] The amygdala detects uncertainty in the environment that may be crucial for survival, and responds automatically, even to subliminal stimulation that is not processed with explicit knowledge (Whalen et al., 1998).

structures, responsible for cognitive processing and voluntary control (Ochsner and Gross, 2005).

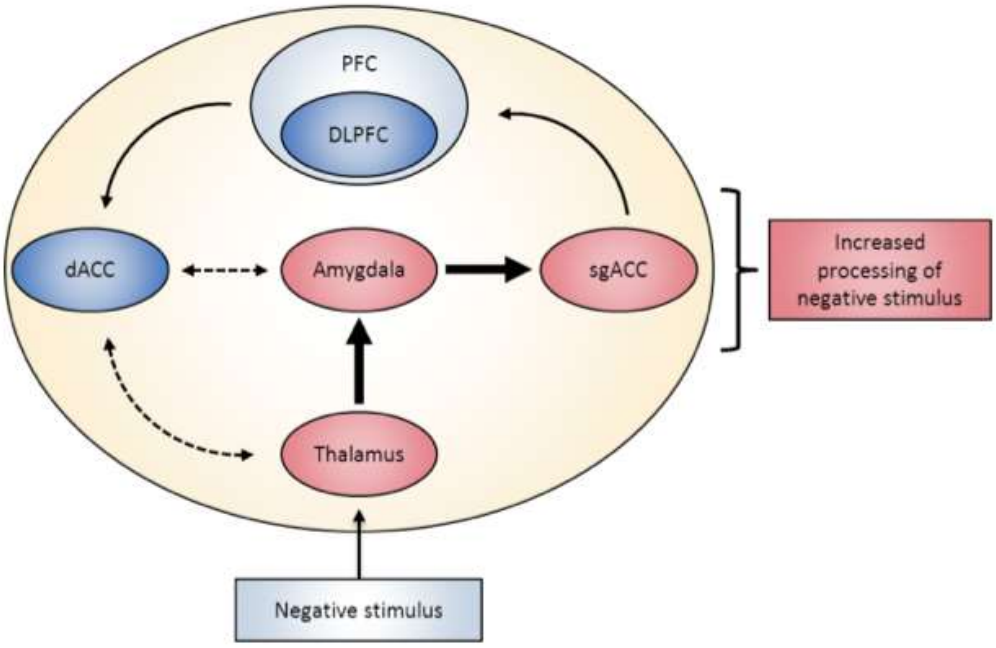

Figure 1. Neural mechanisms of biased emotion processing

Schematic illustration of the refined and extended model of limbic-cortical imbalance in depression. Red colors indicate hyperactivation, blue colors indicate hypoactivation, thicker arrows indicate increased connectivity, dotted arrows indicate reduced connectivity. Abbreviations: dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex; sgACC, subgenual anterior cingulate cortex. The figure is adapted from Disner et al., 2012.

Meta-analyses of fMRI studies support the limbic-cortical imbalance model in patients with depression (Fitzgerald et al., 2008; Graham et al., 2013; Kaiser et al., 2015; Lai, 2014; Sacher et al., 2012; Zhong et al., 2011). However, this does not solve the puzzle of the pathogenesis of the disorder, since limbic-cortical imbalance might be a correlate of the depressed state, a result of the (chronic) disease or its treatment, or a biological vulnerability factor (Kessler et al., 2011). In order to separate depressed state from biological vulnerability, a promising approach is to investigate individuals who are at increased genetic risk for depression but have never been affected by the disorder.

Limbic-cortical imbalance, an intermediate phenotype?

In *imaging genetics* research, aberrant cortico-limbic functioning has been associated with genetic risk for depression in healthy individuals, suggesting it to be an *intermediate phenotype (IP)* (Fornito and Bullmore, 2012; Hasler and Northoff, 2011; Pezawas et al., 2005; Savitz and Drevets, 2009; Scharinger et al., 2011). IPs (Meyer-Lindenberg and Weinberger, 2006), also termed *endophenotypes* (Gottesman and Gould, 2003), are conceptualized as quantitative, reliably measurable biomarkers that mediate between the

genetic predisposition and the behavioral manifestation of a disorder. Per definition of five validity criteria, an IP is associated with the disorder, heritable, state-independent, co-segregated with the disorder within families and found in unaffected family members at a higher rate than in the general population (Gottesman and Gould, 2003).

Hyperactivity of the amygdala and aberrant amygdala-prefrontal FC have been proposed as IPs for genetic depression risk in fMRI studies of the *implicit emotion processing* task[5] (Hariri et al., 2002; Pezawas et al., 2005). During this task, which provokes a strong response of the amygdala, participants are presented with trios of photographs of angry or fearful faces and are instructed to identify the matching pair. Carriers of the short variant of the 5′ promoter region (5-HTTPLR) of the human serotonin[6] (5-HT) transporter gene SLC6A4, which is associated with reduced 5-HT transporter binding in the brain (Heinz et al., 2000), showed a stronger response of the amygdala than the non-risk group. In later studies, the risk variant was associated with altered amygdala FC with the pgACC and the ventromedial PFC (Heinz et al., 2005; Pezawas et al., 2005; Schardt et al., 2010a), suggesting a limbic-cortical imbalance of brain activation and connectivity to be an IP of genetic risk for depression.

Investigation of unaffected first-degree relatives

In the present study, we aimed to test the validity of this proposed IP by investigating it in a familial risk group. Even though the heritability of depression is relatively low (Sullivan et al., 2012), there is robust evidence of its increased familial load (Sullivan et al., 2000), suggesting it to be passed across generations via *familial transmission*, a process involving shared genetic and environmental risk factors, implicit learning of negative cognitive styles, as well as dysfunctional interpersonal interactions (Ulrich et al., 2011). First-degree kinship with a depressed family member is one of the strongest predictors of depression onset (Klein et al., 2013) and meta-analyses report a 2-3-fold increased risk to develop the disorder in first-degree relatives (Li et al., 2008; Sullivan et al., 2000; Wilde et al., 2014).

[5] In contrast, in *explicit emotion processing* tasks, participants are asked to label the presented emotion, which involves more cognitive processing and is associated with an increase of prefrontal activity and a decrease of subcortical limbic activity. It is classified as a process of voluntary emotion regulation, while the implicit processing task is classified as a process of automatic attentional control (Phillips et al., 2008).

[6] Serotonin plays an important role in the pathogenesis of depression, which is assumed from the symptom-reducing effects of serotonin re-uptake inhibitors in depression and anxiety (Nemeroff and Owens, 2002). Serotonin is an important neurotransmitter in limbic-cortical circuits and patients with depression show reduced serotonin receptor expression in limbic, temporal, and occipital regions, and in the ACC (Wang et al., 2016).

So far, familial risk for depression has been investigated only rarely with respect to limbic-cortical functioning, and, to the best of our knowledge, no study has yet assessed implicit emotion processing or limbic-cortical FC in familial risk samples. However, some fMRI studies of familial risk have been conducted, investigating emotional conflict and regulation. Some of these studies reported hyperactivity in ventral limbic and paralimbic emotion processing structures such as the amygdala, insula and the ventral prefrontal cortex (Joormann et al., 2012; Monk et al., 2008; Pilhatsch et al., 2014), and hypoactivity of the dorsal PFC in first-degree relatives of MDD patients (Amico et al., 2012; Joormann et al., 2012; Mannie et al., 2011, 2008), supporting a limbic–cortical imbalance in familial risk. Yet, these studies had relatively small sample sizes (risk group size ranged from n=11-30), reported divergent results, and were focused only at child and adolescent offspring of MDD patients.

Aims and hypotheses

Here, to provide conclusive evidence for the hypothesis that a limbic-cortical functional imbalance is an IP of depression (Hariri et al., 2002; Pezawas et al., 2005), we assessed brain activity and amygdala FC during implicit emotion processing in adult first-degree relatives of MDD patients. To provide conclusive evidence about the implications of amygdala FC for neural mechanisms of emotion processing, we did not only assess FC *across* task conditions, as was done in our study of reference (Pezawas et al., 2005), but also investigated changes of amygdala connectivity *between* the emotion and the control condition. We hypothesized that 1) relatives compared to controls show stronger activity in the amygdala and reduced activity in dorsal limbic and dorsal prefrontal regions and 2) relatives compared to controls show an imbalance of amygdala-prefrontal FC, with increases in ventral, and decreases in dorsal prefrontal regions. We further explored associations between these functional measures and self-reported negative affectivity, tested whether group differences were driven by the type of kinship, and assessed the relationship between amygdala activity and amygdala FC using linear correlations.

Methods

Participants

Seventy adult first-degree relatives of patients with depression and 70 control participants were included in the analyses. Participants were recruited at three cooperating sites, Charité-Universitätsmedizin Berlin, Zentralinstitut für Seelische Gesundheit Mannheim, and Universitätsklinikum Bonn. They were included if they had never experienced a psychiatric disorder[7], did not currently show clinically relevant depression symptoms[8], were native German speakers, and met the requirements to undergo MRI scanning. Relatives were included if they were parent, child, or sibling of a person who had a diagnosis of MDD, and no diagnosis of bipolar disorder, schizophrenia, or substance dependence (except for tobacco)[9]. Controls were included if none of their first-degree relatives had ever had a psychiatric disorder. Participants gave written informed consent, the study was approved by the local ethics committees.

Negative affectivity

Negative affectivity was assessed using self-report inventories of symptoms of state and trait depression and anxiety, the Becks Depression Inventory (BDI-I) (Hautzinger et al., 1994), the depression scale of the Symptom Checklist-90 (SCL-90-R) (Derogatis, 1977), and state anxiety (STAI-S) (Spielberger et al., 1970), NEO-FFI neuroticism (Costa and McCrae, 1992), and trait anxiety (STAI-T) (Spielberger et al., 1970). Based on these measures, a negative affectivity score was computed using factorial analysis in SPSS.

The implicit emotion processing task

Participants completed the implicit emotion processing task for fMRI (Figure 2). They were instructed to identify matching pairs in trios of stimuli. In the emotion condition, the trios contained photographs of angry or fearful faces, counterbalanced for gender and emotion. In the control condition, trios contained shapes (circles, horizontal and vertical ellipses). Four blocks per condition were presented in an alternating order. Each block consisted of an instruction (lasting two seconds) and six trials (lasting five seconds each).

[7] as confirmed by the Screening of the Clinical Interview for DSM (SCID-I, Wittchen et al, 1997), including additional items for depression symptoms.

[8] Becks Depression Inventory (BDI-I) (Hautzinger et al., 1994) > 18

[9] Diagnoses were confirmed using SCID-I (Wittchen et al, 1997), conducted by experienced clinicians, or, in case index patients were unavailable, by medical reports.

The task lasted 274 seconds in total and had the same features as the tasks used in our studies of reference (Hariri et al., 2002; Pezawas et al., 2005).

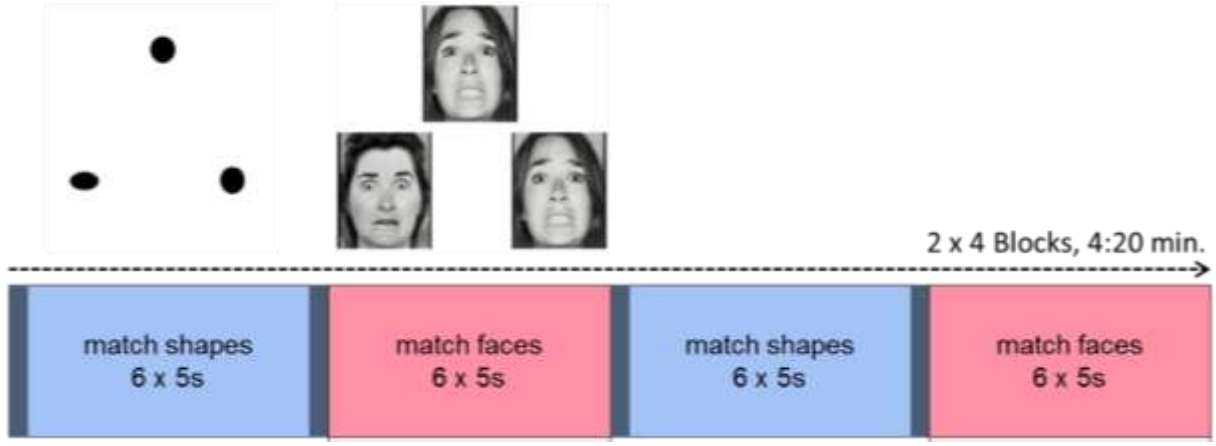

Figure 2. Implicit emotion processing task for fMRI.
Participants are presented with a trio of stimuli and instructed to indicate which one of the objects in the bottom is identical to the object in the top. Four blocks per condition appeared in an alternating order, each containing six trials. For each subject, contrast images of the brain activity and amygdala FC during both conditions were computed and further analyzed in group-level analyses.

MRI acquisition and data processing[10]

MRI was performed at 3T Siemens Trio scanners (Erlangen, Germany) using identical scanning protocols at each site. During the task, 135 whole-head gradient echo planar imaging (EPI) volumes were acquired. Additionally, a field inhomogeneity map was acquired, as well as a T1-weighted anatomical 3D image (for coregistration and normalization purposes), using a magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence with an isotropic spatial resolution of 1 mm^3.

Image processing: Processing of brain images was conducted using the software statistical parametric mapping (SPM)[11]. Images underwent correction for acquisition delay, correction for head motion, unwarping using the field inhomogeneity map, coregistration of the EPI to the individual T1 image, normalization into standard space (3x3x3 mm^3 voxels), and spatial smoothing (8 mm FWHM).

Task-related brain activity: Brain activity and amygdala FC were estimated for each participant in SPM. BOLD signal in each voxel[12] was estimated in a generalized linear model (GLM) that included regressors modeling the task conditions, instructions, button

[10] Technical parameters of image assessment and processing can be found in the original publication.

[11] http://www.fil.ion.ucl.ac.uk/spm/software/spm12

[12] A voxel is the unit in that the three-dimensional image of the brain is built in.

presses, and head motion parameters. Linear contrast images were computed for each task condition ("faces"; "shapes") and entered into group analyses.

Task-related functional connectivity: Amygdala FC was assessed using the generalized psychophysiological interaction approach (gPPI)[13], a method to identify regions in which the temporal correlation (=FC) of BOLD signal with a seed region (physiological factor) is modulated by the experimental context (psychological factor) (Friston et al., 1997). For that purpose, the standard GLM design for statistical interactions is applied to fMRI data: the dependent variable *y* (whole-brain voxel-wise BOLD time course) is modeled by a) a physiological variable *x* (BOLD time course in the seed region), b) a psychological variable *m* (contrast vector representing task conditions) and c) the interaction of *x* and *m* (PPI term). All voxels with significant portions of variance explained by the PPI term significantly differ between task conditions in their correlation strength with the seed region.

In our analyses, for each participant, amygdala FC was assessed both *across* and *between* conditions. As physiological term, time-series were extracted from the right and left amygdala at location of maximum task effect (faces > shapes), which was predominantly (97%) in the basolateral amygdala. As psychological terms, all regressors modeling the task were included. As PPI terms, the psychological term was convolved with the physiological term (right or left amygdala time-series, respectively). Head motion parameters were included as regressors of no interest. Linear contrast images were computed for each amygdala separately: 1) the effect *across* conditions ("PPI faces & PPI shapes"), and 2) the differential effect *between* conditions ("PPI faces > PPI shapes"). The calculated contrast images were entered into group analyses.

Group analyses: We performed analyses of variance for repeated measures (rmANOVAs) for all group analyses. For brain activation, the rmANOVA included the between-subject factor "group" and the within-subject factor "condition". The linear contrast images "activity faces" and "activity shapes" were used as dependent variables. For FC, two rmANOVAs were conducted to assess the FC effects *across* and *between*

[13]The original PPI implementation by Friston et al. (1997) is configured to only detect between-conditions effects of no more than two conditions, which limits the flexibility of analyses and has been criticized to lack power due to collinearity of the task term and the PPI term (O'Reilly et al., 2012). Therefore, we used gPPI (McLaren, Ries, Xu, & Johnson, 2012). It resolves the limitations of standard PPI by allowing to include each task regressor in the model, which enables the assessment of both across and between conditions effects of any number of conditions and thereby increases the specificity and sensitivity of results. We chose gPPI for these reasons and because it has proven the most powerful FC measure especially for block-designed tasks, not only compared to standard PPI but also compared to beta series correlations (Cisler et al., 2014).

conditions. Both analyses included the between-subject factor “group” and the within-subject factor “seed location” (right and left amygdala). For the across conditions analysis, linear contrast images “PPI faces & PPI shapes” were used as dependent variables. For FC effects between conditions, the linear contrasts “PPI faces > PPI shapes” were used. To eliminate task-unspecific between-subject variance, the individual mean over conditions or seed locations were modeled additionally in all rmANOVAs.

Regions of interest and statistical thresholds

For PPI seed regions and hypothesis-driven group analyses, region of interest (ROI) masks were generated for each amygdala and the prefrontal cortex (PFC). The ROI masks for the amygdalae were computed based on coordinates of amygdala activation consistently reported in n=20 comparable studies of the face matching task. A mask of the PFC was created based on the combined anatomical boundaries of the lateral, medial and orbital surfaces of the frontal lobe as provided by the automated anatomical labeling atlas. We applied *Bonferroni-correction* for six tests (two comparisons respectively for activity, FC across, and FC between conditions, p <.0083) to voxel-wise whole-brain familywise error (FWE)-corrected results.

Exploratory analyses

Brain-behavior-correlations: We assessed associations between brain functional measures and negative affectivity (NA). Amygdala response (faces > shapes) was extracted from group level results within the amygdala ROIs. FC estimates were extracted from group level results at the locations of maximum group difference. Due to large inter-correlations of the NA measures (BDI, SCL-90 Depression Scale, Neuroticism and STAI-T), and in order to reduce the alpha error probability due to multiple testing, we generated a comprehensive measure of NA by performing a principal component analysis (PCA) with the NA measures in SPSS. Here, the STAI-S was excluded because it was not assessed at study site Mannheim. Due to missing psychometric data, the sample sizes decreased slightly after PCA analysis (Relatives: 64, Controls: 67). Inter-variable correlations of NA measures were significant (p<.0001) and ranged between r = .49 and .72. Both the *Kaiser-Meyer-Olkin* measure of .73 and *Bartlett's* test of sphericity of p<.0001 indicated adequacy. Performing PCA, only one component had an Eigenvalue larger than 1 and was extracted. This extracted NA score explained 68.2% of the total variance (communalities ranged between h^2 = .67 and .69; component loadings ranged

between r = .82 and .83). Correlations of the NA score with measures of NA ranged between .71 and .93.

We investigated the relationship between the z-scaled individual NA scores and functional measures via stepwise fitting into a GLM for relatives and controls separately. The starting models contained the brain response in amygdala as well as amygdala FC with sgACC and pgACC, MFG and SFG as predictors. Each initial model contained five main effect terms, eight twofold interaction terms as well as a constant (14 predictors). During model estimation, all main effects and interactions without a considerable contribution to variance explanation in NA were removed using the *Akaike Information criterion (AIC)*. Variance explanations of the two final models were compared with a constant model via F-test. Alpha error probabilities for these tests were *Bonferroni-corrected* for multiple comparisons. Finally, the models for relatives and controls were compared via Likelihood-ratio-test.

Type of kinship: To test whether group differences in amygdala response and FC were driven by type of kinship, estimates were extracted from group level results at location (1mm sphere) of maximum task effect or group difference and compared between offspring and siblings of MDD patients using two-sample t-tests in SPSS.

Correlations between amygdala response and amygdala FC: Amygdala response was extracted at location of maximum task effect and correlated with amygdala FC estimates at locations of maximum group difference using SPSS.

Results

Sample characteristics

As shown in Table 1, groups did not differ with respect to age, sex, study site, or years of education. Negative affectivity scores were below clinical thresholds and did not significantly differ between groups. The groups did not differ in task performance.

Characteristic	Controls (n = 70)	Relatives (n = 70)	*df*	F χ^2	*p*
Demographics					
Type of family relationship to index patient[a] *N (%)*					
Offspring		50 (71)			
Sibling		17 (24)			
Parent		1 (1)			
Unknown		2 (3)			
Age *mean ±SD, df, F*	29.70 ±8.08	28.03 ±8.82	139	1.37	.24
Years of education *mean ±SD, df, F*	15.28 ±2.25	15.49 ±2.45	139	.25	.61
Sex *N (%), df, χ^2*					
Male	29 (41)	25 (36)	1	.48	.49
Female	41 (59)	45 (64)			
Study Site, *N (%), df, χ^2*					
Charité Berlin	27 (38)	27 (38)			
ZI Mannheim	18 (26)	21 (30)	1	.42	.81
University of Bonn	25 (36)	22 (32)			
Negative Affectivity *mean ±SD, df, F*					
BDI	2.8 ±3.1	3.9 ±3.4	134	3.8	.06
SCL90-R Depression[b]	45.5 ±8.1	46.1 ±8.4	134	.15	.70
STAI-S[c]	31.7 ±5.92	31.4 ±5.6	100	.11	.74
STAI-T	33.7 ±9.25	35.55 ±8.52	134	1.5	.22
NEO Neuroticism	14.7 ±7.2	16.9 ±7.6	134	2.9	.10
Task performance *mean ±SD, df, F*					
Reaction time (s)					
Faces matching	1.25±.22	1.22±.28	139	.47	.50
Shapes matching	1.10±.20	1.11±.26	139	.01	.93
Percentage of correct responses					
Faces matching	98.87±2.4	98.99±2.20	139	.10	.76
Shapes matching	97.20±3.8	97.62±3.7	139	.43	.51

Table 1. Demographic and psychological sample characteristics.

Abbreviations: BDI, Beck's Depression Inventory; NEO, NEO Five Factory Inventory; SCL90-R Depression, Symptom Checklist 90 Revised Depression Scale; STAI-S, State Trait Anxiety Inventory - State Anxiety; STAI-T, State Trait Anxiety Inventory - Trait Anxiety; ZI, Central Institute of Mental Health. [a]Information about family relationship status was missing for two participants; [b]Raw scores were standardized into age-adjusted T-scores. [c]STAI-S was not acquired at study site Mannheim.

Task-related brain activity

Across groups, in the faces compared to the shapes condition, brain activity was increased in the visual cortex, in limbic structures including the amygdala, in pre- and postcentral regions, in the dorsal prefrontal cortex, and in temporal areas. Activity was decreased in parietal regions, in the posterior and perigenual ACC, and in the medial frontal gyrus (Figure 3, Table 2).

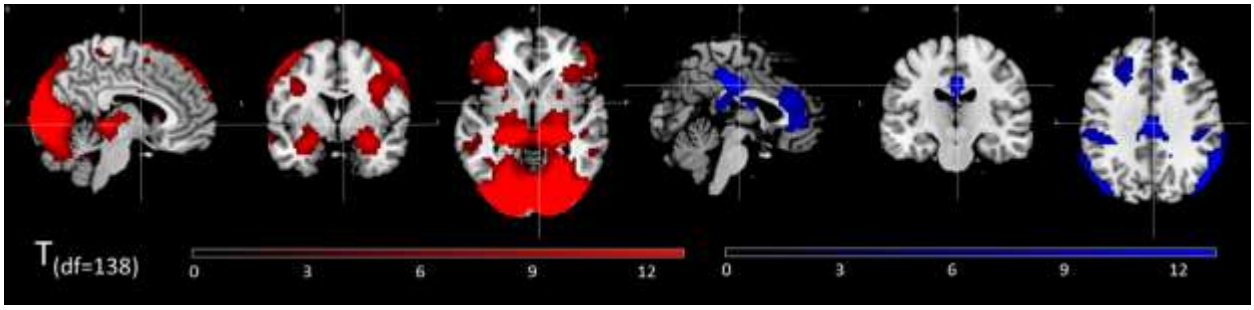

Figure 3. Task effects on brain activity.
Activations (red) and deactivations (blue) in the emotion compared to the control condition.

Faces > Shapes						Faces < Shapes					
Brain region	T	$P_{(FWE)}$	MNI coord. x	y	z	Brain region	T	$P_{(FWE)}$	MNI coord. x	y	z
Cuneus	3.5	<.001	21	-94	14	Angular Gyrus	12.7	<.001	60	-61	32
Lingual Gyrus	3.0	<.001	-12	-91	-7	IPL	11.8	<.001	57	-58	44
Fusiform Gyrus	28.3	<.001	24	-85	-10	SMG	6.9	<.001	48	-31	41
Lingual Gyrus	28.2	<.001	21	-79	-7	Middle Occipital Gyrus	11.1	<.001	-42	-82	38
Calcarine Gyrus	27.8	<.001	-15	-97	2	IPL	6.8	<.001	-57	-61	41
Inferior Occipital Gyrus	27.7	<.001	36	-82	-7	SupraMarginal Gyrus	8.9	<.001	-51	-31	38
Superior Occipital Gyrus	26.7	<.001	-15	-100	14	pgACC	8.2	<.001	-6	32	2
Inferior Occipital Gyrus	26.2	<.001	-30	-88	-4	pgACC	7.8	<.001	3	35	-1
Cerebellum (VI)	25.2	<.001	-18	-82	-10	MFG	6.9	<.001	-24	26	35
Thalamus	24.8	<.001	-24	-31	2	MFG	5.9	.001	27	26	35
Fusiform Gyrus	24.5	<.001	-36	-55	-16	Postcentral Gyrus	5.4	.005	33	-43	62
Thalamus	24.5	<.001	24	-31	2						
Middle Occipital Gyrus	19.9	<.001	-24	-91	20						
Amygdala	16.1	<.001	24	-4	-13						
Amygdala	15.7	<.001	-21	-7	-13						
IFG (p. Triangularis)	15.1	<.001	54	35	20						
MFG	14.9	<.001	54	41	17						
Middle Temporal Gyrus	7.4	<.001	-51	-46	11						
Rectal Gyrus	6.2	<.001	0	32	-19						

Table 2. Task effects on brain activity across groups.
Regions showing a significant effect of condition on BOLD signal during the face matching task. Coordinates are in Montreal Neurological Institute (MNI) space, x, y, z = location in mm with the three axes. Abbreviations: H, hemisphere; IPL, Inferior Parietal Lobule; k, numbers of voxels per cluster; L, left; MFG, Middle Frontal Gyrus; p., pars; pgACC, perigenual Anterior Cingulate Cortex; R, right; SMG, Supramarginal Gyrus.

The Groups did not differ in task-related brain activity, neither in whole-brain, nor in ROI analyses of the amygdala and the PFC at p_{FWE} <.05.

Task-related amygdala functional connectivity

Across groups, bilateral amygdala FC was increased in the faces compared to the shapes condition with the primary visual cortex, inferior and middle occipital gyrus, fusiform gyrus, and the contralateral amygdala, while it was decreased with midline structures (precuneus, cuneus, posterior and mid cingulate gyrus, pgACC, orbitofrontal cortex, and temporal regions (Figure 4, Table 3).

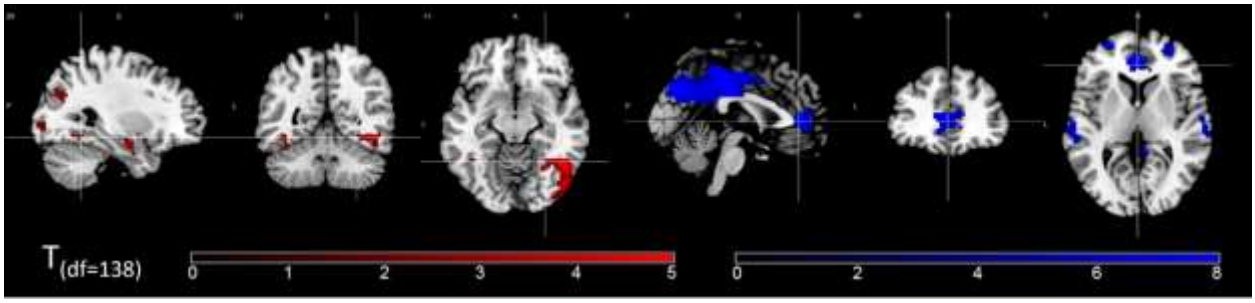

Figure 4. Task effects on amygdala functional connectivity.
Increases (red) and decreases (blue) of amygdala FC in the emotion compared to the control condition.

Faces > Shapes						Faces < Shapes					
Brain region	T	*p* (FWE)	MNI coord. x	y	z	Brain region	T	*p* (FWE)	MNI coord. x	y	z
Amygdala	4.5	<.001	27	-7	-19	Middle Cingulate Cortex	9.7	<.001	0	-28	38
Hippocampus	3.7	<.001	36	-10	-19	Cuneus	8.9	<.001	-6	-73	29
Inferior Occipital Gyrus	4.1	<.001	48	-76	-10	Precuneus	8.3	<.001	6	-67	32
Fusiform Gyrus	2.9	.15	33	-52	-10	Posterior Cingulate	6.7	<.001	12	-52	35
Middle Occipital Gyrus	3.4	.01	-33	-82	5	Postcentral Gyrus	6.5	<.001	33	-34	68
Fusiform Gyrus	3.2	.03	-39	-46	-19	Precentral Gyrus	6.0	<.001	42	-16	53
						Middle Cingulate Cortex	5.7	.001	18	-34	50
						Paracentral Lobule	5.6	.002	15	-34	56
						Precuneus	4.9	.028	-9	-61	14
						Superior Orbital Gyrus	8.4	<.001	-27	59	2
						pgACC	8.0	<.001	0	44	5
						Superior Medial Gyrus	7.0	<.001	-6	47	11
						pgACC	6.2	<.001	9	41	11
						Middle Orbital Gyrus	4.9	.031	3	56	2
						Middle Orbital Gyrus	7.1	<.001	30	53	-1
						Superior Temporal Gyrus	6.9	<.001	66	-13	-4
						Middle Temporal Gyrus	6.2	<.001	66	-25	-1
						Rolandic Operculum	5.3	.007	57	-4	11
						Superior Temporal Gyrus	6.9	<.001	-54	-52	23
						Angular Gyrus	6.1	<.001	-42	-61	38
						Middle Temporal Gyrus	6.7	<.001	-63	-22	5
						Middle Orbital Gyrus	6.4	<.001	-27	29	-16
						Middle Frontal Gyrus	6.4	<.001	-30	26	35
						Insula	5.9	.002	39	-19	20

Table 3. Task effects on amygdala functional connectivity.
Regions showing a significant effect of condition on amygdala FC during the face matching task across groups. Coordinates are in Montreal Neurological Institute (MNI) space, x, y, z = location in mm with the three axes. Abbreviations: pgACC, perigenual anterior cingulate cortex.

In group comparisons of amygdala FC *across* conditions, relatives showed increases in ventral and decreases in dorsal parts of the PFC. Increases were observed in the sgACC and pgACC, the right temporal pole, and clusters at the occipital-parietal junction, including the angular gyrus. Decreases were observed in the precentral gyrus, superior frontal gyrus, and medial frontal gyrus (MFG) (Figure 5, Table 4).

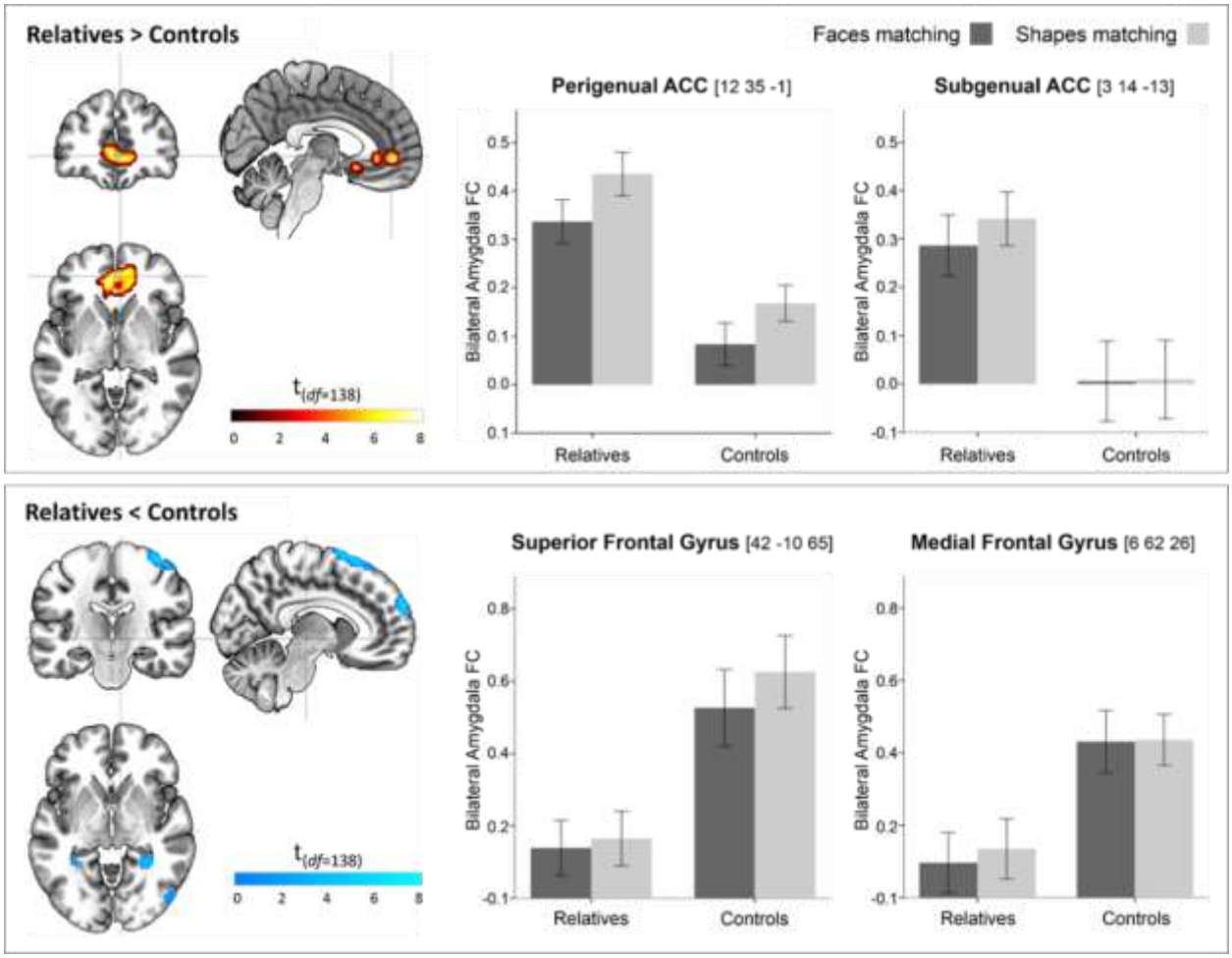

Figure 5. Group differences in amygdala FC across task conditions.

Regions with increased amygdala FC across conditions in relatives compared to controls are shown in the top panel, regions with decreased amygdala FC across conditions in relatives compared to controls are shown in the bottom panel. Results are significant at a whole-brain FWE-corrected significance threshold of $p<.006$. Error bars indicate standard errors of the mean. Abbreviations: ACC, anterior cingulate cortex; amygdala FC, amygdala FC; *df*, degrees of freedom.

Analyses of group-by-condition interactions showed a diminished task-dependent modulation of amygdala FC in relatives in the left superior frontal gyrus (SFG). In the thalamus and visual cortex, controls showed stronger amygdala FC during faces matching compared to shapes matching, while this pattern was inversed in relatives. Amygdala FC with the OFC did not differ between conditions in controls, while it decreased during faces matching in relatives (Figure 6).

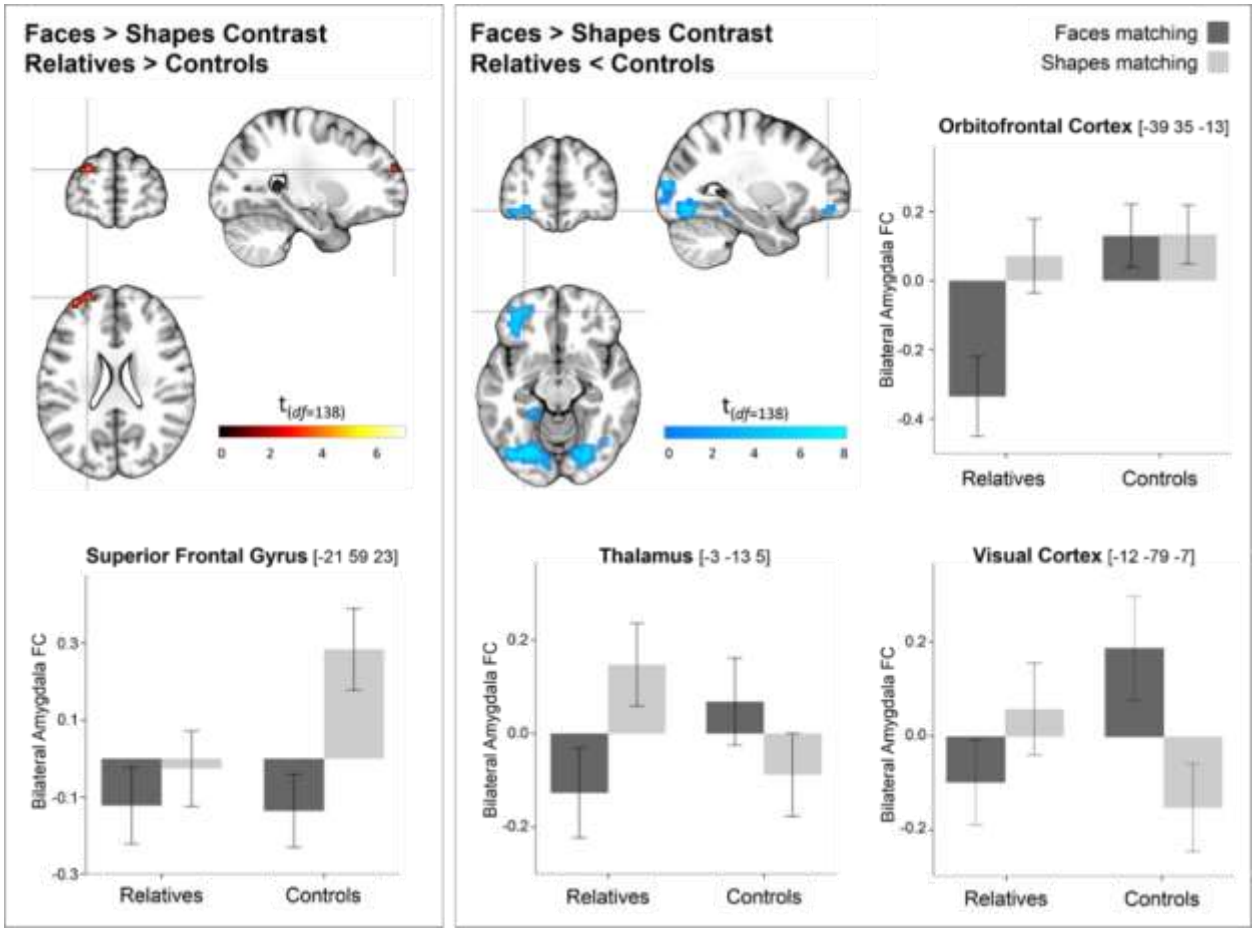

Figure 6. Group by condition interactions in functional amygdala connectivity.

In the left panel, regions with significant group-by-condition interactions (faces > shapes; relatives > controls) are shown, the right panel shows regions with significant group-by-condition interactions in the other direction (faces > shapes; relatives < controls). Results are significant at a whole-brain FWE-corrected significance threshold of p<.006. Error bars indicate standard errors of the mean. Abbreviations: ACC, anterior cingulate cortex; amygdala FC, amygdala FC; *df*, degrees of freedom.

Group effects on amygdala FC were significant at p<.006 (voxel-wise corrected across the whole brain), surviving additional Bonferroni correction for six tests. Coordinates, anatomical labels and statistics of group effects on bilateral amygdala FC are provided in Table 4.

Effects of group on amygdala FC *across* conditions															
Controls > Relatives								Relatives > Controls							
Brain region	k	H	T	$P_{(FWE)}$	MNI coord.			Brain region	k	H	T	$P_{(FWE)}$	MNI coord.		
					x	y	z						x	y	z
Precentral Gyr	217	R	7.9	<.001	42	-10	65	Mid Occ Gyr	79	L	8.0	<.001	-33	-85	41
SMA		L	6.8	<.001	-6	8	74	Angular Gyr		L	6.6	<.001	-45	-73	41
SMA		R	6.4	<.001	6	8	71	pgACC	171	L	8.0	<.001	-3	44	2
SFG (BA6)		R	6.1	<.001	21	-10	74	Mid Orb Gyr		R	7.3	<.001	0	47	-4
Postcentral Gyr		R	5.9	.001	51	-19	59	Mid Orb Gyr		R	6.8	<.001	12	38	-4
SMG (BA10)	44	R	6.8	<.001	6	62	26	MTP	25	R	7.4	<.001	30	11	-34
MFG (BA10)		R	5.8	.001	21	59	32	sgACC	13	M	6.9	<.001	0	14	-13
								sgACC		L	6.0	<.001	-3	14	-16
Effects of group–by-condition interactions on amygdala FC															
Faces > Shapes; Controls > Relatives								Faces < Shapes; Relatives > Controls							
Brain region	k	H	T	$P_{(FWE)}$	MNI coord.			Brain region	k	H	T	$P_{(FWE)}$	MNI coord.		
					x	y	z						x	y	z
Lingual Gyr	180	L	7.7	<.001	-12	-79	-7	SMG	12	R	6.6	<.001	63	-46	38
Fusiform Gyr		L	6.7	<.001	-30	-73	-10	Precentral Gyr	12	R	5.9	.001	57	-10	47
Fusiform Gyr	123	R	7.4	<.001	27	-76	-4	SFG (BA10)	11	L	5.0	.005	-21	59	23
Inf Occ Gyr		R	5.9	.001	42	-67	-7								
Lingual Gyr		R	5.6	.002	18	-85	-7								
Cuneus	80	R	7.3	<.001	21	-94	14								
Mid Occ Gyr		R	6.0	<.001	30	-97	17								
OFC (BA11)	41	L	5.8	.001	-39	35	-13								
MOccG	88	L	6.5	<.001	-21	-94	5								
Inf Occ Gyr		L	5.9	<.001	-24	-94	-4								
Calcarine Gyr		L	5.3	.006	-12	-91	11								
Thalamus	11	L	5.4	.005	-3	-13	5								

Table 4. Results of group comparisons of bilateral amygdala FC.

Abbreviations: Gyr, Gyrus; H, hemisphere; Inf Occ Gyr, Inferior Occipital Gyrus; k, number of voxels per cluster; L, left; MFG, Medial Frontal Gyrus; Mid Occ Gyr, Middle Occipital Gyrus; Mid Orb Gyr, Middle Orbital Gyrus; MTP, Medial Temporal Pole; pgACC, Perigenual Anterior Cingulate Cortex; R, right; SFG, Superior Frontal Gyrus; sgACC, Subgenual Anterior Cingulate Cortex; SMA, Supplementary Motor Area; SMG, Superior Medial Gyrus; OFC, Orbitofrontal Cortex.

Exploratory results

In relatives only, variance in negative affectivity (NA) was significantly explained by a model including the main effects of amygdala-pgACC and amygdala-MFG connectivity and their interaction (NA ~ -.49 * FC_{pgACC} -.63 * FC_{MFG} + .68 * (FC_{pgACC} * FC_{MFG}); $F_{2,60}$ = 3.71, p = .016). This model showed better performance than the final model for controls (χ^2 = 16.43, p < .001). Figure 7 shows a graphical representation of the model.

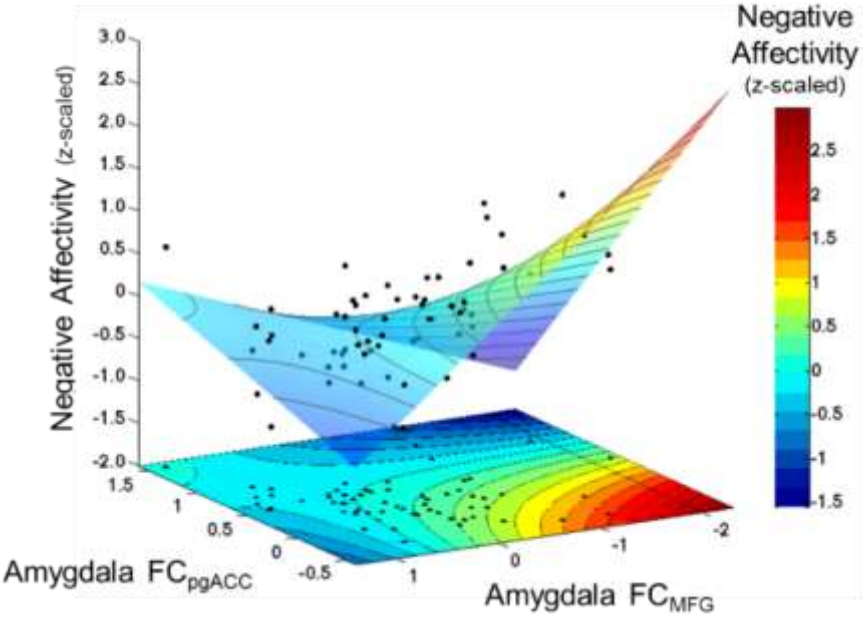

Figure 7. Negative affectivity as a function of amygdala-prefrontal FC.

A three-dimensional representation of the final linear model. Higher negative affectivity was associated with lower estimates of amygdala FC with MFG, pgACC and their interaction. Abbreviations: FC, FC; MFG, medial frontal gyrus; pgACC; perigenual anterior cingulate cortex.

Amygdala FC at locations of group differences did not significantly differ between offspring and siblings. There were no significant associations between amygdala response and amygdala FC – neither across, nor within groups.

Discussion

Aiming to provide insights into the neurobiological pathogenesis of depression, we tested for an imbalance in limbic-cortical activation and FC in first-degree relatives of patients with depression in order to prove its validity as an intermediate phenotype (IP).

No evidence for altered limbic-cortical activity in relatives

As expected, the task induced activation in limbic and prefrontal cortical regions including the amygdala. These effects were comparable to results of a meta-analysis of 105 studies of the face matching task (Fusar-Poli et al., 2009). It needs to be considered that, since the control condition comprised geometric shapes instead of neutral faces, the observed activation patterns may not solely correspond to the emotional expression of the faces, but to face processing in general. However, given that the amygdala, fusiform gyrus, dorsal and ventral PFC were activated in a meta-analysis of studies using neutral faces as a control condition (Sabatinelli et al., 2011), we can assume that the task evoked neural processes critical for emotion processing.

Contrary to our hypothesis, we did not observe group differences in limbic-cortical activation. Previous familial risk studies only inconsistently reported amygdala hyperactivity in offspring of MDD patients, during passive viewing of fearful faces (Monk et al., 2008), negative emotional distraction (Pilhatsch et al., 2014), and sad mood induction (Joormann et al., 2012). No amygdala hyperactivity was observed in familial risk during automatic attentional control studies (Amico et al., 2012; Lisiecka et al., 2013, 2012; Mannie et al., 2008), including a face matching task comparable to the one used here (Mannie et al., 2011). Furthermore, the relationship between amygdala reactivity and the 5-HTTLPR polymorphism has been questioned in a meta-analysis that included unpublished studies (Bastiaansen et al., 2014). It could thus be assumed that amygdala hyperreactivity or prefrontal hypoactivity is not robustly associated with familial or genetic risk, but rather a correlate of the depressed state.

Altered limbic-cortical connectivity in relatives

In the emotion compared to the control condition, amygdala FC was increased with the fusiform gyrus, which plays a critical role in the detection of faces (Petro et al., 2013). At the same time, amygdala FC with the pgACC, OFC, posterior cingulate, and precuneus was decreased in the emotion compared to the control condition. We discussed this pattern as an increased salience-induced visual attention, in which a decreased, or more

negative, amygdala-pgACC FC corresponds to a process of automatic attentional regulation (Phillips et al., 2008).

Across conditions, relatives showed decreases in amygdala FC with dorsal prefrontal regions and increases with the subgenual and perigenual ACC. This pattern was in line with our hypothesis and consistent with the dorsal-ventral connectivity imbalance of the amygdala in depression (Disner et al., 2011). Negative affectivity was negatively correlated with amygdala-MFG FC, amygdala-pgACC FC as well as their interaction, which might suggest that the decrease in amygdala-MFG FC presents a vulnerability marker, which is compensated for by the increase of amygdala-pgACC FC. This is consistent with the role of the pgACC for the dorsal-ventral integration, which was proposed in the initial limbic-cortical model (Mayberg, 1997) as well as with similar observations in imaging genetics studies (Heinz et al., 2005; Schardt et al., 2010b).

We further observed that relatives compared to controls showed differential condition-dependent modulations of amygdala FC with the visual cortex (V1), the thalamus, the lateral orbitofrontal cortex (OFC). Assuming that negative FC reflects an inverse co-activation in terms of an inhibitory process, the stronger modulation in the OFC (decrease during faces matching in relatives, no difference in controls) and blunted modulation in the superior frontal gyrus (decrease during faces matching in controls, no difference in relatives) in relatives suggests a shift from voluntary to automatic regulation pathways in familial risk. This enhanced automatic inhibition might have attenuating effects on the sensory input processing in V1 and thalamus, where relatives showed an inverted pattern (decreased FC during faces processing) compared to controls. Since this was the first study of task-dependent effects on amygdala FC, complementary studies are necessary to generate more conclusive insights into causal relations between brain regions and their pathogenic implications for depression.

Limitations and future directions

While notable strength of this study include the large sample size, the first assessment of amygdala FC in adult first-degree relatives of MDD patients, and the elaborate measure of context-dependent amygdala FC, it is also limited by some aspects. First, since FC is a correlative measure, its implications with respect to the causal relations between the involved regions (e.g. bottom-up excitation, top-down inhibition) need to be validated by complementary measures such as effective and structural functional connectivity. Furthermore, although here the isolated focus at the amygdala was justified by the

specific hypothesis we derived from our studies of reference, the complexity of limbic-cortical functioning should be addressed with network-based approaches, e.g. graph theory (Stam and Reijneveld, 2007) or dynamic causal modeling (Friston et al., 2003). These methods might also provide more conclusive evidence regarding the relationship between functional connectivity and brain activity, which we could not detect in our post-hoc analyses.

In our sample, siblings, offspring and parents of MDD patients were collapsed even though their levels of depression risk might vary given different genetic and environmental risk loads. Although we did not find differences between siblings and offspring in post-hoc comparisons, future studies should control for these potential confounds.

Finally, and crucially, we conducted the study of first-degree relatives, who were at increased risk for depression, but never affected by any psychiatric disorder, to identify biological vulnerability markers independent of depressive symptomatology. Still, in exploratory analyses, we found associations with negative affectivity, indicating that (some of) the identified brain measures were not independent form mental states. To further disentangle pathology, vulnerability, and resilience mechanisms, direct comparisons of risk, patient, and control groups should be conducted. Complementary, prospective studies should assess the predictive value of the imaging measures for risk or resilience, for example by predictive modeling of depression onset vs. quick recovery in the face of adversity based on imaging measures (Kalisch et al., 2017).

Altogether, our study has contributed to a refined understanding of the neurobiological pathogenesis of depression – in particular, it has identified potential neural risk or resilience markers for depressive disorders. Our results can direct the development of therapeutic strategies in *precision psychiatry*, the approach to make therapeutic decisions based on individual biological and psychological features (Stel J. C., 2015).

Conclusion

Our results did not confirm an imbalance of limbic-cortical *activity* as an IP of genetic risk for MDD. Instead, an imbalance of amygdala-prefrontal *connectivity* was observed in the risk group, confirming the tested validity criterion of this putative IP. Provided that, in the next step, the considered pathogenetic implications of our findings can be confirmed, our results might contribute to a person-tailored clinical prognosis and therapeutic prescription in the future, which might improve therapeutic efficacy and economic efficiency in health care and help to reduce the burden of depression.

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Eidesstattliche Versicherung

„Ich, Carolin Wackerhagen, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Limbic-cortical imbalance as intermediate phenotype of depression – investigation of a familial risk sample“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum _____ Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Publikation:
Wackerhagen, C., Wüstenberg, T., Mohnke, S., Erk, S., Veer, I.M., Kruschwitz, J.D., Garbusow, M., Romund, L., Otto, K., Schweiger, J.I., Tost, H., Heinz, A., Meyer-Lindenberg, A., Walter, H., Romanczuk-Seiferth, N., Influence of Familial Risk for Depression on Cortico-Limbic Connectivity during Implicit Emotional Processing., Neuropsychopharmacology, 2017

Beitrag im Einzelnen:
- Rekrutierung, MRT- und testpsychologische Untersuchung von Studienteilnehmer*innen (ein Teil der in Berlin erhobenen Stichprobe)
- Testauswertung und Dateneingabe
- Entwicklung der Fragestellung und Auswahl der Methodik[1]
- Stichprobenauswahl, Datenvorverarbeitung und statistische Auswertung[2]
- Darstellung der Ergebnisse[3]
- Interpretation und Diskussion der Ergebnisse[1]
- Erstellung des Manuskripts, Einarbeitung der Anmerkungen der Koautor*innen

[1]Die Entwicklung der Fragestellung, Auswahl der Methodik und Diskussion der Ergebnisse wurden weitgehend eigenständig, aber in Absprache mit den Koautor*innen durchgeführt.
[2]Zur Durchführung der Datenanalyse erhielt ich von meinem der Koautor Torsten Wüstenberg Unterstützung beim Erstellen der Auswertungsskripte und Erlernen der Programme, führte die Analysen dann auf dieser Basis selbstständig aus.
[3]Abbildung 7 im Manteltext und Abbildung 4 in der Druckversion der Publikation wurden von Herrn Wüstenberg erstellt, alle anderen Tabellen und Abbildungen wurden von mir erstellt.

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

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Unterschrift des Doktoranden/der Doktorandin

Publikationsschrift

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Lebenslauf

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

Publikationsliste

2019

Wackerhagen, C., Veer, I., Erk, S., Mohnke, S., Wuestenberg, T., Romanczuk-Seiferth, N., … Walter, H. (2019) Amygdala Connectivity in Depression - Disentangling Risk, Resilience, and Pathology. Psychological Medicine (*in press*).

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Nina Romaczuk-Seiferth, Nora Skarabis, Patricia Pelz, Paul Cronjäger, Paul Whalen,
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*alphabetisch nach Vorname