Neuroimaging in anxiety disorders

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Received: 6 March 2008 / Accepted: 1 June 2008 / Published online: 21 June 2008
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Abstract Neuroimaging studies have gained increasing importance in validating neurobiological network hypotheses for anxiety disorders. Functional imaging procedures and radioligand binding studies in healthy subjects and in patients with anxiety disorders provide growing evidence of the existence of a complex anxiety network, including limbic, brainstem, temporal, and prefrontal cortical regions. Obviously, “normal anxiety” does not equal “pathological anxiety” although many phenomena are evident in healthy subjects, however to a lower extent. Differential effects of distinct brain regions and lateralization phenomena in different anxiety disorders are mentioned. An overview of neuroimaging investigations in anxiety disorders is given after a brief summary of results from healthy volunteers. Concluding implications for future research are made by the authors.

Keywords Anxiety disorders · Panic disorder · Phobia · Neuroimaging · fMRI · Prefrontal cortex · Limbic system · Insular cortex

Introduction

There has been an enormous increase in studies on anxiety disorders implying neuroimaging procedures. Improved techniques for structural imaging such as computed tomography studies and structural MRI have brought diverse results and hypotheses on the neuroanatomy of anxiety up from the 1980s. However, the findings of these studies hardly correspond.

In 1980, research and classificatory criteria for anxiety disorders have emerged in DSM-III. These made standardized investigations methodologically possible and with the improvement of a neurophysiological and neurobiological understanding of anxiety disorders the idea of a neural anxiety network consolidated. With distinct neocortical, limbic, and brainstem structures involved in the generation and processing of anxiety symptoms and disorders, the need for confirmation has become the incentive of neuroimaging studies. Considering the enormous methodological progress, imaging procedures gain an increasing importance in research on the pathogenesis of anxiety disorders. There is growing evidence that brain areas involved in the stress response, including the prefrontal cortex, hippocampus and amygdala, play a role in the symptoms of anxiety. In the past few years, brain imaging studies have been dedicated to the progress of understanding of the neural circuitry of anxiety disorders (Bremner 2004).

However, it has become obvious that some areas involved in anxiety processing like the amygdalae, distinct brainstem nuclei or the periaqueductal gray (PAG) are hard to detect with sufficient resolution because of their sizes and anatomical locations (closeness to structures of different density like bone or body liquids). Nevertheless, with increasing quality of methods, results become more and more precise and now allow for a consolidation of neuronal network hypotheses in anxiety disorders. Radioligand studies and investigations on regional cerebral blood flow (using e.g. positron emission tomography (PET) and single photon emission computed tomography (SPECT))...
are to assess regional blood flow differences or altered binding of ligands in distinct regions compared to control conditions such as healthy subjects or pre/post treatment differences. The past years have brought about a number of studies using high resolution functional magnetic resonance imaging, which provide valid statements for different stimulation paradigms in patients with anxiety disorders and in stimulated healthy subjects. Such stimulatory conditions can be either psychological or pharmacological and correlate with regional changes of activity.

Investigations incorporated into this review have been chosen on the base of a med-line research with the keywords neuroimaging and either panic disorder, agoraphobia, social anxiety disorder or generalized anxiety disorder. Due to their large amount, research articles on specific phobia have been selected on the base of their impact on disorder specific neuroanatomical models, as judged by the authors. Out of the plenty of animal imaging data and findings in healthy human subjects only few exemplary articles have been chosen to facilitate the introduction to anxiety disorder specific models.

In line with both classificatory systems DSM-IV (American Psychiatric Association 1998) and ICD-10 (World Health Organisation 1993) and in order to make this article as concise as possible, no research articles on post-traumatic stress disorder (PTSD) and obsessive–convulsive disorder (OCD) have been implemented.

Due to the relative unspecificity and the limitations of structural imaging data, their presentation is kept short in this article.

Following a brief introduction about selected findings from animal studies and healthy probands, an overview on neuroimaging research work is given and implications for future perspectives are made. Brief introduction to the clinical syndrome of the respective disorders are given in the beginning of each chapter and preliminary conclusions from the research data are tried to be made.

Implications from animal research

In anxiety paradigms, it has become evident that the medial prefrontal cortex plays an essential role in the inhibition of conditioned fear following extinction. These neuronal pathways inhibit central amygdala nucleus output and inputs from the insula and basolateral amygdala (Quirk et al. 2003). Amat et al. (2005) showed that the ventral medial prefrontal cortex in rats detects whether a stressor is under control of the organism. If this is the case, dorsal raphe activity is blocked.

Milad and Quirk (2002) showed that destruction of the ventral medial prefrontal cortex in animals impairs recall of extinction. This structure might store long-term extinction memory and inhibits fear in subsequent encounters with fear stimuli. Thus, previously learned coping strategies with external and internal stressors would be processed from this region.

Healthy subjects

Functional magnetic resonance imaging (fMRI)

Using fMRI during a fear conditioning paradigm in healthy subjects, amygdalae activation was increased (LaBar et al. 1998). Another investigation showed amygdalae activation on presentation of non-conditioned, fear-related or negatively affect-loaded stimuli, too (Grodd et al. 1995). Gottfried and Dolan (2004) could demonstrate that in humans that orbitofrontal cortex and amygdalae activity were preferably enhanced during extinction learning of previously conditioned aversive stimuli. Etkin et al. (2006) found that activity in the amygdala and dorsomedial and dorsolateral prefrontal cortices reflects the amount of emotional conflict, when a coping-strategy seems not to be directly available. The amygdala activation appears to be personality dependent and correlates with neuroticism (Haas et al. 2007). Final resolution of the emotional conflict goes in line with anterior cingulate cortex (ACC) activity and correlates with reduction of amygdalae activity (top-down inhibition). Herry et al. (2007) suggested that amygdala function increases with the unpredictability of a stimulus or situation. Paulus et al. (2004), however, implied that activation of the ACC and medial prefrontal cortex was significantly higher in high trait-anxiety subjects and was correlated with trait but not state anxiety. Possibly, this feature characterizes subjects who scan their environment more thoroughly for anxiety inducing stimuli but also for coping factors. According to (Phelps et al. 2004), ventromedial prefrontal cortex activation (anterior cingulate) seems to be primarily linked to expression of fear learning during delayed tests of extinction.

Jensen et al. (2003) proposed that the ventral striatum, which is associated with the reward system, is activated in anticipation of adverse stimuli. Yet, Yaguez et al. (2005) showed that actual and anticipated aversive stimuli (pain) elicited similar cortical responses, including activation of ACC, insula, primary and secondary somatosensory cortices. This is in line with Simmons et al. (2004), who observed insula, dorsolateral prefrontal cortex, and parahippocampal gyrus activation during anticipation of aversive affective images. Interestingly, Critchley et al. (2002) demonstrated that conditioning-related neural activity is modulated by both awareness and representations of bodily states and autonomic arousal. Absent
peripheral autonomic arousal, in patients with autonomic
denervation was associated with decreased conditioning
related activity in insula and amygdala.

In a meta-analysis of PET and fMRI studies on emotion
in healthy volunteers, (Phan et al. 2002) proclaimed certain
brain regions to be associated to distinct emotions and
executive functions, e.g. the amygdalae for fear and the
medial prefrontal cortex for emotional processing. In a
recent fMRI study by Dannlowski et al. (2007), however, it
could be demonstrated that amygdala hyperreactivity cor-
related with negative automatic emotion processing (in
depressive patients). Activity in the basolateral amygdala
elicited by unconscious emotional processing was pre-
dicted by individual differences in trait anxiety in healthy
subjects using fMRI. This phenomenon was not detected in
the dorsal amygdala that is modulated by conscious emo-
tional processing (Etkin et al. 2004). High trait anxiety
healthy subjects display higher amygdala and insula acti-
vation during processing of emotional stimuli compared to
a normative group (Stein et al. 2007). State anxiety, how-
ever, is associated with higher ventral amygdala responses
in healthy subjects (Somerville et al. 2004). Application of
the selective serotonin re-uptake inhibitor escitalopram
over 21 days could significantly reduce amygdala activa-
tion during an emotional task compared to placebo in
healthy probands (Arce et al. 2008). This may well fit into a
theoretical framework of negative emotional processing as
indicated by LeDoux (1996) stressing an unconscious,
“fast” way of automatic amygdala mediated responses to
potentially threatening stimuli.

Nevertheless, in a classical conditioning paradigm using
PET, healthy subjects reacted to stimulation with an
increase of cerebral blood flow (CBF) in the thalamus,
hypothalamus, periaqueductal grey (PAG) and cingulate
activity in the cerebellar vermis, both temporal lobes and
related to the dorsal ACC. Effects were independent of the
occurrence of a panic attack, subjective levels of anxiety
correlated with amygdala activation.

Panic disorder

Panic disorder is a condition characterized by repeated
limited episodes of intense somatic and psychic anxiety
symptoms. Symptoms such as dyspnea, palpitations,
tachycardia, sweating, tremor, nausea and depersonaliza-
tion, fear of losing control or dying emerge in specific
situations or “out of the blue” and increase within a few
minutes. Such panic attacks usually result in an intense and
ongoing fear of the next expected attack (phobophobia).
This may lead to avoidance behaviour with patients
refraining situations in which they may become helplessly
panicky. Panic disorder very often is associated with ago-
raphobia, a fear of certain situations (such as elevators,
wide places, crowds of people, theatres) from which fleeing
is expected to be difficult.

Structural imaging

Computed tomography (CT)

In a number of CT studies, some distinct structural alter-
ations in panic disorder patients were detected in low to
medium sample sizes. Most results were rather unspecific
[demonstrating enlarged ventricles in the prefrontal cortex
(Wurthmann et al. 1997)], slight atrophy, diminished brain/
ventricles ratio or lacunary infarctions, and could not be
replicated [e.g. normal brain/ventricles ratio (Uhde et al.
1987)]. Lepola et al. (1990) found structural abnormalities
in 6 of 30 panic patients. In conclusion, CT cannot be
regarded as an appropriate tool for investigating the
neuroanatomy of panic anxiety due to its low resolution.

Magnetic resonance imaging (MRI)

Structural MRI-studies revealed hardly more specific and
conclusive results compared to CT investigations. In panic
patients structural alterations were found in the temporal
lobes, predominantly on the right side (Fontaine et al.
1990; Ontiveros et al. 1989). One investigation reported
diminished volumina of both temporal lobes, despite
unaltered hippocampi (Vythilingam et al. 2000).

Uchida et al. (2003) found a reduced left temporal lobe
volume and a trend to reduced right temporal lobe, left and
right amygdala and the left hippocampal area volume.
One study indicates reduced grey matter density in the
left hippocampus of panic patients (Massana et al. 2003a).

Another morphometric investigation on panic disorder
patients revealed higher grey matter volume in the
mesencephalon of the rostral pons and to a slightly lower extent in the ventral hippocampus combined with less prefrontal cortex volume (Protopopescu et al. 2006). A voxel-based morphometric study found bilaterally diminished putamen volumina (Yoo et al. 2005). Volumetric magnetic resonance imaging (MRI) studies performed by Massana et al. (2003b) found patients to have smaller left-sided and right-sided amygdala volumes than controls. No differences were detected in either hippocampi or temporal lobes.

Functional imaging

Regional cerebral blood flow (CBF) under basal conditions

Three studies investigated basal CBF in patients suffering from panic disorder. In one [18FDG]-PET investigation, a lowered metabolic rate in the left inferior parietal lobe was found compared to controls (Nordahl et al. 1990). Posterior temporal lobe, inferior parietal lobe and cerebellar cortex CBF was decreased bilaterally (Malizia et al. 1998), whereas on study showed increased CBF in the left hippocampus (Bisaga et al. 1998).

Sakai et al. (2005) accessed cerebral glucose metabolism in patients with panic disorder using F-fluorodeoxyglucose positron emission tomography with voxel-based analysis to compare regional brain glucose utilization and showed that patients exhibited significantly higher levels of glucose uptake in the bilateral amygdala, hippocampus, and thalamus, and in the midbrain, caudal pons, medulla, and cerebellum than controls. After successful treatment both cognitive behavioural treatment and antidepressant treatment resulted in comparable decreases of previous activations (Prasko et al. 2004).

On trial implying Tc99m-HM-PAO-SPECT in panic patients detected a bilateral frontal decrease and a right pronounced medial and superior frontal increase of regional blood-flow. CBF asymmetry with a shift to the right side correlated with disorder severity as measured with the Bandelow Panic and Agoraphobia Scale (P&A) (Eren et al. 2003). Comparable results were found by Lee et al. (2006) with patients showing decreased CBF in the right upper temporal lobe. CBF in this region was negatively correlated with panic disorder severity.

GABA-/benzodiazepine receptors

[11C]Flumazenil binding to benzodiazepine receptors was generally diminished in patients compared to controls, especially in the right insular region and in the right orbitofrontal cortex (Malizia et al. 1998). These results could be replicated lately by Cameron et al. (2007) who showed diminished binding in the insular cortices bilaterally correlating with disorder severity and comorbid depression.

Several studies used [123I]Iomazenil-SPECT to investigate benzodiazepine receptor binding. Kuikka et al. (1995) found increased iomazenil signaling in the temporal cortex and in the right laterofrontal gyrus in drug-free panic disorder patients compared to healthy controls. Brandt et al. (1998) compared drug-free patients and controls as well and found increased iomazenil binding in the right orbitofrontal cortex. The left hippocampal area revealed less benzodiazepine-receptor binding (Bremner et al. 2000).

One investigation compared panic disorder patients with patients suffering from epilepsy showing lower iomazenil uptake in the frontal, occipital and temporal cortex (Schlegel et al. 1994).

Comparing panic patients with comorbid major depression to patients suffering from dysthymia, who were all on antidepressant medication, a lower iomazenil binding in both lower lateral temporal lobes, in the left medial inferior temporal lobe and in both orbitofrontal lobes could be demonstrated for panic disorder (Kaschka et al. 1995).

Using 1H-magnetic resonance spectroscopy, a reduced GABA concentration in the occipital cortex could be measured (Goddard et al. 2001).

In a consequent trial, the authors could find a lowering of occipital GABA reduction after benzodiazepine administration (Goddard et al. 2004).

Another study revealed significantly decreased GABA concentration in the anterior cingulate (ACC) and in the basal ganglia in panic patients compared to controls (Ham et al. 2007). Lactate and choline concentrations in the ACC in patients were higher.

Serotonin binding studies

In one PET study, a reduced serotonin-5-HT1A-receptor binding in the cingulate and raphe nuclei could be found (Neumeister et al. 2004).

Maron et al. (2004) found that patients with current PD showed a significant decrease in 5-HT transporter binding in the midbrain, temporal lobes and thalamus compared to controls by SPECT. Regional binding significantly and negatively correlated with the severity of panic symptoms. The binding in patients in remission, however, was comparable to findings in the control group.

Creatine and phosphocreatine are metabolites involved in energy dependent brain systems. In the frontal lobes of panic patients a higher phosphocreatine concentration was found on the left side (Shioiri et al. 1996).

1H-magnetic resonance spectroscopy revealed a reduced creatine/phosphocreatine concentration in the medial prefrontal cortex in one study (Massana et al. 2002).
Anxiety provocation and challenge tests

**Provocation of presentation of visual anxiety-related stimuli**

After presentation of potentially threatening words, panic patients displayed activation in the left posterior cingulum and the left medial frontal cortex (Maddock et al. 2003) in the f-MRI.

On presentation of words with negative emotional valence patients reacted with an activation of the right amygdala and right hippocampus (van den Heuvel et al. 2005).

Stimulation with anxiety related pictures went in line with increased activity in the inferior frontal cortex, the hippocampus, the anterior and posterior cingulate and the orbitofrontal cortex (Bystritsky et al. 2001).

On presentation of anxious faces panic patients displayed, compared to controls, a lower activation of the anterior cingulate cortex and the amygdalae (Pillay et al. 2006). This was discussed in a way that patients had a reduced reaction to acute emotional cues because of a chronic hyperarousal. Happy faces went in line with a bilateral activation of the anterior cingulate cortices but not with amygdala alterations (Pillay et al. 2007).

Domschke et al. (2006) reported correlations between distinct genetic polymorphisms of the serotonergic system and a lower activation of the right prefrontal cortex and increased activity of both amygdalae after presentation of faces with emotional expressions.

**Panic provocation by sodium lactate infusions**

Panic provocation with sodium lactate or other panicogens can be associated with artefacts by induced vasoconstriction (Ball and Shekhar 1997). Also, respiratory changes caused by acute (state anxiety) or continuous (trait anxiety) fear and anxiety may influence results of functional MR imaging (Giardino et al. 2007).

In one PET study by (Reiman et al. 1989) a decreased left to right ratio of parahippocampal CBF was seen in panic disorder patients. However, these results could not be replicated by (Drevets et al. 1992) and turned out to be artefacts by extracerebral signals, namely patients’ gritting of teeth.

In a trial using 99mTc-HM-PAO-SPECT seven sodium-lactate sensitive panic disorder patients were compared to five healthy controls (De Cristofaro et al. 1993). In the patient group, increased CBF in the right orbitofrontal cortex was detected. Additionally, CBF was higher in the left occipital cortex and lower bilaterally in the hippocampus and the amygdalae. Using $^{133}$Xe-SPECT, patients who did not panic after sodium lactate as well as in controls, hemispheric CBF after the infusion was increased (Stewart et al. 1988). This was not the case in patients who had panicked, but maybe because of induced hyperventilation decreasing CBF. Yet, patients who experienced a panic attack had an increase of CBF in the occipital lobe.

Sodium-lactate infusion causes an increased lactate concentration in the brain. The increase is more pronounced in panic disorder patients than in controls. This was demonstrated using proton echo planar spectroscopic imaging (PEPSI). Particular regions not displaying such an increase could not be identified (Dager et al. 1999).

Panic patients had a larger and prolonged sodium lactate increase in the insular cortices (Dager et al. 1994, 1997) as detected by magnetic resonance spectroscopy (MRS).

**Panic provokation by yohimbine**

During yohimbine-induced anxiety, cerebral vasoconstriction was observed. Patients showed an attenuated activation of the frontal cortex compared to controls using HM-PAO-SPECT (Woods et al. 1988).

**Panic provocation by cholecystokinin (CCK)**

After CCK induced anxiety healthy volunteers displayed an increase of extracerebral blood flow in the region of the superficial temporal artery (Benkelfat et al. 1995) as measured by PET. The authors hypothesized that regional blood flow changes that were measured in previous study might be caused by muscular activity.

There is one study which investigated anticipatory anxiety before infusion of the CCK-B agonist pentagastrin. After the challenger there was no more hypothalamic CBF increase but a larger activity of the right amygdala (Boshuisen et al. 2002).

**Panic provocation by doxapram**

In response to the respiratory stimulant doxapram, which can induce panic attacks, panic disorder patients tended to decrease prefrontal activity more than controls, and increased cingulate gyrus and amygdala activity more than controls (Garakani et al. 2007).

**Spontaneous panic attacks**

Pfleiderer et al. (2007) recently reported on a female patient with panic disorder experiencing an (accidental) spontaneous panic attack under an auditory habituation paradigm in fMRI at 3 T. This is the first report on spontaneous panic under such conditions. The panic attack was associated with a significantly increased activity in the right amygdala.
Panic disorder: concluding remarks

Neurocircuitry models of panic disorder have hypothesized that the panic attack itself stems from loci in the brainstem including the ascending reticular system and respiratory and cardiovascular control centres. Panic might be controlled as well as to originate from a dysfunction of frontal and temporal limbic circuitries. According to Gorman et al. (2000) a neuronal “fear network” centered in the amygdala is controlled by medial prefrontal areas via the hippocampus. Amygdala projections to brainstem nuclei might account for many of the somatic anxiety symptoms during a panic attack. Entero- and exteroceptive awareness might be increased by a greater reagibility of the insular cortex. In subsequent phenomena such as expectancies (“fear of fear”) and avoidance prefrontal cortical areas obviously appear to be predominantly involved. Side asymmetries with decreased activity of inhibitory, prefrontal structures and increased activity in limbic areas on the dominant hemisphere are evident. However, many studies cannot be considered conclusive because of several methodological limitations, and challenge paradigms are not easy to perform in this patient group in the scanner. Despite of this, the amount of investigations in panic disorder exceeds the number of those in the other anxiety disorders by far. Volpe et al. (2004) suggested longitudinal and multi-modal studies involving larger patient samples, possibly integrated with population-based and genetic studies, would provide more insight into pathophysiological mechanisms of panic disorder. Nevertheless, a dysfunctional serotonergic system might be of importance since several parameters associated with serotonergic function are altered in panic disorder and treatment with serotonergic drugs can reduce activity of distinct regions of the “fear network” in the direction of controls.

Generalized anxiety disorder (GAD)

Generalized anxiety disorder is a disorder characterized by continuous symptom of anxiety and vegetative hyper-arousal associated with extreme and exaggerated sorrows. Sorrows might deal with thoughts that relatives or family members could be harmed or have an accident when they are out of the patient’s control. Sorrows may also be about financial or occupational issues. Patients are aware that their fear of anything adverse happening is not realistic and that their sorrows are exaggerated (meta-sorrows).

Structural imaging

In comparatively small samples of GAD and panic disorder patients some subjects revealed unspecific CCT alterations such as enlarger ventricles (Lauer and Krieg 1992). Compared to children with panic attacks, children with GAD had a higher grey to white matter ratio in the upper temporal lobe. This was more pronounced on the right side, whereas there were no differences in the thalamus and the frontal cortex (De Bellis et al. 2002).

Functional imaging

Only over the recent years, results from imaging studies allow for differentiated statements about regional CBF alterations (Nutt 2001). Under basal conditions no consistent changes were observed. Under psychological stress, however, a reduction of CBF was found (Nutt 2001). Using xenon-inhalation-technique a negative correlation between CBF and anxiety could be shown. Nevertheless, under resting conditions no differences to controls emerged (Mathews and Wilson 1987).

Positron emission tomography investigations revealed increased metabolism in the occipital, temporal, frontal, and cerebellar region and a lower CBF in the basal ganglia of patients with GAD after presentation of an anxiety-inducing task (Wu et al. 1991). Under comparable conditions an amplification of activity emerged in the basal ganglia (Buchsbaum et al. 1987). Mathew et al. (2004) recently described that GAD patients had a 16.5% higher N-acetylaspartate/creatine ratio, a suggested marker of neuronal viability, in the right dorsolateral prefrontal cortex compared with healthy controls. A total of 13 of 15 matched patient-comparison subject pairs displayed such a difference. In a recent meta-analysis (Etkin and Wager 2007) greater amygdala and also insula activity was reported for GAD in negative emotional processing compared to healthy controls. Patients with GAD had a better treatment response to fluoxetine or cognitive behavioural therapy when pre-treatment amygdala activity was strong (McClure et al. 2007). Treatment response to venlafaxine, however, was predicted by lower amygdala and higher ACC reactivity to fearful faces in the fMRI (Whalen et al. 2008). With regard to prefrontal activity Monk et al. (2006) found greater fMRI BOLD responses in the right ventrolateral prefrontal cortex to emotionally adverse stimuli compared to healthy controls. In adolescents with GAD disorder severity correlated positively with right amygdala activation on presentation of angry faces. This finding was negatively associated to right ventrolateral prefrontal cortex activity, a phenomenon that was evident to an even higher degree in healthy controls (Monk et al. 2008).

There is still a relative paucity of GAD studies. Amygdala and insula function seem to be of importance in this disorder and a dysfunction of the ventrolateral prefrontal cortex could be of relevance.
Social anxiety disorder (SAD)

Social anxiety disorder is characterized by extreme and exaggerated fears of being scrutinized by others and to be a target of criticism leading to awkward situations. Social situations (e.g. public speaking, performances, interactions with authority persons or members of the opposite sex) in which the subjects expects his appearance and behaviour to be evaluated by others (mostly unfamiliar persons) are avoided or tolerated with intense anxiety symptoms which are again expected to be detected by others. Panic attacks may occur in the course of this disorder. A performance type, an interaction type, and a generalized type can be distinguished.

Structural imaging

The study by Potts et al. (1996) found an overall volume reduction of the putamen of patients compared to controls by MRI.

Functional imaging

Phobic stimulation paradigms

Birbaumer et al. (1998) showed bilateral amygdalae activation in SAD patients under phobic stimulation using fMRI. Stein et al. (2002) however, investigated a signal increase in amygdalae, uncus, and gyrus parahippocampalis in patients in the fMRI on presentation of faces expressing negative affectivity, exclusively. This could be confirmed by Evans et al. (2007) and Phan et al. (2006) in generalized SAD patients who were shown aversive faces displaying higher amygdalae activation. The extent of activation correlated with SAD severity and was reversible after antidepressant treatment (Norbury et al. 2007).

Lorberbaum et al. (2004) scanned generalized social phobics anticipating public speaking by fMRI. They showed greater subcortical, limbic, and lateral paralimbic activity (pons, striatum, amygdala, uncus, anterior parahippocampus, insula, temporal lobe), regions important in automatic emotional processing. Cortical activity (dorsal ACC, prefrontal cortex) (important for cognitive processing) was reduced. Interestingly, Campbell et al. (2007) could demonstrate that amygdala and prefrontal cortex responses to emotional faces occurred later in generalized social phobics than in healthy controls.

Kilts et al. (2006) demonstrated in PET scans of SAD subjects that mental imagery resulted in left postcentral gyrus, lenticulate right inferior frontal gyri and medial temporal gyri activity. Mental arithmetic tasks activated medial and left dorsolateral prefrontal cortex, cerebellum, thalamus, insula and ventral striatum. Both conditions went in line with right amygdala and hippocampus activation. In paired conditioning paradigms—simultaneous presentation of a conditioned (neutral facial expression) and an unconditioned stimulus (neutral or aversive odour)—patients displayed a significant increase in amygdalae and hippocampus activity compared to control subjects (Schneider et al. 1999). fMRI scans by Straube et al. (2005) demonstrated increased activity in the extra-striate visual cortex on presentation of faces regardless of expression. Angry faces, however, elicited greater insula activation. Amygdala, parahippocampal gyrus and extra-striate visual cortex were more strongly activated in an implicit subtask (type of picture, not expression) (Straube et al. 2004b). Yoon et al. (2007) also reported higher bilateral amygdala activation in generalized social phobics compared to healthy controls when faces with high emotional intensity were presented.

Kagan described a childhood phenomenon “behavioural inhibition” that is characterized by avoidance of novel stimuli, objects and situations. Adults who had been diagnosed as “inhibited” in the second year of life showed a more pronounced amygdala activation in the fMRI on presentation of unfamiliar faces (Schwartz et al. 2003).

One SPECT-study found no differences with regard to CBF between SAD and healthy subjects (Stein and Leslie 1996).

After provocation by phobic stimuli PET showed a signal increase in the right prefrontal cortex and in the left parietal cortex. This phenomenon did not show under phobic anticipation in controls (Malizia et al. 1997).

Another PET study was performed to measure SAD patient’s CBF in a state of anticipatory anxiety before public speaking. An increased CBF in the right dorsolateral prefrontal cortex, the left inferior temporal cortex and the left hippocampus-amygdala complex was detected, additionally a decrease of CBF in the left temporal pole and bilaterally in the cerebellum.

During and after stimulation SAD patients showed an overall increase of subcortical CBF compared to healthy controls who had an elevation of cortical CBF (Tillfors et al. 2002). Similar elevations of CBF in generalized SAD in the thalamus, midbrain, the lateral, prefrontal and medial cingulum, and the sensomotoric, anterotemporal cortex were stated by investigations by Reiman (1997). Under stimulatory conditions a decrease of activity in the visual- and the mediofrontal cortex could be demonstrated (van Ameringen et al. 1998).

Metabolic changes, treatment effects, and serotonergic function

Davidson et al. (1993) and Tupler et al. (1997) could distinguish different distributions of amino-acids by magnetic resonance tomoscopy in SAD patients for instance in the
thalamus and the caudate nucleus. Relating to these investigations a lower metabolic rate in the basal ganglia of patients with SAD was proposed. Magnetic resonance spectroscopy revealed an increased uptake of fluoxetine in distinct areas of the brain in SAD patients who had improved clinically significantly under this treatment before (Miner et al. 1995). Successful pharmacotherapy reduced activity in the left temporal lobe, left frontal cortex and left cingulum as assessed by HMPAO-SPECT (van der Linden et al. 2000). In a PET study after phobic stimulation, SAD patients who had clinically improved under citalopram treatment had decreased CBF in both amygdala, hippocampus, and in the paraamygdaloid, rhinal, and parahippocampal cortex compared to measurements before pharmacological treatment. Changes correlated obviously with clinical improvement and differed significantly to untreated controls (Furmark et al. 2002). More evidence for a serotonergic dysfunction was given by Lanzenberger et al. (2007) who found a significantly lower 5-HT1A receptor binding in several limbic and paralimbic areas of SAD patients, most significantly in the amygdala followed by the anterior cingulate cortex, insula, and dorsal raphe nuclei.

Recent theories propose a dysfunction of the dopaminergic system in SAD. Using the cocaine analogue $^{[123]}$-Beta-CIT a reduced density of dopamine reuptake sites in SAD patients was demonstrated (Tiihonen et al. 1997). An IBZM-SPECT study found a lower $D_2$-binding capacity in SAD patients (Schneier et al. 2000).

In an open-label treatment trial (Kelsey et al. 2000) with nefazodone correlates of social anxiety under stimulation before treatment were obvious in the cortex bilaterally, the medial temporal lobe, caudate nucleus, frontal lobe, and in the lateral orbitofrontal cortex. Medial frontal lobe CBF correlated with experienced anxiety to a high degree. After treatment, CBF alterations with phobic stimulation still could be seen in the right medial orbitofrontal cortex and in the anterior cingulum. After successful treatment with citalopram or a neurokinin-1 antagonist a reduced response of the rhinal cortex, amygdala and the hippocampal area during a public speaking task was detected in patients with social phobia (Furmark et al. 2005). Another interesting study by the same authors (Furmark et al. 2004) showed that carriers of one or two copies of the short allele of the serotonin transporter gene had, besides elevated levels of trait- and state anxiety, a higher exitability of the right amygdala to anxiety provocation compared to carriers of two long allele copies.

Social anxiety disorder: concluding remarks

Following a neuroanatomical model by (Li et al. 2001) it has been proposed, that in SAD there was a dysfunction of a cortico-striato-thalamic network. This could partially stated by Sareen et al. (2007) showing a striatal dysfunction associated with generalized social phobia. According to Li, the parietal cortex plays an important role in the evaluation of body position and the “social space”. Via connections between thalamus and basal ganglia there is an increased transmission to the frontal cortex. A more negative evaluation of social situations would result and consequently their avoidance. (Veit et al. 2002) presume a hyperactive frontolimbic system that tends to misinterpret potentially anxiety-inducing cues. Amir et al. (2005) stressed the importance of the ACC in SAD in processing negative emotional information. However, compared to patients with posttraumatic stress disorder (PTSD), according to the meta-analysis of Etkin and Wager (2007), SAD patients did not show alterations of the ACC, although amygdala and insula activity was higher than in healthy controls.

Social anxiety disorder seems to be characterized by a hyperreactive (right) prefrontal cortex in combination with a striatal dysfunction and increased hippocampus and amygdalae activity with a lateralization to the left. Insula activity goes in line with somatic anxiety, whereas the ACC is important in anticipation of adverse stimuli. Serotonergic drugs were consistently able to diminish these phenomena according to clinical improvement.

Specific phobia

Specific phobia is a disorder characterized by an intense and exaggerated fear of specific and isolated situations and objects. Animal phobias are the most frequent subtype (spiders, snakes, mice). Extreme anxiety symptoms might emerged in the presence of the feared object, even thinking about it may cause symptoms. Places where a confrontation is expected are usually avoided. This may lead to restrictions in daily life, when e.g. a bedroom cannot be used or the basement or the attic is avoided.

Straube et al. (2006a) found increased activation of the left (but not right) amygdala, left insula, left anterior cingulate, and left dorsomedial prefrontal cortex in fMRI scans in phobics exposed to aversive (spider) versus neutral (mushroom) images. In patients this phobic amygdala activation appears to be stronger and shorter than in nonphobics (Larson et al. 2006).

A greater response to fearful versus neutral faces of the right insular cortex compared to controls was described by (Wright et al. 2003). Amygdala hyperresponsivity was not observed. Straube et al. 2004a, b showed that phobia related words elicited activation in prefrontal cortex, insula, and posterior cingulate cortex.

In patients with specific phobias, SPECT could discover reduced tracer uptake in posterior brain regions under
phobic stimulation (O'Carroll et al. 1993). In spider phobia Schienle et al. (2005) measured greater activation of the visual association cortex, amygdalae, right dorsolateral prefrontal cortex and right hippocampus. The supplementary motor area was activated, too.

Using [¹⁵O]-PET in this patient group, a significant activation under phobic stimulation was measured in the amygdalae and thalamus (Wik et al. 1997). In a population of anxiety disorder patients of which only a part suffered from specific phobias PET could detect regional CBF differences with activation in the right frontal cortex, the right postero-medial orbitofrontal cortex, in both insulae and bilaterally in the nucleus lenticularis, and in the brainstem (Rauch et al. 1995). PET-stimulation with spiders versus butterflies in specific phobia revealed signal enhancement in the left fusiform gyrus and right parahippocampal gyrus. Habituation was seen in the anterior medial temporal lobe bilaterally. State anxiety correlated with left amygdala bilaterally, perirhinal cortex, right fusiform gyrus, and PAG, whereas phobic fear correlated with right hippocampal activity (Veltman et al. 2004).

In an article on pathologic emotions (Reiman 1997), associated brain regions to distinct functions on the base of PET-studies. According to this theory, the anterior temporal lobe is responsible for evaluation processes that attach exteroceptive sensoric information to an emotional component. The anterior insular areas combine potentially fearful cognitive and sensory information to negative emotion. Cingulum, vermis cerebelli, and midbrain regions become activated in both, normal and pathologic anxiety. The orbitofrontal cortex, the anterior insulae and the anterior cingulate appear to be of particular relevance, as they are possibly dysfunctional in all phobic disorders (Malizia et al. 1997). Treatment studies (Straube et al. 2006b), however, showed that in fMRI specific phobics had a reduction of previously hyperactivity of the insula and ACC after successful cognitive behavioural therapy. Goosens et al. (2007a) could demonstrate a reduction of elevated baseline amygdala activation after 2 weeks of exposure treatment to the feared stimuli and also a significant decline in the ACC and insular cortex. In a visual stimulation study, using fMRI, besides amygdala and pulvinar nucleus of the hypothalamus activation increase, ACC and left insula were stimulated more intensively in patients compared to controls (Goosens et al. 2007b). Schienle et al. (2007) reported decreased activation of the medial orbitofrontal cortex in a pre-treatment exposure that increased over the therapeutic process compared to a waiting list group, a finding also reported by Hermann et al. (2007) in patients exposed to phobia-relevant pictures compared to controls. Amygdala and insula activity was reduced with an experienced reduction of somatic anxiety over the course of cognitive behavioural treatment (Schienle et al. 2007). A greater activity of these two structures linked to negative emotional responses was also reported by the meta-analysis by Etkin and Wager (2007). The bed nucleus of the stria terminalis as well as insula, ACC and thalamus had a higher BOLD response in anticipation of phobic versus neutral images in phobics compared to controls. ACC and anterior prefrontal cortex activity correlated with subjective anxiety in the patient group (Straube et al. 2007).

Results from specific phobia investigations underpin the theory of a hyperreactive amygdala more lateralized to the left hemisphere (although no differential investigations on conscious and unconscious perception of stimuli exist) diminishing with successful treatment. Anticipation of phobic stimulation activates the ACC and the insular cortex which may characterize state anxiety or the expectancy of adverse extero- and enteroception. Effects are decreasing with syndrome improvement. The medial prefrontal cortex appears to be hypoactive, although this has not been demonstrated consistently.

Discussion

A multitude of research has been targeting on possible brain regions involved in the origin of anxiety. Numerous studies suggest that the amygdala is critical for the acquisition and expression of fear. Conditioned fear in animals has been considered as a good model for human anxiety disorders, but animal models of anxiety have obvious limitations. Conditioned fear in animals can be directed to a specific stressor and is easily extinguished. Furthermore, animals have a limited or lacking ability to develop the capacity to worry excessively about the future. They do not completely parallel the complex cognitive processes that occur in anxious or even anxiety disorder ridden humans.

It can be assumed that human anxiety disorders are caused to a certain extent by differential activity in certain prefrontal cortex areas, the brain region that most separates us from animals. The human prefrontal cortex has not only been shown to be more developed than that of other mammals, but it also has unique morphology and gene expression. Neuroimaging studies consistently show abnormalities in the prefrontal cortex in anxiety disorder individuals. Thus, (Berkowitz et al. 2007) suggest that the very same cortical complexity that allows us to produce society and culture is also the origin of anxiety disorders.

Interestingly, preclinical and to a growing extent clinical studies have shown that the prefrontal cortex inhibits the amygdalae (the central nuclei). With the current knowledge we have, it can be assumed that the amygdalae are acutely activated when the individual is confronted to novel or generally fearful stimuli. Learned experience that a stressor
can be coped with, is under control or is no longer worth paying attention to, is characterized by distinct regional prefrontal activation. This emotional processing can decrease amygdalae activation or, when a solution is lacking, leads to continuous limbic activation which is lateralizing the more to the non-dominant side the worse the stressor is perceived.

However, there appears to be a distinction between two classes of anxiety disorders. Those disorders involving intense fear and panic (panic disorder and specific phobias) seem to be characterized by a hypoactivity of distinct prefrontal cortex areas, thus desinhibiting the amygdalae. Disorders which involve worry and rumination such as generalized anxiety disorder or cognitions of negative consequences of social behaviour (SAD), on the other hand, seem to be characterized by a hyperactivity of the prefrontal cortex.

Studies of prefrontal cortical function in psychiatric illness should be a fruitful method for identifying effective treatment approaches. With improvements of methods a more sophisticated evaluation of different executive functions of the prefrontal cortex—and a differentiation of orbitofrontal, medial frontal including cingulate cortex, and dorsolateral prefrontal cortex functions will become increasingly inevitable—a more reliable picture of the neurocircuity of anxiety disorders might emerge. In future investigations lateralization phenomena will have to be taken in account as important neurobiological features of anxiety disorders as shifts of activation to the non-dominant hemisphere with growing threat are commonly observed.

While previously mainly limbic structures were focussed on in anxiety, besides the prefrontal areas, distinct areas concerned with the perception of bodily states cannot be neglected. The insular cortices seem to be definitely involved in anxiety disorders contributing initiating and maintaining inputs modulating prefrontal and limbic structures in a way Damasio has described by the somatic marker hypothesis (Damasio 1996).

Neuroimaging studies on the effect of psychotherapy in patients suffering from diverse forms of psychopathology indicate that the mental functions and processes involved in diverse forms of psychotherapy exert a significant influence on brain activity (Beauregard 2007).

Beliefs and expectations can markedly modulate activity in brain regions involved in perception, movement, pain, and diverse aspects of emotion processing. Taken together, the findings of neuroimaging studies strongly support the view that the subjective nature and the intentional content of anxiety-related processes (e.g., thoughts, feelings, beliefs, volition) definitely modulates anxiety-network functioning and plasticity.

Despite an overlap of certain phenomena that cannot be ignored (unspecific alterations), anxiety in healthy subjects does not equal anxiety in anxiety disorders and the different disorders display distinct phenomena (besides expectable unspecific ones) characterizing their particular psychopathologic characteristics. Several controlled studies have pointed out that healthy subjects showed activation of brain region such as anxiety patients. However, phenomena are usually significantly more pronounced in patient groups.

Thus, anxiety syndromes involving a sensitized evaluation of environmental aspects, cognitive dysfunction (such as worries), spontaneous or situational panic detached from higher (prefrontal) cortical control instances, motivational aspects of avoidance combined with perception and appraisal of enteroceptive phenomena of discomfort create demarcable categories of disorders which become increasingly investigable with neuroimaging techniques.

Future perspectives concerning neuroimaging in anxiety disorders could become a useful tool in the control of treatment effects, for the staging of disorder severity and possibly for the identification of variables that predispose individuals to an expectable success or failure of a specific therapeutic approach. Neuroimaging techniques could support the diagnostic process of anxiety disorders and support the inevitable rationale of implying biological variables in the classification of anxiety disorders, characterizing specific endophenotypes.

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