Behavioural Brain Research xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression

Q1 Inga Laeger[a,*], Christian Dobel[b], Udo Dannlowski[a,f], Harald Kugel[d], Dominik Grotegerd[a], Johanna Kissler[e], Katharina Keuper[b], Annuschka Eden[b], Pienie Zwitserlood[c], Peter Zwanzger[a]

Q2 [a] Department of Psychiatry, University of Muenster, Albert-Schweitzer-Campus 1, Building A9, D-48149 Muenster, Germany
[b] Institute for Biomagnetism and Biosignalanalysis, University of Muenster, Malmedyweg 15, D-48149 Muenster, Germany
[c] Institute for Psychology, University of Muenster, Fliednerstr. 21, D-48149 Muenster, Germany
[d] Department of Clinical Radiology, University of Muenster, Albert-Schweitzer-Campus 1, Building A1, D-48149 Muenster, Germany
[e] Institute for Psychology, University of Bielefeld, Postfach 100131, D-33501 Bielefeld, Germany
[f] Department of Psychiatry, University of Marburg, Rudolf-Bultmann-Str. 8, D-35039 Marburg, Germany

HIGHLIGHTS

- The amygdala is activated during negative and positive emotional word reading.
- Subclinically depressed and anxious subjects show increased amygdala activation to negative words.
- Aymgdala–DLPFC connectivity in response to negative words is modulated by trait anxiety.

ARTICLE INFO

Article history:
Received 21 December 2011
Received in revised form 14 May 2012
Accepted 22 May 2012
Available online xxx

Keywords:
fMRI
Amygdala
Emotions
DLPFC
Words

ABSTRACT

Several neuroimaging studies underlined the importance of the amygdala and prefrontal brain structures (e.g. dorsolateral prefrontal cortex [DLPFC]) for the processing of emotional stimuli and for emotion regulation. Many studies used visual scenes or faces as emotion-inducing material, and there is evidence that negative or positive words activate emotion-processing brain regions in the same way. However, no study so far focused on the influence of subclinical measures of anxiety or depression on the neural processing of emotional words. In this fMRI-study, we therefore investigated brain activation to emotional words in relation to subclinical measures of trait anxiety and depression in a sample of 21 healthy subjects. We also assessed effects of subclinical anxiety and depression on amygdala–prefrontal coupling during negative (versus neutral) word reading. Both negative and positive words activated the amygdala, and negative-word processing revealed a positive correlation between amygdala activity and scores of trait anxiety and subclinical depression. During negative versus neutral word reading, subjects with high trait anxiety also showed a stronger functional coupling between left amygdala and left DLPFC. These results suggest a modulation of negative-word processing by subclinical depression and anxiety, as well as possible prefrontal compensatory processes during unintentional emotion regulation in subjects with higher trait anxiety.

1. Introduction

The neural correlates of emotion processing and emotion regulation in healthy subjects, and their alterations in psychiatric disorders, have received plenty of interest for many years. Especially, findings from functional imaging studies (e.g. functional magnetic resonance imaging, fMRI) underscore the relevance of the amygdala as a key structure in limbic emotion processing [1,2]. Moreover, amygdala hyperactivity in response to negative or threatening emotional stimuli, such as the widely used scenes or faces, is assumed to be important for pathogenesis and maintenance of several psychiatric disorders, most prominently anxiety and depression [3–8]. Similar effects are found for linguistic stimuli, such as an increased or sustained response of the amygdala to negative words in depression [6,9], and to disorder-specific words in panic disorder [10] and social phobia [11]. Findings for healthy subjects showed the involvement of the left and/or right

* Corresponding author. Tel.: +49 251 83 52388; fax: +49 251 83 56612.
E-mail addresses: inga.laeger@ukmuenster.de (I. Laeger), dannlow@ukmuenster.de (C. Dobel), dominik.grotegerd@uni-muenster.de (U. Dannlowski), kugel@uni-muenster.de (H. Kugel), cdobel@uni-muenster.de (D. Grotegerd), johanna.kissler@uni-bielefeld.de (J. Kissler), k.keuper@uni-muenster.de (K. Keuper), annuschka.eden@uni-muenster.de (A. Eden), zwitser@uni-muenster.de (P. Zwitserlood), peter.zwanzger@ukmuenster.de (P. Zwanzger).

0166-4328/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbr.2012.05.036

amygdala in both negative- and positive-word processing (e.g. [12–18]), underscoring the strong ability of linguistic stimuli to evoke activations in emotion-related brain areas (see also [19–25] for further results regarding neural correlates of word processing).

Increased amygdala responsiveness might result in negatively-biased emotion processing in healthy subjects and in depressive disorders [26,27], and in an oversensitive threat-detection system in anxiety disorders [28,29]. This is also supported by neuropsychological studies showing attentional biases for disorder-specific words in panic disorder [30–33], social phobia [32–35], generalized anxiety disorder [33,35], and for negative words in depression [30,36]. These results may as well provide an explanation for the disorders' maintenance (e.g. schematic congruent processing of new experiences).

In addition to alterations in limbic activation, the top-down control of emotions by the prefrontal cortex (PFC) [37,38] has also been suggested to be impaired in psychiatric disorders [6,39,40]. Particularly in anxiety disorders, a lack of adequate top-down control mechanisms due to dysfunctional prefrontal activity (e.g. of the DLPFC) is associated with increased neural activity of limbic regions, possibly causing the patients' inadequately increased levels of anxiety [39,41]. Most studies in this area concentrated on the down-regulation of negative emotions or fear, since this process is most often assumed to be impaired in psychiatric disorders (e.g. [39,42]).

Though our understanding of psychiatric disorders is meant to be dimensional, with diagnostic criteria setting more or less artificial cutoff scores for the presence of a disorder, this is often neglected when group comparisons between patients and healthy control groups are conducted. Considering persons that do not fulfill diagnosis criteria, but show some clinical symptoms, will help us understand better the nature of neural mechanisms underlying depression and anxiety. Are phenomena such as amygdala hyperactivity and the impairment of executive down-regulation unique to psychiatric disorders, or are they already present in less severely affected samples? The well-known stress-vulnerability model [43] emphasizes that psychiatric disorders often occur when a susceptible person meets with adverse and stressful conditions. Susceptibility, or vulnerability, includes social background, temperament and personality factors, as well as neurobiological aspects concerning neurotransmitter systems, and the functioning of critical brain systems (e.g. amygdala and prefrontal cortex) even before the onset of a disorder. In search of risk factors for the development and maintenance of psychiatric disorders, research has thus also concentrated on neural correlates of emotion processing in subjects with high trait anxiety as a stable personality factor [44] or with subclinical depressive symptoms. Studies using pictorial stimuli found a relation between the degree of depression and the activation of the amygdala in response to negative facial expressions [45]. Concerning anxiety, a positive correlation between anxiety measures and the activation of the amygdala during emotional or even neutral face processing was observed [46–48]. Subjects with high trait anxiety showed a stronger amygdala responsiveness to emotional stimuli [46]. These results are supported by data from the modified emotional Stroop tasks: attentional biases were found in persons with high anxiety-sensitivity [49] or trait anxiety [50–52] as well as those with panic attacks but without panic disorder [53].

However, the existing body of literature regarding the question of how neural responses in emotional brain regions are altered in subclinical anxiety and depression falls short of the topic's relevance for understanding the biological vulnerability component, which is assumed to lead to an increased risk for the most prevalent psychiatric disorders [43]. This is especially the case for studies using linguistic stimuli. No fMRI-study so far has investigated how trait anxiety or subclinical depression influence the neural processing of emotional words, although words have a long history in research, are a powerful mean to express and comprehend emotional states, and additionally provide methodological advantages: due to their perceptual homogeneity, words can be matched more carefully than images (e.g. for word length and frequency).

In the present study, we therefore investigated emotional-word processing in relation to subclinical measures of depression and anxiety. We hypothesized that both negative and positive emotional words would activate the amygdala as a key structure of emotion processing. We expected that the neural response patterns for these stimuli would be influenced by the degree of subclinical depression and trait anxiety. Furthermore, we studied amygdala–prefrontal functional connectivity during negative versus neutral word reading and hypothesized that this process would also be influenced by the amount of depressive symptoms and by trait anxiety.

2. Material and methods

2.1. Subjects

The 21 healthy subjects (11 women, 10 men; mean age 25.55 ± 3.22 years) that took part were selected from a database of the Institute for Biomagnetism and Biosignalanalysis in Muenster, Germany. All had normal or corrected-to-normal vision. Inclusion criteria were right-handedness, no current or former severe neurological or psychiatric disorder, and general MRI-related requirements (exclusion of ferromagnetic implants, claustrophobia, pregnancy, etc.). These criteria were checked before participation. All participants were assessed by an experienced clinical psychologist and answered a screening questionnaire concerning alcohol or drug use, and neurological disorders. All subjects filled in the Beck Depressions Inventor (BDI [54]) and the Trait form of the State-Trait Anxiety Inventory (STAI [55]). BDI scores were in a normal range for non-clinical populations ($M = 2.90 \pm 3.29$; range: 0–10). The STAI scores of all participants ranged between 21 und 40 points ($M = 32.85 \pm 5.43$) indicating average anxiety in this sample of healthy controls, scoring in the lower half of the STAI-T-range from 20 to 80 points.

2.2. Task and procedures

A total of 180 high-arousing negative (e.g. pain, catastrophe, victim), high-arousing positive (e.g. love, baby, holidays), and low-arousing neutral words (e.g. month, newspaper, detail; all examples translated from German) were taken over from Kissler and colleagues, representing a standardized body of German nouns, rated for valence and arousal, and matched for concreteness, word frequency and word length (for more information see [56]).

The fMRI-paradigm for this study consisting of the negative, positive and neutral words was programmed with Presentation® Software (Version 12.1, Neurobehavioral Systems, Inc., Albany, CA, USA; www.neurobs.com). Words were presented in white colour in the centre of a black screen in alternating 15 s blocks of 15 words per block. Presentation time was 800 ms per word; alternating with a fixed interstimulus interval of 200 ms. Blocks of negative, positive and neutral words were presented in a pseudo-randomized order, to control for sequence effects. A 10 s resting phase (white fixation cross in the centre of a black screen) was following each block of words, allowing subjects to take short pauses. In all, the paradigm took 600 s (10 min), and consisted of 12 word blocks (4 negative, 4 positive, 4 neutral), resulting in a total of 60 words per category. The stimuli were projected onto a screen at the rear end of the MR tunnel, using a beamer shielded against RF interference. Each block was presented twice and subjects were instructed to read the words attentively; no further instruction was given.

All procedures were endorsed by the local Institutional Ethical Review Board. The ethical standards of the Declaration of Helsinki were met. All subjects provided written informed consent and received a small allowance for their participation.

2.3. Image acquisition

MRI data were acquired by using a 3 T scanner (Gyroscan Intera T3.0, Philips Medical Systems, Best, NL) equipped with Quasar Dual gradients (nominal gradient strength 40 mT/m, maximal slew rate 200 mT/m/ms). For spin excitation and resonance signal acquisition, a circularly polarized transmit/receive birdcage head coil with an HF reflecting screen at the cranial end was used. T2* functional data were acquired using a single-shot echo planar (EPI) sequence (whole brain coverage, TE = 30 ms, TR = 2.5 s, FA = 90°, slice thickness 3.6 mm, no gap, matrix 64 × 64, FOV 230 mm, in-plane resolution 3.6 mm × 3.6 mm). The 40 transversal slices were tilted 25° from the AC/PC line in order to minimize drop out artefacts in the orbitofrontal and mediotemporal region.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

2.4. Image analysis

Imaging data were analysed using the Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm). Pre-processing procedures included motion correction, using a set of six rigid-body transformations determined for each image, and unwarping of the functional images to correct the inhomogeneity of the static magnetic field B_0. Additionally, images were normalized to standard MNI space (Montreal Neurological Institute) and smoothed with a Gaussian kernel of 6 mm full width at half maximum (FWHM). A data quality check after pre-processing revealed head movements of more than 2° in one subject that was therefore excluded from further analysis. For the remaining 20 subjects, a statistical analysis based on the general linear model (modelled with a canonical hemodynamic response function) was performed by generating individual fixed-effects contrast maps for the conditions (negative, positive, neutral) and the contrasts of interest (negative > neutral, positive > neutral).

For the 2nd level (group) random-effects analysis, sex was included as a covariate for all calculations to assess possible gender-related effects described in the literature [57,58]. In order to control for multiple statistical testing, all group results were calculated using a combined height and extend threshold based on Monte-Carlo simulations, as implemented in the AlphaSim procedure [59]. Based on this technique, we maintained a corrected false-positive detection rate for the amygdala region of interest analysis at $p < 0.05$, with a cluster extent (k) empirically determined by computing 1000 simulations (yielding $k = 45$ for the bilateral amygdala). For the additional whole-brain analyses, a more conservative uncorrected threshold of $p < 0.001$, and again an empirically determined cluster extent (k) was conducted ($k = 37$ for whole brain analysis). A psychophysiological interaction analysis (PPI) concerning possible modulations of prefrontal activation was conducted at $p < 0.005$, using a mask of the whole frontal lobe [60] (yielding $k = 59$ voxels as the empirically determined cluster extent).

According to our hypotheses, region of interest (ROI) analyses of the bilateral amygdala were performed for both the negative versus neutral and the positive versus neutral word contrast by performing one-sample t-tests including all individual contrast maps. For this purpose, a mask for bilateral amygdala was created using the WFU PickAtlas [60] implemented in the SPM-software, by dilating the defined mask (according to the AAL Atlas [61]) by 1 mm in radius in order to avoid missing relevant structures. The regression analysis was based on our a priori hypothesis concerning the relation between amygdala activity and the degree of subclinical depression and trait anxiety in the negative versus neutral and positive versus neutral word condition. A voxel-wise ROI approach was selected and activity within the amygdalae was correlated with BDI and STAI-T scores separately for each subject. An exploratory whole-brain analysis for the contrasts of interest was also conducted, to ascertain that our ROI analysis did not miss significant results outside the amygdala.

Besides the standard analyses of regional activation, we calculated the modulation by subclinical anxiety and depression of the functional connectivity between the amygdala and cortical areas. Based on the literature mentioned above, we were mostly interested in the regulation of negative affective states related to prefrontal brain activation. Therefore, a psychophysiological interaction analysis [62] was computed in order to capture alterations in the functional coupling between the amygdalae and the frontal cortex (physiological variable) as a function of negative as compared to neutral words (psychological variable). The left and right amygdalae were separately used as seed region in this analysis. Volumes of interest (VOI) were extracted for the negative versus neutral word contrast, based on a statistical threshold of $p = 0.99$, in order to include the time series of the entire anatomically defined amygdala. A mask of the whole frontal lobe (defined according to the WFU PickAtlas [60]) including all prefrontal areas, was used for the PPI analysis.

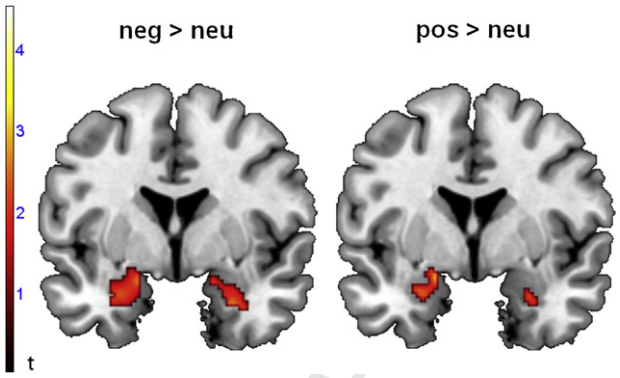

Fig. 1. Coronal view ($y = -4$ for the left and $y = -6$ for the right panel) depicting the region of interest analysis for bilateral amygdala. There were significant activations in the left and right amygdala for the negative versus neutral word contrast (left panel), and for the positive versus neutral word contrast (right panel).

3. Results

3.1. Region of interest (ROI) analysis regarding amygdala responsiveness to emotional words

As expected, for the contrast negative versus neutral words, the ROI analysis yielded strong activations of the left ($x = -18$, $y = -4$, $z = -16$, $t_{18} = 6.15$, $k = 232$ voxels, $p < 0.001$ corrected) and right amygdala ($x = 28$, $y = -2$, $z = -28$, $t_{18} = 3.97$, $k = 130$ voxels, $p < 0.001$ corrected). For the contrast positive versus neutral words, an increased activation was also found for both amygdalae ($x = -16$, $y = -6$, $z = -16$, $t_{18} = 4.55$, $k = 168$ voxels, $p < 0.001$ corrected and $x = 28$, $y = 6$, $z = -28$, $t_{18} = 3.93$, $k = 68$, $p = 0.003$ corrected) (Fig. 1). Direct comparisons of the negative versus positive words and vice versa revealed no significant differences in bilateral amygdala activation.

3.2. Regression analysis with depression- and anxiety scores

The voxel-wise ROI analysis of the amygdalae in the negative versus neutral word condition revealed that significant activity within the left amygdala was positively related to measures of depression and anxiety (BDI: $x = -20$, $y = 2$, $z = -20$, $t_{17} = 3.68$, $p = 0.003$ corrected, $r = 0.67$, $k = 69$ voxels. STAI-T: $x = -24$, $y = 4$,

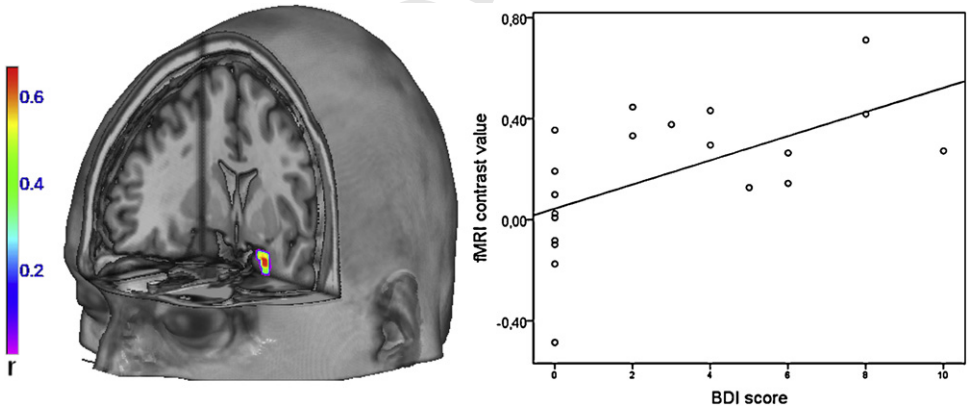

Fig. 2. Subclinical depressive symptoms (BDI score) are positively associated with left-amygdala responsiveness to negative words. Left: association of BDI scores and brain responsiveness to negative words, rendered on an anatomical template in MNI-space. Colour bar, correlation coefficient r. Right: scatter plot depicting the positive correlation of the mean cluster activation values (left panel) and the BDI scores.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

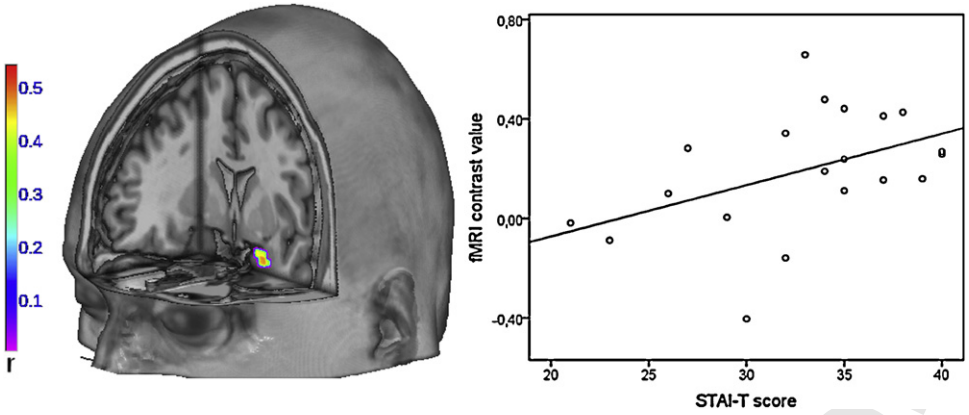

Fig. 3. Measures of trait anxiety (STAI-Trait score) are positively associated with left-amygdala responsiveness to negative words. Left: association of STAI-T scores and brain responsiveness to negative words, rendered on an anatomical template in MNI-space. Colour bar, correlation coefficient *r*. Right: scatter plot depicting the positive correlation of the mean cluster activation values (left panel) and the STAI-T-scores.

$z = -20$, $t_{17} = 2.66$, $p = 0.001$ corrected, $r = 0.54$, $k = 88$ voxels). See Figs. 2 and 3 for these results. Correlations with the right amygdala, or negative correlations, were not found. For the positive versus neutral word contrast, there was no significant association between amygdala activity and the BDI or STAI-T scores.

3.3. Psychophysiological interaction analysis

See Table 1 for an overview of PPI-results. Comparing negative and positive versus neutral words, several frontal brain regions showed enhanced activation simultaneous to the amygdala. Using the left amygdala as seed region generally caused stronger frontal activations as compared to the right amygdala seed. Furthermore, a regression analysis was conducted to find associations between the results of the PPI-analysis (increase in functional coupling of the amygdala in the negative compared to the neutral condition) and BDI and STAI-T scores. The analysis revealed a significant positive correlation between the STAI-T scores and the functional connectivity between the left amygdala and the left middle frontal gyrus (BA 9) as a part of the left DLPFC during the negative versus neutral word contrast ($x = -38$, $y = 30$, $z = 40$, $t_{17} = 4.56$, $p = 0.004$ corrected, $r = 0.74$, $k = 88$ voxels) (Fig. 4). That is, participants with high trait anxiety showed a stronger increase in functional connectivity of the amygdala and the DLPFC in the negative condition than participants with low trait anxiety scores. No association between PPI-analysis and BDI scores were found with a left amygdala seed, and there were no significant correlations between BDI or STAI-T scores and PPI-analysis with the right amygdala as seed region.[1]

3.4. Whole-brain analysis

See Table 2 for an overview of all significant activations for the negative versus neutral and positive versus neutral word contrast.

3.5. Gender effects

In addition to including sex as a covariate in all calculations, the effect of the regressor was studied. The only significant result revealed a stronger functional connectivity in women between the left amygdala and bilateral superior and middle frontal gyrus ($x = -18$, $y = 38$, $z = -2$, $t_{17} = 5.34$, $p < 0.001$ corrected, $k = 152$ voxels; $x = 22$, $y = 24$, $z = 54$, $t_{17} = 4.69$, $p = 0.006$ corrected, $k = 83$ voxels; BA 6,8, and 10), as well as the left pre- and postcentral gyrus and the left inferior parietal gyrus ($x = -42$, $y = -22$, $z = 38$, $t_{17} = 4.50$, $p < 0.001$ corrected, $k = 133$ voxels; BA 3, 4, and 6).

4. Discussion

We used an fMRI block design to examine the neural processing of emotional words in relation to subclinical depression and anxiety. Both negative and positive words activated the amygdala as a main brain structure for emotion processing. Next, subjects with higher scores of subclinical depression and trait anxiety showed increased left-amygdala responsiveness to negative words, while there were no significant associations for the right amygdala, or for the positive versus neutral word contrast. Concerning the functional interplay between amygdala and prefrontal structures, higher trait anxiety was accompanied by an increased functional connectivity between left amygdala and the left DLPFC during negative-word processing. Subclinical depression did not affect the functional coupling of the amygdalae and frontal brain regions for the negative versus neutral word contrast.

The observed activation of the amygdala for both negative and positive emotional stimuli fits with previous results. In contrast to earlier findings indicating that the amygdala is only activated by negative emotional material (e.g. [63]), more recent data and meta-analyses showed that the amygdala is rather a more general emotion-processing structure, regardless of valence [12,13,56,64]. Herbert et al. even reported an advantage for positive emotional words, indexed by left-amygdala activation that was not found for negative words [65]. Nevertheless, a recent review stated that in general, there seems to be a stronger amygdala responsiveness for negative than for positive emotional stimuli [66]. Our results support neither of these findings, since direct comparisons of negative and positive words revealed no significant differences. This supports the assumption that the amygdala does indeed process both positive and negative emotional material [12].

Regarding lateralization effects, results are mixed. Some studies found a more right-lateralized processing of negative emotional stimuli [67], others a left lateralization [63], and still others indicate that the bilateral amygdala is involved in the processing of negative information [68]. It is important to note that linguistic stimuli require a language-based processing, known for its left-hemispheric dominance [69]. In their review, Costafreda et al.

[1] Even though we did not have any hypothesis about the functional connectivity in the positive vs. neutral word contrast we also correlated the results of the corresponding PPI-analysis with BDI and STAI-T scores. Results indicated a significant negative association between BDI scores and the functional coupling between the amygdala and the right middle and superior frontal gyrus (BA10) (left amygdala seed) as well as the right precentral gyrus (BA 4) (right amygdala seed) during positive vs. neutral word reading.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

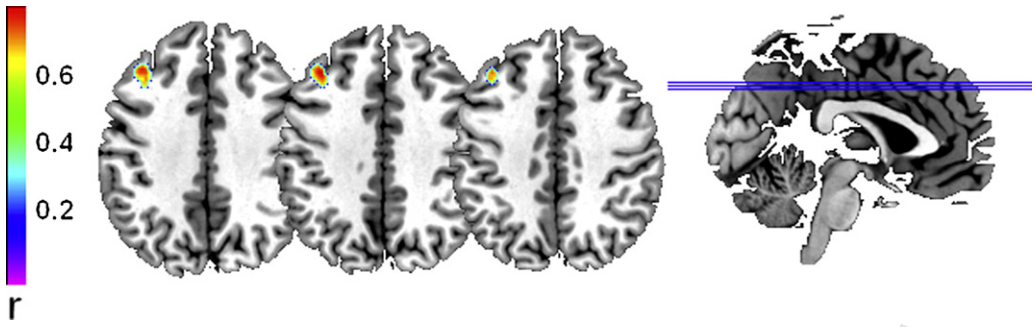

Fig. 4. Functional connectivity between left amygdala and left DLPFC activation during negative-word reading is positively associated with trait anxiety. The axial view (*z*-score of the middle slice = 40) displays DLPFC-regions that show a significant positive correlation with STAI-T scores. Colour bar, correlation coefficient r.

[66] also reported left-lateralized amygdala activation for linguistic stimuli, which fits with our results from the regression- and PPI-analysis, and with other findings [12]. Moreover, and as expected, the whole-brain data for both the negative versus neutral and the positive versus neutral word contrast showed significant activations of limbic, frontal, temporal regions, and of occipital sensory areas.

Examining the neural basis of emotion processing and emotion regulation has a clear relevance for psychiatric disorders, including the search for risk factors and vulnerability components. Amygdala hyper-responsiveness to negative stimuli in healthy individuals has been discussed to increase the risk for depression [70,71]. Moreover, high trait anxiety may lead to increased or sustained amygdala responses to negative emotional stimuli [46,48], and to an increased risk for anxiety disorders [72]. Within this area, our study is the first to show a correlation between subclinical measures of trait anxiety and depression and amygdala responsiveness to negative words. Yet, given a lack of longitudinal studies, it is impossible to determine the direction of influence: does amygdala hyper-responsiveness lead to an increase in trait anxiety and depressive symptoms, or is it a result of these? Nonetheless, our findings demonstrate that even clinically healthy populations can show stronger amygdala responsiveness to negative stimuli, in a similar way to patients, depending on their subclinical degree of depression and anxiety. This fits with the idea that the degree of neural sensitivity for negative information in limbic regions might play a mediating role between a social or biological vulnerability for a disorder – as stated in the stress-vulnerability model [43] – and the onset of a full clinical disorder (see [71,73] for discussion of this question).

We found no significant correlations for positive words, for which we can offer two explanations: first, the overall smaller neural responses to positive words may render it less probable to find correlations between the fMRI- and questionnaire data. Second, current findings in depression and anxiety disorders often suggest that the processing of negative or threatening information is altered [4,10,29,32], while changes in reward processing are discussed in other disorders such as bipolar disorder (e.g. [74]) and drug addiction (e.g. [75]). Our results support this view, with no influence of subclinical depression and trait anxiety on the processing of positive words. Given the importance of language in daily life, an increased sensitivity for the negative connotation of words might further our understanding of anxiety and depression. Moreover, in contrast to the frequently used and often cruel images from the international Affective Picture System (IAPS [76]), emotional words are less burdening and less stressful for subjects to watch, making them interesting especially for clinical research. Our results indicate that words constitute very adequate emotion-inducing materials, since they activate limbic emotion processing areas and even differentiate between different subclinical anxiety- and depression levels.

As mentioned before, alterations in emotion-regulation processes are also considered in the development and maintenance of psychiatric disorders [77]. Emotion regulation includes intentional as well as unintentional processes (e.g. suppression, re-appraisal, distraction), aiming to reduce duration, intensity or expression of emotions [77]. The clinical relevance of the brain areas involved in emotion regulation (e.g. DLPFC) was underlined by Zwanzger et al., who showed that manipulating neural activity in the prefrontal cortex by repetitive transcranial magnetic stimulation (rTMS) can reduce anxiety symptoms [78]. Another study showed that high-frequency rTMS of the right DLPFC led to decreased activity of the DLPFC, and increased amygdala activation, accompanied by problems with the disengagement from angry faces in healthy women [79]. Given the important role of cortical activity for emotion regulation, selective stimulation of cortical areas by means of rTMS may

Table 1
Q4 Results of the psychophysiological interaction analysis for the negative versus neutral and the positive versus neutral word contrast, using either left or right amygdala as seed region. The region of interest analysis based on a mask of the whole frontal cortex was conducted at $p < 0.005$, uncorrected (corrected at $p < 0.05$ at the cluster level, using the AlphaSim procedure that resulted in an empirically determined cluster-extent threshold of $k = 59$ voxels).

Anatomical region	Side	BA	Cluster size	*x*	*y*	*z*	*z*-Score
Negative > neutral							
Left amygdala seed:							
SFG; SFG (medial part); SFG (orbital part)	L	10	65	−16	62	8	3.03
Right amygdala seed:							
Postcentral gyrus	L	4, 6	64	−60	−12	36	3.28
Positive > neutral							
Left amygdala seed:							
SFG; SFG (medial part); superior motor area	R	6	98	12	22	56	4.28
SFG; SFG (medial part); ACC	L	9, 10	232	−4	60	30	4.25
IFG (orbital part); STP	L	10, 11, 47	162	−36	28	−12	3.98
SFG; SFG (medial part)	R	9	62	14	64	24	3.64
SFG; SFG (medial part)	L	6, 8	130	−6	38	56	3.36

Coordinates are given in MNI space. STP, superior temporal pole; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; ACC, anterior cingulate cortex.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

Table 2
Results of a whole-brain analysis for negative versus neutral and positive versus neutral word contrasts, conducted at $p < 0.001$, uncorrected (corrected at $p < 0.05$ on the cluster level using the AlphaSim procedure, which resulted in an empirically determined cluster-extent threshold of $k = 37$ voxels).

Anatomical region	Side	BA	Cluster size	*x*	*y*	*z*	*z*-Score
Negative > neutral							
Hippocampus; amygdala; STP; MTP; parahippocampal gyrus; MTG; ITG; FFG; LGG; thalamus	L	20, 21, 27, 28, 30, 34, 35, 38	1022	−28	−8	−26	4.84
IOG; MOG; CCG; LGG	R	18, 19	89	38	−92	−6	4.75
IFG (orbital part); IFG (triangular part)	L	11, 45, 47	254	−42	34	−8	4.62
IOG; MOG; LGG	L	18, 19	170	−26	−102	−8	4.23
Cerebellum	R		114	16	−82	−38	4.18
STP; MTP	R	38	52	42	14	−26	4.17
SFG; SFG (medial part)	L	10	49	−10	66	26	4.00
FFG; parahippocampal gyrus; amygdala; hippocampus	R	28, 34	143	36	−8	−32	3.83
FFG; IOG; ITG	L		42	−42	−64	−8	3.82
Thalamus	L		38	−2	−10	8	3.81
SFG (medial part)	L	10	51	−2	60	16	3.53
Positive > neutral							
Hippocampus; amygdala	L	28, 34	330	2	−20	−18	5.08
Caudate	R/L		204	12	0	20	4.83
Cerebellum	R		448	24	−76	−38	4.79
Cerebellum; vermis	R/L		121	4	−52	−42	4.72
Thalamus	R/L		209	2	−4	0	4.59
MTG; ITG	R	21	50	54	−6	−20	4.31
STP; IFG (orbital part); insula	L	28, 38, 47	39	−26	10	−24	4.24
STP; MTP; parahippocampal gyrus; IFG	R	28, 38	125	32	14	−32	4.20
SFG; SFG (medial part); ACC	L	9, 10	412	−4	58	8	4.20
IFG (orbital part); IFG (triangular part); STP	L	11, 45, 47	400	−44	26	−18	4.13
Precuneus	L		85	−26	−50	16	4.12
Hippocampus	R		65	32	−34	0	4.00
ACC	R/L	24, 32	59	2	30	−4	3.93
MTG; STP; ITG; MTP	L	20, 21, 38	92	−48	−6	−22	3.85
Caudate	R		48	10	−24	26	3.71
MTG	L	21	44	−54	−26	−12	3.68
Thalamus	L		42	−2	−30	−2	3.54
MTG; angular gyrus	L	39	40	−52	−58	20	3.39

Coordinates are given in MNI space. STP, superior temporal pole; MTP, middle temporal pole; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; LGG, lingual gyrus; IOG, inferior occipital gyrus; MOG, middle occipital gyrus; CCG, calcarine gyrus; FFG, fusiform gyrus; ACC, anterior cingulate cortex.

constitute a potential therapeutic intervention in anxiety disorders [80].

Studies on the neural substrates of emotion regulation demonstrated that down-regulation of negative emotions is associated with an increase of activation in prefrontal areas (e.g. DLPFC), while amygdala activity is decreased, resulting in a negative correlation between these brain regions [81–83]. Accordingly, impaired emotion regulation in psychiatric disorders is often described as a deficient ability of prefrontal areas to down-regulate limbic regions, characterized by increased amygdala and decreased PFC activity [6,39], and resulting in a weaker functional coupling between these brain areas [84]. These assumptions are not supported by our results, because a simultaneous increase in activation of the amygdala and frontal regions was found for negative versus neutral words which was stronger in more anxious subjects. That is, our subjects with higher trait anxiety recruited even more prefrontal areas (left DLPFC) during negative-word reading, while amygdala activation remained high. Although this effect was not significant for subclinical depression, there was a trend for a positive correlation between BDI scores and the association between left amygdala and left medial superior frontal gyrus (also BA 9) during negative- as compared to neutral-word reading. Although this result failed significance by 20 voxels, the trend is in the same direction as for trait anxiety: a positive association between subclinical depressive symptoms and the functional coupling between left amygdala and left DLPFC-underscoring the relevance of this brain region.

At first sight, our results seem to contradict other findings. Yet, a closer look into the literature reveals two patterns: (1) decreased prefrontal activation in psychiatric patients, indicating less efficient emotion regulation, and (2) increased or more widespread recruitment of prefrontal areas in highly anxious subjects [85], and depression [86,87]. The latter pattern was interpreted by Campbell-Sills et al. as deficient down-regulation, taking compensatory processes into account [85]. It was also shown that a stronger functional coupling between left amygdala and prefrontal regions (orbitofrontal cortex, dorsal medial prefrontal cortex) during reappraisal led to less intense negative affect in healthy subjects, indicating that successful emotion regulation does not necessarily include amygdala down-regulation [88]. Thus, although not consistent with all findings in the literature, our results seem to support the idea of an anxiety-driven increase of prefrontal activation, indexing compensatory processes that even exist in subclinical trait anxiety. Thus, the pattern of corticolimbic interaction may well be more complex than a mere unilateral frontal top-down control of subcortical emotion-processing regions such as the amygdala. Note that while others reported an association between PFC activation and subjective intensity of negative affect or anxiety (e.g. [88]), we cannot provide data to this issue. Emotion-regulation processes were not our focus and we thus did not ask for subjective affect.

Concerning the laterality of prefrontal activation, Davidson and colleagues [89,90] postulated that the left hemisphere was involved in the approaching of positive emotional stimuli whereas the right hemisphere was supposed to be responsible for the withdrawal from negative emotional material. This is not evident in our data. Note, however, that linguistic stimuli are very different from those used by Davidson (e.g. film clips designed to induce emotions). It is questionable whether the idea of approach and avoidance applies to words as emotional stimuli, given that they largely rely on a left-hemispheric network [69].

Finally, we considered gender differences, given that differences between men and women were reported for brain activation in response to positive and negative words [57] and to fearful faces

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

[58]. We thus included sex as a covariate in all our analyses, and found only one significant result indicating a stronger functional connectivity between the left amygdala and several frontal regions (frontal gyrus and postcentral gyrus) in women.

This result agrees with Hofer et al. [57], who found stronger hippocampal-gyrus activation for women versus men during negative-word reading. Killgore et al. [58] found a trend towards a stronger activation of the prefrontal lobes in women, which is also in accordance with our results. However, since covaried out, all our results are independent of gender effects and it must be considered that the influence of gender on brain activation was not the focus of our study. Therefore, our sample size of 10 female and 10 male subjects can provide neither the sufficient statistical power nor the methodological quality (e.g. no matching for age and between the groups, no control for the women's menstrual phase) to draw meaningful conclusions from the observed effects.

Some other limitations should be pointed out in the current study. First, because the words used here has been rated before by Kissler et al. [56], we did not include any behavioural or subjective measure or rating of the stimuli. We have no reason to believe that our sample is different from the one from Kissler and colleagues, as the demographic background and cultural upbringing is most similar. Our approach thus was to use standardized stimuli (as with emotional pictures or sounds [76,91]), and to rely on the available ratings. Next, the assessment of our main variables, subclinical depression and anxiety, was only performed by self-report measures, possibly limiting overall validity. On the other hand, both BDI and STAI are frequently used research instruments [46,48,92,93]. Nevertheless, future studies investigating associations between neural activation and aspects of subclinical depression or anxiety should use a broader spectrum of rating instruments, and should consider the influence of genetic variables or familial aggregation as potential risk factors. Note also that we did not include a structured diagnostic screening instrument such as the SCID interview, which limits overall reliability. However, all our subjects were carefully screened by an experienced clinical psychologist for any current or former psychiatric symptoms. In view of the well-known symptom overlap and the high rate of comorbidity between anxiety and depression the scores of our self-assessment instruments BDI and STAI-Trait were not independent (Pearson correlation $r = 0.64$, $p < 0.05$, Spearman's rho $r = 0.68$, $p < 0.05$), thus not allowing for a complete discrimination between effects of trait anxiety and effects of depressive symptoms. This of course is a limitation of our study, since we cannot provide information concerning the unique influence of trait anxiety and depression on brain activation. It must however be noted that discriminating anxiety- and depression-related symptoms is not without problems in the clinical area and might be hardly possible in a subclinical sample. Furthermore, variances within the STAI-T and especially the BDI scores are relatively small in our non-clinical and healthy study sample. However, we do not believe that this constitutes a genuine problem, since it reflects the normal distribution of a clinically unaffected sample, and also indicates that our results represent strong effects. Finally, we did not focus on emotion-regulation processes, but it would have been interesting to include a more explicit instruction, asking subjects to intensify or re-appraise their negative feelings.

In sum, this is the first study to show an association between subclinical anxiety and depression, and the neural basis of the processing and unintentional regulation of emotional words. Our results highlight the importance of studying subclinical samples, in addition to group comparisons between patients and controls, and underscore the relevance of limbic and prefrontal structures for understanding the neural basis of normal and impaired emotion processing.

Conflict of interest

All authors state that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence or bias their work.

Acknowledgements

This study was supported by grants of Interdisziplinäres Zentrum für klinische Forschung (IZKF) of the Medical Faculty of Muenster University (Do3/021/10 to CD and PZ) and the SFB TRR 58 subproject C1 to PZ. The named funding sources were not involved in study design, collection, analysis or interpretation of data.

References

[1] Davis M, Whalen PJ. The amygdala: vigilance and emotion. Molecular Psychiatry 2001;6:13–34.
[2] Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 2005;48:175–87.
[3] Etkin A, Wager TD. Brain systems underlying anxiety disorders: a view from neuroimaging. In: Simpson HB, Schneier F, Neria F, Lewis-Fernández R, editors. Anxiety disorders: theory, research, and clinical perspectives. Cambridge University Press; 2010. p. 192–203.
[4] Suslow T, Konrad C, Kugel H, Rumstadt D, Zwitserlood P, Schöning S, et al. Automatic mood-congruent amygdala responses to masked facial expressions in major depression. Biological Psychiatry 2010;67:155–60.
[5] Stuhrmann A, Suslow T, Dannlowski U. Facial emotion processing in major depression: a systematic review of neuroimaging findings. Biology of Mood & Anxiety Disorders 2011;1.
[6] Siegle GJ, Thompson WK, Carter CS, Steinhauer SR, Thase ME. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biological Psychiatry 2007;61:198–209.
[7] Domschke K, Dannlowski U. Imaging genetics of anxiety disorders. NeuroImage 2010;53:822–31.
[8] Straube T, Mentzel HJ, Miltner WHR. Common and distinct brain activation to threat and safety signals in social phobia. Neuropsychobiology 2005;52:163–8.
[9] Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biological Psychiatry 2002;51:693–707.
[10] Van den Heuvel OA, Veltman DJ, Groenewegen HJ, Witter MP, Merkelbach J, Cath DC, et al. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. Archives of General Psychiatry 2005;62:922–33.
[11] Schmidt S, Mohr A, Miltner WHR, Straube T. Task-dependent neural correlates of the processing of verbal threat-related stimuli in social phobia. Biological Psychology 2010;84:304–12.
[12] Hamann S, Mao H. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. Neuroreport 2002;13:15–9.
[13] Straube T, Sauer A, Miltner WHR. Brain activation during direct and indirect processing of positive and negative words. Behavioural Brain Research 2011;222:66–72.
[14] Isenberg N, Silbersweig D, Engelien A, Emmerich S, Malavade K, Beattie B, et al. Linguistic threat activates the human amygdala. Proceedings of the National Academy of Sciences of the United States of America 1999;96:10456–9.
[15] Herbert C, Herbert BM, Pauli P. Emotional self-reference: brain structures involved in the processing of words describing one's own emotions. Neuropsychologia 2011;49:2947–56.
[16] Cunningham W, Raye CL, Johnson MK. Implicit and explicit evaluation: FMRI correlates of valence, emotional intensity, and control in the processing of attitudes. Journal of Cognitive Neuroscience 2004;16:1717–29.
[17] Kanske P, Kotz S. Emotion triggers executive attention: anterior cingulate cortex and amygdala responses to emotional words in a conflict task. Human Brain Mapping 2011;32:198–208.
[18] Strange BA, Henson RN, Friston KJ, Dolan RJ. Brain mechanisms for detecting perceptual, semantic, and emotional deviance. NeuroImage 2000;12:425–33.
[19] Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, et al. In search of the emotional self: an fMRI study using positive and negative emotional words. American Journal of Psychiatry 2003;160:1938–45.
[20] Maddock RJ, Buonocore MH. Activation of left posterior cingulate gyrus by the auditory presentation of threat-related words: an fMRI study. Psychiatry Research 1997;75:1–14.
[21] Maddock RJ, Garrett AS, Buonocore MH. Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. Human Brain Mapping 2003;18:30–41.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

[22] Lewis P, Critchley HD, Rotshtein P, Dolan RJ. Neural correlates of processing valence and arousal in affective words. Cerebral Cortex 2007;17:742–8.
[23] Tabert MH, Borod JC, Tang CY, Lange G, Wei TC, Johnson R, et al. Differential amygdala activation during emotional decision and recognition memory tasks using unpleasant words: an fMRI study. Neuropsychologia 2001;39:556–73.
[24] Hsu DT, Langenecker SA, Kennedy SE, Zubieta J-K, Heitzeg MM. fMRI BOLD responses to negative stimuli in the prefrontal cortex are dependent on levels of recent negative life stress in major depressive disorder. Psychiatry Research 2010;183:202–8.
[25] Kuchinke L, Jacobs AM, Grubich C, Võ ML-H, Conrad M, Herrmann M. Incidental effects of emotional valence in single word processing: an fMRI study. NeuroImage 2005;28:1022–32.
[26] Dannlowski U, Ohrmann P, Bauer J, Kugel H, Arolt V, Heindel W, et al. Amygdala reactivity to masked negative faces is associated with automatic judgemental bias in major depression: a 3 T fMRI study. Journal of Psychiatry and Neuroscience 2007;32:423–9.
[27] Dannlowski U, Ohrmann P, Bauer J, Kugel H, Arolt V, Heindel W, et al. Amygdala reactivity predicts automatic negative evaluations for facial emotions. Psychiatry Research 2007;154:13–20.
[28] Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology 2010;35:169–91.
[29] Kim J, Gorman J. The psychobiology of anxiety. Clinical Neuroscience Research 2005;4:335–47.
[30] Lim S, Kim JH. Cognitive processing of emotional information in depression, panic, and somatoform disorder. Journal of Abnormal Psychology 2005;114:50–61.
[31] McNally RJ, Riemann BC, Louro CE, Lukach BM, Kim E. Cognitive processing of emotional information in panic disorder. Behaviour Research and Therapy 1992;30:143–9.
[32] Maidenberg E, Chen E, Craske M, Bohn P, Bystritsky A. Specificity of attentional bias in panic disorder and social phobia. Journal of Anxiety Disorders 1996;10:529–41.
[33] Mathews A, Klug F. Emotionality and interference with color-naming in anxiety. Behaviour Research and Therapy 1993;31:57–62.
[34] Amir N, McNally RJ, Riemann BC, Burns J, Lorenz M, Mullen JT. Suppression of the emotional Stroop effect by increased anxiety in patients with social phobia. Behaviour Research and Therapy 1996;34:945–8.
[35] Becker E, Rinck M, Margraf J, Roth WT. The emotional Stroop effect in anxiety disorders: general emotional or disorder specificity. Journal of Anxiety Disorders 2001;15:147–59.
[36] Mitterschiffthaler MT, Williams SCR, Walsh ND, Cleare AJ, Donaldson C, Scott J, et al. Neural basis of the emotional Stroop interference effect in major depression. Psychological Medicine 2008;38:247–56.
[37] Ochsner KN, Gross JJ. The cognitive control of emotion. Trends in Cognitive Sciences 2005;9:242–9.
[38] Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron 2008;59:1037–50.
[39] Bishop SJ. Neurocognitive mechanisms of anxiety: an integrative account. Trends in Cognitive Sciences 2007;11:307–16.
[40] Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: implications for major psychiatric disorders. Biological Psychiatry 2003;54:515–28.
[41] Cisler JM, Olatunji BO, Feldner MT, Forsyth JP. Emotion regulation and the anxiety disorders: an integrative review. Journal of Psychopathology and Behavioral Assessment 2010;32:68–82.
[42] Maletic V, Robinson M, Oakes T, Iyengar S, Ball SG, Russell J. Neurobiology of depression: an integrated view of key findings. International Journal of Clinical Practice 2007;61:2030–40.
[43] Monroe SM, Simons AD. Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. Psychological Bulletin 1991;1:406–25.
[44] Spielberger CD. Anxiety current trends in theory and research, vol. 1. New York, NY: Academic Press; 1972.
[45] Gaffrey MS, Luby JL, Belden AC, Hirshberg JS, Volsch J, Barch DM. Association between depression severity and amygdala reactivity during sad face viewing in depressed preschoolers: an fMRI study. Journal of Affective Disorders 2010;129:364–70.
[46] Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, et al. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron 2004;44:1043–55.
[47] Somerville LH, Kim H, Johnstone T, Alexander AL, Whalen PJ. Human amygdala responses during presentation of happy and neutral faces: correlations with state anxiety. Biological Psychiatry 2004;55:897–903.
[48] Sehlmeyer C, Dannlowski U, Schöning S, Kugel H, Pyka M, Pfleiderer B, et al. Neural correlates of trait anxiety in fear extinction. Psychological Medicine 2011;41:789–98.
[49] Stewart SH, Conrod PJ, Gignac M, Pihl R. Selective processing biases in anxiety-sensitive men and women. Cognition Emotion 1998;12:105–33.
[50] Li W, Zinbarg RE, Paller KA. Trait anxiety modulates supraliminal and subliminal threat: brain potential evidence for early and late processing influences. Cognitive Affective & Behavioral Neuroscience 2007;7:25–36.
[51] MacLeod C, Hagan R. Individual differences in the selective processing of threatening information, and emotional responses to a stressful life event. Behaviour Research and Therapy 1992;30:151–61.
[52] Hout van den M, Tenney N, Huygens K, Merckelbach H, Kindt M. Responding to subliminal threat cues is related to trait anxiety and emotional vulnerability: a successful replication of Macleod and Hagan (1992). Behaviour Research and Therapy 1995;33:451–4.
[53] Ehlers A, Margraf J, Davies S, Roth WT. Selective processing of threat cues in subjects with panic attacks. Cognition Emotion 1988;2:201–19.
[54] Beck AT, Steer RA. Beck Depression Inventory: manual. San Antonio, TX: Psychological Corporation Harcourt Brace Jovanovich; 1987.
[55] Spielberger CD. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.
[56] Kissler J, Herbert C, Peyk P, Junghofer M. Buzzwords: early cortical responses to emotional words during reading. Psychological Science 2007;18:475–80.
[57] Hofer A, Siedentopf CM, Ischebeck A, Rettenbacher MA, Verius M, Felber S, et al. Sex differences in brain activation patterns during processing of positively and negatively valenced emotional words. Psychological Medicine 2007;37:109–19.
[58] Killgore WD, Oki M, Yurgelun-Todd DA. Sex-specific developmental changes in amygdala responses to affective faces. Neuroreport 2001;12:427–33.
[59] Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magnetic Resonance in Medicine 1995;33:636–47.
[60] Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 2003;19:1233–9.
[61] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 2002;15:273–89.
[62] Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 1997;6:218–29.
[63] Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996;383:812–5.
[64] Murray EA. The amygdala, reward and emotion. Trends in Cognitive Sciences 2007;11:489–97.
[65] Herbert C, Ethofer T, Anders S, Junghofer M, Wildgruber D, Grodd W, et al. Amygdala activation during reading of emotional adjectives – an advantage for pleasant content. Social Cognitive and Affective Neuroscience 2009;4:35–49.
[66] Costafreda SG, Brammer M, David AS, Fu CHY. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. Brain Research Reviews 2008;58:57–70.
[67] Shin LM, Kosslyn SM, Mcnally RJ, Alpert NM, Rauch SL, Macklin ML, et al. Visual imagery and perception in posttraumatic stress disorder. Archives of General Psychiatry 1997;54:233–41.
[68] Yoon KL, Fitzgerald DA, Angstadt M, McCarron RA, Phan KL. Amygdala reactivity to emotional faces at high and low intensity in generalized social phobia: a 4-Tesla functional MRI study. Psychiatry Research 2007;154:93–8.
[69] Indefrey P, Levelt WJM. The spatial and temporal signatures of word production components. Cognition 2004;92:101–44.
[70] Wolfensberger SPA, Veltman DJ, Hoogendijk WJG, Boomsma DI, de Geus EJC. Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. NeuroImage 2008;41:544–52.
[71] Joormann J, Cooney RE, Henry ML, Gotlib IH. Neural correlates of automatic mood regulation in girls at high risk for depression. Journal of Abnormal Psychology 2012;121:61–72.
[72] Chambers JA, Power KG, Durham RC. The relationship between trait vulnerability and anxiety and depressive diagnoses at long-term follow-up of generalized anxiety disorder. Journal of Anxiety Disorders 2004;18:587–607.
[73] Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biological Psychiatry 2012;71:286–93.
[74] Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, et al. Emotional bias and inhibitory control processes in mania and depression. Psychological Medicine 1999;29:1307–21.
[75] Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annual Review of Neuroscience 2006;29:565–98.
[76] Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): affective ratings of pictures and instruction manual (Techn. Rep. No. A-8). Gainesville, FL: University of Florida; 2008.
[77] Gross JJ. Emotion regulation: affective, cognitive, and social consequences. Psychophysiology 2002;39:281–91.
[78] Zwanzger P, Fallgatter AJ, Zavorotnyy M, Padberg F. Anxiolytic effects of transcranial magnetic stimulation – an alternative treatment option in anxiety disorders. Journal of Neural Transmission 2009;116:767–75.
[79] De Raedt R, Leyman L, Baeken C, Van Schuerbeek P, Luypaert R, Vanderhasselt MA, et al. Neurocognitive effects of HF-rTMS over the dorsolateral prefrontal cortex on the attentional processing of emotional information in healthy women: an event-related fMRI study. Biological Psychology 2010;85:487–95.
[80] Diemer J, Vennewald N, Domschke K, Zwanzger P. Therapy-refractory panic: current research areas as possible perspectives in the treatment of anxiety. European Archives of Psychiatry and Clinical Neuroscience 2010;260(Suppl.):127–31.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036

[81] Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR, James W, et al. Neocortical modulation of the amygdala response to fearful stimuli. Physiology and Behavior 2003;53:494–501.
[82] Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biological Psychiatry 2005;57:210–9.
[83] Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, et al. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. Journal of Neuroscience 2006;26:4415–25.
[84] Dannlowski U, Ohrmann P, Konrad C, Domschke K, Bauer J, Kugel H, et al. Reduced amygdala–prefrontal coupling in major depression: association with MAOA genotype and illness severity. The International Journal of Neuropsychopharmacology 2009;12:11–22.
[85] Campbell-Sills L, Simmons AN, Lovero KL, Rochlin AA, Paulus MP, Stein MB. Functioning of neural systems supporting emotion regulation in anxiety-prone individuals. NeuroImage 2010;54:689–96.
[86] Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. Journal of Neuroscience 2007;27:8877–84.
[87] Demenescu LR, Renken R, Kortekaas R, van Tol M, Marsman JBC, van Buchem MA, et al. Neural correlates of perception of emotional facial expressions in outpatients with mild-to-moderate depression and anxiety. A multicenter fMRI study. Psychological Medicine 2011;41:2253–64.
[88] Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL. Amygdala-frontal connectivity during emotion regulation. Social Cognitive and Affective Neuroscience 2007;2:303–12.
[89] Davidson RJ. Anterior cerebral asymmetry and the nature of emotion. Brain Cognition 1992;151:125–51.
[90] Davidson RJ. Emotion and affective style: hemispheric substrates. Psychological Science 1992;3:39–43.
[91] Lang PJ, Bradley MM. International affective digitized sounds (IADS): stimuli, instruction manual and affective ratings (Tech. Rep. No. B-2). Gainsville, FL: University of Florida; 1999.
[92] Fakra E, Hyde LW, Gorka A, Fisher PM, Muñoz KE, Kimak M, et al. Effects of HTR1A C(-1019)G on amygdala reactivity and trait anxiety. Archives of General Psychiatry 2009;66:33–40.
[93] Abercrombie HC, Schaefer SM, Larson CL, Oakes TR, Lindgren KA, Holden JE, et al. Metabolic rate in the right amygdala predicts negative affect in depressed patients. Neuroreport 1998;9:3301–7.

Please cite this article in press as: Laeger I, et al. Amygdala responsiveness to emotional words is modulated by subclinical anxiety and depression. Behav Brain Res (2012), http://dx.doi.org/10.1016/j.bbr.2012.05.036