The neural correlates of symptom relief after interventions in anxiety disorders.

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Introduction

People who are suffering from anxiety disorders have intense and prolonged feelings of fear and distress for no obvious reason, affecting their normal way of life. Anxiety disorders include panic disorder with or without agoraphobia, specific phobia (e.g. spider phobia), social phobia, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), acute stress disorder, and generalized anxiety disorder (GAD).

Symptoms of the different anxiety disorders are outlined in the book entitled *Anxiety Disorder*s written by the National Institute of Mental Health (NIMH) [2009], and are presented in table 1.

Table 1. Anxiety disorders and its symptoms [NIMH 2009].

Anxiety disorder	Symptoms
Panic disorder	''It is characterized by sudden attacks of terror, usually accompanied by a pounding heart, sweatiness, weakness, faintness, or dizziness. During these attacks, people with panic disorder may flush or feel chilled; their hands may tingle or feel numb; and they may experience nausea, chest pain, or smothering sensations. Panic attacks usually produce a sense of unreality, a fear of impending doom, or a fear of losing control.''
OCD	''People with obsessive-compulsive disorder (OCD) have persistent, upsetting thoughts (obsessions) and use rituals (compulsions) to control the anxiety these thoughts produce. Most of the time, the rituals end up controlling them.''
PTSD	''Post-traumatic stress disorder (PTSD) develops after a terrifying ordeal that involved physical harm or the threat of physical harm.''...''People with PTSD may startle easily, become emotionally numb (especially in relation to people with whom they used to be close), lose interest in things they used to enjoy, have trouble feeling affectionate, be irritable, become more aggressive, or even become violent.''
Social phobia	''Social phobia, also called social anxiety disorder, is diagnosed when people become overwhelmingly anxious and excessively self-conscious in everyday social situations. People with social phobia have an intense, persistent, and chronic fear of being watched and judged by others and of doing things that will embarrass them. They can worry for days or weeks before a dreaded situation.''
Specific phobia	''A specific phobia is an intense, irrational fear of something that poses little or no actual danger. Some of the more common specific phobias are centered around closed-in places, heights, escalators, tunnels, highway driving, water, flying, dogs, and injuries involving blood. Such phobias aren't just extreme fear; they are irrational fear of a particular thing.''
GAD	''People with generalized anxiety disorder (GAD) go through the day filled with exaggerated worry and tension, even though there is little or nothing to provoke it.'' ... ''People with GAD can't seem to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants.''

Abbreviations: OCD; obsessive compulsive disorder, PTSD; post-traumatic stress disorder, GAD; generalized anxiety disorder.

Fortunately, different kinds of psychotherapy have shown to be effective in these patients like cognitive behavioral therapy (CBT) and exposure therapy. Also, a combination of pharmacological and psychological treatment has shown to be very effective in treating anxiety disorders [Chambless and Ollendick 2001; Nathan and Gorman 2007].

But, when focusing on one patient in particular, there are still many uncertainties in finding the right kind of therapy. The number of available therapies is big, especially when taking into account combinations of therapies. It would be of great value if we could predict which therapy has the biggest chance of successful treatment for a patient suffering from an anxiety disorder.

For that reason, it is important to increase our knowledge about the underlying biological mechanisms of anxiety disorders, and about biological consequences of therapeutic interventions. This is where psychotherapy and neuroscience come together. Sigmund Freud, being a neurologist, was also interested in this mind-brain interaction and studied it in his project entitled *The Project for a Scientific Psychology* [Freud 1895]. Regardless of his neurobiological roots, he chose to focus on the mind, because back then it was hard to study the brain, given the immature state of neuroscience at that time. Psychopharmacology only arose around the 1980s and brain scanning techniques around the 1990s.

Using neuroscience in psychotherapy could increase our knowledge about the development of the disorder and it can help us developing new therapies and therefore help improving the psychotherapeutic process. Increasing our knowledge of anxiety disorders can help developing more efficient ways of treating these patients and might even lead to new therapies.

Much research has been done to understand the pathological features underlying anxiety disorders. Recently, the number of neuroimaging studies that have investigated potential physiological changes in the brain after different kinds of therapy that have shown to be successful in patients suffering from anxiety disorders has increased.

In this thesis I will critically review neuroimaging studies that have focused on either structural or functional brain changes after successful therapy in anxiety disorders in order to establish a frame of reference where the changes can be expected. I will include as many neuroimaging studies as possible that have investigated brain changes after interventions that have resulted in symptom relief. Though, I will only include studies that involve adult subjects, hence 18 years and older. Furthermore, I will focus on whether it is possible to draw any conclusions from these findings of these studies, and whether it can add up to developing new therapies or improve already existing ones. Therefore, this thesis may serve as a basis for future research in the improvement of therapeutic interventions in anxiety disorders.

First, I will explain the basics of a fear response, as it is thought that an exaggerated fear response underlies anxiety disorders. I will discuss which brain structures are said to be involved in the emotional memory of the fear response and how we cognitively can control our emotional response to a fearful stimulus. Second, I will review published studies that have investigated the symptomatology of each anxiety disorder separately in order to define the differences between patients suffering from anxiety disorders compared to healthy subjects. Third, I will review studies that have investigated neurological changes after effective interventions. At last but not least, I will report findings of studies that have focused on the identification of pre-therapeutic brain marker predictors of treatment success.

Chapter 1 - Fear response

Anxiety disorders may reflect dysregulation in the neural fear systems. Thus, in order to understand the underlying mechanisms of anxiety disorders, I will first focus on the fear response. In this chapter, I will discuss

the basics of a fear response and the brain structures that have shown to be involved in the emotional memory of the fear response. Also, I will present studies on our ability to cognitively control our emotions.

Fear, anxiety, and stress

The body's reaction to a threat or fearful stimulus elicits a fear response. It is triggered when signals have been recognized as fearful, which is followed by a release of different neurochemicals. There is an increased release of glucocorticoids (GCs) (cortisol in humans) from the adrenal gland and catecholamines, particularly epinephrine and norepinephrine (NE), from the sympathetic system. This reaction to a stressor is called the fight-or-flight response. Through this response energy is mobilized and cardiovascular output and muscular tone are increased, thus leading to increased physical performance. At the same time, aspects of the parasympathetic nerve system like digestion, growth and immune response are inhibited [Szyf et al., 2005; Meaney and Szyf, 2005].

Stress, fear, and anxiety are all warning signals of the body and are involved in anxiety disorder. Stress, fear, and anxiety are all names for the fight-or-flight response, thus increased muscular tone, increased heart rate etc. But there are differences between these concepts, and consequently it is important to define these features first, to get a clear view of the role they play in different anxiety disorders.

Phenomenologically, fear is an emotional and physiological response to a recognized external threat, such as pain for example [Grillon and Baas, 2003]. Fear can have positive as well as negative effects to the body. It can help us safely cross the street, encourage us to step away from a cliff, and help us to double check if we have signed our tax forms, before we seal the envelope [Cozolino, 2002]. But in anxiety disorders, stimuli that normally seem harmless can be perceived as fearful and people become anxious in daily life [Kaplan et al., 2007]. Then again, anxiety is a feeling that warns for potential danger and enables a person to take action. It is defined as an unpleasant emotional state for which the cause is often a response to an imprecise or unknown threat [Grillon and Baas, 2003, Walker et al., 2003]. Anxiety is likely to occur when a person is walking through a dark forest on its own [Kaplan et al., 2007]. Stress is the body's reaction to a change that requires a physical, mental or emotional adjustment or response. Though, the difference between stress and anxiety is that stress can last on a long-term, and anxiety is mostly on a short-term.

When preparing a presentation, a person can feel anxious about how the presentation might proceed in the near future. Whether stress is experienced due to this upcoming event, depends on whether the person can cope with the level of anxiety. For some people the anxiety level can increase that much, that stress will turn into panic. Panic is characterized by the abruptness of the fear response [Barlow, 2002].

The different kinds of warning signals, thus fear, anxiety and stress, play different roles in each anxiety disorder. Therefore, it is important to keep in mind that, although the anxiety disorders have similarities because they all involve warning signals, they do differ in their outcome. People suffering from phobias are dealing with an exaggerated anxiety response which is persistent or irrational, triggered by harmless stimuli or situations [Friedman et al., 2008]. But, OCD is characterized by anxiety that drives to obsessions. In order to relief the anxious feeling, people show compulsive behavior. People with panic disorder are suffering from

spontaneous panic episodes, typically occurring spontaneously, without any demonstrable threat. And for PTSD, stress is occurring due to trauma, and it is believed that fear-conditioning is involved in explaining the characteristics [Rauch et al., 2003].

Emotional memory: induction of fear response via fast and slow pathway

LeDoux and colleagues [1994] were interested in how memories of emotional events are formed. He and his colleagues investigated the neural basis of emotional memory in rats by using fear conditioning in case of a sound associated with a footshock, which leads to freezing posture, comparable to the conditioning experiment of Pavlov which will be discussed later on. In combination with lesion studies in these rats, they designed a model for two separate, but interrelated fear circuits that induce the fear response, and called them the slow and the fast pathway (see figure 1 and 2). The models of LeDoux can explain why we sometimes act before thinking.

The fast pathway is also called the direct pathway. The information from the sense organs, like the nose, ears, skin, eyes, tongue, goes directly through the thalamus to the amygdala via the unconscious thalamoamygdalar pathway. In figure 2 the fast pathway is illustrated in the example of seeing a snake on the ground while walking through the forest. LeDoux et al [1994] showed that after a lesion in the auditory cortex, the freezing behavior had still been established after the administration of the sound, meaning that the auditory cortex is not needed for fear conditioning. These findings are suggesting that freezing behavior or fight-or-flight behavior is established via the direct pathway. This response is quick and functional for survival [Miller et al., 2005; LeDoux, 1994; Cozolino, 2002].

The slow pathway is also called the indirect pathway, with the hippocampus and cortex at its core. After the sensory information has entered the thalamus, this information is send to hippocampal and cortical circuits for further evaluation. This response is slower, because it involves more synaptic transmission and conscious awareness is involved. The sensory cortices, in conjunction with other brain regions such as the hippocampus, parahippocampal, association, and prefrontal cortices, assign significance to sensory stimuli based upon context and prior experience. The orbital and mPFC appear to exert a predominantly inhibitory influence upon the amygdala by activation of inhibitory interneurons [Miller et al., 2005; LeDoux, 1994; Cozolino 2002].

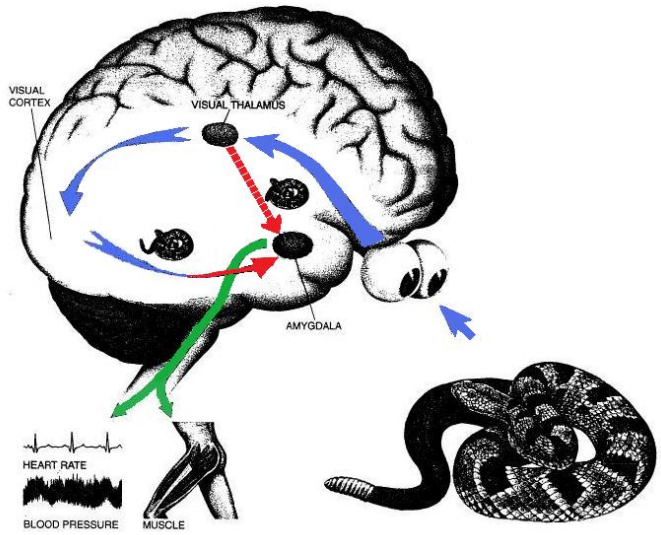

Figure 1. Cortical and subcortical pathways. Taken and modified from [LeDoux, 1994]. A visual stimulus is processed by the thalamus and goes directly to the amygdala (red). This quick transmission allows the brain to start to respond to the possible danger as in increased heart rate, increased blood pressure and muscle contraction (fight-or-flight reaction) (green). Meanwhile the visual cortex also receives information from the thalamus. Via this pathway it is determined whether it is indeed a snake that is seen (blue). This information is passed on to the amygdala, and if it is indeed a snake, the fear response of the body increases. In case the visual stimulus was false alarm, and thus no snake, but for example a wooden stick, the message to the amygdala will suppress the fear response.

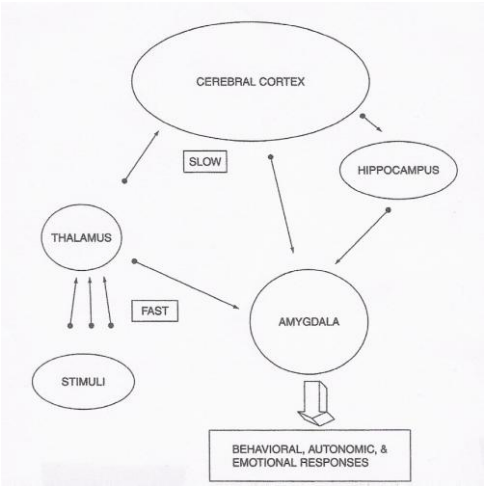

Figure 2. Schematic presentation of the direct and indirect pathway; fast and slow fear circuits; subcortical and cortical pathways [Cozolino, 2002].

In summary, this model is presenting two memory systems which are activated when a traumatic event occurs. One is the conscious memory, through which we can tell what had happened during the traumatic event (thus the slow circuit). At the same time also unconscious emotional memory is formed that is generated from the amygdala with specific details about the surroundings, sounds, smells, etcetera, that were there when it happened (thus is the fast circuit). This is beneficial for survival, because the next time a person is picking up the same stimuli the body is ready to react as if the traumatic event is happening again. The fast pathway is believed to play a role in the symptoms of patients suffering from PTSD. The association between the specific details of the surrounding and the traumatic event is that strong, that these patients can fully re-experience this traumatic event due to a trigger such as a certain smell [Shalev et al., 1992].

Research on anxiety disorders: Implications from animal research

Many studies have shown that in anxiety disorders the HPA-axis is hyperactive due to hyperactive CRF-releasing neurons [Coplan et al., 1996], but there are also many studies that show no involvement of the HPA-axis in anxiety disorders. It is also thought that underlying mechanism of fear conditioning and fear extinction are involved in anxiety disorders. To investigate this, animal models have been used to examine the exact underlying neural mechanisms in fear response and fear conditioning.

Ivan Petrovitsj Pavlov [1926] is famous for his conditioning experiment with dogs. In those experiments, he measured the amount of saliva produced by a dog when food was presented. Prior to the presentation of the food, a bell would sound. Soon the dog associated the sound of the bell with the food, and was salivating as soon as the bell would sound, without seeing the food. The food was in this case called the unconditioned stimulus (US) and the sound of the bell is called the conditioned stimulus (CS). The unconditioned response (UR) is the salivation to the food, and the conditioned response (CR) is the salivation to the sound. Pavlov showed that after several trials presenting the CS, without presenting the US, the ability of the CS to elicit the CR weakened.

Besides studying the conditioning and extinction of salivation in response to CS that predicts food, Pavlov also studied defensive CRs. These were responses elicited by a CS paired to aversive stimulation, such as pairing a tone (CS) and the footshock (US) in rats, leading to freezing behavior (CR) in response to a tone after a period of learning.

Extinction of Pavlovian fear conditioning is an important form of emotional regulation that is thought to have direct relevance to the treatment of anxiety disorders. Much research has been done in order to understand the process of fear extinction [Phelps et al., 2004; Delgado et al., 2008; Sotres-Bayon et al., 2004, 2006; Rauch et al., 2006, Morgan et al., 1993]. The medial prefrontal cortex (mPFC) has received a considerable amount of attention as a component of a brain's extinction circuitry. Certain emotional disorders are characterized by the inability to extinguish learned emotional reactions to fearful stimuli [Mineka and Ohman, 2002].

In the article of Sotres-Bayon et al [2006], a model for fear extinction was created based on several fear extinction studies in rats. In summary, they conclude that extinction could involve either mPFC activation of inhibitory lateral amygdala (LA) interneurons [Rosenkranz et al., 2003], or mPFC activation of inhibitory projections from the intercalated cell masses to the central amygdala (CE) [Quirk et al., 2003]. In short, they propose that the amygdala is involved in fear conditioning and that cortex is involved in fear extinction.

These studies on fear conditioning and fear extinction point to the cortex (especially the mPFC), amygdala, and hippocampus as being interesting brain regions in explaining anxiety disorders.

But we have to take into account that these findings are based on animals, and not on human beings. Still, these models can serve as a scaffold in investigating the underlying mechanisms of anxiety disorders.

The role of the amygdala, hippocampus, and neurochemicals in the fear response

It is thought that in people suffering from anxiety disorders, the role of the amygdala and hippocampus in a fear response is distorted. The amygdala plays an important role in the fear response. Like the hippocampus, the lateral areas of the amygdala are capable of long-term potentiation (LTP), thus learning [Clugnet and LeDoux, 1990]. The role of the amygdala in the fear response is reinforcing connections between neurons and therefore pairing any stimulus with anxiety or fear. Through lesion studies many information about the role of the amygdala in the fear response has been revealed. It was found that the amygdala can modulate memory consolidation [McGaugh et al., 1996]. But how is that accomplished?

The amygdala is known to project to other structures with the result of the fearful stimulus being exaggerated or not. This results in different fear responses such as freezing behavior when projecting for example to the central gray, or having a fearful facial expression when projecting to the trigeminal facial motor nerve [Davis, 1992] or the release of norepinephrine when projecting to the locus coeruleus (see figure 3). In this way a certain kind of weight can be put to the fearful stimulus [Cozolino, 2002].

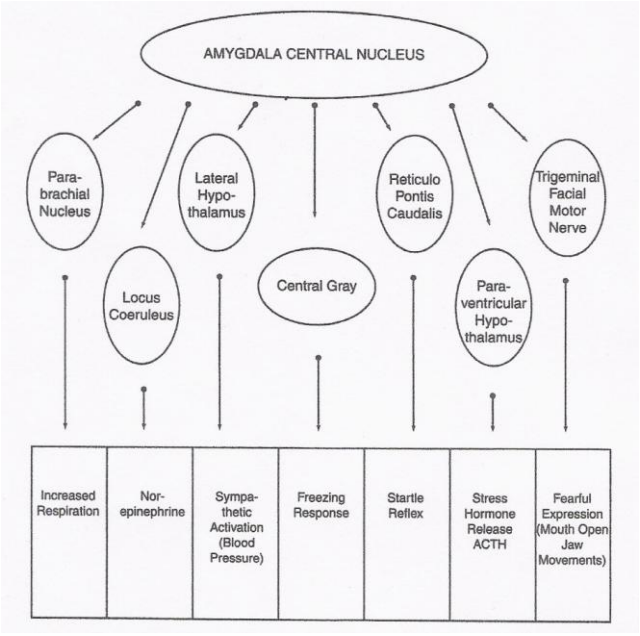

Figure 3. When being activated due to a fearful stimulus, the amygdala can project to other brain structures. Through connections to these brain structures, the fearful stimulus can be modulated and certain weight can be put to the fearful stimulus [Cozolino, 2002].

It has been shown that several neurochemicals can enhance long-term memory when being administered to animals shortly after training in inhibitory avoidance tasks as well as other types of learning tasks. Post-training injections of norepinephrine and epinephrine have shown to enhance memory. Next to that, adrenal catecholamines, thus glucocorticoids, have also shown to promote consolidation and/or storage of novel information [McGaugh et al., 1996, Roozendaal, 2002]. Furthermore, opioids and GABAergic drugs have shown to be involved in memory storage by modulating the release of norepinephrine within the amygdala. Benzodiazepines are known to act by binding to $GABA_A$ receptor complex, and are known to impair memory. But these adrenergic, glucocorticoid, opioid, and GABAergic influences on memory storage differ in the way the

amygdala is influenced. The influence on the amygdala is mediated by the release of NE [for review see McGaugh et al., 1996].

The hippocampus is believed to link information about physical contexts with the emotional context provided by the amygdala [Fanselow and Gale, 2003]. This process is called contextual fear conditioning [LeDoux, 2000].

Cognitive control of emotion

The ability to cognitively regulate emotional responses to aversive events is important for mental and physical health. Many studies have focused on the cognitive control of emotion. In these studies participants were presented negative stimuli which would elicit a fearful or negative emotional response, and they were asked to cognitively change what they were feeling. During these cognitive tasks brain activation was measured using neuroimaging techniques, like positron emission tomography (PET), single photon emission computed tomography (SPECT), electroencephalography (EEG), functional magnetic resonance imaging (fMRI), or blood-oxygen-level dependent (BOLD) response.

Different types of cognitive control are proposed in order to find the functional architecture underlying the cognitive control of emotion [Ochsner and Gross, 2005]. Behavioral regulation (e.g. suppressing expressive behavior) can be distinguished from cognitive regulation (e.g. attending to or interpreting emotion-eliciting situations in ways that limit emotional responding). Cognitive regulation neutralizes the negative experience and this can be established via attentional control or cognitive change. Attentional control is established by simply drawing the attention to something else than the fearful stimulus. Cognitive change involves mental processes like reappraisal. Reappraisal can be described as the cognitive transformation of emotional experience [Ochsner and Feldman Barrett, 2002]. For example, when seeing a picture of a woman crying in front of a church, this could be experienced as emotionally negative. But through reappraisal the picture can be reinterpreted in a less negative context, for example the woman is crying tears of joy at a wedding [Delgado et al., 2008].

One example of a study on attentional control is a study of attentional distraction. Participants are administered painful stimuli and at the same time are asked to fulfill a secondary task, which distracts them from the painful stimulus. The attention to the secondary task may limit attention to emotional stimuli. It has been shown that the 'thought of something else' diminishes the aversiveness of pain [Tracey et al., 2002]. Brain activity in subcortical regions, such as the thalamus and insula, decreases, whereas brain activity in the orbital frontal cortex (OFC), anterior cingulate cortex (ACC), and medial and lateral PFC regions increases [Phan et al., 2005].

An example of a study on cognitive control of emotion is by Ochsner and Feldmann Barrett [2002]. In their article researchers presented participants aversive picture and asked the participants to either attend to their emotions, without trying to alter their feelings ('attend trials'), or reappraise their feelings, and thus interpreting the picture so that they no longer felt negative in response to them ('reappraise trials'). The results showed that during the reappraise state the lateral and medial prefrontal regions were activated, essential for

working memory and cognitive control [Miller and Cohen, 2001] and self-monitoring [Gusnard et al., 2001]. Next to that, they measured a decreased activation in regions involved in emotion processing, i.e. the amygdala and medial orbito-frontal cortex [Dolan, 2002].

The results of these different kinds of studies in the investigation of cognitive change are showing discrepancies in the brain regions involved, and this is most probably due to differences in study design [for review on study design see Ochsner and Gross, 2005]. Learning to associate new emotional responses with stimuli, or distraction from the emotional stimulus due to a secondary task, can result in different brain regions to be involved. Also, different forms of emotional stimuli are used, such as painful shocks or the presentation of pictures of fearful faces.

In general, the ability to control emotions both involves activation of prefrontal cortex inhibitory systems (top-down) and decreased activity in subcortical areas, such as the amygdala (bottom-up) [Sotres-Bayon et al., 2004; Davidson 2002]. In anxiety paradigms, it has become evident that the medial prefrontal cortex plays an essential role in the inhibition of conditioned fear with reference to the amygdala, following extinction [Quirk et al., 2003; Engel et al., 2009]. It is thought that the same mechanisms that are involved in the cognitive control of emotions are modulated due to psychotherapy in anxiety disorders [De Raedt, 2006].

Therapy

Feelings and behavior are largely influenced by the way a situation is interpreted. Interpretation might lead to dysfunctional thoughts that create and exacerbate psychiatric symptoms. Dysfunctional thoughts like: ''I am going to die, or I will faint'', may impact the life of an individual to such a degree that it may develop into an anxiety disorder. In cognitive behavioral therapy (CBT) patients learn to recognize these dysfunctional thoughts and learn to test and modify them as they arise. In that way emotions are combined with cognitive understanding, so patients learn to re-interpret the situation or stimulus that they fear so much [Beutel 2003, Rauch 2003]. In research examining the underlying mechanisms of CBT, the cognitive process of reappraisal is investigated.

In fact, psychotherapy is a controlled form of learning that occurs in the context of a therapeutic relationship. In exposure therapy the patient is confronted with several sets of presentation of the fearful stimuli, in order to diminish the anxious response. Exposure training is often used in combination with relaxation training. During exposure therapy, patients learn new adaptive responses to their fearful stimulus. From this perspective, the biology of psychotherapy can be understood as a special case of the biology of learning. Learning has a measurable impact on the brain, so successful psychotherapy is likely to lead to measurable change [Beutel et al., 2003, Kandel, 1999].

Psychotherapy can be seen as an enriched environment, where brain plasticity is increased. In several animal studies it is shown that enriched environment impacts on both the neural architecture and neurochemistry [Meaney and Szyf, 2005]. Interestingly, successful psychotherapy indeed has shown to impact relative activation or inhibition of brain regions [Schwartz et al., 1996]. This is promising for people suffering from anxiety disorders, because it means that neural circuitry related to symptoms can be plastic [De Raedt,

2006]. Factors that have shown to be important for the therapeutic process are a safe and empathic relationship with the therapist [Schore, 1994] and the activation of anxiety and stress [Cowan and Kandel, 2001]. A good bond between the therapist and his or her client is important in better tolerating the stress that comes with and at the same time is required for neural reorganization. Optimal levels of arousal and stress result in increased production of neurotransmitters and neural growth hormones that enhance LTP, learning and cortical reorganization [Cowan and Kandel, 2001].

Moreover, pharmacotherapy has shown to be effective in treating anxiety disorders. Antidepressants (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors etc.) and tranquilizers (e.g. benzodiazepine) are widely used to help patients stabilize their mood and reduce anxiety [Chow and Tsang, 2007].

In general, there is plenty of evidence that CBT and pharmacotherapy are effective in symptom treatment of anxiety disorders [Lydiard et al., 1996; Rauch et al., 2003, Nathan and Gorman, 2007]. Nevertheless in order to improve the quality of therapy, understanding the biological mechanisms that are underlying the mental healing process can be of great help.

Current theories hypothesize that the same mechanisms that are involved in cognitive control of emotions or fear extinction are involved in the effect of psychotherapy in anxiety disorders [De Raedt, 2006]. Psychotherapy is said to involve activation of prefrontal cortex inhibitory systems (top-down) and decreased activity in subcortical areas, such as the amygdala (bottom-up) [Sotres-Bayon et al., 2004, Davidson, 2002].

Chapter 2 - Studying anxiety disorders

There are many ways in investigating neural correlates of symptom relief after interventions in anxiety disorders. In neural state paradigms data from patients is recorded during resting state and is compared to controls in order to determine the functional anatomy. In order to record brain activities associated with specific symptoms, symptom provocation studies are applied, in which anxiety disordered patients are presented items related to their symptomatology (e.g. expose a spider to a spider phobic) during neuroimaging [Beutel et al., 2003]. Other types of studies are correlation studies and factoranalysis, in which, for example, regional cerebral blood flow (rCBF) and clinical symptoms are checked for correlation. Furthermore, in activation studies brain activity of participants is scanned during execution of cognitive tasks [Rauch et al., 2003].

Designing neuroimaging studies in which brain activity of one person is compared to the other involves creating an activation condition and a control condition. Depending on the activation task, the control condition may often be a resting state, or another task that controls for non-specific sensorimotor aspects (e.g. visual perception, reading, pressing a button) of the activation task [Beutel et al., 2003].

Repeating the same experimental task in the pre- and posttreatment condition can bring bias to the data because the participant already has gone through the whole scanning procedure and knows what to expect from the experiment. During the second scanning session the participant is more used to the scanning

environment and therefore presumably less anxious. Also, when investigating long-term treatments, due to a big interval between pre- and posttreatment measurements, the chance of intermediate changes (e.g. due to health status) accumulating with the data increases [Beutel et al., 2003]. Therefore it is necessary to scan comparable control subjects on both occasions.

When comparing studies, people need to take possible heterogeneities between these studies into account. In several studies, although the intervention that is used is called one thing (e.g. CBT), the description of the psychotherapeutic process in fact is more closely resembling another (e.g. BT). Also, methodological inconsistencies have to be taken into account when comparing studies. Studies can differ in the way the treatment was designed, for example if the therapy involved single or multiple therapists, or how many psychotherapy sessions the participant had to practice, or if the participants were in group therapy or individually. Also, when neuroimaging results are compared it is important to keep in mind that when comparing data from studies which used different imaging techniques, the resolution may be different, or the patient could have possibly experienced the neuroimaging techniques in a specific way [Roffman et al., 2005].

In the previous chapter I have discussed the basic fear response and the cognitive control of fear. Now, I will try to create a clear picture of brain differences between patients suffering from anxiety disorders compared to healthy subjects. I will highlight the studies that have investigated brain activity during resting state, followed by studies that have measured stimulus induced brain changes. Next to that, I will review studies that have measured structural or functional brain changes before and after effective treatment of anxiety disorders, the so called pre- and posttreatment studies. In that way, I tend to create a clear picture of the characteristics of an anxiety disorder without treatment and report measurable neurological changes after effective interventions.

As I have mentioned earlier, patients with an anxiety disorder have shown decreased activity in inhibitory, prefrontal structures, and increased activity in limbic areas [Quirk et al., 2003, Engel et al., 2009]. Also, it is thought that patients suffering from an anxiety disorder have disturbed functionality in brain mechanisms involved in fear extinction or in the cognitive control of emotions. Moreover, the ability to control emotions is believed to both involve activation of prefrontal cortex inhibitory systems (top-down) and decreased activity in subcortical areas, such as the amygdala (bottom-up) [Sotres-Bayon et al., 2004, Davidson et al., 2002]. Therefore, I hypothesize that the involved brain regions in the cognitive control of emotion and fear extinction are involved in the pre-and posttreatment studies.

It has been found that the cognitive ability to reappraise involves an increased activation in the lateral and medial prefrontal areas, which is essential for working memory and cognitive control [Miller and Cohen, 2001] and self-monitoring [Gusnard et al., 2001], and decreased activation in regions involved in emotion processing, i.e. the amygdala and medial orbito-frontal cortex [Dolan, 2002]. Interestingly, it has also been shown that during the thought of something else, and therefore not focusing on the anxiety-related trigger, brain activity in subcortical regions, such as the thalamus and insula, decreases, whereas brain activity in the orbital frontal cortex (OFC), anterior cingulate cortex (ACC), and medial and lateral PFC regions increases [Phan et al., 2005]. Fear extinction is suggested to involve mPFC activation resulting in inhibition of the amygdala [Rosenkranz et

al., 2003; Quirk et al., 2003]. Consequently, these brain regions might be of interest for this study, hence the general known function of these brain regions in explained in table 2.

Table 2. The general known function of brain regions involved in anxiety disorders.

Brain region	**General known function**
Amygdala	Emotion (putting weight to the event)
Hippocampus	Learning (putting weight to the event)
Prefrontal cortex (PFC)	Inhibition
Ortbital frontal cortex (OFC)	The OFC is said to be required for decision making and involved in the mediation of emotional responses to biologically significant stimuli, as well as inhibition of behavioral responses [Zald and Kim, 1996]. Regulation of planning behavior associated with sensitivity to reward and punishment [Bechara et al., 1994].
Anterior cingulate cortex (ACC)	The ACC is said to be involved in action monitoring, such as conflict detection in pain and error monitoring [Bush et al., 2000].
Caudate nucleus	The caudate nucleus is said to play an important role in learning and memory [Graybiel, 2005], including the ability to acquire new habits and skills necessary for the successful initiation of approach or avoidance behaviors [Mittleman et al., 1990, Packard and White, 1990].
Thalamus	Filtering information that comes from the sensory system (with the exception of the olfactory system) and sends relevant information to the associated primary cortical area, for example input from the retina goes via the thalamus to the visual cortex
Insula	The insula plays a role in emotion processing; body representation (i.e. self-awareness) and subjective emotional experience (i.e. feelings), cognitive functioning, and interpersonal experience (i.e. the sense of disgust by smell or visual disgusting stimuli when observing or imagining painfulness), empathy, drug craving. Next to that, it is also linked to the regulation of the body's homeostasis (pain and temperature sensation, regulation of immune system) and motor control (balance, movement, swallowing, and perception). The insula has output to other limbic-related structures, such as the amygdala and OFC.

Obsessive compulsive disorder

Symptoms

Obsessive compulsive disorder (OCD) is characterized by intrusive unwanted thoughts, ideas, or images that are distressing (obsessions) and urges to perform ritualistic behaviors or mental acts (compulsions) to reduce this distress [Whiteside et al., 2004].

Resting state, stimulus induced

In a nutshell, many studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) have identified elevated activation during resting state in the orbital frontal cortex (OFC), caudate nucleus, anterior cingulate cortex (ACC), putamen, and thalamus in patients with OCD compared to various control subjects [Baxter et al, 1987, 1988, 1989, 1992; Benkelfat et al., 1990; Nordahl et al., 1989; Perani et al., 1995; Sawle et al., 1991; Swedo et al.,1989]. Similar brain regions have been reported in studies investigating stimulus induced brain changes in OCD patients [Breiter et al., 1996; Kwon et al., 2003; McGuire et al., 1994; Rauch et al., 1994].

Pre- and posttreatment studies

In the study of Baxter et al [1992] OCD patients were scanned using a FDG-PET scan during resting state. These patients were either treated with fluoxetine (n=9; 3 men, 6 women) or behavioral therapy (BT) (n=9; 4 men, 5 women) and brain data was compared to a control group (n=4; 2 men, 2 women) which consisted of healthy subjects. Fluoxetine is a medical drug that has indirect connections to the dopamine system, because it affects serotonin. Patients in the fluoxetine group were given oral fluoxetine hydrochloride for 2 weeks and six patients responded to the treatment. Patients in the BT group underwent exposure and response-prevention (EX/RP) for approximately 10 weeks. Once or twice a week patients met with their therapist (3 different therapist in total were available in this study) for approximately 1 hour. Six patients also attended a CBT group which was run by one of the therapists. Seven patients responded to BT. OCD patients in all groups were rescanned after approximately 10 weeks. The results were that glucose metabolism in the right anterior cingulate gyrus and left thalamus was significantly decreased in responders to fluoxetine treatment. Though fluoxetine as well as BT responders, showed a decrease in glucose metabolism in the head of right caudate nucleus. Non-responders did not show significant changes in glucose metabolism.

The reason why Baxter et al used fluoxetine was that they knew a similar study was in progress using the tricyclic antidepressant clomipramine hydrochloride by Benkelfat et al [1990]. Clomipramine has significant direct interactions with the dopamine system and SRI properties. Benkelfat and colleagues examined eight OCD patients using FDG-PET scanning during resting state before and after 16 weeks of treatment with clomipramine hydrochloride. Well responders compared to poor or partial responders showed a significant decrease only in the left caudate of patients who responded well to the drug. Though, Benkelfat found a decrease in the left caudate nucleus after treatment with clomipramine, Baxter found a decrease in the right caudate nucleus after treatment with fluoxetine or behavioral therapy. In the discussion, Baxter proposes that

the differences possibly had occurred due to the severity of symptoms in OCD patients used in these studies, by which he meant that one side could be more disordered than the other [Baxter et al., 1992, Hollander et al., 1990].

A comparable study to the study of Baxter and Benkelfat is the study of Swedo et al [1992]. In this study researchers administered clomipramine or fluoxetine to OCD patients. These patients were rescanned during resting state after approximately 1 year (mean of 20 months). The patients showed a decrease in right orbitofrontal metabolism which correlated with only 2 measures of OCD symptom improvement. Therefore, Swedo and colleagues concluded that orbitofrontal hypermetabolism may be a feature of OCD and may be normalized after successful treatment, but is regardless of whether that improvement is drug induced or spontaneous.

When comparing the PET studies of Baxter, Benkelfat, and Swedo, different brain region changes were measured after symptom improvement with fluoxetine, clomipramine or BT. Baxter et al [1992] hypothesize in their discussion that discrepancies between these studies could be due to the interval between pre- and posttreatment scanning procedures. Interestingly, the study of intermediate length found both caudate nucleus and orbital changes, while the shorter and longer studies found only caudate nucleus and orbital changes respectively.

Schwartz et al [1996] performed a replication of the study of Baxter et al [1992]. They used [^{18}FDG]-PET scanning in 9 patients with DSM-III-R OCD and measured changes before and after 8 to 12 weeks of structured exposure and response prevention behavioral and cognitive treatment, which is comparable to the behavioral treatment of the study of Baxter et al, explained earlier, but they used different therapists. Co-morbid diagnosis with cyclothymic disorder, panic disorder, and acrophobia was the case in one subject each. Two subjects had major depression in the past but were now euthymic. Interestingly, they used the data from the controls of the so-called ‘similar study’ of Baxter et al in their statistical analysis. I disagree on their decision to do this because it is commonly known how important a healthy subject control is to base your findings on. The study of Schwartz was performed four years after the study of Baxter, and I think the study loses reliability by not including an adequate control.

Either way, the results showed that treatment responders had significant decreased brain glucose metabolism in the right caudate nucleus compared to before treatment in those judged as treatment responders. They conclude that a prefrontal cortico-striato-thalamic brain system is implicated in mediation of symptoms of OCD. These findings correspond with the findings of Baxter et al [1992].

As the caudate nucleus is said to be involved in learning and memory, including the ability to acquire new habits and skills necessary for the successful initiation of approach or avoidance behaviors [Mittleman et al., 1990, Packard and White, 1990], it is not surprising that it is involved in extinguishing OCD symptoms through CBT. The corticostriato-thalmic system of which the caudate nucleus is a key element might therefore be involved in symptom relief in OCD [Schwartz et al., 1992].

Perani et al. [1995] used [^{18}FDG]-PET scanning to study nine OCD patients before and after 3 months of pharmacotherapy with various SRIs. They compared OCD patients (n=9; 3 men, 6 women) to healthy controls (n=15; 11 men, 4 women). Treatment of the OCD patients was with fluvoxamine (n=4), fluoxetine (n=2), or

clomipramine (n=3). They found decreased activity in the cingulate cortex after treatment. This is in line with Baxter et al [1992], who also found decreased activity in the ACC but after fluoxetine treatment. However these findings are the exact opposite of Saxena et al [2009] who found increase in dACC after CBT.

In the pre-posttreatment study of Saxena et al [2009], researchers examined 10 adults with OCD (6 men, 4 women) and the control group which existed of 12 participants (8 women, 4 men). During resting state, they obtained [^{18}F]-fluorodeoxyglucose positron emission tomography ([FDG]-PET scan) brain scans of both groups that were exposed to brief, intensive, daily CBT using exposure and response prevention (ERP) for only 4 weeks. The therapy involved 90-minutes individual CBT sessions for 5 days a week and 4 weeks continuously. During these CBT sessions homework was discussed and ERP, cognitive techniques, and mindful exercises were done. All patients had one and the same therapist. Before and after these 4 weeks of CBT treatment cerebral glucose metabolism was measured with PET-scanning. Controls were scanned before and after 10-12 weeks, to control for habituation to the scanning procedure and environment on brain metabolism. Next to the PET scan, all subjects received a 3D MRI scan of the brain performed with a 1,5 Tesla scanner. The researchers used an MRI-based region of interest (ROI) analysis. ROIs were chosen a priori based on previous findings in OCD, namely dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), OFC, dorsal anterior cingulate cortex (dACC), ventral anterior cingulate cortex (vACC), caudate nucleus, putamen, and thalamus. Ratios of each ROI were normalized to ipsilateral hemispheric glucose metabolism (ROI/hem).

The posttreatment results showed that OCD patients had a decreased glucose metabolism in bilateral thalamus/hem, and increased glucose metabolism in right dACC/hem compared to controls. Controls, on the other hand, showed decreased glucose metabolism in left dACC/hem compared to OCD patients. There was a significant inverse correlation between change in OCD severity and change in right dACC/hem measurements, indicating a strong association between improvements in OCD symptoms and increasing normalized glucose metabolism in right dACC. The dACC can be divided in two subregions, namely the perigenual ACC and the anterior middle cingulate cortex (aMCC). The aMCC is said to be involved in the cognitive process of reappraisal [Ochsner and Feldmann Barrett, 2002]. Therefore, the authors suggest that the increase in aMCC activity after intensive CBT could represent an improved ability to reappraise and suppress negative emotional responses. They considered this being a process of inhibiting exaggerated amygdala responses to stimuli that previously provoked obsessional fears and compulsive urges.

Notably, the result of increased activity after CBT is contradictory to many other pre-and posttreatment studies, in which a decrease is mostly reported after successful treatment.

Limitations of this study are that six OCD patients were taking medication, but the doses were unchanged 12 weeks prior to starting CBT and during the study. The concerning medications were SRI's, adjunctive buspirone, adjunctive risperidone, and adjunctive clonazepam. It has to be taken into account that the measured effect after CBT in these six patients are a result of an interaction between the medical drug they were using and the CBT, not solely the effect of CBT as the authors propose.

Furthermore, they found that lower pretreatment metabolism in both left and right OFC predicted better improvement in OCD severity with CBT. These results add to evidence indicating that orbitofrontal-subcortical circuit function mediates the symptomatic expression of OCD [Saxena et al., 1999]. The orbitofrontal-

subcortical circuit is known to mediate motor activity and behavior in humans and links specific areas of the frontal cortex to the striatum, basal ganglia and thalamus [Tekin and Cummings, 2002].

In the study of Nakatani et al [2003] Xenon-enhanced computed tomography scanning was used. In this technique, CT scans obtained during and after the inhalation of non-radioactive xenon are utilized to record the movement of lipid-soluble and radio-dense gas into the brain tissues. The end-tidal xenon concentration is utilized to indirectly record the arterial concentration during the wash-in and wash-out of xenon. The xenon concentrations in the arterial blood flow are estimated by the end-tidal xenon concentrations and the hematocrit value. Twenty-two OCD patients were investigated on brain changes measured with (Xe-CT) after successful BT. No fixed time between pre-and posttreatment scanning was determined a priori, but they performed the post-treatment scan after ''significant symptom improvement'' or ''until they received adequate daily function.'' Before the start of the experiment several patients were using clomipramine, but with no symptom improvement. Between the pre-and posttreatment period 13 OCD patients maintained clomipramine dosage, 5 decreased dosage, 4 increased dosage, and 9 patients were clomipramine free. The second scan was after 7.55 (+/- 4.68) months.

The results show a significant decrease of rCBF in the right caudate nucleus after successful treatment. However, there are quite a few limitations in this study. No exact information on the numbers of therapists was reported in the article. Also, the authors did not give information on substance abuse or co-morbid disorders. Even if there were no co-morbidities, it is customary to report this. Furthermore, they involved patients in this study who had been using clomipramine during the study and patients who did not. They simply assume that symptom improvement after clomipramine, or clomipramine and BT, or only BT, is established though one and the same mechanism(s). Furthermore, the researchers did not fix the period between pre-and posttreatment scanning sessions, but they performed the posttreatment scan after the symptoms had improved. I think it is more adequate to design a pre-posttreatment study in a way that separate groups are compared, namely a group consisting of OCD patients that undergo treatment, an OCD patient group that does not undergo treatment, and a healthy control group. Then, after a set amount of time patients can be divided into treatment responders versus non-responders. As I mentioned earlier, Baxter et al [1992] suggested that different brain regions are involved in symptom improvement after 10 weeks compared to 1 year of treatment. Therefore, the results of Nakatani are hard to compare with findings of other pre-posttreatment experiments.

In investigating the effects of interventions on symptom provocation in OCD Nakao et al [2005] performed a cognitive task (Stroop task) and a symptom provocation task during fMRI scanning using a 1,5T scanner. OCD patients were treated with either fluvoxamine (n = 4) or BT (n = 6) for a period of 12 weeks. Patients were scanned pre-and posttreatment and the results revealed that after treatment during symptom provocation the related activation in the orbitofrontal (OFC), dorsolateral–prefrontal (DLPFC), and anterior cingulate cortices (ACC) decreased. Conversely, during the Stroop task, the related activation in the parietal cortex and cerebellum increased. They concluded that after treatment, the hyperactivation of the frontal lobe (related to a symptom-provocative state) decreases, and posterior brain activity (related to action-monitoring function) increased. Limitations of this study are that they did not use healthy control to test for re-scanning bias.

Predictors of effectiveness

Brody et al [1998] did a study in order to find predictors in response to BT, based on the study of Swedo et al. [1989] who found that responders to 2 months of clomipramine had lower pre-treatment absolute rates of metabolism in the right OFC and right AC than did non-responders. Brody and colleagues performed [^{18}FDG]-PET scans during resting state before and after treatment with either BT (n=18; 6 men, 12 women) or 60 mg/day of fluoxetine (n=9; 3 men, 6 women), as described previously by Baxter et al [1992] and Schwartz et al [1996]. The OCD patients that underwent BT were co-morbid diagnosed with some disorder, namely cyclothymic disorder, panic disorder, and acrophobia was diagnosed in one subject each. The researcher used a ROI analysis. Also, they calculated a normalized ratio (ROI/Hem) for each ROI, by dividing the metabolic activity in each ROI by the activity in the ipsilateral hemisphere (including both grey and white matter).

The authors found that higher normalized left OFC metabolism correlated with better response to behavior therapy and worse response to fluoxetine. In explaining this, they found that pre-treatment left OFC showed a trend toward a positive correlation with symptom severity measured with Y-BOCS. This is in line with Swedo et al [1989] who found that higher OFC metabolism was associated with worse OCD symptomatology. Interestingly, this matches clinical findings, which indicate that more severe OCD at baseline is predictive of poorer outcome with medication [Alarcon et al., 1993; Dewulf et al., 1995].

Summary

In summary, many studies using positron emission tomography or functional magnetic resonance imaging (fMRI) have identified abnormally high activation at resting state in the OFC [Baxter et al., 1987, 1988; Nordahl et al., 1989; Swedo et al., 1989; Sawle et al., 1991], caudate nucleus [Baxter et al., 1992, 1988; Benkelfat et al., 1990, Lucey et al., 1997a], and ACC [Swedo et al., 1989; Perani et al., 1995] in patients with OCD compared to various control subjects [Baxter et al., 1989]. Symptom provocation studies of OCD symptoms shown that activation in areas such as the OFC, caudate nucleus, thalamus, and ACC is involved [Rauch et al., 1994].

After successful treatment, several studies have reported that decreased activity in the OFC, thalamus, ACC and caudate nucleus is achieved [Schwartz et al.,1996; Baxter et al., 1992; Benkelfat et al 1990; Swedo et al., 1992], though other studies report increased glucose metabolism in the dACC after successful CBT [Saxena et al., 2009].

There are commonalities found in brain changes after psycho- and pharmacotherapy [Linden, 2006]. But notably, studies that have focused on predictors of the effectiveness of treatment [Swedo et al., 1989, Brody et al., 1998] have shown that higher OFC glucose metabolism was associated with worse OCD symptomatology. Also, clinical studies found that more severe OCD symptoms at baseline is predicting poorer outcome with medication treatment, but this was not the case after BT [Alarcon et al., 1993, Dewulf et al., 1995]. In predicting the outcome of CBT, it was found that lower pretreatment metabolism in both left and right OFC predicted greater improvement in OCD severity with CBT [Saxena et al., 2009].

Post traumatic stress disorder

Symptoms

Post traumatic stress disorder (PTSD) can occur after a person had been exposed to a traumatic event. One speaks of a traumatic event if the situation had been experienced as life-threatening. A person is suffering from PTSD when there is a matter of re-experiencing the traumatic event in a vivid way (hallucinations, nightmares), avoidance of any stimuli that might remember the patient of aspects of the traumatic event (antisocial behavior), and hyperarousal due to a constant active sympathetic nervous system (irritable mood, bursts of anger) [DSM-VI, 2000]. Physical changes that have shown to be involved in PTSD are changes in the limbic system, in particular the hippocampus and amygdala. As I have mentioned earlier, the fast circuit in the model for emotional memory described by LeDoux et al [1994] is said to play an important role in the onset of PTSD.

Via the fast pathway the unconscious emotional memory, involving the amygdala, has linked surrounding stimuli that were present during this event, to the traumatic experience. A certain smell or noise can trigger the powerful unconscious memory that activates the amygdala into the release of hormones that brings the body into the fight-or-flight response. In PTSD patients, this emotional memory can be that strong, that these patients cannot function normally in daily life, because they are suffering from delusions and hallucination as if the life-threatening event occurs again [Shalev et al., 1992].

The hypothesis of involvement of the fast pathway in PTSD is in line with a model for neurocircuitry in PTSD presented by Rauch and Baxter [1998]. They hypothesize that presentation of threat-related stimuli to patients with PTSD results in hyper-responsivity within the amygdala, and next to that, an inadequate top-down governance over the amygdala by the mPFC (specifically, the rostral anterior cingulate cortex) and hippocampus. In this model, the hyperactivity of the amygdala explains the persistent emotional memory for the traumatic event. Decreased hippocampal activity explains the deficits in identifying safe contexts and memory difficulties. And the inadequacy of the anterior cingulate might underlie the deficits of habituation.

In treating PTSD using psychotherapy, the goal is to help shift the memory and to reprogram this excessive amygdala response. This is attempted by prolonged-exposure therapy in combination with relaxation exercises. The patient is asked to slowly re-experience the traumatic event by visualizing and describing in words what had happened in every detail. In that way memories can lose the emotional contact and the amygdala can be triggered to set off a different behavior, instead of the excessive fight-or flight response. The patient is learning new associations via cognitively activating brain mechanisms and therefore neural plasticity [Beutel et al., 2003]. Through cognitive processing therapy, such as CBT, the patient is searching for distorted thinking patterns or misunderstandings, such as the thought of what they had experienced was their fault. Also, stress-inoculation therapy, meditation, and Eye Movement Desensitization and Reprocessing (EMDR) have shown to relief PTSD symptoms.

Patients that partially respond to medication benefit greatly from prolonged exposure therapy (PE). But patients who responded fine to the medication (sertraline) did not benefit from PE. However, when stopping

the medication, those who had combined medication treatment with PE did not relapse, whereas of those who had used only medication 30% relapsed [Cahill et al., 2003].

Resting state

Only a few neuroimaging studies have been published during resting state in PTSD patients [Francati et al, 2007]. In the SPECT study of Lucey et al [1997b] a reduction in rCBF was found in the superior frontal cortex and the right caudate in PTSD patients. Furthermore, no changes were reported in the cerebellum, medial frontal cortex, and thalamus. Mirzaei et al [2001] found an elevation in left hemisphere rCBF in patients with PTSD who survived torture episodes. The most recent results, reported by Bonne et al [2003] showed that PTSD patients had higher cerebellar rCBF compared to controls. Furthermore, they found reduced rCBF in the right precentral, superior temporal, and fusiform gyri, in PTSD patients compared to healthy controls.

Stimulus induced

Symptom provocation studies of PTSD contained mainly presentation of trauma-related visual or acoustic stimuli or on script-driven imagery. Shin et al [2004] performed a PET scan in which they measured regional cerebral blood flow (rCBF) during a word-stem completion task. They used 16 firefighters of which 8 were diagnosed with PTSD and 8 were not. All firefighters had been exposed to several types of specific firefighting-related traumatic events earlier (e.g., witnessing the death or serious injury of others, handling burned bodies). Results showed that the PTSD group had higher rCBF in bilateral hippocampus and left amygdala than the control group, and within the PTSD group, symptom severity was positively associated with rCBF in hippocampus and parahippocampal gyrus.

Shin et al [2005] presented pictures of fearful and happy faces to PTSD patients (n=13) and trauma-exposed non-PTSD individuals (n=13). With the use of fMRI they examined whether emotional pictures unrelated to the trauma itself, would also evoke abnormal responses, thus a hyperactive amygdala response. Interestingly, they found that fearful faces led to greater amygdala activation and hypoactivation of the ACC.

In the fMRI study of Lanius et al [2001] it was found that subjects with PTSD showed less brain activation in the thalamus, the medial frontal cortex, and the anterior cingulate gyrus than comparison subjects during a script-driven symptom provocation paradigm. They used nine subjects who had developed PTSD as a result of sexual abuse/assault (N=6) or motor vehicle accidents (N=3). Comparison subjects were nine subjects who met DSM-IV criterion A but who did not meet the full DSM-IV criteria for the disorder.

Next to SPECT, PET and fMRI, brain asymmetries in the alpha band of the electroencephalogram (EEG) are used as an inverse index of brain activation. It was shown that greater left frontal activation is associated with approach motivation, emotion, and behavior, whereas greater right frontal cortical activation is associated with withdrawal motivation, emotion, and behavior [Sutton and Davidson, 1997]. This is in line with the findings of the study of Heller et al [1997], in which they measured EEG in PTSD patients during rest and during an emotional narrative task designed to elicit anxious arousal. They found that during the task anxious participants showed a selective increase in right parietal activity. McCaffrey et al [1993] searched for EEG asymmetries in Vietnam veterans with PTSD and they indeed reported increased right anterior activation during symptom

provocation. Furthermore, Metzger et al [2004] examined the relationship among PTSD, anxiety, and depressive symptoms and frontal, temporal, and parietal EEG alpha asymmetry in female Vietnam War nurse veterans. They found that PTSD arousal symptoms were associated with increased right-sided parietal activation.

Pre- and posttreatment studies

In the pre- and posttreatment study of Rabe et al [2008] they investigated spontaneous EEG activity from left and right anterior and posterior regions during baseline and during confrontation to neutral, positive, negative, and trauma-related pictures before and after CBT treatment. They used motor vehicle accident (MVA) survivors with PTSD (n=10), or subsyndromal PTSD (n=7) receiving CBT, and wait-list controls with PTSD (n=7) or subsyndromal PTSD (n=11) without any treatment. Subsyndromal means that the participants were exhibiting symptoms that were not severe enough for diagnosis as a clinically recognized syndrome. Pretreatment scanning in participants with PTSD and subsyndromal PTSD showed a pattern of enhanced right anterior and posterior activation in response to the trauma-related accident pictures. This is in line with the studies of Metger et al [2004] and McCaffrey et al [1993]. Furthermore, they found that this trauma-specific increase in relative right hemisphere activation was correlated with increased negative affect and PTSD symptoms. Interestingly, at posttreatment scanning there was a greater reduction of right anterior activation in the CBT group as compared to wait-list controls. The amount of reduction in the right anterior region was associated with reduction in PTSD severity. Therefore, they concluded that effective CBT treatment may be accompanied with adaptive changes in asymmetrical brain function.

Limitations of this study were that participants were diagnosed with comorbid disorders, yet the patients were matched on comorbidity between groups. In addition, a high rate of comorbidity is typical of PTSD and they stated that exclusion would have resulted in a nonrepresentative sample.

Farrow and colleagues [2005] were interested in the physiology of social cognition in PTSD patients. They scanned non-combat related PTSD patients (n=13; 9 men, 4 women) before and after CBT while they engaged in tasks that (i) involved speculation on another's intention, (ii) invoked empathy and (iii) involved making judgments of the forgivability of others' actions, each versus baseline social reasoning judgments. The CBT was accomplished by the same psychotherapist for all subjects. They found that CBT led to a degree of normalization of the neural response to these social cognition tasks.

Post-treatment fMRI scanning revealed increased activity in the left middle temporal gyrus in response to empathy judgements. This brain region is mostly associated with depth of semantic processing [Castillo et al., 2001]. They also found increased activity in the posterior cingulate gyrus to forgivability judgements. This brain region is thought to be involved in monitoring of the internal visceral state and self-behavior evaluation [Vogt 1992]. Limitations of this study are that they did not use a suitable control group. Therefore they could not check for rescanning effects. Normally rescanning is associated with decreased brain activation for a range of paradigms [Brannen et al., 2001].

Felmingham et al [2007] investigated neural networks using MRI after exposure-based treatment of PTSD. They scanned 8 individuals with PTSD following assault (n=4) or car accidents (n=4). Four subjects had co-

morbid depression and two subjects were medicated with SSRI's during the period when the testing session took place. The treatment involved eight once-weekly sessions of imaginal exposure and cognitive restructuring. Scanning took place prior to and 6 months following treatment, during which they viewed 120 fearful and 120 neutral standardized facial expressions. Regions of interest (ROI) were the rostral anterior cingulate cortex (rACC) and amygdala. After treatment, they had found greater activation in bilateral rACC compared to the pretreatment scan. The activity in the amygdala before or after treatment was not significantly different. Also, a positive correlation was found between scorings on a scale for PTSD symptom severity (CAPS: Clinician- Administered PTSD Scale) and activity change in right rACC from before to after treatment, and a negative correlation was found between activation in bilateral amygdala. Therefore, as CAPS scores improved, rACC activity increased and amygdala activity decreased during fear processing.

As the authors mention themselves, a wait-list control condition was needed in order to prove that the differences are not due to scanning conditions or other factors that might have lead to bias. Furthermore, I disagree on the conclusion the authors draw in the last discussion session. They state that this study is providing evidence that successful exposure therapy for PTSD is associated with increased rACC and reduced amygdala activation. With regard to amygdala activity, they had reported no significant activation of the amygdala before and after treatment, so they can only base this statement on the negative correlation found between CAPS and amygdala activity. Therefore, I think this conclusion is drawn too hasty.

Levin et al [1999] measured rCBF with SPECT during recall of the traumatic memory in one male PTSD subject before and after treatment with EMDR (Eye Movement Desensitization and Reprocessing). This patient had experienced an abusive childhood, had witnessed violence between his parents and occasionally had been beaten. After three 90-minute session of EMDR sessions at 1-week intervals the patient experienced improvement in his level of distress. The patient was spending less time scanning the environment for threats measured with the Hypervigilance Index. Upon recall of the traumatic memory two brain areas were hyperactive post- EMDR treatment relative to pretreatment, namely the anterior cingulate gyrus and the left frontal lobe. These findings indicate that the improvement of PTSD symptoms may not be mediated by decreased activation of the amygdala, as is proposed by others, but instead, is caused by an increased activation of the anterior cingulate and prefrontal area.

This in line with the study of Felmingham et al [2007] where they also found increased activation in bilateral rACC compared to the pretreatment scan, but no pre-and posttreatment effect for the amygdala activity. Levin et al [1999] conclude that the ability to distinguish between real and imagined threats is likely to underlie the successful treatment of PTSD. The major limitation of this study is that it involves only one participant.

Results of pre-posttreatment studies using pharmacotherapy have shown that serotonin reuptake inhibitors (SSRI's) lead to increased orbitofrontal and medial prefrontal activity in PTSD patients [Fernandez et al., 2001, Seedat et al., 2004].

Summary

In a nutshell, most functional neuroimaging studies of PTSD reveal reduced vmPFC activity, particularly in rostral anterior cingulate cortex (rACC) [Lanius et al., 2001; Shin et al., 2005]. Also, there is enough evidence to state that PTSD also holds increased amygdala and hippocampus activity in threat processing and fear conditioning [Shin et al., 2005, Bremner et al., 2004]. Furthermore, increased right-hemispheric activation measured with EEG has been replicated in PTSD patients [McCaffrey et al., 1993; Metzger et al., 2004]. Until now, only a few resting state studies have been reported and they have shown discrepant results.

The pre-and posttreatment studies highlight the role of the medial prefrontal cortex, amygdala, and hippocampus mediating symptom formation in PTSD. Despite the findings in the study of Levin [1999], there is enough evidence to state that PTSD holds increased amygdala and hippocampus activity in threat processing and fear conditioning [Shin et al., 2005, Bremner et al., 2004]. Most functional neuroimaging studies on the symptomatology of PTSD reveal reduced vmPFC activity, particularly in rostral anterior cingulate cortex (rACC) [Lanius et al., 2001, Shin et al., 2005]. Posttreatment studies revealed that increased activity in this region correlates with symptom improvement after exposure-based treatment [Felmingham et al., 2007; Levin et al., 1999; Farrow et al., 2005].

In PTSD, increased amygdala activity during fear conditioning and reduced vmPFC activity during extinction have been reported [Bremner et al., 2004]. As fear extinction is mediated by inhibitory control of the vmPFC over amygdala-based fear processes, it is hypothesized that PTSD may develop from impaired extinction of conditioned fear responses, with the vmPFC and amygdala involved.

Furthermore, increased right-hemispheric activation seems to be one of the characteristics of PTSD [McCaffrey et al., 1993, Metzger et al., 2004]. Posttreatment studies have reported a significant decrease of this increased right-hemispheric activation after symptom improvement in PTSD patients [Rabe et al., 2008].

Phobia

Symptoms

Phobia can be divided into two general types. One is social phobia (also called social anxiety disorder) which is characterized by an intense, persistent, and chronic fear of being watched and judged by others and of doing things that will embarrass them. Patients are conscious about their behavior being irrational, but they try to avoid social situations or these situations are endured with intense fear or suffering [DSM-IV, 2000].

The other type of phobia is called specific phobia, formerly described as simple phobia, which is characterized by intense, irrational fear of something that poses little or no actual danger. The most common forms of specific phobia are related to small animals, such as snakes, spiders or rodents [Fyer, 1998]. People with spider phobia experience persistent and intense fear when confronted with spiders and develop avoidance behavior of all contexts related to this animal [DSM-IV, 2000].

Resting state

Unfortunately, studies investigating brain activity during resting state in patients suffering from phobia have not been published.

Stimulus induced

Symptom provocation studies in investigating phobias are relatively straightforward. Symptoms of spider phobia can be investigated by showing standardized images or film sequences of spiders, contrasted with innocuous animals or natural objects. In the study of Paquette et al [2003] for example, brain activity was compared during the presentation of spiders and presumably innocuous butterflies. Consequently, this use of identical stimulus material across participants removes a source of variance that is especially undesirable in studies with small sample sizes. In contrast, studying the symptomatology of an anxiety disorder like PTSD or OCD is less straightforward as disorder-related triggers need to be personalized to the trauma or obsession of the individual, thus is the data more prone for bias [Linden, 2006].

There are many studies that have published data on stimulus induced brain changes in phobics, but they have shown discrepant results. The aim of the symptom provocation study of Davidson et al [2000] was to determine the brain electrical correlates of anticipatory anxiety provoked by the making of a public speech between social phobics and healthy controls. Using PET scanning, they measured increased right-sided activation in the anterior temporal and lateral prefrontal scalp regions in social phobics compared to controls.

Several previous positron-emission tomography (PET) studies examining the neural substrates involved in specific phobia found increased regional cerebral blood flow (rCBF) in extrastriate visual cortex but not in other brain regions during visual phobogenic stimulation compared to neutral stimulation in patients with animal phobia. Also, phobic as compared to neutral stimulation elevated relative rCBF in the secondary visual cortex but reduced relative rCBF in the hippocampus, prefrontal, orbitofrontal, temporopolar, and posterior cingulate cortex [Fredrikson 1993, 1995]. This increase of rCBF in the visual cortex is suggested by Paquette et al [2003] to be related to increased visual attention to the significance (potential threat) of the stimulus. At the same time, the reduced rCBF activity in limbic and paralimbic cortices might reflect reduced conscious cognitive processing during the cerebral response associated with the defense reaction.

In another PET scanning study [Rauch 1995] subjects suffering from specific phobias were asked to close their eyes and to allow their thoughts to focus on their individualized phobogenic stimulus, for example a container with the feared animal inside which was placed near the subjects. The specific phobics showed a significant increase of rCBF in the ACC, insula, thalamus, anterior temporal, somatosensory, and posterior medial orbitofrontal cortex during symptom provocation. Similar results were found in other PET studies to the presentation of real feared animals or pictures of these animals [Reiman, 1997; Carlsson et al., 2004]. Also, in several fMRI studies an increase in activation in the insula, ACC, and prefrontal cortex in response to visually presented phobia-related stimuli in animal phobics was reported [Dilger et al., 2003].

In a nutshell, it has been found that in specific phobics, ACC and insula activity is increased compared to healthy controls. But not all studies report this ACC and insula increase [Fredrikson et al., 1993, 1995; Tillfors et al., 2002]. As suggested elsewhere [Straube et al., 2004a] an important aspect might be the amount of

attentional distraction by cognitive tasks. Straube et al [2006b] have shown that activation of the insula and ACC was blocked when spider phobics were requested to solve a demanding cognitive task that was displayed in the foreground of phobia-relevant pictures. In accordance to this, Paquette et al [2003] suggested that attentional distraction that is self-induced as a kind of avoidance or coping behavior might lead to a decrease in insula activity.

Also, most functional brain imaging studies of specific phobia have implicated amygdala hyperactivity in response to phobia-related threats [Paquette et al., 2003; Rauch et al., 1995; Stein et al., 2002]. But again not all studies report this. Straube and colleagues [2006b] propose this could be due to the sustained periods of symptom provocation used in these studies, leading to an attenuation of amygdala responses. They suggest that the amygdala has a crucial function in the initial processing of phobia-related stimuli and in the induction of fear, but that amygdala activity is not crucial for sustained processing of phobia-related stimuli, such as confrontation with real, imagined, or filmed feared objects [see also Rauch et al., 1997; Walker et al., 2003]. Straube et al [2006b] propose that the crucial function of the amygdala is to fire when there is a stressor, but is not involved during confrontation with feared objects.

Pre- and posttreatment studies

There are only three studies to my knowledge that have investigated brain changes in phobics after successful therapy, namely the study of Paquette et al [2003] (spider phobia), Straube et al [2006] (spider phobia), and Furmark et al [2002] (social phobia). The effect of CBT was investigated in the first two studies and both CBT as well as drug treatment with citalopram was investigated in the study of Furmark et al [2002].

CBT in social phobia focuses on the core fears of negative evaluation by others and the cognitive biases and avoidance patterns that prevent disconfirmation of these fears [Otto et al., 2004]. CBT in specific phobia consists of exposure-based treatment to the phobogenic stimuli (e.g. spiders) combined with education for changing negative cognitive misattributions related to these stimuli [Linden et al., 2006].

In the study of Paquette et al [2003] the regional brain activity of subjects (n=12 women) suffering from spider phobia was measured using fMRI, before and after CBT, while they were viewing video passages showing either living spiders (activation task) or living butterflies (reference task). These data were compared to that of normal control subjects (n=13 women), who were scanned once while watching the same video passage. Brain activity associated with viewing butterflies was subtracted from that associated with viewing spiders. In that way they found that right dorsolateral prefrontal (dlPFC) cortex and the right parahippocampal gyrus were significantly activated before CBT but not after CBT. Based on the pretreatment scanning data, it was suggested that the activation of the dlPFC may reflect the use of metacognitive strategies aimed at self-regulating the fear triggered by the spider video passages, whereas the parahippocampal activation might be related to an automatic reactivation of the contextual fear memory that led to the development of avoidance behavior and the maintenance of spider phobia. They suggest that after successful CBT the normalized frontal function has returned in patients with spider phobia.

This pattern is consistent with the findings in the fMRI study of Ochsner et al [2004] in which they correlated right ventral PFC activity with down-regulation of negative emotions either by focusing internally on

the self-relevance of aversive scenes or by focusing externally on alternative meanings for pictured actions and their situational contexts. Thus following therapy, a shift of activity to the ventral PFC could prompt down-regulation of limbic activity, and consequently dampen the fear reaction [Roffman et al., 2005].

One limitation of the study design of Paquette et al [2003] is that no untreated phobic control group was included in this study. Since repeated scanning sessions may be associated with confounding variables such as habituation, anticipation, and novelty effects [e.g., McGonigle et al., 2000], a phobic waiting-list control group offers the possibility to properly control for these influences. Furthermore, the videos, which were used in the pre- and posttreatment scanning sessions, were also presented between scanning sessions as part of the therapy. Therefore, no clear conclusion was possible whether the modification of brain activation was due to effects of the psychotherapy applied, or to other factors such as stimuli-specific habituation [Straube et al., 2006].

The suggested involvement of the dlPFC in symptom relief [Paquette 2003] is rejected in the study of Straube et al [2006]. In this fMRI study spider phobics (n=28 women) and healthy control subjects (n=14 women) were scanned before and after CBT. They divided the phobics to a therapy-group and a waiting-list group. Though they call the therapy which they used CBT, it contained mainly components of exposure therapy because it consisted of rapid gradual exposure to the feared animals during two sessions with a duration of 4 to 5 hours each. Pretreatment scanning showed that spider phobics showed increased activity in insula and ACC compared to the controls when being presented to spider videos, which is in line with the findings of many symptom provocation studies [Carlsson et al., 2004; Dilger et al., 2003; Rauch et al., 1995; Reiman, 1997]. After CBT, phobic symptoms strongly reduced in the therapy group compared to the waiting-list group. Post-treatment scanning revealed a decrease in the response in the insula and ACC. Thus, they did not find a significant effect for the involvement of the PFC, or parahippocampal regions.

In response to the findings of Paquette et al [2003], Straube et al [2006] proposed that activation of the dlPFC during anxiety provocation paradigms might reflect coping strategies and inhibitory control and not representing the neural mechanisms underlying the effects of successful treatment. They support this statement with the findings of Johanson et al [1998]. Johanson et al [1998] have investigated rCBF in spider phobics during the presentation of video showing living spiders. They found an increase of prefrontal rCBF in patients that were not in panic during the presentation of the video, compared to the patients that were in panic. This frontal rCBF increase was hypothesized to be correlated with the use of cognitive strategies for coping with the phobic situation. So the involvement of the dlPFC might be an aspect of cognitive control of the feared response. Remarkably, no phobia-related activation of the insula, ACC, or other areas was detected in the study of Johanson and colleagues, while these brain areas have shown to be essential in many previous symptom provocation studies [Carlsson et al., 2004; Dilger et al., 2003; Rauch et al., 1995; Reiman, 1997].

Both the study of Paquette et al [2003] as well as Straube et al [2006] did not reveal evidence of the involvement of the amygdala in the processing of fear stimulus of the subjects with phobia. Though, Straube et al [2006] did find activation of the amygdala in the healthy comparison subjects.

Until recently, the only pre-and post treatment study that has been performed on social phobia is that of Furmark et al [2002]. Patients with social phobia respond favorably to SSRIs [Van Ameringen et al., 1999] and

CBT [Taylor, 1996], therefore Furmark and colleagues chose to focus on the neural networks participating in the response to citalopram and CBT. They measured rCBF using PET scanning in 18 (10 men, 8 women) previously untreated patients with social phobia during an anxiogenic public speaking task. They divided these patients into three groups which were matched for sex, age, and phobia severity: a citalopram medication group, CBT group, and a waiting list control group. The CBT and citalopram treatment lasted for 9 weeks, as did the waiting period for the waiting-list group. Symptom improvement was accompanied by a decreased rCBF response to public speaking bilaterally in the amygdala, hippocampus, and anterior and medial temporal cortex, including the entorhinal, perirhinal, parahippocampal, and periamygdaloid areas in both the citalopram and CBT group. These results imply that CBT and citalopram therapy for social phobia might dampen limbic response by different mechanism.

Summary

In conclusion, increased right-sided activation in the anterior temporal and lateral prefrontal scalp region has been found in social phobics [Davidson et al., 2000]. Also, many studies suggest increased activation in ACC and insula in specific phobics [Carlsson et al., 2004; Dilger et al., 2003; Rauch et al., 1995; Reiman, 1997]. This is in line with the pre-and posttreatment study of Straube et al [2006a] in which a decrease in ACC and insula activity was found *after* in comparison to *before* CBT. This is suggested to be caused by attentional distraction leading to symptom improvement [Paquette et al., 2003, Straube et al., 2006b]. Increased right dorsolateral prefrontal (dlPFC) cortex and right parahippocampal gyrus activity was found before CBT compared to after CBT in specific phobics [Paquette et al., 2003]. It is suggested that increased activity measured in the dlPFC is a function of cognitive control over the phobic response and is accepted by many researchers [Johanson et al., 1998, Straube et al., 2006a, Paquette et al., 2003, Ochsner et al., 2004]. The only pre-posttreatment study on social phobia of Furmark et al [2002] revealed decreased rCBF response to public speaking bilaterally in the amygdala, hippocampus, and anterior and medial temporal cortex after citalopram or CBT, suggesting that psycho-and pharmacotherapy have similar outcomes. Still, there are many uncertainties, such as the role of the amygdala in phobia. Therefore more pre-and posttreatment studies on phobia are needed to understand the neurobiology of effective therapies in social and specific phobia.

Panic disorder

Symptoms

A panic attack is characterized by an unexpected episode of intense fear or feeling of distress. During a panic attack a person may be experiencing tremor, the feeling of suffocation, heart racing, sweating, nausea, and/or shortness of breath. A person is suffering from panic disorder when he or she is experiencing intense and ongoing fear of the next expected attack. Panic disorder can be diagnosed with or without agoraphobia. Agoraphobia is fear of leaving the house or being in a situation from which fleeing is expected to be difficult [DSM-IV, 2000].

In panic disorder (PD) cardiovascular and respiratory reactivity is abnormal, pointing to brainstem involvement [Gorman et al., 2000]. In general, researchers have hypothesized on neurocircuitry models of PD that the panic attack originates from loci in the brainstem, including the ascending reticular system and respiratory and cardiovascular control centers. It is also hypothesized that the amygdala, which is projecting to the brainstem nuclei, might be involved [Engel et al., 2009].

Gorman et al [2000] have recently revised their previous neuroanatomical hypothesis of PD [1989]. Their revised hypothesis holds that patients with PD inherit an especially sensitive central nervous system fear mechanism. This fear mechanism has at its center the central nucleus of the amygdala and includes the hippocampus, thalamus, and hypothalamus, as well as the periaqueductal gray (PAG) region, locus ceruleus, and other brainstem sites. They also hypothesize that medications such as SSRIs may reduce panic attacks by decreasing the activity of the amygdala and interfering with its ability to stimulate projection sites in the hypothalamus and brainstem. Psychotherapeutic interventions, such as CBT, may work upstream from the amygdala, via extinction of contextual fear conditioning at the level of the hippocampus and decreasing cognitive misattribution and abnormal emotional reactions by strengthening the ability to inhibit the amygdala.

Resting state

Using [^{18}FDG]-PET and voxel-based analysis on 12 (3 men, 9 women) nonmedicated PD patients and 22 healthy controls during resting state, Sakai et al [2005] demonstrated elevated regional glucose metabolism in PD patients with heightened state anxiety relative to that in normal controls in the bilateral amygdala, hippocampus, and thalamus, and in the midbrain around the PAG, caudal pons, medulla, and cerebellum,. These results support the presence of an activated “panic neurocircuitry” including a fear network proposed by Gorman et al [2000].

In the study of Bisaga et al [1998], cerebral metabolic activity was measured during resting state using [^{18}FDG]-PET scanning method. Data of six healthy female volunteers was compared to data of six female PD patients. A significant elevation in glucose metabolism was found in the left hippocampus and parahippocampal area of the panic disorder subjects in comparison with healthy subjects. In addition, a significant decrease in metabolism was found in the right inferior parietal and right superior temporal brain regions of the panic disorder subjects in comparison with that of the healthy subjects.

Using (SPECT) and ^{99m}Tc-hexamethylpropyleneamine oxime (HM-PAO), De Cristofaro et al [1993] assessed brain perfusion in seven patients with PD and in five age-matched normal subjects at rest. They found a significant L/R asymmetry in the inferior frontal cortex of the PD patients with a relative increase in perfusion on the right hemisphere. They also observed a significant blood flow increase in the left occipital cortex and a significant decrease in the hippocampal regions bilaterally. They suggest that hippocampal structures may play an important role in the pathophysiology of PD as hippocampal hypoperfusion appears to be one of the characteristics.

When looking at the results of these studies in PD patients during resting state, only a few studies report activity changes in brain regions that converge with the model proposed by Gorman et al [2000]. These last two studies during resting state are difficult to compare, as one has measured glucose metabolism, and the other

brain perfusion. It is important to keep in mind that a region of the brain could have increased glucose metabolism due to increased activation but have reduced blood flow due to constriction of blood vessels [Whiteside et al., 2004]. Therefore, the findings of these two studies during resting state do not have to be contradictory.

Stimulus induced

Studies investigating stimulus induced brain changes have mainly reported increased glucose metabolism in the right hemisphere. Nordahl et al [1990] found an asymmetry in the hippocampal region with trends towards significant increases in the right hippocampal region using [^{18}FDG]-PET scanning during performance of an auditory discrimination task. They also found metabolic decreases in the left inferior parietal lobule and in the ACC (trend) and an increase in the metabolic rate of the mOFC (trend) of PD patients were found.

Reiman et al [1989] investigated PD patients who were vulnerable to lactate-induced anxiety attacks. These patients showed abnormal hemispheric asymmetries of parahippocampal (left less than right) regional blood flow in the resting, nonpanic state. Lactate-induced panic was associated with increases in blood flow bilaterally in the temporal poles and in the insular cortex, claustrum and lateral putamen, bilaterally in or near the superior colliculus, and in or near the left anterior cerebellar vermis.

Based on these findings, Nordahl et al [1998] investigated the differences in cerebral metabolic activity between chronic imipramine-treated patients with PD and unmedicated PD patients during an auditory discrimination task using [^{18}FDG]-PET scanning. Similarly to the previous studies, they found increased metabolic activity in the right hemispheric hippocampus and posterior inferior prefrontal cortex in the imipramine-treated PD patients. Interestingly, activity in posterior OFC was significantly lower in the imipramine treated patients compared to unmedicated patients. This decrease may reflect direct or indirect effects of imipramine treatment in panic disorder patients.

Pre- and posttreatment studies

Only two studies have been published on pre-and posttreatment effects in PD. The pre-post treatment study of Prasko et al [2004] was carried out to compare changes in cerebral glucose metabolism during pharmacotherapy or psychotherapy of panic disorder in a within-subject design. They investigated 12 patients with PD and examined brain changes after either CBT (n=6, 3 females, 3 males) or antidepressants (n=6, 3 females, 3 males) using [^{18}FDG]-PET scanning during resting state. The treatment period lasted for 3 months. The antidepressant that were used were sertraline (SSRI) (n=2), venlafaxine (SNRI)(n=1), and citalopram (SSRI) (n=3).

Remarkably, they did not use a healthy control group, and therefore data of the pre-treatment scanning session are lacking. After treatment, the antidepressant group showed a decrease in glucose metabolism in the right hemisphere, in the superior, middle, medial and inferior frontal gyrus, superior and middle temporal gyrus. Also, increases in glucose metabolism were detected in the left hemisphere in medial and middle frontal gyrus, superior, middle and transverse temporal gyrus. The CBT group showed decreases in glucose metabolism in the right hemisphere in the inferior temporal gyrus, superior and inferior frontal gyrus. Also,

increases were detected in the a priori hypothesized region, mostly in the left hemisphere: inferior frontal gyrus, middle temporal gyrus and insula. They did not detect changes in [^{18}FDG] uptake in the limbic region (hippocampus, parahippocampal gyrus or amygdala). Based on these findings the authors propose that effective treatment, whether with antidepressants or CBT, results in a decrease of right hemispheric hyperactivity.

A disadvantage of this study is that it only held six subjects in each treatment group and thus may have lacked power to detect additional, perhaps more subtle, neural effects unique to CBT and pharmacotherapy [Kumari, 2006]. Also, researchers had chosen to use three different antidepressants in this small group of participants and may therefore not be a homogeneous group. Next to that, because patients had been treated before the beginning of the study with various antidepressants, they had chosen for antidepressant medication that had previously never been used before by the patients. For these reasons and with the fact that they did not use a healthy control group, this study is hardly of any value as it is difficult to compare the results with other studies that have investigated brain changes after drug treatment in PD patients.

In contrast to the findings of Prasko et al [2004], Sakai et al [2006] performed a PET study in which they compared regional brain glucose metabolism before and after CBT or antidepressant treatment. Pretreatment scanning 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 CBT and antidepressant treatment resulted in comparable decreases of previous activations. In 11 of 12 patients who showed improvement after CBT, decreased glucose metabolism was detected in the right hippocampus, left ACC, left cerebellum, and pons, whereas increased glucose metabolism was seen in the bilateral mPFC.

Summary

In summary, elevated regional glucose metabolism levels in limbic regions during resting state have been reported in PD patients [Sakai et al., 2005], which is in line with the proposed model for PD by Gorman et al [2000]. An elevation in blood glucose metabolism in hippocampal and parahippocampal regions has been reported with mostly right hyperactivity [Bisaga et al., 1998; Reiman, 1997]. Furthermore, decrease in regional blood flow during resting state has been reported in bilateral hippocampus [De Cristofaro et al., 1993] and right parahipocampal regions [Reiman, 1997].

Stimulus induced studies reported mainly hyperactivity of the right hemispheric hippocampus and decrease in left inferior parietal lobe [Nordahl et al., 1990]. Overall, increased activity was measured in limbic regions [Reiman]

Taken together, side asymmetries with decreased activity of inhibitory, prefrontal structures and increased activity in limbic areas such as the hippocampus on the dominant hemisphere have been suggested for being important features in PD [Engel et al., 2009]. Panic might be controlled as well as to originate from a dysfunction of frontal and temporal limbic circuitries, such as hypoactivity in the hippocampal regions [De Cristofaro et al., 1993]. Pre and posttreatment studies showed pretreatment increase in glucose metabolism in limbic regions and after successful CBT and antidepressant treatment decreased glucose metabolism in these

regions [Sakai et al., 2006]. Though there are many uncertainties about the involved brain regions in PD, let alone the brain changes after successful therapy.

Generalized anxiety disorder

Symptoms

Patients with generalized anxiety disorder (GAD) experience worry for feeling anxious and a number of physical and psychologic symptoms. After multiple revisions of the concepts of GAD, it was revised once again in 1992 in DSM-IV. Three of six symptoms are required for the diagnosis of GAD, namely restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance. GAD is seen as a separate disorder that persists at least for some time in episodes distinct from those of other disorders, so GAD symptoms cannot fully occur during another disorder [DSM-IV, 2000]. GAD has been conceptualized as a worry-based rather than a fear-based disorder [Hoge et al., 2004].

Unfortunately, the amount of published neuroimaging findings of GAD is scarce. In most settings, generalized anxiety disorder (GAD) has co-morbidities with major depressive disorder (MDD) and is therefore hard to examine.

Resting state, stimulus induced

Until today, there are no reports published of studying brain activity in GAD during resting state. Though, there are a few symptom provocation studies. In the fMRI study of Monk et al [2006] greater BOLD responses were found in the right vlPFC to emotionally adverse stimuli in GAD patients compared to healthy controls. They compared brain activity of 18 adolescents diagnosed with GAD to 15 healthy controls while viewing angry or neutral face pairs during fMRI acquisition. The participants had to indicate whether a subsequent asterisk appeared on the same (congruent) or opposite (incongruent) side as the angry face by pressing a button. Reaction time differences between congruent and incongruent face trials provided a measure of attention bias to angry faces. In analysis of the degree of anxiety and brain activation, the authors found that as vlPFC activation increased, severity of anxiety symptoms diminished. Furthermore, symptom severity correlated positively with right amygdala activation on presentation of angry faces.

Predictors of effectiveness

With regard to predictability of the effectiveness of pharmacotherapy in treating GAD, McClure et al [2007] showed that GAD patients had a better treatment response to fluoxetine or CBT when pretreatment amygdala activity was strong. However, Whalen et al [2008] found that treatment response to venlafaxine, was predicted by lower amygdala and higher ACC reactivity to fearful faces in the fMRI. Fluoxetine and venlafaxine both are antidepressants, but fluoxetine belongs to the group of Selective Serotonin Inhibitor (SSRI) and venlafaxine belongs to Serotonin and Noradrenalin Reuptake Inhibitor (SNRI's).

Pre- and posttreatment studies

Wu et al [1991] published the first article on differences in regional cerebral metabolism between normal controls and patients with GAD before and after drug treatment. In this [FDG]-PET study they examined 18 patients (8 men, 10 women) that met DSM-III criteria for GAD. We have to take into account that DSM-III criteria for GAD differ from the DSM-IV criteria which are used nowadays. Patients were divided in a drug treatment group (benzodiazepine) (n=8) or in a placebo group (n=10). The control group consisted of 15 healthy participants (5 men, 10 women).

Since disturbed and/or hypervigilant attention is one of the characteristics of GAD, researchers had chosen to perform a cognitive vigilance task during uptake of FDG. In this task the participants were presented numbers on a screen and they were asked to actively identify these target stimuli by pressing a button each time they detected a zero and not to respond if they detected non-zeros. The numbers were blurred, thus making it harder to distinguish them. Also, false feedback was given that was designed to stimulate anxiety.

Pretreatment scanning consisted of one baseline scan, during which the participants had to observe the numbers passively. In the second pretreatment scan the participants had to execute the cognitive vigilance task, thus had to react to the visual stimuli. Posttreatment scanning consisted of the cognitive vigilance task after placebo or medication administration.

Baseline results of the pretreatment scanning during the passive task revealed that patients showed lower absolute metabolic rates in basal ganglia and white matter compared to healthy subjects. Also, relative metabolism was increased in the left inferior occipital lobe, right posterior temporal lobe, and the right precentral frontal gyrus.

Pretreatment execution of the cognitive vigilance task showed activation of relative basal ganglia metabolism in patients. Posttreatment scanning showed that benzodiazepine therapy resulted in decreases in absolute metabolic rates for cortical surface, limbic system, and basal ganglia and was not associated with normalization of patterns of glucose metabolism. Based on these finding they suggest that the basal ganglia may play an important role in GAD. Also, the change seen in this region after benzodiazepine treatment is revealing a possible interesting feature for symptom improvement [Wu et al., 1991].

Summary

Clearly, neuroimaging studies in GAD are at a very early stage. Nevertheless, it seems that basal ganglia, amygdala and insula function are of importance in this disorder and a dysfunction of ventrolateral prefrontal cortex could be of relevance [Monk et al., 2008; Engel et al., 2009].

Chapter 3 - Anxiety disorders integrated

In this last chapter, I will integrate findings of the previously discussed studies of anxiety disorders and investigate whether these findings show commonalities between the different anxiety disorders.

Commonalities between anxiety disorders

Based on the findings of this review in investigating the shared mediating neuroanatomy of anxiety symptoms, it can be concluded that findings regarding activation of the insula and ACC during symptom provocation are in accordance with different anxiety disorders. For example, insula activation was shown in social phobia [Stein et al., 2002; Tillfors et al., 2001, 2002], panic disorder [Reiman, 1997], and PTSD [Rauch et al., 1997]. Furthermore, studies investigating EEG asymmetries in anxiety disorders reported increased right anterior activation during symptom provocation in PD patients [Wiedemann et al., 1999], social phobics [Davidson et al., 2000], and Vietnam veterans with PTSD

Nowadays, the role of the amygdala in anxiety disorders is still not clear. Some functional imaging studies have demonstrated hyperexcitability of the amygdala during fear processing in anxiety disorders, in particular PTSD [Shin et al., 2004, 2005; Bremner et al., 2004], social phobia [Furmark et al., 2002], specific phobia [Paquette et al., 2003; Rauch et al., 1995; Stein et al., 2002], PD [Sakai et al 2005, 2006], and GAD [Monk et al., 2006]. Though, other studies have specifically rejected this, namely for PTSD [Felmingham et al., 2007; Levin et al., 1999], specific phobia [Paquette et al., 2003; Straube et al., 2006b], and PD [Prasko et al., 2004]. Straube et al [2006a] suggest that amygdala activity is not crucial for sustained processing of phobia-related stimuli, but rather is crucial for the initial processing of phobia-related stimuli and in the induction of fear [see also: Rauch et al., 1997; Walker et al., 2003].

Pre-posttreatment studies

Most pre-and posttreatment studies reveal that abnormal brain functioning measured in anxiety disorder patients seems to change to normal brain functioning levels after effective treatment. This suggests that brain changes due to effective treatment are quite straightforward, namely anxiety disorder symptoms are present together with a specific abnormal brain activity, and as symptom relief is established after treatment the specific abnormal brain activity has turned to normal levels. As for example studies of CBT effects in OCD were consistent in showing decreased metabolism in the right caudate nucleus, whereas an increased activity in the caudate nucleus showed to be characteristic for OCD patients [Baxter et al., 1992; Schwartz et al., 1996]. Also, CBT in phobia resulted in decreased activity in limbic and paralimbic areas [Paquette et al., 2003; Furmark et al., 2002], and were reported before treatment to be significant for both specific and social phobics.

Next to that, results of pre-and posttreatment studies have shown to support the hypotheses that in anxiety disorders neural mechanisms for fear extinction and the cognitive control of emotion are distorted. Namely, CBT has shown to result in increased activity of inhibitory cortical structures and decreased activity in limbic structures. This is in line with the model for fear extinction of Sotres-Bayon et al [2006] mentioned earlier, in which they propose that extinction could involve either mPFC activation of inhibitory lateral amygdala (LA) interneurons [Rosenkranz et al., 2003], or mPFC activation of inhibitory projections from the intercalated cell masses to the central amygdala (CE) [Quirk et al., 2003]. Also, the findings of the anxiety disorders are in line with the model for how we control our emotions. Namely, the cognitive control of emotions is said to involve activation of prefrontal cortex inhibitory systems (top-down) and decreased activity in subcortical areas, such as the amygdala (bottom-up) [Sotres-Bayon et al., 2004, Davidson, 2002].

Though, not all pre-and posttreatment studies report increased activation in prefrontal cortical brain regions, together with activity differences measured in limbic brain areas after successful treatment. Some studies measured only limbic brain activity changes, and others only inhibitory prefrontal structures. Levin et al [1999] proposed that the improvement of PTSD symptoms may not be mediated by decreased activation of the amygdala, as is proposed by others, but instead, is caused by an increased activation of the anterior cingulate and prefrontal area [see also Felmingham et al., 2007].

Psycho- and pharmacotherapy

Whether successful treatment contained psycho- and pharmacotherapy did not matter for the observed effects after successful intervention for most cases. This is suggesting that there are commonalities in the biological mechanisms of psycho- and pharmacotherapy [Linden, 2006].

Though there are differences between psycho-and pharmacotherapy on the long-term. The relapse-rate seems to be much higher after drug treatment, compared to psychotherapy [Pollack and Smoller, 1996]. CBT appears to offer long-standing benefits after quitting the formal treatment [Otto et al, 2005]. Studies on this topic have investigated the neurophysiology of these different types of treatment or a combination of the two. Combining drug therapy with psychotherapy has shown to decrease the risk of relapse. With psychotherapy, patients have learned to cognitively deal with the disorder, making them less prone for relapse after stopping the medication. Medication can help psychotherapy by controlling emotions, as emotions become less severe and therefore easier to cognitively learn to handle [Ribeiro Porto et al., 2009]. Conversely, psychotherapy can help the effect of medication in a way that it can decrease the risk of relapse after stopping taking the drug. Psychotherapy can also be used as a replacement strategy for patients wishing to discontinue their medications [Beutel et al., 2003].

Future research

Nowadays, it is difficult to match the right kind of therapy to one patient diagnosed with an anxiety disorder. In order to determine which kind of therapy is best for which patient, it is necessary to increase our knowledge about brain changes after effective interventions. In that way it might be possible to predict the outcome of one kind of therapy for a patient and create the right type of therapy for a patient.

This thesis has shown that there are many difficulties in the investigation of brain changes after successful interventions due to the cost, inconvenience and difficulty of conducting and evaluating a complete course of psychotherapy under controlled conditions. Patient groups were often not homologous, as in almost every study the participating patients were diagnosed with co-morbidities. Patients often had been using medication or psychotherapy in the past, which could have caused bias in the results but obviously it is unethical to ask the participants not to use any medication for their disorder. Furthermore, due to the fact that it is difficult to find a group of patients who are around the same age and are willing to participate in an experiment, sample sizes have been relatively small in general [Etkin et al., 2005]. But most importantly, these discrepant results could also be caused by no clear DSM criteria for one disorder meaning that these criteria are not set correctly.

Nevertheless, considering the beneficial effects of psychotherapy, it is of great interest if we could understand how psychotherapy changes the brain. A highly interesting question for future research might be how different components of psychological therapy (e.g., cognitive restructuring, imaginable/behavioral exposure, or relaxation training) are related to changes in brain function [Rabe et al., 2008]. Perhaps more subtle, neural effects unique to psychotherapy and pharmacotherapy may inform about particular mechanisms leading to clinical improvements [Kumari, 2006].

In the future, the successfulness of one kind of therapy might be determined by relative brain activity in different brain regions, and therefore biological changes might become part of an accepted method for determining the success of psychotherapy. Perhaps even, neuroscience can add up to the formation of new DSM criteria to improve the diagnostics of anxiety disorders and other mental disorders.

Until now, neuroscience has not been of great assistance for improving the quality of therapy much, as it is a new field of research. Neuroimaging studies have shown effects of therapies on group level, but no clear findings have been reported for the individual. Therefore, in order to help to improve therapies with neuroscience, more neuroimaging studies are needed, with good controls, no diagnosis of co-morbidities in the patient group, and with clear DSM criteria for the anxiety disorder. Only in that way, neuroscience can help improving the quality of therapy.

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