

# Anticipation of aversive stimuli activates extended amygdala in unipolar depression <sup>☆</sup>

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## Abstract

According to cognitive theories, negative cognitions including negative attitudes towards the future are key factors associated with depressive disorder. We investigated the neural correlates of anticipation of emotional stimuli in patients with unipolar depression to reveal influences of future thinking on brain activity. We used functional magnetic resonance imaging (fMRI) to study 12 female patients with stable antidepressant medication and 12 healthy women. Subjects were presented with positive, negative and neutral pictures that were announced by a congruent cue. Subjects were instructed to expect and subsequently watch the pictures. After scanning, subjects filled the Emotion Regulation Questionnaire (ERQ) to assess the regulation strategies suppression and reappraisal. Compared to the healthy control group, during expectation of negative vs. neutral or positive stimuli the patients showed significantly more activation within the sublenticular extended dorsal amygdala (SLEA) bilaterally but did not differ from controls upon expecting positive stimuli. Hamilton depression scores of the patients correlated positively with activation of the left and right ventral amygdala during expectation of negative stimuli. Furthermore, we found a negative correlation of ventral amygdala activation in the patients with reappraisal scores comprising the ability to limit emotional responding by re-interpreting emotion-eliciting situations. We interpret enhanced activation in the amygdala/SLEA as a possible consequence of altered future thinking in patients suffering from depression. Supporting cognitive theories, this finding does represent evidence that altered cognitions as potentially involved in expectation result in differences in brain activity.

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## 1. Introduction

Negative attitudes towards future events, together with feelings of hopelessness in general, are important symp-

toms of depressive disorders. Patients often are not able to look forward to upcoming positive events and take potentially negative prospects more grave than healthy subjects. According to cognitive theories of mood disorders (Beck et al., 1979), a systematic bias in processing of information from the environment has been proposed as a psychological explanation for these phenomena.

Recently, functional neuroimaging has made important contributions towards a better understanding of the pathophysiology of depression. Metabolic activity of the amygdala could be predicted by scores of negative affect and depression (Abercrombie et al., 1998; Drevets et al., 1992) and activity in the anterior cingulate cortex was

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<sup>1</sup> Location where work was conducted.

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related to response to antidepressant treatment (Buchsbbaum et al., 1997; Davidson et al., 2003; Mayberg et al., 1997, 2000). Furthermore, functional imaging studies revealed task-related differences between patients and healthy controls: Activation of the amygdala in acute depression was increased in response to sad faces (Fu et al., 2004; Surguladze et al., 2005) negative pictures (Davidson et al., 2003) and words (Siegle et al., 2002). Besides amygdala, prefrontal and cingulate cortex, basal ganglia and secondary visual areas showed altered responses to emotional stimuli in depression (Davidson et al., 2003; Fu et al., 2004; Surguladze et al., 2005).

Up to now, imaging studies of depression have mainly investigated altered *perception* of emotional stimuli. But from a psychological point of view alterations in *attitudes* towards stimuli or events may play an even greater role in the pathophysiology of depression. According to cognitive theories (Beck et al., 1979; Teasdale et al., 1998) cognitions actually may be the cause for altered perception of environmental stimuli, and cognitive styles have been found to predict vulnerability to depression (Alloy et al., 1999). Biased future thinking in depression has been suggested to rely on an easier access to negative (but not positive) memories or cognitions and on altered simulation processes of future events resulting for example in an overestimation of the probability of negative future events (MacLeod and Ruthersford, 1999). The way how dysphoric patients think about a certain event, how they attribute it, was found to influence the perception of the likelihood of similar experiences in the future (Cropley and MacLeod, 2003). This supports the notion that expectations towards a certain event seem to be biased by cognitions or attitudes towards such events and by past experiences with it. We suggest from this, that the investigation of the anticipation of emotional stimuli has the potential to reveal influences of attitudes biasing expectation processes in depression as well. Furthermore, in healthy subjects, expectation of negative stimuli like fear, pain or aversive pictures has been shown to activate brain regions involved in depression – like the amygdala, prefrontal, insular, and cingulate cortex (Nitschke et al., 2006; Ploghaus et al., 1999; Porro et al., 2003; Ueda et al., 2003).

It has been suggested that the information processing bias in affective disorders arises from a dysfunctional interaction of bottom-up emotional activation and top-down attentional control (Mathews and MacLeod, 2005). The assessment of emotion regulation strategies can be a means to further characterize the control processes involved. Gross and John (2003) proposed two major forms of emotion regulation strategies: reappraisal and suppression. Cognitive reappraisal is defined as a form of cognitive change that involves construing a potentially emotion-eliciting situation in a way that changes its emotional impact (Lazarus and Alfert, 1964) while suppression is defined as a form of response modulation that involves inhibiting of ongoing emotion-expressive behavior. Reappraisal is considered an antecedent strategy apt to successfully reduce the behavioral and experiential component of negative

future emotions. In contrast, suppression is considered a response-focused strategy primarily modifying the behavioral aspect of negative emotional responses but not their experience. It has been suggested that suppression is related to negative cognitions and depressive thinking while reappraisal has a rather protective effect (Gross and John, 2003) concerning mood disturbances.

We investigated the neural correlates of the anticipation of visual emotional stimuli with positive or negative affective valence. Anticipating negative events may easily elicit anxiety and comorbid anxiety is frequently seen in depression. Amygdala and insula are not only relevant in depression, but were found activated as well in anxiety disorders, e.g. when socially phobic patients anticipated making public speeches (Lorberbaum et al., 2004).

To put an emphasis on depression in comparison to classical anxiety disorder we used clearly negatively valenced pictures from the IAPS of disgusting but assumably not fear-inducing content. Previous studies on the anticipation of aversive events including our own found involvement of insula (Simmons et al., 2004), prefrontal and cingulate cortex (Herwig et al., *in press*) and amygdala. Hereby, rather the dorsal part of the amygdala within the region of the sublenticular extended amygdala seemed to be involved (Nitschke et al., 2006).

Using functional magnetic resonance imaging (fMRI) we tested two hypotheses concerning cognitions and future thinking in depression:

First hypothesis: Expectation of future emotional stimuli is biased in depression. Based on Beck's theory and the notion that attitudes have an influence on emotional reactions, we expected to find altered brain activity in subjects suffering from depression compared to healthy subjects, especially in regions previously identified to be involved in the processing of aversive stimuli.

Second hypothesis: Preferential emotion regulation strategies of subjects with a diagnosis of depression will differ from those in healthy subjects and may help to explain altered brain activities.

## 2. Methods

### 2.1. Subjects

13 female patients with a diagnosis of a moderate or severe depressive episode or recurrent depressive disorder according to the International Classification of Diseases (ICD-10: F32.1, F32.2, F33.1 or F33.2) and 12 healthy female control subjects were primarily included in the study (Table 1). Diagnoses were assessed with a psychiatric interview by a specialist psychiatrist involved in the patient's treatment after admission of the patient and confirmed before enrollment. Interviews comprised a general part concerning the patient's history and a structured part to confirm the diagnosis according to ICD-10 criteria. All

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