Neuroimaging in Social Anxiety Disorder – a meta-analytic review resulting in a new neurofunctional model

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Abstract

Social anxiety disorder (SAD) is one of the most frequent anxiety disorders. The landmark meta-analysis of functional neuroimaging studies by Etkin & Wager (2007) revealed primarily the typical fear circuit as overactive in SAD. Since then, new methodological developments such as functional connectivity and more standardized structural analyses of grey and white matter have been developed. We provide a comprehensive update and a meta-analysis of neuroimaging studies in SAD since 2007 and present a new model of the neurobiology of SAD. We confirmed the hyperactivation of the fear circuit (amygdala, insula, anterior cingulate and prefrontal cortex) in SAD. In addition, task-related functional studies revealed hyperactivation of medial parietal and occipital regions (posterior cingulate, precuneus, cuneus) in SAD and a reduced connectivity between parietal and limbic and executive network regions. Based on the result of this meta-analysis and review, we present an updated model of SAD adopting a network-based perspective. The disconnection of the medial parietal hub in SAD extends current frameworks for future research in anxiety disorders.

Keywords:

Social anxiety disorder; neurobiology; MRI; connectivity; anxiety; treatment, network; brain structure

1. Introduction

Anxiety disorders are the most frequent mental disorders, affecting 7-14% of the general population at any given time point (Baxter et al., 2013; Wittchen et al., 2011) and over 25% at least once in a lifetime (Kessler et al., 2005). Within anxiety disorders, Social Anxiety Disorder (SAD) is the second largest group (Wittchen et al., 2011). Clinically, patients with SAD are afraid of and avoid situations associated with potential exposure to unfamiliar people or to possible scrutiny by others or endure such situations only with intense anxiety or distress (American Psychiatric Association, 2000).

In 2007, Etkin and Wager collated the then available functional magnetic resonance imaging (fMRI) studies in a meta-analysis and formulated a neurobiological model based on these studies (Etkin and Wager, 2007). This model comprised brain regions known as the "fear circuit" (e.g. Etkin, 2010; LeDoux, 2000; Marek et al., 2013), namely the amygdalar region, insula and the adjacent inferior frontal gyrus, in addition to the fusiform gyrus and superior temporal gyrus. Further neuroimaging methods such as Positron Emission Tomography (PET) and Single Positron Emission Tomography (SPECT) at that time were in agreement with this model reporting an increased blood flow in the amygdala (Tillfors et al., 2001; Tillfors et al., 2002), hippocampus (Tillfors et al., 2002) and insula (Warwick et al., 2006), which decreased ("normalized") with psychopharmacological therapy (Fehm et al., 2005; Tillfors et al., 2002; Warwick et al., 2006) or exposure therapy (Van Ameringen et al., 2004).

Since this landmark meta-analysis of Etkin and Wager in 2007, a large number of studies have added important information regarding brain function in SAD. In addition, connectivity and network-based methods have extended the perspectives of understanding brain systems (Park and Friston, 2013). Recent reviews have covered specific issues relating to anxiety disorders and SAD. One meta-analysis addressed functional correlates of facial emotion recognition in SAD (Hattingh et al., 2013), other reviews focused on structural changes in SAD either in white matter (Ayling et al., 2012) or in grey matter (Ferrari et al., 2008), and the comprehensive review from Freitas-Ferrari (Freitas-Ferrari et al., 2010) has covered studies until 2009. But none of these reviews provided a new or updated model of the neurobiology of SAD integrating the findings of the different methodological approaches.

Therefore, this review aims at giving an overview of neuroimaging studies from the last six years, now also including methods which address a) connectivity as a new analytical method aiming at uncovering networks in addition to specific brain regions with more or less isolated dysfunctions, b) structural methods showing differences between patients with SAD and healthy subjects in white and grey matter and c) changes due to therapy or therapeutic strategies, which tend to uncover mechanisms of successful treatment and treatment prediction factors. Summarizing these results in an updated neurofunctional model of SAD, we aim to provide further insight into the psychopathological mechanisms of SAD and highlight open questions in this field.

2. Methods

2.1. Literature search and selection

We searched Medline and PsycInfo reference lists using the following keywords: 'MRI', 'functional', 'tomography', 'tractography', 'DTI', 'cortical thickness', 'voxel-based morphometry', 'connectivity' and 'resting state' crossed one by one with the terms 'social anxiety disorder' and 'social phobia'. Studies available from *October 2006* to 1st May 2014 were included (including studies in press). A second search included functional MRI studies published before 2006. Each hit was cross-checked and evaluated resulting in 104 references after elimination of duplicates and the first screening of titles and abstracts (PRISMA diagram (Moher et al., 2009): see figure 1). To be eligible studies must have included a group of adult patients with social anxiety disorder and a comparison group of healthy subjects, examining grey or white matter volume, functioning or changes in functioning after intervention. We had to exclude 28 of the 104 references for they did not meet the inclusion criteria. Exclusion was due to: review paper (n=4), references turned out to be no original research study of neuroimaging (n=5), studies using SPECT or PET (n=6, Ahs et al., 2006; Åhs et al., 2009; Evans et al., 2009; Laukka et al., 2011; Schneier et al., 2009; Warwick et al., 2008), age of participants (n=4, e.g. Battaglia et al., 2012; Guyer et al., 2008), mixed samples including patients without a diagnosis of SAD (n=3, Krain et al., 2008), studies about anxiety disorders other than SAD (n=2), studies being included in the meta-analysis by Etkin and Wager (n=1), no clear comparison between SAD patients and healthy control subjects (HCS, n=2), focus on time-related instead of location-related questions (n=1). In those studies, where effects of therapy and therapeutic interventions were the focus, we also included studies which contrasted within groups of patients (pre/post therapy) or between groups of patients (with/without intervention). Overall, 76 studies were included into the review.

There are 4 main categories of the studies: a) functional, b) changes after intervention, c) connectivity and d) structural. An overview of the included studies and the demographic data of the included samples are given in the supplementary table 1. A number of studies have more than one focus and therefore are mentioned in more than one category.

The vast majority of studies investigated functional alterations in subjects with SAD. We included a total of 40 studies, which could be subdivided into two groups: One group used stimuli that activate the typical fears of social anxiety disorders, such as faces, phobia related words, or social situations (32 studies). Within this group, two studies focused on temporal aspects of habituation. The second group (8 studies) used non-specific emotional or general cognitive tasks without relation to social fears.

In total 19 studies investigated functional changes in relation to a therapeutic intervention. Six of these studies applied psychotherapy and tested changes due to therapy (Goldin and Gross, 2010, Goldin et al., 2012, Goldin et al., 2012, Goldin et al., 2013, Mansson et al., 2013, Klumpp et al., 2013a). Five other studies investigated the effects of pharmacotherapy with selective serotonin inhibitors (SSRI, 6-

12 weeks) in SAD (Schneier et al., 2011, Cassimjee et al., 2010, Phan et al., 2013, Pantazatos et al., 2014, Gimenez et al., 2014). Five studies looked at the neural circuits of emotion regulation in SAD, which is one of the most important aspects of psychotherapy (Goldin et al., 2009b, Goldin et al., 2009a, Ziv et al., 2013b, Brühl et al., 2013, Gaebler et al., 2014). Three other publications focused on the effects of a single application of intranasal oxytocin (Labuschagne et al., 2010, , in press, Dodhia et al., in press) in SAD patients.

One study investigated which functional activations during confrontation with angry facial expressions and threatening natural scenes were correlated with symptom changes after 12 weeks of cognitive behavioural therapy (CBT, Doehrmann et al., 2013) and could therefore serve as possible predictors for response to CBT. This study did not investigate the biological effects of a therapeutic intervention and is therefore not given in the results table (table 4), but was included due to the outstanding and very innovative approach.

Most studies on connectivity in SAD used ROI or seed based approaches. In total, the search revealed 20 studies in this field, of which four (Ding et al., 2011; Liao et al., 2010a; Liao et al., 2010b; Liao et al., 2011) are based on (presumably strongly) overlapping subjects in both the patients and the healthy participants (personal information from corresponding author H. Chen, but no clear information on the degree of overlap). Of these 20 studies, eleven used resting state as acquisition method, eleven measured functional connectivity during classical task-related fMRI (two studies did both methods). Two studies compared extended networks between patients with SAD and healthy subjects (Liao et al., 2010a, Arnold Anteraper et al., 2014), another focused on regional homogeneity measures in resting state (Qiu et al., 2011). Due to the different methods, these three studies are only reported in the results section (not in the table 5).

Overall, 14 studies addressed structural changes in SAD. Seven studies focused on grey matter changes using whole-brain analyses (Syal et al., 2012, Talati et al., 2013, Liao et al., 2011, Frick et al., 2013a, Liao et al., 2011, Meng et al., 2013, Bruhl et al., 2014), two others did only region of interest (ROI)-based analyses (Irle et al., 2010, Machado-de-Sousa et al., 2014). One of the studies reported on two independent samples, which we here present as two studies (Talati et al., 2013). One other of the included studies described changes in grey matter in SAD patients due to treatment with escitalopram (Cassimjee et al., 2010) and is therefore included in the section on intervention effects.

Seven studies investigated white matter alterations in SAD. Of these, two measured only white matter volume (Machado-de-Sousa et al., 2014, Meng et al., 2013). Three studies used ROI-based approaches (Baur et al., 2011, Baur et al., 2013a, Liao et al., 2011). Two used a whole brain approach (Phan et al., 2009, Qiu et al., 2014), while two others combined ROI-analyses and fibre tracking (Baur et al., 2013a; Liao et al., 2011).

Results of one multimodal study including structural data together (Frick et al., 2014) are reported in the results section of the text.

2.2. ALE Meta-analysis procedure

We investigated functional differences between patients suffering from SAD and healthy control subjects with activation likelihood estimation (ALE, Eickhoff et al., 2012; Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) using GingerALE2.3.1 (http://www.brainmap.org/ale/). We extracted the coordinates of cluster given as different between SAD and HCS in a whole-brain analysis from the publications (n=36), but excluded studies that used an approach based on anatomical regions of interest (ROIs, n=2) and studies not investigating whole-brain group contrasts (n=2). The steps involved in this estimation are explained in detail in the documentation and elsewhere (Turkeltaub et al., 2012). The ALE represents the likelihood of observing activity in a voxel in at least one group of participants (Turkeltaub et al., 2012). For studies reporting their results in MNI space, the coordinates were transformed into the Talairach system using the MNI2Tal function in GingerALE. The statistical threshold was set at $p<0.05$ FDR corrected using a minimum cluster size of 200 mm^3. Furthermore, we computed one ALE meta-analysis including the peak voxel reported by Etkin & Wager 2007. To test for effects due to the type of stimulation, we computed the same two ALE meta-analysis including only those studies using SAD-specific stimuli (results see supplementary material). All results are given in Talairach coordinates and were overlaid onto a standard brain (Colin) using Mango (http://ric.uthscsa.edu/mango) for presentation purposes (Lancaster et al., 2010).

3. Results

3.1. Functional magnetic resonance imaging in SAD

Of the 40 included fMRI studies, 32 used stimuli specifically addressing SAD fears ("specific"), whereas eight studies presented unspecific stimuli to SAD patients compared to healthy controls. The term *specific* here refers to stimuli that activate the social anxiety in SAD, such as for instance negative facial expressions, social situations or respective verbal stimuli. So-called "*unspecific*" tasks examined neurofunctional networks independent of the social fears and social anxiety disorder such as anticipation of emotional stimuli and purely cognitive tasks. Two additional studies examined differences in temporal changes between patients and controls. For details on tasks and participants, please refer to table 1.

3.1.1. Specific tasks (table 2):

The following specific tasks were used: emotional faces (22 studies, including the two studies investigating habituation), social transgression or criticism (Blair et al., 2010; Blair et al., 2011b, Ziv et al., 2013a), self-referential cognitions (Blair et al., 2008a, Ziv et al., 2013a), exposure to scrutiny

(Gimenez et al., 2012), anticipation of public speaking (Boehme et al., in press), pictures of social situations (Nakao et al., 2011), negative emotional voices (Quadflieg et al., 2008) and phobia related words (Schmidt et al., 2010).

Compared to healthy controls the most consistent findings were a higher activation of the bilateral amygdala, bilateral insula, the bilateral medial and ventrolateral prefrontal cortex (MPFC, VLPFC) as well as anterior cingulate (ACC) and bilateral parietal cortex (ParC). Consistent, but in less studies, were increased activations in bilateral hippocampus (HC) and fusiform gyrus (FFG). The most mixed findings were reported for the bilateral dorsolateral prefrontal cortex (DLPFC), where the ratio of increased to decreased activation (frequency) was 5:4 on both sides, as well as for the left caudate/ncl. accumbens region (2:2). All other regions had one or no studies showing reduced activation in SAD. The temporal cortex (TC) region showed the strongest effects of a preponderance of one side with increased activity in eight studies on the right side, however also one study reporting decreased activity. Only two studies reported increased activity in the left temporal cortex.

Two other studies in this group used emotional faces in SAD compared to a HCS group, but focused on differences of habituation over time between the two groups instead of comparing activity in the different regions (Campbell et al., 2007; Sladky et al., 2012). Campbell and colleagues (Campbell et al., 2007) found differential effects of time between the groups only when confronted with fearful, happy and angry faces, but not in the contemptuous facial expression condition. In the bilateral amygdala, this study identified rather a delayed and prolonged increase of amygdala activity, which was paralleled by developments over time in bilateral DLPFC. The other study (Sladky et al., 2012) found rather a continuous decrease of activity over time in bilateral amygdala, orbitofrontal cortex (OFC) and right pulvinar, whereas in healthy controls this decrease or habituation was not detected.

3.1.2. Unspecific tasks (table 2):

The unspecific tasks were the following: anticipation (Brühl et al., 2011) and perception of emotional stimuli without specific social content (Shah et al., 2009, Gaebler et al., 2014), reward anticipation and outcome (Richey et al., 2014), a cognitive task (Sareen et al., 2007), and human vs. computer interaction (trust game, Sripada et al., 2009, Sripada et al., 2013). One study used an unspecific cognitive task, but aimed at performance-induced stress, which is then again a typical fear among SAD patients (Koric et al., 2012), which positions this study slightly between the two groups.

In general, studies using unspecific stimuli showed similar findings as those using specific stimuli, such as increased activation in bilateral amygdala, bilateral insula and left DLPFC, temporal, parietal and occipital cortex, and thalamus. The left caudate/ncl. accumbens area was, similarly to the studies using specific stimuli, more active in two, and also less active in two studies.

Studies using unspecific stimuli differed most strongly from those using specific stimuli in less consistent activation in MPFC, VMPFC/OFC and VLPFC. However, due to the low number of studies

and the variety of tasks and systems in this category (e.g. reward, emotion, cognition), the cumulative results are here less uniform and less bilaterally distributed.

3.1.3. Additional correlation analyses in fMRI studies

Some studies have done post-hoc correlation analyses between brain activation and psychometric measures on top of the between-group comparisons. Most of these correlations were computed either using the Liebowitz Social Anxiety Scale (LSAS, Liebowitz, 1987) or general trait anxiety measured with the STAI-T (Spielberger et al., 1970), single studies used the Social Phobia Inventory (SPIN, Connor et al., 2000) or the Brief Fear of Negative Evaluation Scale (Leary, 1983). As in prior, here not included studies (e.g. Phan et al., 2006), the most consistent result in the here reviewed studies was a positive correlation between amygdala activity and severity of social anxiety symptoms (e.g. Goldin et al., 2009b, Ball et al., 2012, Shah et al., 2009, Evans et al., 2008, Frick et al., 2013b, however negative correlation in Laeger et al., 2014) and with general anxiety (Ball et al., 2012, Richey et al., 2014, Cooney et al., 2006), although a couple of studies found no correlations (e.g. Nakao et al., 2011, Klumpp et al., 2010, Ziv et al., 2013a, Sareen et al., 2007, Blair et al., 2010, Gimenez et al., 2012). Further correlations were reported between insula activity and LSAS (Ball et al., 2012) or SPIN (Schmidt et al., 2010), although here also a number of studies found no correlations (e.g. Shah et al., 2009). Further positive correlations were reported for occipital and occipitotemporal regions (Brühl et al., 2011), cingulate (Ball et al., 2012, Goldin et al., 2009b) and VLPFC (Koric et al., 2012), however, one study reported a negative correlation between LSAS and MPFC activity (Blair et al., 2011b). One study reported a more complex, inverted u-shaped correlation between LSAS and activity in midbrain, thalamus, basal ganglia and orbito- and prefrontal regions (Pujol et al., 2013).

3.2. ALE meta-analysis of functional studies (table 3)

Out of the 40 functional MRI studies, two did only ROI analyses and two other studies did not compute classical between-group comparisons, but focused on time-related questions (habituation). Therefore, data from 36 studies were included in the meta-analysis. In total 51 experiments (some studies contributed with several experiments, e.g. Ziv et al., 2013a) and the results of the previous meta-analysis (Etkin and Wager, 2007) were included in the meta-analysis, comprising 1993 subjects (patients and healthy controls), which resulted in 255 foci. The ALE meta-analysis confirmed statistically the description given before (table 3, figure 2): The most consistent regions which were more active in SAD compared to HCS were bilateral amygdala and adjacent regions (bed nucleus stria terminalis (BNST) and parahippocampal gyrus (PHG)), right insular cortex, ACC, left DLPFC and MPFC and bilateral occipitotemporal regions. In this meta-analysis, the contrast HCS > SAD, thus activity consistently stronger in control participants compared to patients, did not result in any cluster passing the threshold corrected for multiple comparisons (FDR corrected).

Overall, these results did not change when only including those studies using specific stimuli (supplementary table S1, 28 experiments, 174 foci, 1173 subjects). The main difference when not including the studies with unspecific stimuli was a reduced consistency in occipitotemporal regions (SMG, FFG, lingual gyrus). Otherwise, the activation pattern was very similar.

3.3. Results: treatment effects in functional studies (table 4)

Table 4 shows the results of studies on treatment effects (17 studies used FMRI with a whole brain approach, one structural MRI, one functional connectivity).

Studies investigating chronic application of antidepressants (8-12 weeks, Phan et al., 2013, Schneier et al., 2011, Gimenez et al., 2014, Pantazatos et al., 2014) and of psychotherapeutic treatment (MBSR, 8 weeks, Goldin and Gross, 2010, Goldin et al., 2013, Goldin et al., 2012, and CBT, 9 to 12 weeks, Klumpp et al., 2013a, Mansson et al., 2013) consistently found decreased activation in bilateral occipital and temporal cortical regions. Results in frontal regions were less consistent. Antidepressant treatment was associated with reduced activity in the amygdala in three studies, whereas only two studies using psychotherapy showed this effect. Attention bias modification (ABM), a computerized training aiming at reducing attentional biases, seemed to have opposite effects compared to the other psychotherapeutic approaches. On the structural level, bilateral superior temporal cortex thickness was reduced after 12 weeks of treatment with Escitalopram (Cassimjee et al., 2010).

The acute application of a cognitive emotion regulation instruction was investigated in five studies (Brühl et al., 2013, Goldin et al., 2009b, Goldin et al., 2009a, Ziv et al., 2013b, Gaebler et al., 2014). All studies showed effects of these interventions in the temporal cortex, although not a uniform effect. Three study showed decreased activation in all these regions (Brühl et al., 2013, Goldin et al., 2009b, Gaebler et al., 2014), whereas another study (Goldin et al., 2009a) found a differential pattern with increased activations in inferior parietal and superior temporal regions, but decreased activations in superior and ventral (postcentral) parietal regions. Three studies showed decreased activation in the bilateral FFG. Medial prefrontal regions were rather increased when patients with SAD applied cognitive control, but compared to HCS, this activation was lower in two studies. In the DLPFC, this pattern was less clear: increased activation in SAD compared to HCS in one study, but decreased in another and decreased in SAD when compared to no control intervention. Insular activity was rather reduced with regulation, with mixed findings when comparing SAD and HCS during regulation.

The acute application of oxytocin was investigated in two studies (Labuschagne et al., 2010, , in press), which found no clear pattern (decreased activation in bilateral amygdala, MPFC, ACC and temporal cortex, but increased activation in bilateral FFG). Analyzing resting-state functional connectivity in the same sample (Dodhia et al., in press) resulted in enhancement of prior reduced connectivity between both left and right amygdala and rostral mPFC in SAD, which was reversed in

HCS. Similar interactions were described for connectivity between bilateral amygdala and superior temporal cortex.

Pre-treatment occipitotemporal cortex activation correlated positively with treatment response to 12 weeks of CBT (Doehrmann et al., 2013) and was suggested as response predictor.

3.4. Connectivity in SAD (table 5)

In summary, there are some consistent findings over the studies, whereas others are rather mixed to inconsistent (table 5):

Studies analysing amygdala seeds overall found rather increased connectivity to pre- and orbitofrontal regions (Liao et al., 2010b, Prater et al., 2013, Ding et al., 2011, Danti et al., 2010, Blair et al., 2008a), but some also decreased connectivity in SAD patients (Sladky et al., in press, Liao et al., 2010b, Hahn et al., 2011). From amygdala seeds, connectivity to parietal regions was reduced (Liao et al., 2010b, Hahn et al., 2011, Danti et al., 2010, only increased connectivity to right IPS in Danti et al., 2010). Connectivity to temporal regions was mixed, with decreases in one study (Liao et al., 2010b), but increases in others (Danti et al., 2010; Ding et al., 2011; Liao et al., 2011; Pannekoek et al., 2013). However, when using prefrontal and orbitofrontal seeds, studies detected no significant differences in fronto-amygdalar connections (e.g. Liao et al., 2011). Within frontal brain regions, connectivity was rather reduced in SAD (Ding et al., 2011; Hahn et al., 2011), which could point to disturbed processing within and between (pre)frontal hubs. The results of these studies are given in Table 5.

When choosing subcortical regions such as thalamus and bilateral pallidum as seed, connectivity to temporal and frontal regions was increased (Ding et al., 2011; Gimenez et al., 2012). Inversely, the connectivity between MPFC as seed and thalamus and caudate was also increased (Gimenez et al., 2012 Liao et al., 2011). Connections from frontal, temporal and amygdala seeds to occipital cortical regions were homogeneously increased (Ding et al., 2011; Hahn et al., 2011; Liao et al., 2010b; Liao et al., 2011; Pannekoek et al., 2013), whereas fronto-parietal and amygdalo-parietal connectivity was decreased (Danti et al., 2010; Ding et al., 2011; Hahn et al., 2011; Liao et al., 2010b). One study used the left hippocampus as seed and found homogeneously reduced connectivity to inferior frontal and temporal cortex as well as precuneus and thalamus (Frick et al., 2014).

In a network based approach, one study (Liao et al., 2010a) addressed differences between healthy controls and patients with SAD with regard to pre-defined resting state networks (RSNs, Mantini et al., 2009). In this study, patients with SAD had decreased connectivity in the somato-motor network and the visual network, whereas connectivity in the self-referential network was increased. In four other networks (dorsal attention network, central executive network, default mode network (DMN) and the core network) differences were mixed, in some parts increased, in others decreased connectivity. Another study with a network-based approach (Arnold Anteraper et al., 2014)

systematically used subcortical regions involved in emotion processing (basal ganglia, amygdala, thalamus, periaqueductal grey (PAG)) as seeds. They found increased connectivity in SAD between these subcortical areas and many regions belonging to the DMN, such as between caudate and medial frontal areas, also between putamen bilateral and cingulate and DMPFC. For the Globus pallidus as well as the thalamus, particularly the precuneus was more connected in SAD. The amygdala connectivity was increased to supplementary motor area, temporal and occipitotemporal cortex, and PCC.

Another study measured regional homogeneity (ReHo), which has been correlated to local functional connectivity (He et al., 2007). This study showed increased ReHo in SAD in left occipital cortex and right putamen, and decreased ReHo in left MPFC, right DLPFC and ACC, bilateral angular gyrus, right parietal cortex and right fusiform gyrus.

3.5. Structural-anatomical changes in SAD (table 6)

While there are some studies addressing structural-anatomical brain changes in SAD, the results of these studies are mainly mixed.

Cortical thickness and volume reports are overall not very consistent, and more studies report no changes. For instance, in the hippocampus, two studies report increased volumes, two decreases, and four studies report no difference. In OFC and Insula, each two studies report decreased grey matter (Syal et al., 2012, Talati et al., 2013), with no studies reporting increases. In VLPFC and PCC, only one study reported decreases in grey matter, but only at an uncorrected level (Syal et al., 2012). Decreased cortical thickness or volumes are reported by several studies and for different areas of grey matter but results are mostly inconsistent (table 6a).

The global white matter volume was not different in four studies, only one study reported reduced global white matter (Baur et al., 2013a). However, one study reported globally reduced fractional anisotropy (FA, Baur et al., 2013a). Significant FA changes were detected in the left uncinate fasciculus in three studies (Baur et al., 2013a; Baur et al., 2011, Qiu et al., 2014), with one study finding no difference in the left, but reduced FA in the right uncinate fasciculus (Phan et al., 2009). In the superior fasciculus, apparent diffusion coefficient (ADC) was reduced bilaterally in one study, which also reported reduced FA on the left side (Qiu et al., 2014), which is paralleled by another study (Baur et al., 2011). However, two studies found no difference in at least one side of the superior fasciculus (Baur et al., 2011, Phan et al., 2009) No changes in FA were reported for the inferior fronto-occipital fasciculus in two studies (Baur et al., 2013a; Phan et al., 2009), while one study showed reduced ADC (Qiu et al., 2014). There is no evidence for increased FA in white matter in most of the existing studies (Phan et al., 2009, Baur et al., 2013a, Qiu et al., 2014) except for increased FA and fibre density in one study (Liao et al., 2011). Results of white matter alterations are shown in table 6b.

4. Discussion

In the present study, we provide an overview of neuroimaging studies in SAD since the landmark review of Etkin and Wager (Etkin and Wager, 2007) and, based on this overview, integrate these findings into an updated neurobiological model of SAD (Figure 3). The meta-analysis and model presented by Etkin and Wager had been based purely on functional MRI studies and had presented a model comprising primarily increased activation in brain regions known as the "anxiety circuit", namely the amygdalar region, insula and the adjacent inferior frontal gyrus, further in fusiform gyrus and superior temporal gyrus. Since then, technical developments in neuroimaging such as the use of resting-state and functional connectivity measures (e.g. Buckner et al., 2013) as well as an increasing number of studies on structural changes in grey and white matter have advanced our knowledge of the neurobiology of SAD.

4.1. New extended model of the neurobiology of SAD

Summarizing the studies, we propose a model (Figure 1) which extends the previous model of Etkin and Wager (Etkin and Wager, 2007) by adding increased activations in parietal and medial occipital brain regions. These regions, however, are decoupled from the amygdalar/limbic, the cingulo-opercular and the ventral attention network (Tomasi and Volkow, 2011; Yeo et al., 2011). This decoupling was found at the level of functional and structural connectivity (uncinate fascicle, superior longitudinal fascicle).

These parieto-occipital regions, which were hyperactive but less functionally and structurally connected in SAD, were mostly located in the medial part of the brain. Anatomically, they comprised cuneus, precuneus and the PCC. Considering the known role of these structures as general hubs in the brain – PCC and ventral cuneus have been identified before as the most strongly connected regions in the whole brain (Tomasi and Volkow, 2011) – makes disturbances in this region particularly important. This hub is the centre of the so-called Default-Mode-Network (DMN, Greicius et al., 2003; Raichle et al., 2001; Shulman et al., 1997), which is involved in self-reference and emotion regulation (Raichle et al., 2001; Shulman et al., 1997). Supported by strong whole-brain connectivity, this posteromedial region has been associated with information transfer, multimodal integration, processing of spontaneous thoughts and internal awareness and consciousness (Tomasi and Volkow, 2011). Moreover, this PCC/ventral cuneus region is also involved in the so-called Dorsal Attention Network (DAN, Corbetta and Shulman, 2002). The DAN has functionally been associated with attention, alertness, externally driven cognition and working memory (summarized in Tomasi and Volkow, 2011). The precuneus itself has strong connections to prefrontal, parietal and thalamic regions (Cavanna and Trimble, 2006) and has been related to higher-order cognition, particularly with integrative functions such as visuospatial imagery and control, episodic memory retrieval, self-referential processes, and voluntary shift of attention (Cavanna and Trimble, 2006). The adjacent

cuneus in the occipital cortex has more circumscribed functions in the field of visual information integration and processing (Tomasi and Volkow, 2011).

A decoupling of this posteromedial region from other brain networks could result in a preponderance particularly of cingulo-opercular, limbic and ventral attention networks, which provide bottom-up information of relevance, salience, and stimulus-driven attention (Sylvester et al., 2012).

One important hub linking the DMN with the executive or fronto-parietal network could be located in the anterior insula (Dennis et al., 2011; Sridharan et al., 2008). The anterior insula has long been associated with salience and interoceptive processes (e.g. Craig, 2009; Menon and Uddin, 2010), but also with multiple other processes (Chang et al., 2013). The insula is typically coactivated together with the amygdala (Kohn et al., in press; Robinson et al., 2010), particularly during emotion processing (Stein et al., 2007a), and has strong afferent anatomical connections to the amygdala in rodents (Shi and Cassell, 1998), nonhuman primates (Aggleton et al., 1980; Mufson et al., 1981) and humans (Baur et al., 2013b). In healthy humans, increased insular activity is associated with anxiety (Carlson et al., 2010; Stein et al., 2007b), particularly state anxiety (Baur et al., 2013b). With increasing anxiety, the insula becomes more part of the DMN in healthy humans (Dennis et al., 2011). The particular correlation of insula-amygdala connectivity with *state* anxiety might explain why we found no change in this connection in the here summarized studies in SAD. Another reason for this null-finding here might be that only one study placed a seed into the insula (Klumpp et al., 2012).

Connectivity between the amygdala and pre- and orbitofrontal regions was *decreased* in one study in highly anxious healthy subjects (Kim and Whalen, 2009). In our meta-analysis, however, the connectivity pattern in SAD in this regard was overall not consistent, but showed rather a tendency towards *increased* connectivity.

Overall, the disturbance of the normally well-balanced network system in the human brain in SAD shown here might be an equivalent of the dysbalance between heightened emotional arousal and the enhanced perception of potentially threatening or feared stimuli (Cisler and Koster, 2010) on the one hand and the difficulties to activate and apply top-down control and regulation mechanisms in anxiety disorders (Beck and Clark, 1997; Cisler and Olatunji, 2012; Sylvester et al., 2012). In SAD, the here assembled evidence and the proposed model emphasize for the first time the role of parietal and occipital regions in anxiety disorders in addition to prefrontal and limbic circuits. As previous research had a strong focus on the so-called "fear circuitry" (e.g. LeDoux, 2000; Marek et al., 2013), this study supports the additional role of particularly medial parietal regions in the field of anxiety and anxiety disorders, here shown in the example of SAD. However, as there are no meta-analyses on the neurofunctional circuit in other anxiety disorders except for PTSD (Hayes et al., 2012; Simmons and Matthews, 2012) we cannot make any inferences about the specificity of this model for SAD.

4.2. Fear circuitry in SAD

The circuit of fear and anxiety (e.g. Etkin, 2012; LeDoux, 2000; Marek et al., 2013; Paulus and Stein, 2006) typically comprises amygdala, insula, ACC and prefrontal cortex. All these brain regions were more active in SAD in our analysis. Within the fear/anxiety circuit, amygdala activation is particularly associated with arousal and negative valence (Sergerie et al., 2008), and studies have shown a correlation between amygdala volume and trait anxiety (Baur et al., 2012). The increased activity in the FFG, which was already evident in the meta-analysis by Etkin and Wager (Etkin and Wager, 2007), might represent a specific aspect in SAD, where particularly negative facial expressions are feared by the patients. However, besides its role in face processing (Weiner and Grill-Spector, 2012), the FFG has also consistently been activated with emotional scenic stimuli (Sabatinelli et al., 2011). Therefore, the increased FFG activation in SAD might reflect both, the increased sensitivity to facial stimuli and the heightened reactivity of the emotional system as a whole in SAD.

Prefrontal regions which are more active in SAD in the current meta-analysis, have been associated with emotion regulative functions (recent meta-analyses: Buhle et al., in press; Diekhof et al., 2011; Kalisch, 2009; Kohn et al., in press; Ochsner et al., 2012). However, parietal regions have sparsely been addressed in this field: Amongst the recent meta-analyses in HCS, Kalisch found the angular gyrus bilaterally involved in reappraisal, but discussed parietal activation not specifically (Kalisch, 2009). Diekhof et al. linked increased activations in temporal and parietal cortical regions to the voluntary redirection of attention (Diekhof et al., 2011). Kohn et al. incorporated the superior temporal gyrus and angular gyrus in their model of cognitive emotion regulation (Kohn et al., in press), whereas Buhle et al. associated (lateral) parietal regions with general regulatory and monitoring functions (Buhle et al., in press). Parietal regions, particularly around the intraparietal sulcus, are generally involved in top-down attention control or reorienting (e.g. Corbetta et al., 2008, Hutchinson et al., 2009, Langner and Eickhoff, 2012), which supports the interpretations given in the field of emotion regulation.

From the emotion regulation perspective, there are a number of possible interpretations of the increased activity of prefrontal regions in SAD in studies without explicit top-down control instruction:

One interpretation could be that patients try to use top-down control (reflected in activation in regions as DMPFC/MPFC/DLPFC) but this regulatory effect does not reach the amygdala (because of disturbed connectivity) or is not strong enough to control and regulate the hyperactive amygdala (a).

Another interpretation builds upon studies that show during suppression (which is a less efficient control strategy) an increased activation in about the same prefrontal regions as during reappraisal (e.g. Goldin et al., 2008; Lerner et al., 2009; Phan et al., 2005). Considering these findings, one could also argue that patients with SAD might engage rather suppression than the more successful

reappraisal, which would then be reflected in increased activation in control regions, but insufficient control over amygdalar activity (b).

A third line of interpretation has been brought forward by C. Grillon: He proposes rather a bottom-up effect of amygdala activity increasing MPFC activity (Robinson et al., 2012) which is increased in anxiety and anxiety disorders (c).

All of these interpretations would explain the increased activity in prefrontal areas in SAD vs. HCS in studies without explicit control strategy. Increased connectivity between amygdala seed regions and PFC would be explained with the last interpretation (c). As there are no clear findings about changes in connectivity to amygdala when using PFC seed regions, the first and second interpretation (a, b) cannot be dismissed yet. The second interpretation (b) does not assume any changes/disturbances in MPFC/amygdala connectivity. The first interpretation (a) would be supported by findings in studies on white matter structure: Reduced FA (corresponding to reduced white matter integrity) in the uncinate fascicle (connecting orbito- and maybe also prefrontal regions with the amygdala) was the most consistent finding in DTI studies in this review. This could explain why PFC regions are activated, but don't exert their controlling/regulating effect upon the amygdala.

The results of studies in SAD investigating emotion regulation in fMRI are, unfortunately, based on few studies and quite mixed. In healthy participants, reappraisal/cognitive control during emotional stimulation is associated with very consistent increases of MPFC/DMPFC/PreSMA areas extending into the dACC (e.g. Buhle et al., in press; Diekhof et al., 2011; Kohn et al., 2014). Compared to HCS, MPFC seems to be rather less active in SAD (but see Ziv et al., 2013b), whereas DLPFC and VLPFC are not clearly different and rather not less active in SAD. ACC was reported to be less active in SAD during emotion regulation. These findings could support either a deficient recruitment of PFC areas in SAD or, together with the findings of increased PFC activity without control instruction, support interpretation b.

Interestingly, there seems to be no difference in amygdala activation between SAD and HCS when patients are instructed to reappraise. This, too, would support the second interpretation (b). When comparing patients with and without reappraisal instruction, it is however remarkable that there is no clear pattern of increased recruitment of PFC regions with reappraisal, and also no clear tendency on the level of the amygdala.

Etkin et al. suggested a differentiation between anterior and dorsal parts of prefrontal areas with regard to their function in emotion regulation (Etkin et al., 2011). They proposed that DMPFC/PreSMA, dACC and DLPFC are more involved in evaluative aspects such as appraisal, whereas VMPFC/OFC and sub- and pregenual ACC areas are the primary regions involved in regulating emotional circuits. When considering functional connectivity studies in SAD, one could argue that there might be a disturbance in the communication between the posterior and the anterior parts of this network (see

reduced connectivity to PFC when using OFC seeds in SAD). This could explain why patients with SAD show no clear increase of recruitment of PFC with regulation, but still rather signs of disturbed regulation (mediated by VMPFC/OFC). From a structural perspective, the reduced FA in the uncinate fascicle would support this interpretation.

Overall, these findings point to disturbed emotion regulation networks with maybe a disturbed communication between dorsal evaluative and ventral regulative frontal areas, from which the regulatory information then cannot reach the amygdala fast enough due to structural disturbances.

When interpreting the parietal hyperactivation in SAD together with the disconnection of these parietal regions from other circuits, this could possibly reflect heightened efforts to regulate the increased bottom-up activation coming from the amygdalo-insular circuit. This is evidenced by the increased activation found in studies investigating emotion regulation in SAD. However, these efforts are overall not successful (as visible in the symptoms of SAD) – maybe because the disturbed connectivity hinders regulations. This hypothesis, however, needs further investigation, on the level of resting state and task related connectivity as well as on the structural level. Eventually, studies using transcranial magnetic stimulation (TMS) could further elucidate the connectivity or connectivity failure in SAD.

When comparing these findings to a recent meta-analysis in PTSD (Sartory et al., 2013) which has in the recent version of the DSM-5 (American Psychiatric Association, 2013) been moved out of the anxiety disorders group into a category of its own, a very prominent finding there was a hyperactivity of the precuneus during confrontation with trauma-related stimuli. This was interpreted as enhanced self-referential processing. Another meta-analysis in PTSD (Hayes et al., 2012) found in a network approach more activity in areas associated with salience such as middle and dorsal ACC, SMA and superior temporal gyrus. In contrast to SAD, however, was the lack of increased activity in the amygdalar region in PTSD. A recent meta-analysis in specific phobias (Ipser et al., 2013) found a more similar pattern as here in SAD with an increased activity in bilateral amygdala and also occipital cortical areas, but reduced activation in bilateral temporo-occipital areas in comparison to HCS. In comparison to the here described pattern in SAD, in OCD which has also been regrouped into a category of its own, the most consistent findings until now are in the field of structural differences, both white and grey matter (Radua et al., 2014, Piras et al., 2013; Radua et al., 2010, de Wit et al., 2014, Rotge et al., 2010). Until now, there is no meta-analysis on fMRI findings in OCD, which might be due to the overall lower number of published fMRI studies in OCD. Besides reasons at the level of the number of published studies, the much higher consistency in structural studies might point to a different underlying biology with a focus on midline structures such as corpus callosum and middle/dorsal cingulum, and additionally basal ganglia structures (putamen).

4.3. Implications of the model

From a basic scientific perspective, the extension of the neurofunctional model of SAD and eventually also of other anxiety disorders can serve to generate new hypotheses about vulnerability, development and chronic course of anxiety disorders. The specificity of these findings has not yet been investigated. Eventually, this extended model might hold a potential for the identification of neurocognitive endophenotypes in anxiety, affective and obsessive-compulsive disorders (Robbins et al., 2012).

From a clinical point of view, this perspective of anxiety as a problem of involving central regulatory structures in addition to an overactive amygdalo-insular system could support specific training methods particularly in psychotherapy: For instance meditation training and specific attention trainings could help improving the efficacy of top-down control (Beard et al., 2012; Kozasa et al., 2012) including the connectivity in the respective circuits (Tang et al., 2012). Furthermore, meditation could also influence the emotional arousal 'at baseline' or in rest (Herwig et al., 2010; Larson et al., 2013) and the reactivity to emotional stimuli (Taylor et al., 2011). Therapeutic effects of mindfulness-based treatments have been shown to reduce ('normalize') parietal cortical activity (Goldin and Gross, 2010). However, the effect of treatment in general and of specific types of treatment on connectivity in SAD has not yet been investigated, but might hold further relevant information.

4.4. Summary of the overall data quality

One main strength of the here reviewed studies in SAD is the overall comparability of the samples. This could reflect a characteristic of SAD where patients typically seek treatment (and get diagnosed) around a certain age (mean age of most of the studies around 30 years). The characterization and description of the participant samples is overall of high quality, nearly all studies used the LSAS to characterize the severity of illness. The mean LSAS of the included studies was 75.5 points, with only one study including exceptionally severely affected patients with a mean LSAS of 133, few studies included patients with rather low scores below 60. In all other studies, the range of severity was between 60 and 100. About 50% of the included patients were taking medication, mostly SSRI, which makes the included samples more homogeneous than studies in depression or PTSD. The reporting of the data could in some studies be improved by giving the handedness of the participants.

Research on the neural correlates of the perception of facial expressions in SAD is based on quite a strong amount of studies. However, few studies have used other paradigms such as general emotional stimuli, cognitive tasks, or other SAD-specific stimuli. Therefore, the available data in these areas could be strengthened by further investigations in these functional domains.

In pharmacological treatment studies, the dosage and duration of treatment followed the guidelines, making this group of studies homogeneous and the results rather consistent. Compared to other anxiety disorders, it is interesting that only one study investigated the effects of CBT (Klumpp et al., 2013a), another internet-delivered CBT (iCBT, Mansson et al., 2013), although CBT is the most

frequently used and per guidelines recommended psychotherapy in SAD (Pilling et al., 2013). Despite being very effective, there is still a proportion of patients not responding to classical CBT. Therefore, further research into treatment and response mechanisms is desirable. The studies on therapeutic mechanisms of mindfulness-based stress reduction (MBSR) are of good quality regarding number of participants and duration of the treatment (Goldin and Gross, 2010, Goldin et al., 2013, Goldin et al., 2012). Attentional bias modification (ABM) is a fairly recent treatment approach that has been shown to be successful in reducing social anxiety symptoms in SAD (e.g. Boettcher et al., 2013). However, the one study investigating ABM compared to CBT (both administered via internet) showed rather opposite effects compared to CBT (Mansson et al., 2013). This therapeutic approach should be investigated in future studies with respect to efficacy and neural mechanisms.

The field of functional connectivity in SAD suffers from two main problems: Despite the neurobiological model being quite consistent, the seed regions used so far are widely distributed throughout the brain. With the exception of the amygdalar region many other seed regions have therefore been investigated only single to few studies, such that the convergence in connectivity is rather weak. Using standardized seed regions for analyzing functional connectivity could improve the comparability of studies. The other problem refers to the analytical method used in resting-state fMRI studies. Although resting-state data can be compared (and even pooled) more easily than functional connectivity in task-based data, there is until now no clear gold standard of analysis. Besides multiple measures with possible different meanings (e.g. graph theoretical analyses, regional homogeneity (REHO), amplitude of low frequency fluctuations (ALFF), effective connectivity), the comparison of whole networks between patients and HCS is interesting, but difficult to replicate due to the variability of methods. Furthermore, repeated publications of identical datasets only differing in the analytical method should be clearly labeled as re-analyses. The field of functional connectivity could be strengthened by a) using pre-defined (not functionally defined) seed ROIs and b) reporting at least one standard measure of connectivity in resting state studies making comparisons between studies possible. Alternative, an initiative similar to fMRI reporting guidelines (Poldrack et al., 2008) could help improving the overall standard of reporting resting state and task-related functional connectivity.

The here included structural anatomical studies in SAD used different analytical methods,

4.5. Limitations:

In this meta-analytical review, the available number of studies using facial stimuli in fMRI was overall sufficient (nearly 1400 participants). In the field of non-specific stimuli, the number of studies was rather low, and heterogeneity was high. In the group of studies investigating treatment effects the heterogeneity was even bigger. Studies focusing on functional connectivity in SAD are hampered by general approaches (task-related connectivity versus resting state connectivity). Furthermore,

methodological differences (connectivity, varying seeds, network based analyses, regional homogeneity measures), and the inclusion of four studies which are based on a vastly overlapping dataset, though analyzed with varying methods, was not ideal. These four studies represent a third of all connectivity studies, and more than half of the resting state studies, and can thereby inflate specific effects in this sample on the general results of functional connectivity of this review. In the field of structural brain alterations in SAD, the limitations are primarily the small sample sizes and, to a lesser extent in grey matter studies, methodological differences of data analysis. Another limitation of our meta-analysis is that most studies included mixed samples of patients with and without psychopharmacological medication (mostly antidepressants) such that influences of the medication itself cannot be distinguished from the effects of the disorder. However, prior studies showed that medication in patients diminished the differences between patients and healthy subjects rather than inflating them (Lanius et al., 2010), such that purely medication free samples would be expected to rather show stronger differences than the currently included studies.

4.6. Open questions and outlook:

This review identified a number of open questions that warrant further investigation.

The main result of this study is that the role of parietal and occipital brain regions, particularly of medial parietal regions with their widespread connections and presumed integrating, monitoring and regulating functions has been overlooked thus far in the field of anxiety disorders and more generally in emotion research. These regions and their functions might hold a central role in the inability of patients to overcome their fears and their ongoing fearful rumination.

Within the network perspective, the role of hub regions, such as medial parietal cortex and insula might warrant further investigation in SAD, preferably within methodically combined approaches, e.g. resting state and task-related functional connectivity, causal models, structural connectivity, and eventually direct measures of connectivity using TMS in anxious states and in anxiety disorders.

One general point is the specificity of the here summarized alterations with regard to the disorder. Are these alterations specific to SAD or more general to specific anxiety disorders? Or rather are they reflective of an underlying disturbance of emotion processing and regulation in general, which might be found in those disorders characterized by increased anxiety, comprising also OCD and depressive disorders? Therefore, comparisons between disorders using identical sets of stimuli and studies testing the neural basis of general emotional (and non-emotional) stimuli could offer valuable information (e.g. Killgore et al., in press).

Another, more technical point is the investigation of structural brain differences associated with SAD and anxiety in general. The shortage of studies on white and grey matter changes in SAD and the

heterogeneity of measures and analytical methods preclude strong conclusions. Therefore, studies in larger groups of patients and using well-established methods might in future help identify not only brain regions with structural changes compared to healthy controls, but also those brain regions which are preserved and therefore, potentially, not related to the disorder. With larger sample sizes (see for instance Bruhl et al., 2014), longitudinal study designs and more comparable and standardized analytical methods, future studies could help address these questions.

Another field of interest in SAD could and should be in the neural mechanisms of treatment effects and different treatment types. There are until now no studies that directly compare differential and common neurobiological changes in the course of pharmacological and psychotherapeutic treatment. In particular, changes of functional connectivity might hold the potential to detect early signs of response to treatment. Such studies could help identifying neurobiological characteristics of patients who respond better to pharmacological or to psychological treatment or a combination of both. This knowledge could improve clinical decisions and lead to targeted and individualized treatments resulting in faster and more successful treatment response and improved recovery and quality of life.

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6. Legends

Figure 1 PRISMA diagram of study selection

Figure 2 Results of the ALE meta-analysis

Brain regions with consistently stronger activations in SAD>HCS are given in red. There were no regions with consistent activations in the contrast HCS>SAD.

Figure 3 Proposed neurobiological model of SAD

All regions shown here are more active in SAD than in HCS. The red marked connections are increased in SAD, the blue connections decreased.

Abbreviations: DL/MPFC Dorsolateral/Medial Prefrontal cortex, ACC anterior cingulate cortex, Ins Insula, Amy Amygdala, Thal Thalamus, PCC posterior cingulate cortex, Par Cort parietal cortex, Precun precuneus, Occ Cort occipital cortex, FFG fusiform gyrus, R right, L left

Table 1 Studies included in this review with demographic and psychometric information

Abbreviations: SAD: Social anxiety disorder; m: male, f: female, LSAS: Liebowitz Social Anxiety Scale (sum score), HCS: healthy control subjects, MRI: Magnet resonance tomography, WM: white matter/diffusion tensor imaging; GM: grey matter/structural studies, n.g. not given, R – right handed, L – left handed, A, ambidextrous, RS resting state, PD panic disorder, GAD generalized anxiety disorder, CBT: cognitive-behavioural therapy, MBSR: mindfulness-based stress program, DMN: default-mode network; iCBT – internet delivered CBT; ABM attention bias modification, SVM support vector machine analysis; studies marked with * are not included in the meta-analysis

Table 2 Results in functional studies

Abbreviations: SAD Social anxiety disorder; HCS healthy control subjects; ↓ decreased in SAD, ↑ increased in SAD; ø no difference between SAD and HCS, MPFC medial prefrontal cortex (superior frontal gyrus, medial frontal gyrus), DLPFC dorsolateral prefrontal cortex (superior frontal gyrus, middle frontal gyrus, BA 6, 8, 9, 46), VLPFC ventrolateral PFC (inferior frontal gyrus, BA 44, 45, 47), Ins Insula, OFC orbitofrontal cortex, VMPFC ventromedial prefrontal cortex, ACC anterior cingulate cortex, BA 32, 33, 24, PCC posterior cingulate cortex, BA 23, 31, ParC parietal cortex (superior/inferior parietal lob(ul)e, intraparietal sulcus), TC temporal cortex, PC (pre)cuneus, OccC occipital cortex (excl. FFG), FFG fusiform gyrus incl. medial occipitotemporal gyrus, BA 37, 19, Amy Amygdala, HC Hippocampus/Parahippocampal gyrus, NAc Ncl. Accumbens/ventral striatum, caud caudate, Thal Thalamus

The studies highlighted in grey used non-specific stimuli.

Two studies focusing on habituation effects are mentioned in the results section (Sladky et al., 2012, Campbell et al., 2007), they are not included in the ALE meta-analysis.

Table 3: Result of ALE meta-analysis of functional MRI studies

Abbreviations: SAD Social anxiety disorder; HCS healthy control subjects, BA Brodmann Area, x/y/z Talairach coordinates, L left, R right, ACC anterior cingulate cortex, BNST bed nucleus of stria terminalis, DLPFC dorsolateral prefrontal cortex, FFG fusiform gyrus, Lat Occipitotemp Gyrus Lateral occipitotemporal gyrus, MFG medial frontal gyrus, MidFG middle frontal gyrus, MPFC Medial prefrontal cortex, PHG parahippocampal gyrus, SFG superior frontal gyrus, SMG supramarginal gyrus

Table 4 Effects of interventions

Abbreviations: ↓ decreased in SAD, ↑ increased in SAD; ø no difference between SAD and HCS, post/pre contrast between activation after versus before the intervention, AE Aerobic exercise, MBSR Mindfulness based stress reduction, CBT cognitive behavioural therapy, cogn. reap. cognitive reappraisal, Ox Oxytocin, plc Placebo, w/wo with/without, MPFC medial prefrontal cortex (superior frontal gyrus, medial frontal gyrus), DLPFC dorsolateral prefrontal cortex (superior frontal gyrus, middle frontal gyrus, BA 6, 8, 9, 46), VLPFC ventrolateral PFC (inferior frontal gyrus, BA 44, 45, 47), Ins Insula, OFC orbitofrontal cortex, VMPFC ventromedial prefrontal cortex, ACC anterior cingulate cortex, BA 32, 33, 24, PCC posterior cingulate cortex, BA 23, 31, PMC (pre)motor cortex, ParC parietal cortex (superior/inferior parietal lob(ul)e, intraparietal sulcus), TC temporal cortex, PC (pre)cuneus, OccC occipital cortex (excl. FFG), FFG fusiform gyrus, medial occipitotemporal gyrus, BA 37, 19, Amy Amygdala, HC Hippocampus/Parahippocampal gyrus, NAc Ncl. Accumbens/ventral striatum, caud caudate, Thal Thalamus

One study investigating correlations between pre-treatment brain activation and response to treatment (Doehrmann et al., 2013) is reported in the results section.

Table 5 Seed based Connectivity Contrast SAD>HCS

Abbreviations: ACC anterior cingulate cortex, ant anterior, DLPFC dorsolateral prefrontal cortex, IFG inferior frontal gyrus, Inf par inferior parietal lobe, IOG inferior occipital gyrus, ITG inferior temporal gyrus, L left, Lat occ lateral occipital cortex, mACC middle ACC, MFG medial frontal gyrus, MidFG middle frontal gyrus, mid occ middle occipital cortex, mOFC middle orbitofrontal cortex, MTG middle temporal gyrus, OFC orbitofrontal cortex, olf cortex olfactory cortex, operc opercular gyrus, pallid pallidum, PCC posterior cingulate cortex, PHG parahippocampal gyrus, PMC premotor cortex, PostC postcentral gyrus, precun precuneus, R right, SFG superior frontal gyrus, SMG supramarginal gyrus, STG superior temporal gyrus, Sup occ G superior occipital gyrus, vis cortex visual cortex

Two studies reporting resting state networks (Liao et al., 2010a, Arnold Anteraper et al., 2014) and another on regional homogeneity of resting state (Qiu et al., 2011) are both presented in the results section.

Table 6 Structural alterations in SAD patients

No differences were reported in bilateral ventral striatum, caudate and thalamus in any of these studies.

If not otherwise indicated, the analyses were done in whole brain.

Abbreviations: ROI region of interest, SAD Social anxiety disorder; HCS healthy control subjects, ↓ decreased in SAD, (↓) uncorrected data, no significance after multiple testing corrections, ↑ increased in SAD; ø no difference between SAD and HCS, n.a. no data available, FA fractional anisotropy, ADC apparent diffusion coefficient, MPFC medial prefrontal cortex (superior frontal gyrus, medial frontal gyrus), DLPFC dorsolateral prefrontal cortex (superior frontal gyrus, middle frontal gyrus, BA 6, 8, 9, 46), VLPFC ventrolateral PFC (inferior frontal gyrus, BA 44, 45, 47), OFC orbitofrontal cortex, ACC anterior cingulate cortex (BA 32, 33, 24), PCC posterior cingulate cortex (BA 23, 31), PMC (pre)motor cortex, Par parietal cortex (superior/inferior parietal lob(ul)e, intraparietal sulcus), Ins insula, TC temporal cortex, PC (pre)cuneus, Occ occipital cortex (excl. FFG), FFG fusiform gyrus (including medial occipitotemporal gyrus, BA 37, 19), Amy Amygdala, Thal Thalamus, HC Hippocampus/Parahippocampal gyrus

Table 1 included studies

Study	**Pat** **N (M/F)**	**Age**	**LSAS**	**HCS** **N (M/F)**	**Age**	**LSAS**	**R/L** **(Pat/HCS)**	**Type of** **Stimulation**	**Induced** **contrasts**	**Symptom-** **provocation**
a) functional differences										
Cooney et al., 2006 (1)	10 (4/6)	28.7 (8.5)	n.g.	10 (3/7)	28.8 (5.3)	n.g.	R (10/9) L (0/1)	Emotional faces	SAD vs. HCS	Specific
Hahn et al., 2011 (2)	10 (9/1) Incl. PD	28.6 (4.3)	n.g.	27 (11/16)	27.7 (7.2)	n.g.	R (6/25) L (1/1) A (1/1)	Emotional faces	SAD vs. HCS	Specific
Klumpp et al., 2012 (3)	29 (12/17)	24.7 (5.9)	81 (15.2)	26 (10/16)	26.2 (6.3)	8.2 (7.7)	R	Emotional faces	SAD vs. HCS	Specific
Labuschagne et al., in press (4)	18 (18/0)	29.4 (9.0)	n.g.	18 (18/0)	29.9 (10.2)	n.g.	R	Emotional faces	SAD vs. HCS	Specific
Prater et al., 2013 (5)	20 (9/11)	26.0 (5.4)	79.4 (15.4)	17 (7/10)	25.7 (7.2)	7.9 (7.1)	R	Emotional faces	SAD vs. HCS	Specific
Klumpp et al., 2010 (6)	12	28.2 (8.6)	n.g.	12	33.6 (9.6)	n.g.	R	Emotional faces	SAD vs. HCS	Specific
Evans et al., 2008 (7)	11 (4/7)	29.0 (7.5)	82.4 (21.5)	11 (4/7)	27.9 (10.6)	n.g.	R	Emotional faces	SAD vs. HCS	Specific
Yoon et al., 2007 (8)	11 (5/6)	27.0 (6.1)	70.9 (20.0)	11 (5/6)	26.9 (6.2)	9.6 (8.4)	R	Emotional faces	SAD vs. HCS	Specific
Gentili et al., 2008 (9)	8 (4/4)	39 (7)	69.6 (1.01)	7 (4/3)	30 (7)	24.7 (1.25)	R	Emotional faces	SAD vs. HCS	Specific
Gentili et al., 2009 (10)	8 (4/4)	39 (7)	n.g.	7 (4/3)	30 (7)	n.g.	R	Emotional faces + RS	SAD vs. HCS	Specific
Blair et al., 2008b (11)	17 (9/8)	29.0 (8.7)	68.3 (20.7)	17 (9/8)	31.2 (9.1)	22.3 (14.5)	R	Emotional faces	SAD vs. HCS	Specific

Phan et al., 2013 (12)	21 (8/13)	25.9 (5.5)	82.3 (13.0)	19 (10/9)	27 (8.1)	9.2 (7.4)	R	Emotional faces	SAD vs. HCS	Specific
Blair et al., 2011a (13)	25 (10/15)	32.2 (9.1)	73.2 (20.4)	23 (13/10)	29.7 (8.3)	n.g.	R	Emotional faces	SAD vs. HCS	Specific
Schneier et al., 2011 (14)	16 (6/10)	29.8 (9.0)	81.4 (15.6)	16 (6/10)	30.3 (9.7)	8.2 (5.4)	R (15/15) L (1/1)	Faces simulating eye gaze	SAD vs. HCS	Specific
Nakao et al., 2011 (15)	6 (4/2)	31.7 (7.9)	80.8 (24.1)	9 (6/3)	32.8 (5.0)	12.3 (6.9)	n.g.	Social situation task	SAD vs. HCS	Specific
Schmidt et al., 2010 (16)	19 (9/10)	23.8 (2.8)	n.g.	18 (9/9)	23.7 (2.7)	n.g.	R	Phobia related words	SAD vs. HCS	Specific
Gimenez et al., 2012 (17)	20 (5/15)	24.2 (5.2)	80.7 (16.2)	20 (6/14)	24.4 (5.6)	11.8 (8.5)	R	Scrutiny task	SAD vs. HCS	Specific
Blair et al., 2010 (18)	16 (9/7)	35.1 (9.6)	67.1 (23.4)	16 (7/9)	30.0 (8.37)	16.2 (11.7)	R	Social transgression	SAD vs. HCS	Specific
Blair et al., 2011b (19)	15 (8/7)	30.3 (8.5)	67.7 (21.8)	15 (9/6)	31.1 (6.4)	17.5 (11.8)	R	Response to own / other opinions	SAD vs. HCS	Specific
Blair et al., 2008a (20)	17 (11/6)	35.1 (2.5)	61.4 (5.1)	17 (8/9)	29.7 (2.3)	18.9 (3.2)	R (16/17) L (1/0)	Self vs. other reference	SAD vs. HCS	Specific
Laeger et al., 2014 (21)	21 (0/21)	29.2 (8.0)	n.g.	21 (0/21)	29.3 (9.1)	n.g.	R (16/17) L (5/4)	Emotional faces, pseudonames	SAD vs. HCS	specific
Demenescu et al., 2013 (22)	17 (6/11)	36.1 (10.0)	n.g.	16 (5/11)	33.6 (9.6)	n.g.	R (16/14) L (1/2)	Emotional faces + connectivity	SAD vs. HCS	specific
Pujol et al., 2013 (23)	20 (5/15)	24.2 (5.2)	80.7 (16.2)	20 (6/14)	24.4 (5.6)	11.8 (8.5)	R	Public self-exposure (video)	SAD vs. HCS	specific
Ziv et al., 2013a (24)	67 (35/32)	33.0 (8.8)	84.1 (17.5)	28 (15/13)	32.6 (9.5)	15.3 (9.1)	R	emotional faces, social criticism, neg. self-beliefs	SAD vs. HCS	specific
Gaebler et al., 2013 (25)*	21 (5/16)	31.0 (7.3)	87.4 (20.5)	21 (5/16)	29.1 (5.9)	18.5 (16.7)	R	Emotional faces	SAD vs. HCS	specific
Boehme et al., in press (26)	17 (10/7)	31.1 (10.5)	75.1 (19.7)	17 (11/6)	30.8 (8.6)	19.7 (10.5)	R	Anticipation of public and evaluated speaking	SAD vs. HCS	specific

Klumpp et al., 2013b (27)	29 (11/18)	24.9 (6.3)	77.3 (15.4)	27 (12/15)	24.9 (5.9)	7.8 (6.3)	R	Emotional faces	SAD vs. HCS	specific
Frick et al., 2013b (28)	14 (14/0)	32.4 (8.8)	72.1 (25.7)	12 (12/0)	28.0 (8.2)	n.g.	R	Emotional faces + connectivity	SAD vs. HCS	specific
Pantazatos et al., 2014 (29)	12 (4/8)	28.3 (7.8)	85.8 (15.3)	7 (5/2)	35.0 (13.0)	7.7 (6.0)	n.g.	Emotional faces	SAD vs. HCS	Specific
Quadflieg et al., 2008 (30)	12 (6/6)	23.3	SPIN: 39.8	12 (6/6)	24.0	SPIN: 9.7	R	Emotionally spoken words	SAD vs. HCS	Specific
Koric et al., 2012 (31)	15 (7/8)	34.3 (3)	72.6 (6.79)	15 (6/9)	34.7 (3)	36.0 (6.79)	n.g.	Performance induced stress	SAD vs. HCS	(un)specific
Bruhl et al., 2011 (32)	14 (7/7)	33 (12)	63 (17.8)	16 (6/10)	31 (7.2)	n.g.	R	General emotional pictures	SAD vs. HCS	Unspecific
Sareen et al., 2007 (33)	10 (6/4)	29.1 (9.1)	84.5 (22.9)	10 (6/4)	28.4 (8.6)	11.6 (15.0)	R	Stop-Reaction Task	SAD vs. HCS	Unspecific
Shah et al., 2009 (34)	11 (8/3)	27.5 (9.0)	75.9 (14.9)	11 (6/5)	30.6 (7.7)	13.7 (14.3)	R	General emotional pictures	SAD vs. HCS	Unspecific
Sripada et al., 2009 (35)	25 (13/12)	32.7 (8.1)	77.3 (18.4)	25 (9/16)	28.0 (8.2)	15.6 (11.9)	R	Trust game, mentalizing	SAD vs. HCS	Unspecific
Richey et al., 2014 (36)	15 (9/6)	26.9 (5.3)	133.0 (13.2)	19 (13/6)	25.3 (7.0)	n.g.	SAD: n.g.; HCS: R	Reward anticipation + outcome	SAD vs. HCS	unspecific
Sripada et al., 2013 (37)*	36 (15/21)	27.0 (7.6)	76.9 (16.7)	36 (14/22)	29.5 (8.3)	n.g.	R	Trust game (ROI analysis)	SAD vs. HCS	unspecific
Gaebler et al., 2014 (38)	21 (5/16)	30.5 (7.2)	88.4 (18.2)	23 (18/5)	30.0 (8.0)	17.4 (16.4)	R	General emotional pictures	SAD vs. HCS	unspecific
Additional functional studies										
Sladky et al., 2012 (39)*	15 (7/8)	26.6 (8.6)	75.6 (22.7)	15 (8/7)	25.4 (3.4)	5.3 (7.3)	n.g.	Emotional faces	Habituation effects	Specific
Campbell et al., 2007 (40)*	14 (10/4)	38.2 (12.1)	87.4 (26.7)	14 (10/4)	37.6 (11.6)	15.5 (13.9)	R	Emotional faces	Habituation effects	Specific
b) changes after intervention										

Doehrmann et al., 2013 (41) CBT (12 weeks)	39 (25/14)	29.3 (7.9)	81.8 (13.4)	n.g.	n.g.	n.g.	R (34) L (5)	Faces	pre CBT – treatment response	Specific
Klumpp et al., 2013a (42) CBT (12 weeks)	14 (5/9)	28.1 (8.6)	71.2 (9.6)	14 (6/8)	23.3 (5.4)	9.7 (6.5)	R	Emotional faces	SAD vs. HCS, Pre/post CBT	Specific
Goldin and Gross, 2010 (43) MBSR (8 weeks)	16 (7/9)	35.2 (11.9)	68.7 (21.2)	-	-	-	R	Negative self-beliefs	Pre/post MBSR	Specific
Goldin et al., 2013 (44) MBSR vs. Aerobic exercise (AE), incl. GAD, MDD, PD, OCD	MBSR 31 (19/12)	MBSR 32.9 (8.8)	n.g.	AE: 25 (10/15)	AE: 32.9 (8.0)	n.g.	R	Negative self-beliefs	Pre/post MBSR	Specific
Goldin et al., 2012 (45) MBSR vs. Aerobic exercise (AE), incl. GAD, MDD, PD, OCD (see (44))	MBSR 31 (19/12)	MBSR 32.9 (8.8)	n.g.	AE: 25 (10/15)	AE: 32.9 (8.0)	n.g.	R	Self-referential words	Pre/post MBSR	Specific
Mansson et al., 2013 (46) iCBT (9 weeks) vs. ABM (4 weeks)	iCBT 13 (2/11)	iCBT 32.5 (8.6)	iCBT 76.0 (20.3)	ABM 13 (2/11)	ABM 32.1 (10.9)	ABM 75.3 (19.2)	R	Emotional faces	Pre/post iCBT or ABM	specific
Brühl et al., 2013 (47) Regulation	14 (8/6)	35.2 (9.3)	71.1 (22.2)	Basic: 14 (7/7)	Basic: 33.4 (12.0)	Basic: 69.7 (16.2)	R	General emotional pictures	w/wo cognitive control	Unspecific
Goldin et al., 2009b (48) Regulation	15 (6/9)	31.6 (9.7)	67.6 (21.1)	17 (8/9)	32.1 (9.3)	29.3 (20.9)	R	Social and physical threat	SAD vs. HCS x cogn. regulation	Specific
Goldin et al., 2009a (49) Regulation	27 (15/12)	32.1 (9.2)	80.1 (16.8)	27 (15/12)	32.2 (9.5)	15.7 (8.7)	R	Cognitive reappraisal of neg. self-beliefs	Early vs late BOLD	Specific
Ziv et al., 2013b (50) Regulation	27 (15/12)	31.1 (7.6)	99.3 (11.8)	27 (14/13)	32.6 (9.5)	15.3 (9.1)	R	Social-emotional task – reappraisal	SAD vs. HCS x cogn. regulation	specific
Gaebler et al., 2014 (38) Regulation	21 (5/16)	30.5 (7.2)	88.4 (18.2)	23 (18/5)	30.0 (8.0)	17.4 (16.4)	R	Mixed IAPS pictures + reappraisal	SAD vs. HCS x reappraisal	unspecific
Phan et al., 2013 (12) Sertraline (12 weeks)	21 (8/13)	25.9 (5.5)	82.3 (13.0)	19 (10/9)	27 (8.1)	9.2 (7.4)	R	Emotional faces	Group x time pre/post	Specific
Schneier et al., 2011 (14) Paroxetine (8 weeks)	16 (6/10)	29.8 (9.0)	81.4 (15.6)	16 (6/10)	30.3 (9.7)	8.2 (5.4)	R (15/15) L (1/1)	Faces simulating eye gaze	Pre/post	Specific

Pantazatos et al., 2014 (29) Paroxetine (8 weeks)	12 (4/8)	28.3 (7.8)	85.8 (15.3)	7 (5/2)	35.0 (13.0)	7.7 (6.0)	n.g.	Emotional faces + GM	Pre/post	Specific
Gimenez et al., 2014 (51) Paroxetine vs. placebo (8 weeks)	Parox 17 (3/14)	Parox 24 (n.g.)	Parox 80.1 (18.5)	PLC 16 (2/14)	PLC 22 (n.g.)	PLC 79.1 (16.2)	n.g.	Public exposure, emotional faces	Pre/post	specific
Cassimjee et al., 2010 (52) Escitalopram (12 weeks)	14 (5/9)	40.6 (11.7)	84.4 (21.9)	n.g.	n.g.	n.g.	n.g.	Structural/GM	Pre/post	-
Labuschagne et al., in press (4) Intranasal Oxytocin	18 (18/0)	29.4 (9.0)	n.g.	18 (18/0)	29.9 (10.2)	n.g.	R	Emotional faces	SAD vs. HCS x Oxy/ PLC	Specific
Labuschagne et al., 2010 (53) Intranasal Oxytocin (see (4))	18 (18/0)	29.4 (9.0)	81.7 (17.5)	18 (18/0)	29.9 (10.2)	13.9 (8.3)	R	Emotional faces	SAD vs. HCS x Oxy/ PLC	Specific
Dodhia et al., in press (54) Intranasal Oxytocin (see (4))	18 (18/0)	29.4 (9.0)	81.7 (17.5)	18 (18/0)	29.9 (10.2)	13.9 (8.3)	R	RS	SAD vs. HCS x Oxy/PLC	Unspecific
c) connectivity differences										
Liao et al., 2010a (55)	20 (14/6)	22.9 (4.0)	53.9 (11.5)	19 (14/5)	21.9 (3.8)	19.2 (7.7)	R	RS	SAD vs. HCS	Unspecific
Liao et al., 2010b (56)	22 (16/6)	22.6 (4.0)	51.5 (9.7)	21 (15/6)	21.7 (3.6)	20.5 (8.4)	R	RS	SAD vs. HCS	Unspecific
Qiu et al., 2011 (57) cf. (55), but mismatch							R	RS	SAD vs. HCS	Unspecific
Ding et al., 2011 (58)	17 (13/4)	23.5 (4.2)	52.6 (11.7)	19 (14/5)	21.9 (3.8)	19.2 (7.7)	R	RS	Within SAD	Unspecific
Hahn et al., 2011 (2) Incl. PD	10 (9/1)	28.6 (4.3)	n.g.	27 (11/16)	27.7 (7.2)	n.g.	R (25/6) L (1/1) A (1/1)	RS	SAD vs. HCS	Unspecific
Liao et al., 2011 (59)	18 (12/6)	22.7 (3.8)	54.4 (12)	18 (13/5)	21.9 (3.7)	19.1 (7.9)	R	RS	SAD vs. HCS	Unspecific
Pannekoek et al., 2013 (60)	12 (5/7)	34.8 (8.8)	n.g.	12 (5/7)	34.0 (7.2)	n.g.	R	RS	SAD vs. HCS	Unspecific
Liu et al., in press (61)	20	22.9	53.9	20	21.8	20.0	n.g.	RS	SAD vs. HCS	unspecific

	(14/6)	(4.0)	(11.5)	(14/6)	(3.7)	(8.3)				
Arnold Anteraper et al., 2014 (62)	17 (8/9)	24.7 (6.3)	77.9 (14.1)	17 (8/9)	25.0 (7.5)	n.g.	R	RS network	SAD vs. HCS	unspecific
Blair et al., 2008a (20)	17 (11/6)	35.1 (2.5)	61.4 (5.1)	17 (8/9)	29.7 (2.3)	18.9 (3.2)	R (16/17) L (1/0)	Self vs. other reference + connectivity	SAD vs. HCS	Specific
Danti et al., 2010 (63)	8 (4/4)	39 (7)	69.6 (1.01)	7 (4/3)	30 (7)	24.7 (1.25)	R	Emotional faces + connectivity	SAD vs. HCS	Specific
Klumpp et al., 2012 (3)	29 (12/17)	24.7 (5.9)	81 (15.2)	26 (10/16)	26.2 (6.3)	8.2 (7.7)	R	Emotional faces + connectivity	SAD vs. HCS	Specific
Gimenez et al., 2012 (17)	20 (5/15)	24.2 (5.2)	80.7 (16.2)	20 (6/14)	24.4 (5.6)	11.8 (8.5)	R	Scrutiny task + connectivity	SAD vs. HCS	Specific
Prater et al., 2013 (5)	20 (9/11)	26.0 (5.4)	79.4 (15.4)	17 (7/10)	25.7 (7.2)	7.9 (7.1)	R	Emotional faces + RS	SAD vs. HCS	Specific + Unspecific
Pantazatos et al., 2014 a (29)	16 (2/14)	33.6 (7.1)	n.g.	19 (11/8)	31.7 (8.0)	n.g.	n.g.	Emotional faces + connectivity	SAD vs. HCS	specific
Pantazatos et al., 2014 b (29)	14 (4/10)	27.3 (7.5)	86.7 (18.1)	17 (7/10)	31.0 (10.7)	7.8 (5.3)	n.g.	Emotional faces + connectivity	SAD vs. HCS	specific
Demenescu et al., 2013 (22)	17 (6/11)	36.1 (10.0)	n.g.	16 (5/11)	33.6 (9.6)	n.g.	R (16/14) L (1/2)	Emotional faces + connectivity	SAD vs. HCS	specific
Frick et al., 2013b (28)	14 (14/0)	32.4 (8.8)	72.1 (25.7)	12 (12/0)	28.0 (8.2)	n.g.	R	Emotional faces + connectivity	SAD vs. HCS	specific
Frick et al., 2014 (64)	14 (14/0)	32.4 (8.8)	n.g.	14 (14/0)	28.0 (8.2)	n.g.	R	Emotional faces + RS + GM	SAD vs HCS	specific
Sladky et al., in press (65)	13	n.g	n.g	13	n.g	n.g	n.g.	Emotional faces and object discrimination task	SAD vs HCS	specific + unspecific
d) Structural differences WM/GM										
Irle et al., 2010 (66)	24 (12/12)	32 (10)	67 (n.g.)	24 (12/12)	31 (9)	n.g.	R (23/22) L (1/2)	GM	SAD vs. HCS	-
Syal et al., 2012 (67)	13 (8/5)	35.3 (11.8)	103.3 (17.0)	13 (8/5)	33.6 (11.2)	n.g.	R	GM	SAD vs. HCS	-

Frick et al., 2013a (68)	14 (14/0)	32.6 (8.7)	n.g.	12 (12/0)	27.9 (7.9)	n.g.	R	GM	SAD vs. HCS	-
Talati et al., 2013 a (69)	16 (3/13)	34.1 (6.7)	n.g.	20 (11/9)	31.4 (7.8)	n.g	n.g.	GM	SAD vs. HCS	-
Talati et al., 2013b (69)	17 (6/11)	29.1 (8.9)	81.4 (15.6)	17 (7/10)	31.3 (10.7)	8.1 (5.4)	n.g.	GM	SAD vs. HCS	-
Frick et al., 2014 (64)	14 (14/0)	32.4 (8.8)	n.g.	14 (14/0)	28.0 (8.2)	n.g.	R	Emotional faces + RS + GM – SVM	SAD vs HCS	specific
Phan et al., 2009 (70)	30 (15/15)	27.2 (7.8)	76.7 (17.3)	30 (10/20)	29.9 (8.1)	13.4 (11.3)	R	WM	SAD vs. HCS	-
Baur et al., 2011 (71)	25 (18/7)	32 (10.4)	66.0 (23)	25 (18/7)	32 (10.1)	n.g.	R	WM	SAD vs. HCS	-
Baur et al., 2013a (72)	25 (18/7)	31.6 (10.4)	66.0 (23.0)	25 (18/7)	32.3 (10.1)	n.g.	R	WM	SAD vs. HCS	-
Qiu et al., 2014 (73)	18 (12/6)	22.7 (3.9)	54.1 (11.9)	18 (12/6)	21.8 (3.9)	19.5 (8.5)	R	WM	SAD vs. HCS	-
Liao et al., 2011 (59)	18 (12/6)	22.7 (3.8)	54.4 (12)	18 (13/5)	21.9 (3.7)	19.1 (7.9)	R	GM + WM	SAD vs. HCS	-
Machado-de-Sousa et al., 2014 (74)	12 (7/5)	20.2 (n.g.)	n.g.	14 (11/3)	19.8 (n.g.)	n.g.	R	GM + WM	SAD vs. HCS	-
Meng et al., 2013 (75)	20 (14/6)	21.8 (3.7)	52.8 (11.7)	19 (13/6)	21.6 (3.7)	21.5 (8.7)	R	GM + WM	SAD vs. HCS	-
Bruhl et al., 2014 (76)	46 (29/17)	33.1 (10.6)	66.2 (20.4)	46 (29/17)	33.0 (8.9)	n.g.	R	GM + WM	SAD vs. HCS	-

Table 2: Results in functional studies (contrast SAD>HCS)

Study No.	MPFC		DLPFC		VLPFC		Ins		OFC VMPFC		ACC		PCC		ParC		TC		PC		OccC		FFG		Amy		HC		Caud NAc		Thal	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
(1)																									↑	↓						
(2)																										↑						
(3)	↑				↑	↑	↑	↑								↑	↑								↑	↑	↑			↑		
(4)	↑	↑										↑			↑		↑				↑	↑		↑								
(5)																									↑							
(6)			↓		↑		↑	↑											↑									↑		↑		↑
(7)			↓	↑			↑				↑			↑		↑	↑						↑	↑	↑							
(8)			↑					↑							↑						↑	↑			↑	↑						
(9)				↓		↑		↑									↑	↑	↓	↑		↑		↓		↑						
(10)													↑	↑																		
(11)		↑	↑	↑	↑	↑				↑		↑					↑				↓				↑							
(12)			↑	↓	↑				↓	↓															↑	↑						
(15)													↓	↓						↓												
(16)									↑																	↑						
(17)																					↑	↑										
(18)	↑	↑					↑	↑		↑															↑							
(19)	↑	↑	↑	↑			↑	↑		↑			↑		↑	↑	↑					↑			↑							
(13)											↑						↓				↓					↑						
(20)	↑	↑	↑									↑							↑	↑					↑	↑						
(14)							↑	↑							↑		↑				↑				↑	↑	↑					
(21)																																
(22)	ø	ø						ø	ø		ø	ø													ø	ø						
(23)	↓		↓	↓																	↑											
(24)	↑	↑	↓	↑													↑	↑	↓			↑					↑					
(25)*																					ø	ø			ø	ø					ø	ø
(26)							↑																		↑					↓		
(27)							↑	↑				↓																				
(28)				↑																			↑	↑								
(29)				↓																				↑								
(30)									↑																							
(31)			↑	↓	↑																											
(32)	↑			↑		↓				↓				↑		↑	↑	↑			↑	↑	↑	↑		↑		↑		↑	↑	↑
(33)							↑	↑								↑														↑		
(34)							↑	↑									↑								↑	↑		↑				
(35)	↓		↑		↓										↓	↑				↓				↓								
(36)																														↓		
(37)*																													↓	↓		
(38)												↑			↑	↑	↑	↑														

The studies highlighted in grey used non-specific stimuli. Two studies focusing on habituation effects are mentioned in the results section (Sladky et al., 2012, Campbell et al., 2007). Two studies conducted only ROI analyses (marked with *). These four studies are not included in the ALE meta-analysis.

Table 3 Result of ALE meta-analysis of functional MRI studies

	Anatomic regions (BA)	Peak coordinates x/y/z (Tal)	Volume (mm3)	Max. ALE (x 10-3)
SAD > HCS				
Subcortical/ limbic	Amygdala / BNST / PHG R	19 / -4 / -7	2744	22.13
	Amygdala / BNST / PHG L	-23 / -3 / -14	3304	30.69
	ACC L (31)	-15 / -31 / 39	416	16.25
	Insula R (13)	28 / 17 / -10	232	11.45
Frontal	MPFC / MFG L (10)	-6 / 54 / 10	1288	17.26
	DLPFC / SFG L (10)	-16 / 60 / 15	232	13.04
	DLPFC / MidFG L (8)	-24 / 34 / 37	224	14.10
Temporal/ occipital	FFG R (19)	31 / -66 / -7	320	13.17
	Lat Occipitotemp Gyrus R (19)	40 / -63 / -19	456	15.87
	SMG L (40)	-59 / -52 / 25	464	15.79
	Lingual gyrus L (18)	-25 / -70 / -10	432	15.12
HCS > SAD	No cluster			

Table 4 Effects of treatment/interventions

	Treatment	Contrast	MPFC		DLPFC		VLPFC		Ins		OFC VMPFC		ACC		PCC		PMC		ParC		TC		PC		OccC		FFG		Amy		HC		caud		Thal	
			R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
(42)	CBT	Post/pre	↓						↓		↓											↓										↓				
(43)	MBSR	post/pre																↓	↓	↓			↓		↓	↓	↓		↓		↓					
(44)	MBSR vs. AE	Between txs. (post)					↓												↑		↓					↓	↓	↓								
(45)	MBSR/AE	Between txs	ø	↑	ø	↑	↑	↑					ø	ø			↑	↑																			
	MBSR	Post/pre				↑	↑	↑	↑	↑			↑	↑			↑	↑				↑		↑	↑	↑											
(46)	iCBT	Post/pre				↓								↓																		↓				↓	
	ABM	Post/pre																↑	↑			↑								↑	↑					
	iCBT/ABM	Between txs.												↓						↓										↓	↓				↓	
(47)	Cogn. reapp.	w/wo regulation	ø		ø		↓	↓			↓								↓	↓	↓	↓	↓		↓				↓	↓	↓		↓				
(48)	Cogn. reapp.	w/wo regulation	↑						↑	↑	↓	↓							↑	↓	↑	↓	↑	↓	↑						↑	↑				
		SAD/HCS	↓				↓				↓				↓		↓		↓		↓		↓						↓	↓						
(49)	Cogn. reap.	SAD/HCS	↓	↓	↑	↑	↑	↓	↑	↑			↓					↑	↑		↑		↑													
(50)	Reapp	SAD/HCS						↓				↓	↓	↓										↓			↓	↓	↓						↓		
(38)	Reapp	w/wo regulation												↓								↓	↓													
(12)	Sertraline	post/pre					↓				↑											↓		↓	↓	↓	↓	↓		↓						
(14)	Paroxetine	post/pre								↓							↓					↓		↓			↓									
(51)	Paroxetine	post/pre		↓										↓																↓				↓	↓	
(29)	Paroxetine	post/pre						↑		↑		↑											↓							↓		↑	↓				
(52)	Escitalopram	Gray matter																			↓	↓														
(4)	Ox/plc	Sad faces																											↓	↓						
(53)	Ox/plc	Sad faces																									↑	↑								
		Happy faces	↓	↓									↓	↓							↓	↓												↓		

One study investigating correlations between pre-treatment brain activation and response to treatment Doehrmann et al., 2013 and another study on the effects of Oxytocin on functional connectivity in SAD Dodhia et al., in press are both reported in the results section.

Table 5 Seed based Connectivity Contrast SAD>HCS(for network-based studies: see text)

Seed	Frontal Lobe	Temporal Lobe	Parietal Lobe	Occipital Lobe	Subcortical regions
Frontal lobe					
MPFC	DLPFC ↑ (17) ø (59)	ø (59)	ø (59)	ø (59)	Thalamus ↑ (17) Caudate ↑ (17) ø (59)
OFC/MFG R	IFG L, R ↓ (58) MCC R ↓ (58) MCC R ↑ (58) DLPFC ↓ (65)		IPL R, L ↓ (58)	L, R ↑ (58)	Caudate R ↓ (58) Amygdala ↓ (65) Amygdala ↑ (65)
mOFC L	ACC ↓ (2)				
SFG(orbital) R	IFG L, R ↓ (58)	STG L ↓ (58)		L, R ↑ (58)	
SFG(orbital) L		STG L ↓ (58)			
dACC				Precun L ↑ (60) Lat occ L ↑ (60	
Temporal lobe					
Ant Insula R	dACC ↓ (3)				
STG R				Occ cort L ↑ (58)	
STG L		MTG L, R ↓ (64)		Occ cort L,R ↑ (58)	PHG/HC L ↓ (64)
STS R	IFG L, R ↑ (63)		IPL/S L ↓ (63)	Precun L ↓ (63)	
ITG R				Inf occ G L ↑ (59)	
Parietal Lobe					
PCC	Olfcort L,R ↓ (58) ø (60)	ø (60)	ø (60)	ø (60)	Pallid L ↓ (58) ø (60)
Postcentral G L				Sup occ G L ↓ (58)	
IPL R		R ↑ (58)			
Occipital lobe					
Visual cortex	ø (17)	ø (17)	ø (17)	ø (17)	ø (17)
FFG R	VMPFC L ↓ (28)		PCC R ↓ (63) PostC L ↓ (63)	Precun R ↓ (63)	Amy R ↑ (28)
Subcortical regions					
Amygdala R	mOFC ↑ (56) OFC ↓ (65) DLPFC R ↑ (5) ACC ↑ (5) SFG R ↓ (56) DLPFC ↓ (65) ø (22)	R ↓ (56) L ↓ (56) MTG L ↑ (60) SMG L ↑ (60) ø (22)	All ↓ (56) ø (22)	All ↑ (56) mid occ R ↑ (2) Lat occ L ↑ (60) ø (22)	PHG ↑ (56) ø (22)
Amygdala L	MidFC ↑ (56) PMC L ↑ (58) ACC ↑ (5) mOFC ↓ (2) SFG L ↓ (56) SFG R ↑ (63) IFG R ↑ (63) MPFC ↑ (20) ø (22)	L ↑ (58) L ↓ (56) R ↓ (56) MTG R ↓ (56) STG R ↑ (63) MTG L ↑ (59) ø (22)	PostC R ↓ (56) PostC L ↓ (56) PCC L ↓ (2) PostC R ↓ (63) IPS R ↑ (63) ø (22)	Vis cortex ↑ (56) ø (22)	ø (22)
Hippocampus L	IFG L ↓ (64)	TP L ↓ (64)		Precun L ↓ (22)	Thal R ↓ (64)
Thalamus	mACC ↑ (17) PMC R ↑ (58)	STG R,L ↑ (58)			
Pallidum L		Operc L ↑ (58) SMG L ↑ (58)			
Pallidum R		Operc L ↑ (58) STG L ↑ (58)			

Table 6 Structural alterations in SAD patients

a)	GM	Frontal cortex						Parietal cortex			Temporal cortex		Occipital cortex		Subcortical structures		
Study		MPFC	DLPFC	VLPFC	OFC	PMC	ACC	PCC	Par	PC	Ins	TC	Occ	FFG	Amy	HC	Thal
(6)		(↓)	(↓)	(↓)	↓	ø	ø	(↓)	↓	ø	↓	↓	ø	↓	(↓)	ø	
(66)	ROI	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	↓	↓	
(69)a		↓	ø	ø	ø	↓	↓	ø	ø	ø	↓	↑	↑	↑	ø	↑	
(69)b		ø	↓	ø	↓	↑	ø	ø	↑	ø	ø	↑ ↓	ø	ø	ø	ø	
(59)		↑	ø	ø	ø	ø	ø	ø	ø	ø	ø	↓	ø	ø	ø	↓	
(68)		ø	ø	ø	ø	ø	ø	ø	ø	ø	ø	↑	ø	↑	ø	ø	
(74)	ROI	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	↑	↑	
(75)										↓					↓		↓
(76)	ROI	n.a.	n.a.	n.a.	ø	n.a.	↑	n.a.	n.a.	n.a.	ø	ø	n.a.	ø	ø	ø	
			↑						↑	↑							

b)	WM alterations	Uncinate fasciculus		Superior longitudinal fasciculus		Inferior longitudinal fasciculus		Inferior fronto-occipital fasciculus		Arcuate fasciculus	Global white matter
		R	L	R	L	R	L	R	L		
(72)	Volume ROI	ø	↓	n.a.	n.a.	n.a.	n.a.	ø	ø	ø	ø
	FA ROI	ø	↓	n.a.	n.a.	n.a.	n.a.	ø	ø	ø	↓
(71)	FA ROI	ø	↓	ø	↓	n.a.	n.a.	n.a.	n.a.	n.a.	ø
(70)	FA	↓	ø	ø	ø			ø	ø	ø	n.a.
(59)	Fiber density/ tracking	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	↑	n.a.
	FA ROI	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	↑	n.a.
(73)	FA		↓		↓						n.a.
	ADC			↓	↓			↓	↓		n.a.
(74)	Volume	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	ø
(75)	Volume	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	ø

No differences were reported in bilateral ventral striatum, and caudate in any of these studies.
Results of one multimodal study(Frick et al., 2014) are reported in the results section of the text.

Fig. 1

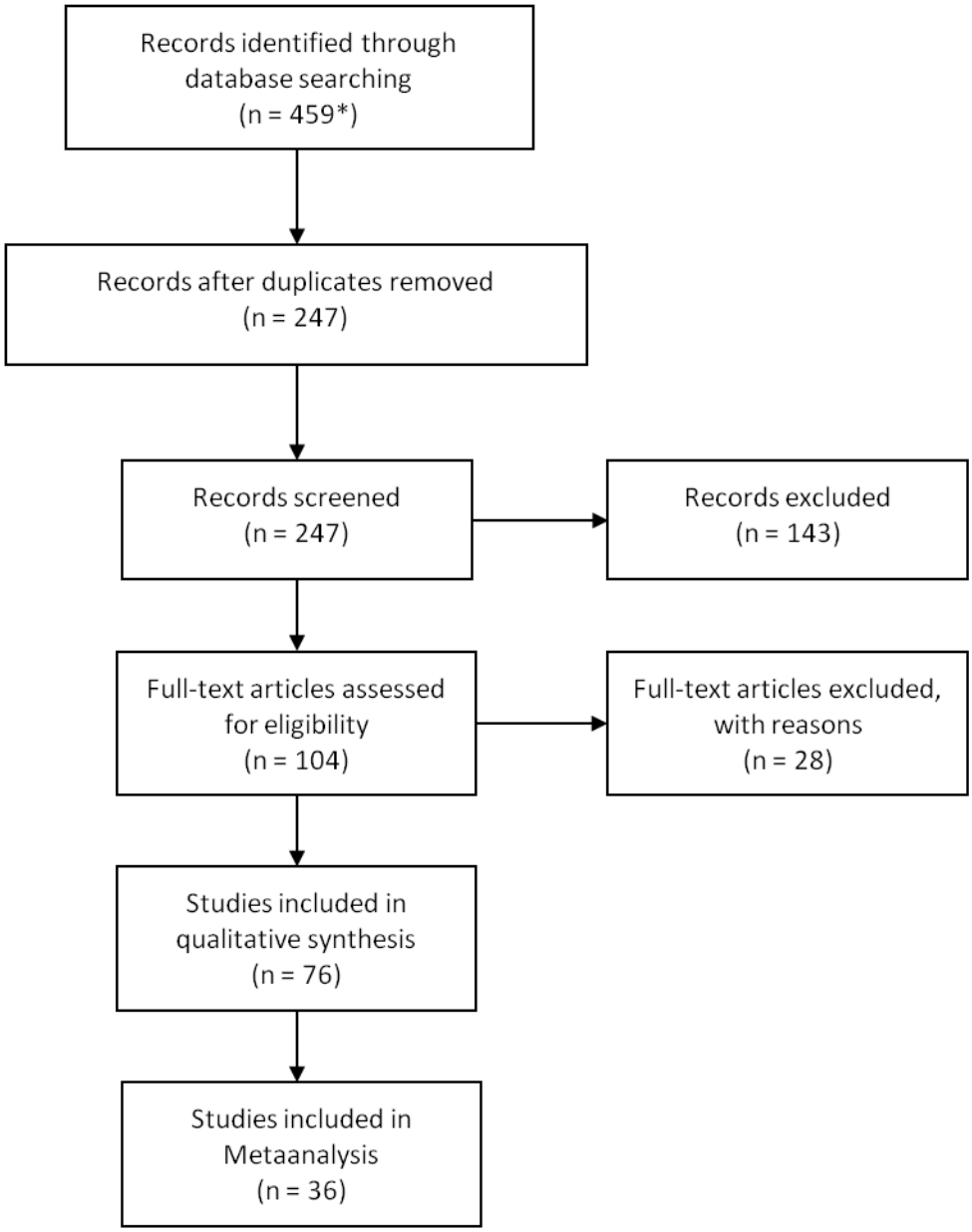

Records identified through database searching (n = 459*)
Records after duplicates removed (n = 247)
Records screened (n = 247)
Records excluded (n = 143)
Full-text articles assessed for eligibility (n = 104)
Full-text articles excluded, with reasons (n = 28)
Studies included in qualitative synthesis (n = 76)
Studies included in Metaanalysis (n = 36)

Fig. 2

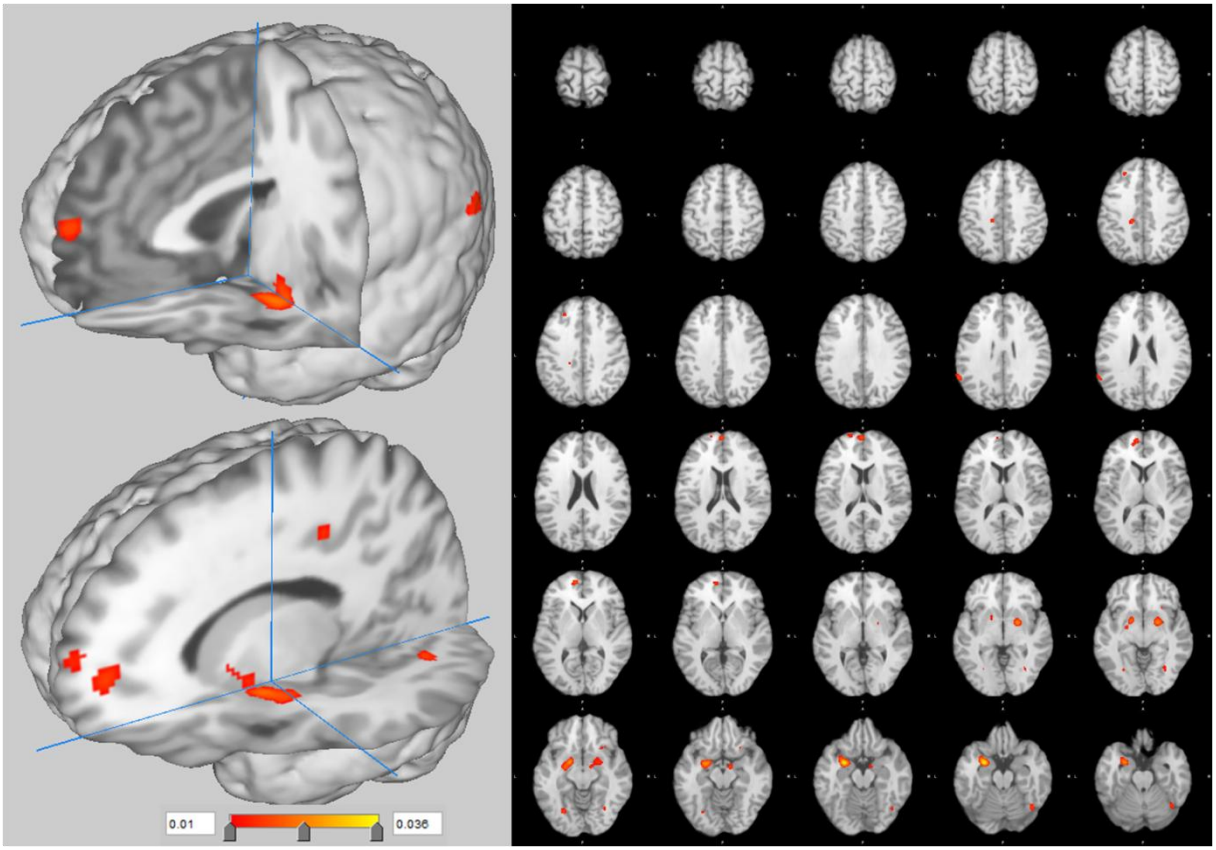
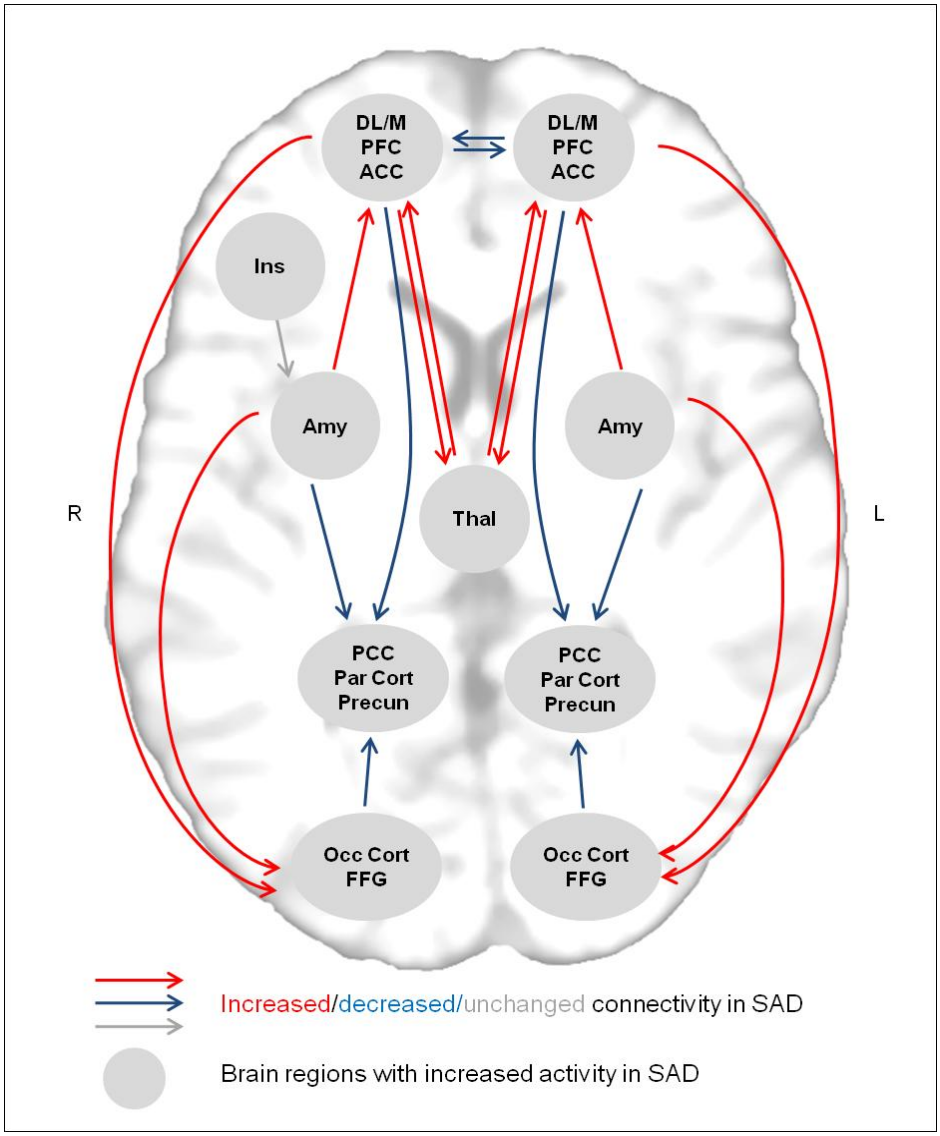


Fig. 3


DL/M
PFC
ACC
DL/M
PFC
ACC
Ins
Amy
Amy
R
L
Thal
PCC
Par Cort
Precun
PCC
Par Cort
Precun
Occ Cort
FFG
Occ Cort
FFG
Increased/decreased/unchanged connectivity in SAD
Brain regions with increased activity in SAD