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Cognitive emotion regulation through reappraisal in an anticipatory anxiety paradigm

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Abstract

Humans have the ability to cognitively control their emotions. Reappraisal is a cognitive emotion regulation technique that works through re-interpretation of the meaning of a stimulus or situation and can be used to down-regulate negative emotions, including anxiety. There is currently a strong interest in identifying the cognitive processes and neural substrates that mediate reappraisal.

We demonstrate, using a detachment-from-threat paradigm and concurrent skin conductance monitoring and functional magnetic resonance imaging (fMRI), that attenuation of anxiety is based not only on re-interpretation but also on further processes accompanying reappraisal. We establish a reappraisal technique in an anticipatory anxiety paradigm (*Study I*) that is anxiolytic when compared to a simple 'observe' condition. However, when compared to a control condition that is matched for all aspects (including cognitive load) apart from re-interpretation, the observed anxiolytic effect of reappraisal is substantially diminished (*Studies II,III and IV*). We further show that besides re-interpretation and cognitive load, developing a positive outcome expectation influences the anxiolytic character of reappraisal (*Study V*). Finally we experimentally test the distinction between an early and a late reappraisal phase, currently hypothesised by the implementation-maintenance model or IMMO (*Study VI*).

Taking everything into consideration, the results from the studies presented in this thesis show that anxiolysis via cognitive reappraisal relies on at least three subcomponents: re-interpretation, cognitive demand and a placebo-like expectation-effect. Neurally, the reappraisal process involves late right anterior lateral frontal cortex activation that we interpret as reappraisal maintanace activation, as supported by IMMO.

Glossary

ACC	anterior cingulate cortex	PET	positron emission tomography
ad	anterior dorsal	PFC	prefrontal cortex
ANOVA	analysis of variance	pg	perigenual
BOLD	blood oxygenation level dependent	PPI	psychophysiological interaction
CS	conditioned stimulus	RA	reappraisal
dl	dorsolateral	RF	radiofrequency
dm	dorsomedial	rm	rostromedial
FDR	false discovery rate	RSI	reappraisal success index
fMRI	functional megnetic resonance imaging	s	second
IMMO	implementation maintanace model	SCL	skin conductance level
HF	high frequency	SC	skin conductance
l	lateral	SD	standard deviation
IAPS	international affective picture system	SDS	social desirability scale
m	medial	sg	subgenual
M	mean	STAI	state-trait anxiety inventory
MHz	megahertz	t	tesla
MNI	montreal neurological institute	T	threat
MRI	magnetic resonance imaging	UCS	unconditioned stimulus
NA	no-reappraisal	UR	unconditioned response
NT	no-threat	US	unconditioned stimulus
pd	posterior dorsal	vm	ventromedial

Contents

Part I

Introduction

1 Emotion and Emotion Regulation

This chapter will describe what emotions and emotion regulation are. Fear and anxiety are in the centre of attention as the studies described later deal with humans' reactions during anticipation of a feared stimulus, named 'anticipatory anxiety' (see below).

1.1 Definition of Emotion

There has been much debate on finding a definition of 'emotion' that is agreed on by the different groups of scientists that work in the field of emotion-research. The following definition comprises aspects of emotion that most researchers agree on (Kleinginna P.R., 1981):

> Emotions are "a complex set of interactions among subjective and objective factors, mediated by neural/hormonal systems, which can: (a) give rise to affective experiences such as feelings of arousal, pleasure/displeasure; (b) generate cognitive processes such as emotionally relevant perceptual effects, appraisals, labelling processes; (c) activate widespread physiological adjustments to the arousing conditions; and (d) lead to behaviour that is often, but not always, expressive, goal directed, and adaptive" (p. 355).

The definition emphasises on the one hand the subjective and on the other hand the objective side of emotions: objectively identical stimuli (external excitations) will be perceived subjectively different by different individuals.
In addition, the working definition emphasises the multi-channel consequences of emotions: a subjective (or feeling) level, a cognitive level, a physiological and a behavioural

reaction. In experimental settings it is possible to measure the emotional outcome on different levels.

Although it is stressed that emotions are complex processes, they can be categorised in different taxonomies. Many scientists, for example Russell, divide between different dimensions of emotion like pleasure/displeasure and high/low arousal (Russell, 1980). Other researchers like Ekman describe few innate basic emotions like disgust or happiness, which can not be broken down further and that differ regarding their characteristics like physiologic or behavioural responses (Ekman & Friesen, 1969).

Fear and anxiety

If one assumes that basic emotions exist, fear is one of them (Ekman & Friesen, 1969; Schmidt-Atzert, 1995). Fear serves to prevent us from harm by initiating avoidance or flight behaviour (Öehman, Lewis & Haviland-Jones, 2000). Anxiety is an aversive emotional state, characterised by a feeling of dread and apprehension or fear (Blakemore & Jennett, 2002). Fear must be distinguished from anxiety, in that it is a more basic phylogenetically old mechanism involved in the reaction to environmental threat. Anxiety develops from fear if an individual is not able to cope with an aversive situation. The situation becomes uncontrollable and anxiety arises (Manstead, Frijda & Fischer, 2004). Concluding from this, fear is a reaction to a certain stimulus that we perceive, while anxiety is a feeling not necessarily bound to the appearance of a specific stimulus. Nevertheless, there is ongoing debate about the exact classification of fear and anxiety.

With a 12-month prevalence of 14 percent anxiety disorders form the largest diagnostic group of psychological disorders (Wittchen, Jacobi, Rehm, Gustavsson, Svensson, Jönsson, Olesen, Allgulander, Alonso, Faravelli, Fratiglioni, Jennum, Lieb, Maercker, van Os, Preisig, Salvador-Carulla, Simon & Steinhausen, 2011). It is estimated that 61.5 million people in Europe were affected by an anxiety disorder in the year 2010. The ICD-10 (International Classification of Disease) divides this heterogeneous group in 1) phobic anxiety disorders, 2) other anxiety disorders (with panic disorder and generalized anxiety disorder), 3) obsessive-compulsive disorder, 4) reaction to severe stress and adjustment disorders (with acute and posttraumatic stress disorder) and 5) dissociative disorders.

Although theses disorders vary in many aspects they all share the core symptom of irrational, excessive fear.

This thesis describes experiments that use "anticipatory anxiety" paradigms: participants anticipate a threat that they fear (painful electrical shock), which then elicits an aversive state of anxiety.

1.2 Learning and Anxiety

Learning is a process by which the individuals behavior changes due to experiencing a situational event (Mazur & Roberts, 1999). Learning theories explain the acquisition, maintenance and extinction of fear and anxiety with the help of classical and operant conditioning.

1.2.1 Classical Conditioning

The typical classical conditioning experiment presents pairings of an unconditioned stimulus (US) that elicits an unconditioned response (UR), with a first neutral and later conditioned stimulus (CS) (Mazur & Roberts, 1999). In fear conditioning the US is a stimulus that evokes fear (e.g. an electric shock). The CS can for example be visual (a picture) or auditory (a certain tone, a spoken word). The success of fear conditioning can be quantified with different measures (see methodological introduction). The CS can be followed by the US (CS+) or not (CS-).

With classical (fear) conditioning a model of anxiety acquisition and extinction can be brought into experimental setting (Manstead, Frijda & Fischer, 2004). This is important, as controlled experimental settings are necessary to make underlying processes of the rather complex anxiety disorders explicit and (at least partly) observable. Also, fear conditioning is an accepted animal model for anxiety disorders; fear conditioning experiments in rodents helped develop and test hypotheses in patients with anxiety disorders (Milad & Quirk, 2012).

There are several phenomena around classical conditioning that are important for learning processes.

During the acquisition phase the participant experiences several CS-US pairings. In the beginning the learning curve is step and the participant learns quickly. After several pairings learning is slower. The "asymptote of conditioning" is reached (Mazur & Roberts, 1999). The stronger the US (e.g. more painful), the faster learning takes place and the quicker the asymptote is reached (Mazur & Roberts, 1999). Extinction describes the

reduction or even disappearance of the CR (conditioned response) after repeated presentations of CS- (Mazur & Roberts, 1999).

Several mechanisms contribute to the current understandning of extinction learning as an active learning process where new, inhibitory associations are learned. First, extinguished responding can reappear after some time of no stimulus presentation. This is called 'spontaneous recovery'. Second, 'reinstatement' refers to the phenomenon that formerly extinguished CRs return after presentation of the USs alone. Third, also 'rapid reacquisition ', which is the accelerated return of the CS-US association after extinction, can be observed.

Phenomena like spontaneous recovery, reinstatement or rapid reacquisition suggest that after extinction the memory trace about the CS-US connection is not wiped out completely but at least in parts is preserved. This has important implications for patients with anxiety disorders, as it suggests that rather than initiating a 'deletion' of the learnt during confrontational therapy a new behaviour is learned that dominates the former maladaptive, pathological behaviour. Behavioural therapy builds on this knowledge about extinction-processes to reduce unwanted fear-reactions like observed in patients with specific phobias or panic disorder by exposing them to a feared stimulus or situation (CS), allowing them to make the experience that the expected consequences (US, e.g. fainting in public) does not occur.

It is accepted that the extinction process relies on a new learning process rather than on a deletion of the already existing knowledge (Bouton, 2002). The drop in CR is again, quick in the beginning and reaches asymptotic level in the end (Mazur & Roberts, 1999). The temporal relationship between CS and US is important for the strength of conditioned responding. Fast learning can be reached if the CS comes before the US (forward conditioning). Within forward conditioning short delays lead to the strongest and quickest conditioning (Mazur & Roberts, 1999). Two subforms can be described: the CS starts and is after a short delay accompanied by the US (delay conditioning) or the CS is presented and, after a short time-interval of no stimulus presentation, the US is presented (trace conditioning).

1.2.2 Operant Conditioning

In operant conditioning the behaviour is not elicited by one specific stimulus. Operant conditioning tries to find general principles that can predict a person's behaviour in a given situation. In operant conditioning the *behaviour* of a participant is in the centre of observation. The participant has to get active and show a certain behaviour, that is, in a second step, followed by a particular stimulus, the *reinforcer*. One important principle is the *Law of Effect* described by Thorndike (Mazur & Roberts, 1999). It states that behaviours that are followed by a satisfying or desirable state will be shown more often in the future. Behaviours, that are followed by an aversive or undesirable state are shown less often.

Reinforcement can be conducted in four ways: positive reinforcement (presenting a reward), negative reinforcement (removing a negative stimulus, avoidance), punishment (presenting an unpleasant stimulus) and negative punishment (removing a pleasant stimulus, omission). Reinforcement can be continuous or variable, immediate or delayed, leading to differences in conditioning strength. Intermittent reinforcement, not given after every successful trial, but at only a part of the trials, is more persistent.

1.2.3 Two-Factor Theory and Conditioning

Mowrer (1947) stated in his *two-factor theory* that in avoidance learning both factors, classical and operant conditioning, occur.

For Mowrer, fear can be seen as a response to a stimulus. Avoiding fear-eliciting stimuli reduces fear (negative reinforcement) and therefore reinforces the avoidance of fear. In other words: reduction of fear is a reinforcer for the avoidance response. Consequently, in a person showing avoidance behaviour a self-catalysing process is initiated: a cycling of avoidance behaviour and reduction of fear. For instance, a neutral stimulus (spider) after being paired with a traumatic event (loud noise) could become associated with an anxiety state (classical conditioning). Subsequently avoiding the stimulus reduces the anxiety state and reinforces the fear-spider association (operant conditioning).

Mowrers theory was later criticised for its incomplete explanatory account, for example in connection with missing CRs during avoidance. By now expectancy-based models are an alternative theoretical framework (Lovibond, Saunders, Weidemann & Mitchell, 2008).

Expositiontherapy for patients with anxiety disorders is based on these concepts. After successful exposure therapy the CS will not be followed by the CR (e.g. uncontrollable conditioned fear) any more. Aim of every exposure therapy is extinction of the CR in terms of classical conditioning. As explained above, the aspect of operant conditioning can explain why maladaptive behaviour is maintained.
Many patients with anxiety disorders (e.g. specific phobias) are able to describe a specific conditioning experience, such as being attacked by a dog in childhood as the beginning for a specific phobia of dogs (Hamm, 2006). However some patients cannot recall a specific learning event or did not experience a classical conditioning event as a trigger for their maladaptive anxiety reaction. The answer of learning theorists is that even purely observing an anxiety reaction to a certain stimulus in another person can function as a conditioning event for oneself (observational/vicarious conditioning). However, in this case no associative learning in terms of classical conditioning takes place.

In the studies described later in the experimental section instructed conditioning is applied: participants are informed about the CS-US association before start of the experiment. Cognitive processing of this information is sufficient to arouse anticipatory anxiety at the first presentation of the CS, without prior pairings of CS and US. Over the course of the experiment classical fear conditioning takes place (the participant experiences several CS-US pairings).

1.3 Emotion and Cognition

There are many different definitions of cognition. Cognition can be understood as a collective term describing higher processes of the brain such as memory, reasoning, problem solving, perception or attention and is often meant to be unique to humans (Eysenck, 2006; Pessoa, 2008). After the reorientation of psychological research from behaviouristic to more cognitivistic paradigms ('kognitive Wende') the amount of research concerned with cognition and emotion grew substantially. Does emotion genesis need cognition or not? There is evidence that emotions arise without any cognitive processing. On the other hand, emotions are under the influence of cognition. Individuals are able to cognitively control their emotions (Solomon, 2003; Beck & Clark, 1997). Thinking about "cognition" in the context of emotion genesis means one is dealing with appraisals of certain events. "Cognitive" in this context does not necessarily mean "goal-directed" or "conscious". The cognitive process in focus is the step between occurence of the (emotional) stimulus and the associated reaction (appraisal process). This evaluation of a stimulus/situation can be conscious or non-conscious (Pessoa, 2008).

1.3.1 Cognition influences emotion

The first to even the ground for cognition in emotion research was Magda Arnold (Merten, 2003). A prominent example, that cognitive evaluation has an influence in emotion genesis is the comparison of seeing a bear in a zoo or standing in front of a bear in wildlife. The bear in the zoo is no threat, because it is kept behind a fence. Opposing to that, a bear in wildlife is a threat to life that should be noticed as such by our fight-or-flight system. Consequently, an emotional reaction, as just described, is influenced by the evaluation (or appraisal) of the situation in terms of its relevance (threat) to the organism.
Magda Arnold's theory built on the hypothesis that a person would appraise a situation or event in a certain way that directly influences quality and intensity of the resulting emotion. In addition to this first appraisal, 'evaluative cognitions' are necessary to make assumptions about desirability or undesirability of the situation or event. Appraisal and

evaluative cognitions are prerequisites for emotion-genesis.

This means that cognition can very well influence affective behaviour. In a social situation it might be wrong to simply act out every impulse that comes up. Sometimes it is better to consciously re-appraise a situation and change one's goals in a controlled process.

This effortful appraisal is essential in Lazarus' cognitive-motivational-relational theory. For Lazarus emotions are reactions to the world surrounding us (Merten, 2003). A situation is judged according to its direct consequences for the individual. If the situation brings the individual closer to a positive goal, the emotion will be positive and vice versa. For Lazarus an emotion can only arise after detailed evaluation of the situation. He divided this cognitive appraisal process into three subforms:

1. Primary appraisal: a stimulus or situation is evaluated as pleasant, unpleasant or irrelevant
2. Secondary appraisal: the individual evaluates if sufficient coping resources are available
3. Re-appraisal: the relation between situation and coping potential is monitored and adjusted if necessary

Within this appraisal process Lazarus especially pointed out the importance of coping mechanisms for the individual[1]. The individual reaction to stressful situations depends on the differing coping potential a person has. Lazarus stated that a stress reaction is always an emotional reaction (Reisenzein R., 2003).

Lazarus' and Kleinginnas' definition of the consequences of emotions are very similar: four components (cognitive, subjective, connotative/behavioural and physiologic) constitute the nature of emotions.

In disagreement with Lazarus, current opinion is, that emotions are also influenced by the state a person is in (e.g. bodily constitution or alcohol level) and time-invariant traits

[1]To explain the differences in emotional reactions to critical life events, Lazarus introduced the concept of coping. Coping mechanisms are the individually different problem solving strategies a person has. Lazarus and colleagues distinguished between problem focussed (taking action) and emotional (distraction, relaxation, seek help, etc.) coping.

(e.g. neuroticism or extraversion) (Schmidt-Atzert, 1995). Therefore, the most important criticism on the cognitive-motivational-relational theory is that emotions are not just the result of evaluation of the external world, like Lazarus proposes, but also are influenced by other variables.

Some scientists argue that the described appraisal or cognitive evaluation is not necessary in emotion-genesis. For instance, the "mere exposure effect[2]" shows that participants can develop a preference (a positive emotional valuation) for a subliminally presented stimulus (Eysenck, 2006). One could conclude that emotion does not necessarily need conscious appraisal. Still, as cognitive evaluations can take place unconsciously emotion genesis can be influenced by cognition in different (also unconscious) ways.

1.3.2 Emotion influences cognition

Emotions have an informational and motivational function for the individual (Frijda, 1994). Emotions lead to certain action tendencies that influence future behavior or future aims a person has. Also, if we react emotionally to a stimulus, this is information that the individual will process in addition to other information about the stimulus. For example, in a well-known study by Solarz (1960) participants had to push or pull a lever. Just a few milliseconds before the instruction to push or pull was given, the scientists presented a positive or negative adjective. The reaction time was lowest in the combination "pull" and "positive adjective". This shows that emotional information can influence behaviour, in this case in an automated way, without conscious appraisal.

In many cases emotions have a strong impact on cognition. Supporting evidence for the influence of emotion on cognition arises from numerous behavioural studies. A reaction time study presenting IAPS pictures (International Affective Picture System (Lang, Oehman & Vaitl, 1988)) showed that highly arousing pictures lead to shorter reaction times in a recollection task than less arousing pictures (Bradley, Greenwald, Petry & Lang, 1992). This effect could be observed immediatly after the first presentation of the pictures and at

[2]The effect that individuals ascribe a positive value to repeatedly presented stimuli, simply because they are familiar with it.

1-year follow-up. The results suggest that emotional arousal influences cognition in form of memory performance. Furthermore, attention processes like visual search for target stimuli are influenced by emotion. It could be shown that threatening schematic faces were detected quicker than friendly or neutral faces among the distractor cues in a visual search task (Öhman, Lundqvist & Esteves, 2001). Also, emotional information can interfere with cognitive performance as shown in studies employing high and low working memory load tasks and emotional cues or distractors (Mathews & MacLeod, 2002).
The integration of emotion and cognition can also be found on a neural level. This will be discussed later in this chapter.

1.3.3 Theory of cognitive reappraisal

As stated above, cognitive processes can influence the emotional reaction. Cognitive emotion regulation is applied with the goal to reduce, keep or enhance negative or positive emotions, although mostly the attenuation of negative emotions is discussed in the literature. In this work I will also concentrate on the downregulation of negative emotions.
The strategies individuals use for emotion regulation can be subdivided into three classes (Gross, 2002):

1. action-oriented strategies (attempts to change emotionally relevant properties of the environment, antecedent-focussed)

2. cognitive strategies (alter cognitive processing of stimulus or situation, antecedent-focussed)

3. response-focussed strategies (modulating the emotional response itself)

In his *process model of emotion generation* Gross describes how antecedent- and response-focussed emotion regulation strategies take place in different phases of the emotion regulation process and therefore differ in their regulatory impact. He implements "timing" of emotion regulation as an important factor deciding about the consequences of emotion regulation (Gross, 1998). According to Gross' model, antecedent-focussed strategies

can alter emotional outcome during the first phases in the emotion generation process. Possible emotion modulations are: situation selection, situation modification, attentional deployment and cognitive change. Response-focussed modulation can take place during the last phase in emotion generation: during the experiential, behavioural or physiological response.

Reappraisal is a type of antecedent-focussed emotion regulation. It employs a cognitive process of reinterpreting a given situation or stimulus in a way that changes its emotional meaning. Usually the intensity of stimuli or situations that elicit negative emotions are reinterpreted to be less negative. Following Gross, successful reappraisal should lead to a reduction of experiential, behavioural and physiological responses as it steps in early, before the emotional response already started. Expessive suppression is a well-studied example for a response-focussed emotion regulation technique. The aim of this technique is to suppress the overt behavioural expression during the emotional experience, for example inhibit a facial expression during the feeling of disgust. Suppression is applied while the emotional response to a stimulus is already elicited. It aims at inhibiting ongoing emotion-expressive behaviour (Gross, 2002).

Studies often contrast reappraisal and expressive suppression to gain deeper insight into the processes underlying cognitive emotion regulation. Both strategies lead to a change in the emotional response through different ways. Gross and colleagues contributed a huge amount of research in this field. In earlier experiments they found that suppression leads to a decrease of the outward expression of disgust while watching disgust-arousing films. However sympathetic arousal accompanying the feeling of disgust was not attenuated (Gross & Levenson, 1993). Later this result was supplemented by the finding that reappraisal as well reduces the overt expression of negative emotions, but additionally reduces the experience of negative emotions with all its consequences for the individual (Gross, 1998).

Following Gross (2003), individuals can be divided in habitual "reappraisers" and "suppressors". In the emotion regulation literature more frequent use of reappraisal is associated with greater well-being, closer relationship to friends, fewer depressive symptoms, less negative affect and reduced physiological arousal. On the opposite, expressive sup-

pression is found to be connected to less positive affect, more depressive symptoms and greater social anxiety and increased activation in the cardiovascular system (Kashdan & Steger, 2006; Gross, 2003, 1998; Moore, Zoellner & Mollenholt, 2008; Davidson, 1993).

Reappraisal activity: an early and a late phase

Our group's on-going studies point to a critical role of timing within the reappraisal process. The theoretical framework called *implementation-maintenance model* (IMMO) established on the basis of a meta-analysis of reappraisal studies (Kalisch, 2009) could recently be confirmed in an fMRI experiment (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011).

The model also successfully integrates the at first sight contradictory neuroimaging results (Kalisch, 2009). Comparable to Gross' model it focusses on the 'timing' factor in the emotion regulation process. The IMMO concept accounts for the fact that cognitive reappraisal is often operationalised in a way that does not control for the temporal microstructure of the regulation process. Most neuroimaging reappraisal studies measure reappraisal-related brain activation during a set phase of several seconds after the cue to reappraise occurred (Kalisch, 2009) implying that reappraisal-related activity follows a 'switch-on' 'switch-off' pattern. However, it is unlikely that a process as complex as reappraisal can be modeled optimally with such a function. The criticism of Kalisch (2009) is that this simplification does not account for the dynamic and recurrent nature of the reappraisal process. In accordance with this hypothesis our group could show that reappraisal-related activation patterns support the existence of a distinguishable early and a late phase. It seems that a temporal shift of reappraisal activity from the left to the right hemisphere and from posterior to anterior (all in the lateral frontal cortex) takes place over the course of a reappraisal-trial. This shift might reflect two different phases in the reappraisal process: an early phase, which is used for memory retrieval and implementation of the reappraisal technique and a late phase that is needed to keep up the reappraisal processes (maintenance). Taking this into consideration, the supposedly heterogeneous study results can be explained based on the IMMO concept: depending on how reappraisal was operationalised, different temporal aspects of the reappraisal pro-

cess bring about diverting neural correlates in the different studies. Studies in which reappraisal trials are short mainly step into early implementation processes and therefore mainly activate left posterior frontal sites. By contrast studies with long reappriasal trials also activate maintenance processes and thus, additionally, right-anterior sites.

A first empirical verification of IMMO was recently published by our group (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011). The study used an anticipatory anxiety paradigm and emotion regulation through reappraisal. As hypothesized by IMMO early activation was found in more posterior left frontal parts of the brain and later activation was found frontally more right anterior. Still further evidence will be needed to verify and maybe generalize the IMMO concept.

To sum up, reappraisal is a cognitive complex process that is applied to reduce the emotional intensity of a stimulus or situation. Following the *process model of emotion regulation* reappraisal happens early in the emotion generation process. It changes the emotional response in a way that is positive for the individual. It is difficult to conclude about the underlying neural mechanisms because of heterogenic study results, but one could summarise that reappraisal-related brain activation is mostly found in the frontal cortex, most consistently in the lateral frontal, prefrontal and adjacent anterior cingulate cortex. The *implementation-maintenance model of reappraisal* identified a temporal relationship between neural activation site and different stages of the reappraisal-process (Kalisch, 2009).

The studies described later in this thesis are designed with respect to these results. The time-length of the reappraisal-phases is long enough to include all possible early and late reappraisal-related neural activation.

1.3.4 Emotion regulation as a cognitive placebo effect

Placebos are "substances, given in the guise of active medication, but which in fact have no pharmacological effect on the condition being treated" (Kirsch, 1985, p. 238). Placebo analgesia is the effect that individuals feel less pain when treated with a supposedly pain-

diminishing drug or cream. For the success of the placebo treatment the participants' positive outcome expectations are important. Some researchers strengthen the participants' belief in the placebo drug or cream in administering a trial with objectively less pain prior to the experiment with the placebo on board(Eippert, Bingel, Schoell, Yacubian, Klinger, Lorenz & Büchel, 2009; Price, Milling, Kirsch, Duff, Montgomery & Nicholls, 1999).

Humans use a range of cognitive techniques to control their emotions (Gross, 2002). So far, regulation studies have not addressed the issue that the employment of a regulation strategy might be associated with the expectation of a beneficial outcome. For example, it is unlikely that a patient or anyone under emotional distress would make extended regulation efforts in the absence of success expectations and, in the laboratory, participants most likely come to believe that a emotion-regulation strategy tought by the experimenter will actually influence their emotions in the desired direction.

It is possible that cognitive regulation success at least partly represents a placebo effect driven by expectancy. This question is relevant as it has repeatedly been shown that expectancy-effects can have a strong influence on emotional states, wether in the context of experimental placebo manipulations (Petrovic, Dietrich, Fransson, Andersson, Carlsson & Ingvar, 2005; Zhang, Qin, Guo & Luo, 2011; Enck, Benedetti & Schedlowski, 2008) or in 'real-life' situations like psychotherapy (Dew & Bickman, 2005; Furmark, Appel, Henningsson, Ahs, Faria, Linnman, Pissiota, Frans, Bani, Bettica, Pich, Jacobsson, Wahlstedt, Oreland, Långström, Eriksson & Fredrikson, 2008) or anti-depressant pharmacotherapy (Kirsch, 2009).

Several functional imaging studies describe brain activation and deactivation related to placebo analgesia: painful stimulation in connection with placebo analgesia leads to brain deactivation in the amygdala, cingulate cortex, insula and thalamus and to activation in the prefrontal cortex (rostral cingulated, dorsal and ventral LPFC) (Lieberman, Jarcho, Berman, Naliboff, Suyenobu, Mandelkern & Mayer, 2004; Petrovic, Kalso, Petersson & Ingvar, 2002; Wager, Rilling, Smith, Sokolik, Casey, Davidson, Kosslyn, Rose & Cohen, 2004). The regions activated and deactivated during reappraisal of painful stimulation are very similar to those just mentioned for placebo analgesia (Kalisch, 2009). The con-

cepts of placebo analgesia and reappraisal of aversive stimuli share the cognitive aspect of positive outcome expectation. Ochsner interprets that (re-)appraisal is the cognitive component behind the placebo effect (Ochsner & Gross, 2005).

1.3.5 Distraction and cognitive reappraisal

Distraction from aversive stimuli, as in using selective attention to limit the processing of emotional stimuli, is a successful form of emotion regulation (Delgado, Nearing, Ledoux & Phelps, 2008; McRae, Hughes, Chopra, Gabrieli, Gross & Ochsner, 2010). For example distraction from pain through performing cognitively demanding tasks lowers self-reported aversiveness and pain-intensity (Wiech, Seymour, Kalisch, Stephan, Koltzenburg, Driver & Dolan, 2005; Terkelsen, Andersen, Mølgaard, Hansen & Jensen, 2004). The question if cognitive demand alone might make an important contribution to emotion regulation success was asked before (Van Dillen & Koole, 2007; Urry, van Reekum, Johnstone & Davidson, 2009). One could imagine that the different components of an imaging reappraisal experiment (e.g. scanner noise and narrowness, keeping task instructions in mind, concentrating on reappraisal technique) have high cognitive demand and lead to distraction from the threatening stimuli. As a consequence, rather than because of reappraisal, anxiety levels would decline because the participant was busy with situational and task requirements.

An imaging experiment directly compared reduction of negative affect through reappraisal and distraction (McRae, Hughes, Chopra, Gabrieli, Gross & Ochsner, 2010). They found that reappraisal reduced negative affect more than distraction. In addition, reappraisal and distraction activate a shared neural network as well as distinct brain areas. The authors conclude that although reappraisal and distraction both reduce negative affect, reappraisal seems to be a more effective technique.

Another way to distract oneself from the emotional content of a visually presented stimulus is to simply look away. Van Reekum and colleagues designed an imaging reappraisal study to answer the question of how participants visually scan the presented IAPS pic-

tures during reappraisal (van Reekum, Johnstone, Urry, Thurow, Schaefer, Alexander & Davidson, 2007). Participants where asked to control (increase, decrease, attend) their emotional response to neutral and negative pictures. The results suggest that participants spent less time spent looking at the aversive pictures and fixating emotionally relevant aspects of the pictures when asked to decrease their affecive response (compared to attend and increase). As a main proportion of reappraisal studies use aversive IAPS pictures to induce negative emotions one has to ask the question to what an extent these studies might be confounded by changes in gaze fixation. Bebko and colleagues could show in a very similar experimental setting that the amount of time, looking away from the emotionally relevant aspects of negative IAPS pictures differes for different emotion regulation techniques (Bebko, Franconeri, Ochsner & Chiao, 2011).

In summary one can conclude that reappraisal studies have to be designed with special focus on choosing the right experimental procedure to disentangle reappraisal effects from distraction or cognitive demand and on choosing the right method of anxiety induction to avoid effects of gaze fixation and attentional deployment.

1.4 Neuroanatomy of anxiety and emotion regulation

In neurobiological theories the anatomical and physiological bases of anxiety in health and disease are highlighted. Neurotransmitter systems (dopamine, serotonin, noradrenalin and neuropeptide S) evidently play a role in fear processing in animals (Sullivan, Coplan, Kent & Gorman, 1999; Pape, Jüngling, Seidenbecher, Lesting & Reinscheid, 2010; Reinscheid, Xu & Civelli, 2005) and humans (Raczka, Gartmann, Mechias, Reif, Büchel, Deckert & Kalisch, 2010, 2012; Lonsdorf, Weike, Nikamo, Schalling, Hamm & Ohman, 2009; Furmark, Appel, Henningsson, Ahs, Faria, Linnman, Pissiota, Frans, Bani, Bettica, Pich, Jacobsson, Wahlstedt, Oreland, Långström, Eriksson & Fredrikson, 2008; Baldwin, Anderson, Nutt, Bandelow, Bond, Davidson, den Boer, Fineberg, Knapp, Scott, Wittchen & for Psychopharmacology, 2005; Fadok, Dickerson & Palmiter, 2009), but will not be described in more detail. Because of higher relevance, I will concentrate on human data although a large body of evidence comes from animal studies. Various cortical and subcortical regions involved in emotion processing can be identified through (functional) neuroimaging. Selected regions connected to fear-related processing and emotion regulation will be discussed below.

1.4.1 Amygdala and insula

The amygdala is involved in learning, expression and extinction of fear. Evidence comes for example from animal work (Milad & Quirk, 2012; Helmstetter, 1992; Fanselow, 1994), lesion studies (Bechara, Tranel, Damasio, Adolphs, Rockland & Damasio, 1995; LaBar & LeDoux, 1996) and studies with healthy participants (Buechel, Morris, Dolan & Friston, 1998; Hariri, Bookheimer & Mazziotta, 2000; Knight, Cheng, Smith & Stein, 2004). Joseph LeDoux is one of the best known scientists studying emotional processing, especially fear, in rodents (LeDoux, 1998). He proposed to distinguish between a quick, emotional processing of fear-relevant stimuli via the amygdala and a more elaborate, slower, cognitive processing of the same stimuli by cortical structures. Both neural pathways play a role in (human) fear conditioning.

The human amygdala has strong interconnections with the insular cortex (Paxinos, 2003). A meta-analysis of neuroimaging studies of patients with anxiety disorders found the amygdala and the insula to be part of an anxiety-network (Etkin & Wager, 2007). They conclude that these structures are part of a complex system of hyper- and hypoactivation in the diseased neural anxiety-circuits as well as in normal fear. Intense states of fear in health and disease correlate with hyperactivation of the insula and amygdala and likely reflect normal and excessive generation of fear (Etkin & Wager, 2007).

In a meta-analysis of fear conditioning neuroimaging studies the bilateral anterior insula was found to be consistently activated (Mechias, Etkin & Kalisch, 2010). Additionally it has also been suggested that the anterior insula helps integrate visceral and other affective signals with more cognitive processing outcomes, based on its close functional association with limbic and medial prefrontal regions in a meta-analysis of emotional processing studies (Kober, Barrett, Joseph, Bliss-Moreau, Lindquist & Wager, 2008).

Still, the role of the amygdala in the generation and experience of emotion is not entirely clear. As described above the amygdala is seen as a core region of fear processing. However just about half the fear studies find neural activation in the amygdala as detected by meta-analysis (Murphy, Nimmo-Smith & Lawrence, 2003; Phan, Wager, Taylor & Liberzon, 2002; Mechias, Etkin & Kalisch, 2010).

Next to the processing of fear, the amygdala might as well have a role in overall affect processing (both positive and negative) and detection of significance of affective stimuli (i.e., their predictive value) (reviewed in Kober, Barrett, Joseph, Bliss-Moreau, Lindquist and Wager, 2008). The diversity of findings might among others originate from the functional and anatomical complexity of the amygdala. Costafreda et al. included PET and fMRI studies in their large meta-analysis of amygdala activation (Costafreda, Brammer, David & Fu, 2008). Again amygdala activity was seen in connection with positive and negative emotions. Additionally, attentional employment (passive $>$ active task instructions) and aversive learning lead to higher probability of amygdala activation.

1.4.2 The prefrontal cortex

Another core-structure of fear and anxiety processing is the prefontal cortex (PFC). The PFC is involved in effortful, working-memory demanding, higher cognitive functions (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005). It is proposed, that the PFC has a role in the regulation of emotions, including the cognitive regulation of fear and anxiety (Hariri, Bookheimer & Mazziotta, 2000; Taylor, Phan, Decker & Liberzon, 2003). In this section I will first discuss the role of the PFC in (conscious) appraisal, then its role in regulation with a main focus on reappraisal and finally briefly describe frontal-limbic connectivity.

Because of the formerly identified importance of the PFC and additional evidence from our research groups own former studies (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005; Kalisch, Wiech, Critchley & Dolan, 2006a; Kalisch, Wiech, Herrmann & Dolan, 2006b), we conducted a meta-analysis of anticipatory anxiety studies to identify a possible candidate area for conscious threat appraisal in the brain (Mechias, Etkin & Kalisch, 2010).

In the meta-analysis, we systematically reviewed the existing literature dealing with instructed and uninstructed fear conditioning studies. This approach was used to disentangle the neuroanatomy of controlled cognitive versus uncontrolled automatic processes in anxiety regulation (Mechias, Etkin & Kalisch, 2010): in classical fear conditioning, the CS comes to be evaluated as threatening due to its association with an aversive UCS, and elicits fear. In a subtype of fear conditioning paradigms, called instructed fear or anticipatory anxiety, participants are made aware of the CS-UCS association prior to actually experiencing it. Initial fear elicitation during this type of conditioning results from the negative evaluation of the CS as a consequence of CS-UCS contingency awareness. Prior reports had suggested that this conscious appraisal process is mediated by a variety of brain regions, including rostral dmPFC/dorsal (d) ACC, lateral PFC, posterior cingulate, hippocampus/parahippocampus, and nucleus accumbens (reviewed in Mechias, Etkin and Kalisch, 2010), but there is little overlap between results. In our meta-analysis we found

consistent activation in instructed-fear studies in the rostral dmPFC but not in the other candidate areas.

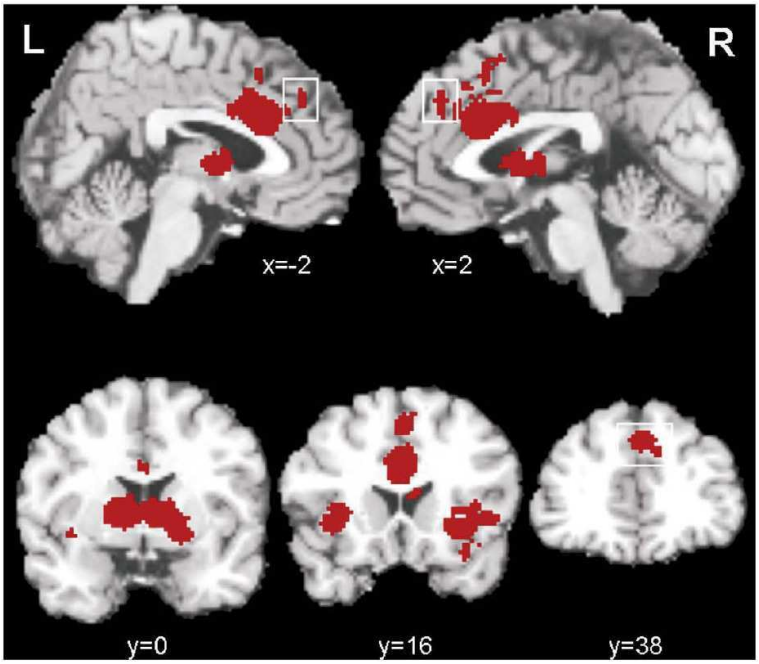

Figure 1: Meta-analysis of instructed fear conditioning studies. Instructed fear paradigms consistently activated, among other areas, mid and rostral parts of the bilateral dmPFC/dACC (all panels), bilateral caudate, putamen and right pallidum (bottom row, left panel), and bilateral anterior insula (bottom row, middle panel). The rectangle demarcates the rostral dmPFC area earlier identified as a candidate region for conscious appraisal. Voxels significant at False Discovery Rate (FDR) $q<0.01$ are superimposed on a canonical structural brain image. X,Y-Coordinates: Montreal Neurological Institute (MNI). Source: Mechias, Etkin and Kalisch, 2010.

The results allow to maintain the theory that the rostral dmPFC is involved in conscious threat appraisal. We also conducted a meta-analysis of uninstructed (classical) fear conditioning studies in which we found activation in more posterior parts of the dmPFC/dACC that overlapped with some of the instructed fear activations. The data suggest that mid regions of the dmPFC/dACC are part of a "core" fear network that is activated irrespective of how fear was learned. [3]

The hypothesized involvement of the rostral dmPFC in appraisal processes is further supported by a meta-analysis summarising evidence from neuroimaging studies of explicit

[3]For a detailed description of the meta-analysis see Appendix B.

emotional evaluation (Lee & Siegle, 2009). They found the rostral dmPFC to be part of a common neural network activated by explicit evaluation of (positive and negative) emotions. In particular selected studies applying online tasks of emotional valence and intensity identification termed 'evaluation of one's own emotions' resulted in spread activation in the dmPFC extending to the rostral ACC. The authors interpret that the rostral dmPFC might have an integrating role in the emotion evaluation process connecting emotional to more cognitive aspects of the evaluation process.

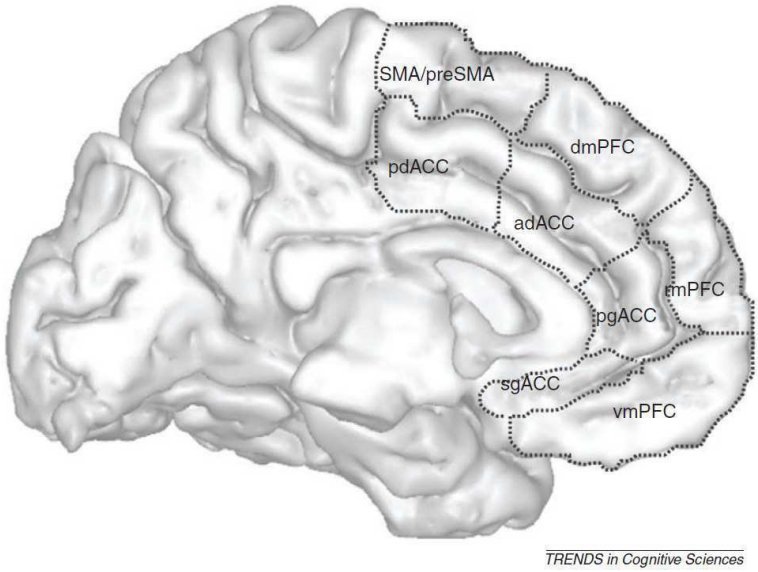

Figure 2: Parcellation of anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) subregions. Abbreviations: sg, subgenual; pg, pregenual; vm, ventromedial; rm, rostromedial; dm, dorsomedial; ad, anterior dorsal; pd, posterior dorsal. Source: Etkin, Egner and Kalisch, 2001.

The PFC further plays a major role in emotion *regulation*. It is proposed in the literature that a distributed cortical network including *regulating* PFC regions (medial, inferior, dorsolateral and ventral PFC) and *regulated* limbic[4] regions (amygdala and insula) underlies the process of cognitive downregulation of negative emotions (Goldin, McRae, Ramel & Gross, 2008; Phan, Fitzgerald, Nathan, Moore, Uhde & Tancer, 2005; Ochsner, Bunge, Gross & Gabrieli, 2002; Ochsner, Ray, Cooper, Robertson, Chopra, Gabrieli &

[4]There is an ongoing debate if the term "limbic" should be used more carefully in neuroscientific discussions. It is often used in connection with the functional neuroanatomy of emotion. As there is neither a common definition of the limbic system nor of emotion the term 'limbic' has limited descriptive power (reviewed in Pessoa, 2008).

Gross, 2004; Beauregard, Lévesque & Bourgouin, 2001; Banks, Eddy, Angstadt, Nathan & Phan, 2007).

Etkin et al. reviewed human and animal literature and found evidence for a separable role of the anterior cingulate cortex (ACC) and medial PFC (mPFC) in appraisal/expression on the one side and regulation of fear and anxiety on the other side (Etkin, Egner & Kalisch, 2011). It seems that particularly the ventral and rostral parts of the ACC/mPFC are involved in the regulation of fear. The fear-regulation process is discussed in the light of extinction of conditioned fear as well as emotion regulation through reappraisal. Emotion regulation through reappraisal seems to involve the dorsal ACC/mPCF region directly, while the ventral ACC and mPFC might have a mediating role between dorsomedial and lateral PFC and the amygdala.

Results from neuroimaging studies which investigate the neural correlates of cognitive reappraisal are heterogeneous. Ochsner and Gross (2008) reviewed functional imaging reappraisal studies and proposed that the heterogeneity of the results stems from heterogeneous operationalisations. Although all studies included in this review employ cognitive reappraisal different subforms of reappraisal are used in the different studies. The different reappraisal techniques are all applied in affect regulation, but might rely on different neural mechanisms. Taking everything into consideration, they state that the lateral prefrontal/dorsal anterior cingulate cortices are commonly activated by cognitive reappraisal.

It is possible that the integration of emotion (in particular fear) and cognition is mediated by frontal-amygdalar interconnections (Ochsner & Gross, 2005; Hariri, Mattay, Tessitore, Fera & Weinberger, 2003; Lee & Siegle, 2009). Anatomically, among all PFC regions the orbitofrontal PFC shows the highest amount of direct connections to the amygdala. Other PFC regions (ventral, dorsal) can interact with the amygdala via projections to the orbital PFC, thalamic and striatal circuits (Hariri, Mattay, Tessitore, Fera & Weinberger, 2003). Hariri states that especially the interplay between lateral PFC regions and the amygdala (possibly mediated through orbital PFC regions) enables cognitive emotion regulation. Prefrontal-amygdala projections connect prefrontal areas involved in feed-forward systems to inhibitory interneurons in the amygdala (Carmichael & Price, 1995; McDonald,

1991). This points to prefrontal control of the amygdala in a top-down fashion.
Banks et al. (2007) analysed frontal-amygdala connectivity in an emotion regulation task (Banks, Eddy, Angstadt, Nathan & Phan, 2007). While functional imaging was performed, participants had to reappraise or simply observe aversive pictures from the International Affective Picture System (IAPS) (Lang, Oehman & Vaitl, 1988). A psychophysiological interaction analysis[5] revealed that the strength of coupling between the amygdala and orbital frontal cortex and dorsomedial (dm)PFC was a predictor for reappraisal success. The stronger the coactivation between amygdala and orbital frontal cortex and dmPFC was during reappraisal, the more successfull participants could reduce their self-reported negative affect. The authors stress that the findings do not inform about the directionallity of the influence (amygdala - frontal areas). Still, the results further support a functional interplay between the amygdala and frontal areas during regulation of negative affect.

Perspective

Taking information from both learning and neurobiological theories together, one might be able to explain interindividual differences in emotion regulation in health and disease. Unimpaired emotion regulation seems to be a requirement for psychological well-being. It is not fully understood, why seemingly same events/stimuli lead to excessive fear-reactions that might generalize to uncontrollable feelings of anxiety in one person but not the other. Individual differences in learning history, regulation style as well as genetically differing vulnerabilities and neuroanatomical variations might be one explanation for the observed variance. Still more research is needed to gain deeper insight into these processes and how they interact.

[5]A psychophysiological interaction (PPI) analysis can be performed on functional imaging data to understand the coupling of different brain regions. The discovered functional connectivity between certain defined brain regions is task-dependent. Importantly the PPI analysis does not allow to conclude about the directionallity of the effect. It just informs about an increase or decrease of regional coactivation during the performed tasks.

1.5 Hypotheses

The studies presented in this thesis investigate the influence of cognitive effort and expectancy-effects on emotion regulation through cognitive reappraisal as well as the neural correlates of cognitive reappraisal.

The aim is to find and establish a reappraisal technique that helps to successfully down-regulate anticipatory anxiety and, in a second step, to gain deeper insight into (neural) mechanisms underlying this anxiolysis.

In *Study I* a potentially anxiolytic reappraisal technique will be established in an anticipatory anxiety paradigm. We expect to see a down-regulation of anxiety in the reappraisal condition compared to a no-regulation condition. Successful reappraisal should lower subjectively felt levels of anxiety and objective physiological measures (skin conductance).

Studies II and III compare the established Reappraisal technique with a new No-reappraisal strategy that also involves the cognitive operations of implementing and maintaining an appraisal strategy that is howerver not thought to be anxiolytic. Before the experiment participants are trained intensly to apply the techniques until the (low) cognitive effort needed for strategy implementation and maintenance is comparable between the Reappraisal and No-reappraisal techniques. If cognitive effort leads to attenuation of anxiety levels generally in reappraisal (see chapter 1.3.5) we should observe much less reduction of anxiety in Reappraisal compared to No-reappraisal as Reappraisal is now compared to a control condition (No-reappraisal) that is matched for cognitive effort. Again subjective (ratings) and objective (skin conductance) measures are taken.

In*Study IV* participants are treated similarly as in *Studies II and III* apart from the training aspect. Training of the Reappraisal and No-reappraisal technique will be moderate instead of intense before the experiment, leading to a higher cognitive demand of technique application during the experiment. The influence of this higher cognitive demand on the relatively anxiolytic effect of the Reappraisal technique will be investigated.

Study V asks the question wether expectancy-effects have an influence on anxiolysis in the already established paradigm. Two groups of participants (Normal and an Inverse group) learn and apply the formerly used Reappraisal and No-reappraisal techniques to regulate

emotions in an anticipatory anxiety paradigm. However, the Inverse group is instructed in a modified way such that they expect the No-reappraisal, not the Reappraisal, technique to be anxiolytic. In case expetancy-effects have an influence on reappraisal success this should cancel out or maybe even invert the anxiolytic effect of Reappraisal relative to No-reappriasal in the Inverse group.

Study VI adds functional magnetic resonance imaging as a dependant variable. *Study VI* investigates the neural architecture of cognitive reappraisal with special focus on the (late) maintanance processes in reappraisal as described in IMMO (see above). We expect to see late maintenance activation in the right anterior lateral prefrontal cortex.

2 Introduction to the methods

In the following section, the experimental methods, which were used to perform the different studies, will be described. As the studies described in this thesis are methodologically closely matched, the methods commonly used in all studies (like pain stimulation or skin conductance recording) are described here. More study-specific details will be given in the experimental section.

2.0.1 Recruitment of participants

Participants were recruited a) from the institute's internal participant-database b) from a genotyped and phenotyped participant pool built up during the years of my doctoral studies and c) by advertisement in an internet-based job-market.
Interested participants were contacted either by telephone or by e-mail and informed about the possibility to take part in the study. If they agreed to take part, they were sent the volunteer sheet and consent form (Appendix C) and details about the time and place of testing.
Participants were included if they were male, between 18 and 50 years old, healthy and native German speakers.
All participants were offered 30 Euros for their attendance or a proportion of the money, if they did not complete the whole experimental procedure. The studies were approved by the ethics committee of the Hamburg Medical Board and conformed to all relevant regulatory standards.
Overall exclusion criteria were: pre-existing psychiatric or neurologic illnesses, elevated trait anxiety (as measured by State-Trait Anxiety Inventory, cut-off > 44 (Spielberger, Gorsuch & Lushene, 1970)) or non-responsive skin conductance. If the participants corresponded to these criteria, was assessed before the experiment started.

2.0.2 Experimental procedure

Participants were informed about the study details and gave written informed consent. Then they filled in several questionnaire data: trait social desirability, trait anxiety and descriptive information (SDS, STAI, Allgemeiner Fragebogen: all see Appendix C). Afterwards, they were trained to use the Reappraisal and No-reappraisal technique or how to apply the No-regulation (control) technique.
Anxiety was induced using an instructed fear paradigm (also known as "anticipatory anxiety") which consisted in forewarning participants that they might receive a painful electric stimulus at a probability of 25 % at any time during a approximately 16-second trial (Threat condition). During a control condition (No-threat), participants were told they would not be stimulated during the trial. In a fully balanced, 2x2 factorial design, participants either employed reappraisal (Reappraisal condition) or not (No-reappraisal or No-regulation condition).

Anxiety induction
Participants were forewarned that in Threat trials they might receive painful electrical stimulation. Further, in No-threat trials they would never be stimulated. 28.6% of the Threat trials were reinforced with electric shock (a triple pain stimulus (pulse intervals: 80 milliseconds) which occurred randomly within a time window of 3 to 10 seconds after offset of the auditory instruction) and were excluded from further analysis.

No-regulation technique (Study I)
For the No-regulation condition participants were asekd to simply let their feelings and thoughts arise naturally without changing them. This No-regulation technique was used only in *Study I.*

Reappraisal technique
The reappraisal technique used by us is based on distancing/detachment. For the Reap-

praisal condition, participants were given a short verbal self-statement and an associated visual imagery that both expressed a distanced, detached observer perspective from which participants could see all on-going external and internal events (the stimuli, the situation, their own thoughts or affective reactions...) as not being relevant to them and not directly affecting them. Participants were explicitly given this strategy to allow them to stay calm throughout trials. Detachment-reappraisal has previously been shown to successfully attenuate anticipatory anxiety (Houston & Holmes, 1974; Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005; Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011), depressed mood (Kross & Ayduk, 2008) and affective responding to negative picture material (Ochsner, Ray, Cooper, Robertson, Chopra, Gabrieli & Gross, 2004; Dillon, Ritchey, Johnson & LaBar, 2007; Erk, Mikschl, Stier, Ciaramidaro, Gapp, Weber & Walter, 2010).

In detail, participants were told to imagine a cloud in the sky that would symbolize the emotional aspects of the situation, including all potential threats and accompanying reactions or feelings of tension or anxiety. For the reappraisal condition, they were asked to imagine themselves far away from this cloud, for example standing on a hill and observing the cloud from a distance (but not to look away). In addition to this mental image, they were given a self-statement that expressed the detached perspective: "Die Wolke ist weit weg am Horizont. Ich betrachte sie aus der Ferne." ("The cloud is far out on the horizon. I observe it from a distance.").

No-reappraisal technique (Studies II-VI)

For the No-reappraisal condition, participants were also given a self-statement and imagery whose contents were however chosen to promote immersion into the situation. We considered this to best model a normal and natural appraisal approach to most situations, including threatening ones, as people would usually view events in their closer environment as self-relevant and experience them as directly affecting them. Immersion should have no active anxiolytic component and has also been used as a reference baseline for reappraisal effects on depressed mood (Kross & Ayduk, 2008).

Participants were told to imagine a cloud in the sky that would symbolise the emotional

aspects of the situation, just as in the reappraisal technique. However, participants now had to imagine the cloud closely surrounding them. The corresponding self-statement was adapted ("Ich befinde mich in der Wolke. Sie umgibt mich von allen Seiten." "I am in the cloud. It surrounds me from all sides").
This was supposed to prevent participants from distancing themselves from their feelings and model a more natural, spontaneous appraisal of immersion, where one assumes that a situation is self-relevant and affects one directly. It was hoped that the cognitive effort required for imagery and rehearsal of the verbal self-statement would match the reappraisal technique.

Moderate and intense training

Immediately before the experiment, participants were trained in using the reappraisal technique by first having to read aloud the verbal self-statement then having to freely recall the statement 5 times and finally providing verbal effort ratings (1=not effortful at all to 10=extremely effortful). If a participant made a mistake in recalling the statements, the procedure was repeated until the participant was perfectly able to repeat the statements. In *Studies I, IV, V* and *VI* participants were trained moderately, meaning they had to read the verbal self-statement aloud 15 times before free recall. However in *Studies II* and *III* participants were trained more intensely and had to read out aloud 30 times before free recall. The aim of longer training was to prevent skill learning in strategy rehearsal from taking place during the experiment and thereby to keep effort levels as constant (and low) as possible.

After having learned the self-statement successfully, participants had to spend one minute eyes closed, performing visual imagery, followed by a free description of the imagined scene and ratings of effort (1=not effortful to 10=very effortful), intensity (vividness) of the images (1=not intense to 10=very intense), and emotional valence (1=very negative to 10=very positive). If the imagined scene did not correspond to the respective strategy, if a participant had difficulties producing vivid images (effort rating > 7, intensity rating

< 4) or if a participant attached too much emotional valence to an image (valence rating < 3 or > 8), the procedure was repeated until all criteria were fulfilled.
Participants were supposed to bring up self-statement and imagery at the beginning of an experimental trial when cued, and then to mentally rehearse them throughout. In both conditions, participants were eyes closed.

Two-way analyses of variance (ANOVAs) with the factors Threat (No-threat and Threat) and Regulation (No-regulation and Regulation) were calculated to analyse the subjective ratings and skin conductance data collected during the experiment. The level of significance was set at 5 percent.

Choosing the right reappraisal technique and comparison condition
In all studies presented here (exept *Study I*) the control condition was an "as close as possible" match of Reappraisal.
Critically, the application of a self-statement and a visual imagery in both the Reappraisal and the comparison condition (No-reappraisal) was intended to equate Reappraisal and No-reappraisal for cognitive aspects like implementation and working memory demands and thus to let them differ only in the core component of reappraisal that is, in the semantic re-interpretation of the situation.

The technique instructions used by us were comparably specific. Other studies operationalised reappraisal more freely by giving participants a general direction of how to reappraise and giving examples, but letting the participants choose how exactly to reduce emotional intensity on their own during the experiment (Phan, Wager, Taylor & Liberzon, 2004b; Banks, Eddy, Angstadt, Nathan & Phan, 2007; Ochsner, Bunge, Gross & Gabrieli, 2002). However, we reckoned that giving participants exact and detailed detachment and immersion instructions would reduce inter- and intraindividual variance in strategy use and increase the likelihood that participants actually do apply the intended strategies.

2.1 Skin conductance

In skin conductance (SC) measurements two electrodes that are placed (in most cases) at the palm surface of the hand measure electrical conductivity (Fowles, Christie, Edelberg, Grings, Lykken & Venables, 1981). Conductivity fluctuates because perspiration changes. If a higher amount of sweat is produced, the electrical skin resistance is lowered and in turn the skin conductance rises.

Anxiety and skin conductance

Within 1-5 seconds after onset of an arousing (e.g. feared) stimulus a higher amount of sweat is produced leading to measurable higher skin conductance. This reaction is mediated by the sympathetic nervous system and thus skin conductance is an objective index of the sympathetic arousal that accompanies anxiety. A problem with this measure is the big interindividual variance in participants' responsiveness of the SC. A way to solve this problem is to perform z-transformations on the collected SC-data. In addition, as changes in SC are provoked by all kinds of emotional processes (not just anxiety) it can never be ruled out completely that one is measuring responses to several processes and not only the emotional response. Nevertheless, under the controlled conditions of a fear experiment, the SC rises with higher levels of fear and vice versa. In addition, the SC can also rise with higher levels of effort or intense attention to the task the participant has to perform.

2.1.1 Measurement and Analysis of Skin Conductance Data

A CED micro1401 mkII (Cambridge Electronic Design, Cambridge, UK) and a 2500SA (ED) measurement box were used to record and digitize the skin conductance signal at 1000 Hz. All SCR data were analysed using Matlab R2007b (Mathworks Inc., Natick, USA) and SPSS 17.0 software(SPSS, Chicago, Illinois, USA). The skin conductance data were downsampled to 100 Hz. All trials were normalised to the first time point of the trial.

The skin conductance level (SCL) was defined as the mean value of the whole trial. All trial values were z-standardised within participants (Buechel, Morris, Dolan & Friston, 1998) and then averaged for each condition.

2.1.2 Hard- and software

PCs were used to present the auditory and visual stimuli and record and store skin conductance data with Spike2 6.04 software. All instructions were recorded and presented visually on a computer screen and over headphones using Matlab R2007b (Mathworks Inc., Natick, USA) and Cogent2000 (Wellcome Trust Centre for Neuroimaging, England). For painful electric stimulation a custom-made electrode (Clydes Polo Kit Supplies, Bexley, UK) was attached to the upper surface of the participants' right hand. Trains of three electrical pulses of 2 ms duration up to 99.00 mAmp were generated by a Digitimer DS7A electrical stimulator (Digitimer, Welwyn Garden City, UK).

2.2 Subjective ratings

In experimental paradigms dealing with emotion, subjective ratings reflect the experiential component of the experimental manipulation. Objectively same stimuli can be perceived very differently. Subjective ratings are a way to control for these differences, by applying the same *subjective* cut-offs for example for anxiety levels or pain levels. Still, the drawbacks of subjective ratings are e.g. effects of social desirability or expectancy.

Social desirability

As explained above it is important to collect subjective ratings from the participants. The problem with those self-ratings is the susceptibility to effects of social desirability. Social desirability is defined as the tendency of participants to generate a favourable image of themselves in front of others (Johnson & Fendrich, 2002). It is proposed that social desirability is a trait component. This means that individual differences in the urge to appear 'favourable' in the sight of others are intrapersonally time-stable and vary interpersonally. The trait component of social desirability can be measured with the Social Desirability Scale (Crowne & Marlowe, 1960). Individuals scoring high on this instrument are shown to over-report socially desirable information (Carstensen & Cone, 1983; Kozma & Stones, 1987).

As we cannot directly observe the cognitive process of "reappraisal", we have to rely on subjective ratings or indirect measures. In order to have at least minimum insight into the reliability of those self reports we employed the Social Desirability Scale in *Study I to IV*.

2.2.1 Measurement and analysis of subjective ratings

Subjective ratings were analysed using Matlab R2007b (Mathworks Inc., Natick, USA) and SPSS 17.0 software (SPSS, Chicago, Illinois, USA). Self-ratings of anxiety-levels were averaged over all trials within the 4 experimental condition-subgroups.

2.3 The principles of Magnetic Resonance Imaging

2.3.1 The properties of the proton

In MRI the magnetic properties of protons are used to create images of the body inside the MRI scanner.
Protons are positively charged particles that constitute, together with neutrally charged neutrons, the nucleus of any atom. Additionally to being positively charged protons also move around themselves, they spin. Electric charges in motion give rise to a magnetic field. As a consequence protons have a small magnetic field, or a magnetic momentum. Under natural circumstances the orientation of the particles and their magnetic fields are random. The phenomenon of *Antiferromagnetism* can be observed, meaning that the magnetisation of two particles of same charge next to each other is cancelled out, if they are conversely aligned. The same principle can be applied to protons: if the alignments of two protons are opposing, they cancel each others magnetic fields out.
However, if a strong enough external magnetic field is applied, the protons start aligning parallel or anti-parallel to this field and a higher net magnetisation is found. The rise and fall in net magnetisation can be measured and manipulated by controlling the external magnetic field. Atoms of different elements have differing spinning properties due to unpaired (parallel and anti-parallel) neutrons and protons. Since it is the difference in proportion of parallel and anti-parallel alignment we are detecting a net spin is required. Some nuclei have a net magnetization of zero due to opposing orientation of their magnetic moments. Therefore not all nuclei are detectable in the scanner.

Protons do not only spin, they also rotate with a certain resonance frequency around an imaginary axis. This property is called angular momentum for a moving body consisting of many particles and precession for any body including protons. The precession frequency, the speed of the circular movement, is not constant. It depends, among other things, on the external magnetic field and on temperature. The stronger the external magnetic field, the higher the precession frequency. To calculate the precession frequency

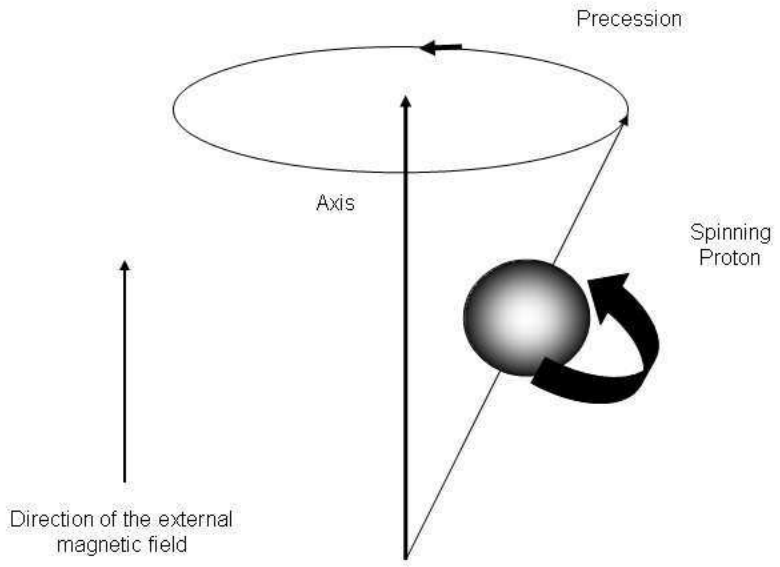

Figure 3: The spin of the proton. The proton is illustrated simplified as a gyroscope.

or angular momentum we use the Larmor equation:

$$\omega_0 = \gamma B_0$$

with ω_0 being the precession frequency measured in megahertz (MHz), γ being the constant gyromagnetical ratio of the nuclei measured in MHz/Tesla (T) and B_0 being the strength of the external magnetic field measured in T. The gyromagnetic ratio differs for different atoms and is fixed to 42.58 MHz/T for the hydrogen proton.
Hydrogen-1 has optimal properties for being detected in the scanner. It has a spin and resonates with a high precession frequency of 42.58 MHz/Tesla (Jezzard, 2001). The higher the precession frequency, the easier the detection is, as we can think of the frequency as one component defining the magnetic properties of the proton. The strength of the precession or angular momentum increases the magnetic momentum. So, the high resonance frequency of Hydrogene-1 is caused by a strong angular momentum. Additionally, hydrogen is very abundant in the human body, as 70% of the body is H_2O. In the following paragraphs I will refer to the proton of hydrogen-1 when discussing protons.

The direction of the alignment of the proton can be parallel or anti-parallel to the external net magnetic field B_0. The parallel alignment is more stable referring to energy levels. Some protons align anti-parallel, although a system always aims for being in the lowest possible and most stable energy state some protons align anti-parallel. A rough estimate for the difference between alignment is roughly 7 in one million (Schild, 1992). That means that one million protons are aligned anti-parallel while 1 million and 7 protons are aligned parallel. Remembering that protons in opposite alignment cancel each other out (see above: antiferromagnetism) we can conclude that only a fraction of the protons in the tissue are actually important for measuring the signal.

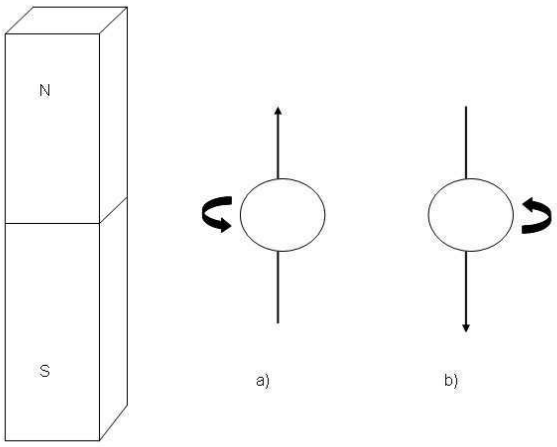

Figure 4: This figure shows two aligned protons. Proton "a" is aligned parallel and proton b is aligned anti-parallel to the external magnetic field. N and S refer to north and south, the two magnetic poles of the proton.

Which energy state is preferred by the protons, parallel or anti-parallel depends on the force of the surrounding magnetic field and the temperature and hence both entities have an effect on the signal measured in MRI.

2.3.2 Detecting a signal in MRI

These properties of the protons in the human body can be used to detect a signal in MRI. The moment the participant is put into the scanner, the protons in the body start aligning to the external magnetic field. The magnetisation of the protons can be thought of as a sum vector indicating the added up magnetic vectors of the aligned protons. This magnetisation will be referred to as longitudinal magnetisation.
In this static magnetic field the longitudinal magnetisation can not be measured directly, as it is parallel to the external magnetic field and therefore signals of small magnetic fields inside the body mix with the total magnetic field and it is impossible to filter out how strong the signal coming from the longitudinal magnetisation is. The solution is to apply a second non-static, but alternating magnetic field that is at exactly 90 degree right angle, transverse, to the net magnetic vector and B_0 to the static magnetic field.

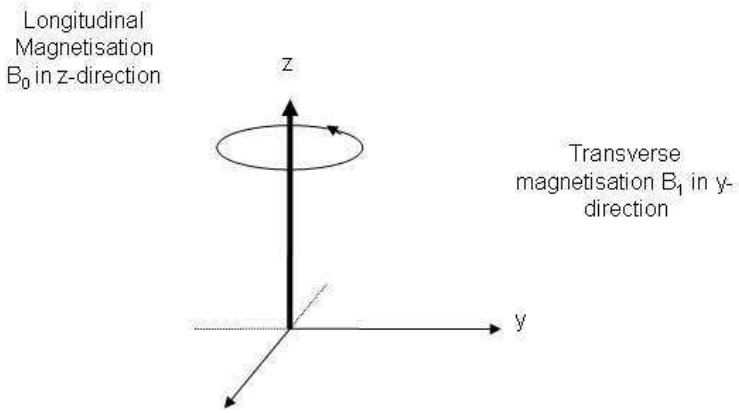

Figure 5: Illustration of longitudinal and transverse magnetisation. Magnetic fields are shown as vectors.

To bring the protons that are precessing in longitudinal direction into the transverse, we apply a short high-frequency RF (radio frequency) pulse B_1. The HF-pulse has to have exactly the same frequency as the precession frequency, called Larmor frequency, described earlier otherwise the protons will not absorb the HF energy.

The HF-pulse lifts the protons on a higher energy level and makes them precess synchronised in the transverse x-y-plane. At same time the net magnetisation in longitudinal direction diminishes. Because of this synchronisation the magnetic properties of the protons add up in the transverse plane and a magnetic sum vector, the transverse magnetisation, is formed.

As soon as the brief HF-pulse is turned off, the protons start moving back from the transverse plane to the longitudinal plane to align again with the static magnetic field. Since the HF-pulse artificially held the protons on a higher energy level, they give away thermal energy in form of radio waves to the surrounding area until they are back in their initial state. These radio waves can be detected by the receiver coil in the transverse plane. The induced oscillating voltage signals the coil receives are the MR signal.

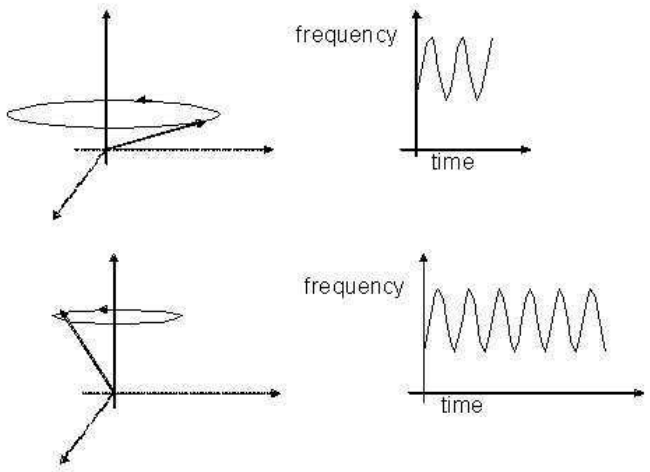

Figure 6: As the protons precess back to their initial position the receiver coil collects the radio wave signal

As the protons precess with that characteristic frequency calculated with the larmor equation they give away energy in waves synchronous with this precession. The received radio waves resonate with the same frequency as the excited protons.

2.3.3 T1 and T2 relaxation time

The way the whole system goes back to its original state after we applied the HF-pulse is defined as the longitudinal and transversal relaxation time. Longitudinal relaxation occurs, because the protons fall back on their former energy level. This process follows a characteristic curve, the T1-curve. The time it takes for the longitudinal magnetisation to be 63% restored is called T1-relaxation time or simply T1. The signal measured during this time is called free-induction decay (FID-signal).

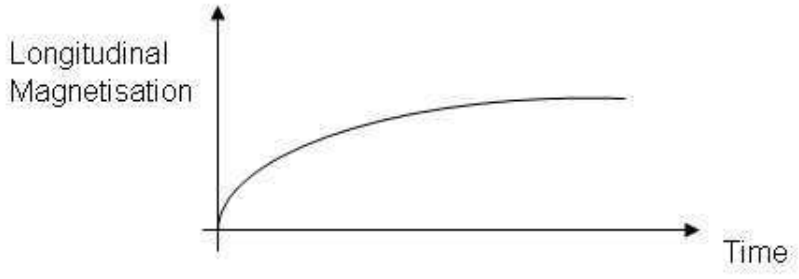

Figure 7: The exponential T1-curve.

Transversal relaxation time is also referred to as T2-relaxation time or simply T2. It describes the way the protons start running out of phase after the HF-pulse is switched off. Two factors make the protons run out of phase: a) molecular interactions (different protons have different precession frequencies) and b) inhomogenities of the external magnetic field B_0. The HF-pulse forces the protons to run in phase, but without the influence of the HF-pulse the protons start dephasing for the two reasons just described. The protons loose coherence and return to their original random state.

Because T1 and T2 vary for different tissue classes, we see different contrasts on the images. T1-relaxation times exceed T2 times. In addition, T1 is longer in stronger magnetic fields. This is due to the higher precession frequency in stronger magnetic fields that complicates the release of energy from the protons. We also can see that the T2 times are not linearly dependent on the strength of the magnetic field.
How does this influence our signal? To be able to differentiate between different tissue

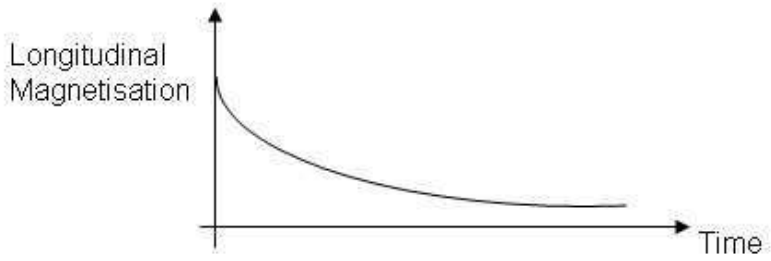

Figure 8: The exponential T2-curve.

classes we have to be able to separate between the signals. This is possible by sending not only one HF-Pulse, but a few in a row (i.e. a sequence). Tissues that have a long relaxation time will not have recovered to baseline by the time the next pulse is given. The time between the pulses is called repetition time (TR). Depending on the length of the TR we will observe differing signals from the different tissues. Depending on other characteristics of the sequence it is important to choose the right TR length. Only the right combination of all influencing factors will lead to a satisfying contrast between the tissues.

2.3.4 Spatial mapping and processing of the received signal

So, now it is clear, how the spin of the protons in a given volume is manipulated to give a signal in the form of a radio-wave that can be received and transformed into an electrical signal which, in turn, is the basis of the images we see. It was also pointed out how the different properties of protons in different tissues account for contrast differences and how this has to be paid attention to in planning a scan sequence. To know where the received signal originates a Maxwell pair of coils is integrated in the scanner-design.
As mentioned before, two magnetic fields act like two vectors. If we place two magnetic coils with opposing magnetic directions next to each other in the z-direction (= B_0 direction) of the scanner, the magnetic vector will be zero in the middle between the two coils and completely controlled by the external magnetic field. Further away from the

middle in +z or −z direction the magnetisation will be slightly more positive or negative, respectively. The consequence for the signal is that not all received radio-waves will oscillate with the same frequency, but with the frequency according to the field strength applied by the two Maxwell coils. By analysing the different frequencies of the received signal it will be possible to quantify the amount of protons that precess with one specific frequency characterising a certain place on the z-axis.
To be able to locate a signal in all three dimensions a gradient coil is integrated, that can induce a magnetic field following the principles of the Maxwell coils.
To analyse the pictures a Fourier transformation is used. A Fourier analysis is used to separate a group of waves with different frequencies into single waves with certain frequencies and amplitudes. The spectrum of these waves, the output of a Fourier analysis, is used to conclude about the composition of the acquired slice and the origin of the detected signal. Using this technique, even very complex signals can be described. The signal is converted from the time into the frequency domain, what enables us to decode the position of the original signal.

2.3.5 The BOLD contrast

Neuronal activity is energy consuming. The energy is brought through the vessels to the cells of the nervous system in form of glucose and oxygen. As energy metabolism (oxidation of glucose) and neuronal activity are closely linked we are able to measure brain activity by measuring changes in relative blood oxygenation. In detail, the deoxygenation of blood distorts the applied magnetic field locally as oxygenated blood is diamagnetic and deoxygenated blood is paramagnetic (Jezzard, 2001). The change from diamagnetic to paramagnetic state gives rise to the signal change from inside a blood vessel. That is why the method applied is called blood oxygenation level dependent (BOLD) contrast imaging or BOLD fMRI.

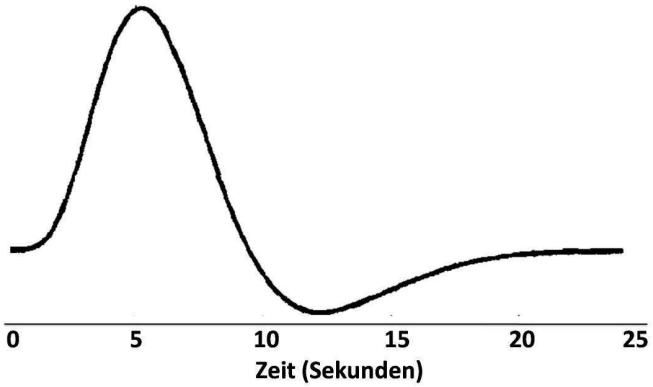

Figure 9: *The temporal resolution of the BOLD contrast* lies within seconds. Within one second after stimulus presentation a decrease of signal intensity can be observed (initial dip). Then, over 2-5 seconds after stimulus onset blood flow increases around 50-70%. The simultaneous increase in deoxygenation leads to the increase in signal intensity. The signal slowly goes back to baseline, when the stimulus stops and neuronal activity and blood flow decrease. An poststimulus undershoot below baseline occurs. It is thought to represent a passive blood volume effect and properties of the stimulus. For a brief stimulus the duration from onset of the response till return to baseline is 12-18 seconds.

2.3.6 Preprocessing of the data

The fMRI data acquired through the method described above has to be prepared for statistical analysis. Data should be corrected for differing acquisition times (slice timing), motion artefacts (realignment), interindividual differences in brain anatomy (spatial normalisation) and optimised for statistical analysis (spatial smoothing). The single steps will now be described in detail.

Slice timing accounts for differences in acquisition times. In subsequent statistical analyses slices from one acquired brain volume are treated as if they were acquired simultaneously. As one slice is actually acquired after the other slice timing corrects for this difference by temporally aligning all slices to one reference slice. To minimise possible limitations from slightly differing acquisition times already before slice timing it is possible to acquire the slices from one brain volume spatially not one after the other but concatenated, as we did in *Study IV*.

Realignment corrects for motion-related artefacts. As in this thesis many researchers have to deal with experimental designs that are confounded by movements. In studies where e.g. electric shock, visual or auditory stimulation is applied, participants will uncontrollably react to stimulation with movement of the head. These (in worst case) systematic confounds are serious and have to be corrected for as thoroughly as possible, as in the statistical analysis following later, this variance will be taken as experimental variance. In fMRI data movement parameters are calculated in reference to the first brain volume acquired. Those movement estimates are then used to realign subsequent images and remove movement-related effects.

Spatial Normalisation is a preprocessing step needed to eliminate inter-participant differences in brain anatomy. Brain anatomy differs between individuals. In later analyses voxels from different participants but same spatial origins will be statistically compared directly. A prerequisit is that voxels from different participants spatially correspond and resemble same underlying anatomical origins. As functionally separate brain regions can neighbour each other this correction has to be performed very accurate. The procedure maps all images from all participants onto one standard anatomical volume preparing for intersubject averaging that is (in most cases) needed for statistical analysis.

Spatial Smoothing is applied for several reasons, one of which is increasing signal relative to noise. The effect of interest physiologically arises from the hemodynamic response that spatially covers several millimetres. Noise is expected to be independent between voxels. Therefor the spatial frequency structures differ between signal and noise and can be separated by filtering. Another reason for spatial smoothing is to fulfil statistical prerequisites for making statistical inferences. Finally, smoothing blurs the images. The bigger the smoothing kernel, the more information from neighbouring voxels is integrated into the voxel of interest. If we know (e.g. from former research) that the functional effect we a re looking for is anatomically large, we will want to apply a big smoothing kernel (for example 10 mm) and vice versa.

Part II

Experimental Section

3 Study I: The anxiolytic effect of reappraisal

3.1 Introduction I

The reappraisal technique employed in the experimental condition relies on distancing. During the control condition (No-regulation, see Introduction to the methods) participants were asked to not alter their feelings, but try and let all feelings arise naturally. A similar control condition was used by other researchers before e.g.(Ochsner, Bunge, Gross & Gabrieli, 2002; Ray, Ochsner, Cooper, Robertson, Gabrieli & Gross, 2005; Ray, McRae, Ochsner & Gross, 2010). A distancing-reappraisal technique similar to the one applied in this experiment was successfully used by us before in an anticipatory anxiety paradigm (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005).
Anxiety was induced by anticipation of painful electrical shocks (Threat condition). Emotion regulation was performed through reappraisal (Regulation condition). Skin conductance levels and self-ratings of anxiety were measured to gather objective and subjective information about success of anxiety reduction.
If induction of anxiety is successful anxiety levels should be higher in Threat compared to No-threat trials. Based on knowledge from former studies we expect our reappraisal technique to be anxiolytic, leading to lower levels of anxiety in Regulation (Reappraisal) compared to No-regulation trials.

3.2 Materials and methods I

3.2.1 Participants

After having given written informed consent, 18 participants took part in the study (2 left-handed, mean age 26,3 years, age range 21 - 38). After completion of the experiment, the skin conductance data of one participant was excluded from further analysis, as the responsiveness was too weak (< 0.01 μmhos)(Fowles, Christie, Edelberg, Grings, Lykken & Venables, 1981).

3.2.2 Experimental Design

We used the instructed fear paradigm, described in the Introduction, to induce anxiety: participants were informed before start of the experiment that they might receive painful electric stimulation at a probability of approximatly 25 % at any time during a 15.6-second Threat-trial (Threat condition). Then they were told that during a control condition they would never receive painful stimulation (No-threat condition). Threat-trials were signaled through a high double beep and No-threat trials through a low double-beep (for more details see Figure 10 on page 48).

Table 1: Overview of the four experimental conditions used in Study I to VI.

	No-Regulation (NR)	Regulation (R)
No-threat (NT)	p(shock)=0%	p(shock)=0%
Threat (T)	p(shock)=25%	p(shock)=25%

In a full 2x2 experimental design participants had to either apply the reappraisal technique to reduce anxiety (Regulation condition) or let their feelings and thoughts arise naturally without changing them (No-regulation condition) (for a detailed description of the techniques see Introduction to the methods).

Procedure

The actual experiment was divided into 6 sessions. Each session consisted of 2 blocks. One block comprised 4 trials (see Figure 10). Each block started with a 20 second pause and was followed by a verbal instruction (via headphones) which technique (Reappraisal or No-regulation) was to use; the instruction was followed by a 30 second establishing phase to give the participants time to establish the reappraisal or no-regulation technique. Participants were asked to sub-vocally rehearse the self-statement and visual imagery after the instruction was given, throughout all trials until the rating phase started. A sound signaled Threat or No-threat and participants had to apply the technique. After 15.6 seconds again a sound signaled if the next trial was under Threat or No-threat. During 28.6% of the Threat trials participants received a triple pain stimulus (pulse intervals: 80 milliseconds) which occurred randomly within a time window of 3 to 10 seconds after offset of the auditory instruction (that is, from approx. 2.7 sec into the trial). After 4 trials the rating phase started with the instruction "Augen auf, Rating!" ("Eyes open, rating.") and a fixation cross (2 seconds) followed by a 5-second presentation of a rating screen with the question "Wie gross war Ihre Angst/Anspannung?" ("How strong was your anxiety/tension?") and a visual analog scale below (separately for Threat and No-threat trials). On the scale, participants could move a red star using their keypad between poles "no anxiety" (0) and "very strong anxiety" (100). The position of the star at the onset of each rating was randomized.

One block took approximately 2.5 minutes (including ratings). In total 6 sessions x 2 blocks x 4 trials=48 experimental trials were conducted. 20 trials (10 No-regulation, 10 Regulation) were under 'No-threat', 28 trials under 'Threat'. 28.6% of the trials of the 'Threat' condition were followed by electric shock and were excluded from further analysis, leaving 20 Threat-trials (10 No-regulation, 10 Regulation) for further analysis.

Finally, participants were paid for their participation.

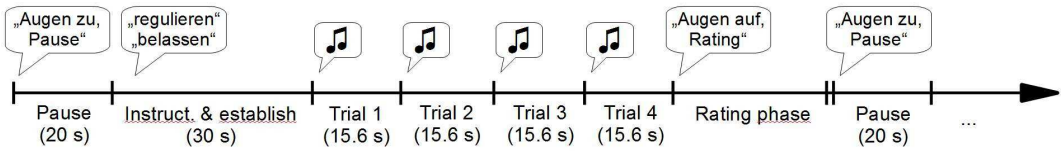

Figure 10: Study I - an experimental block started with a 20 second pause, followed by a verbal instruction which technique ("regulieren"=Reappraisal, "belassen"=No-regulation) to use. After a 30 second establishing phase a double beep (high=Threat, low=No-threat) signaled the trials. After the last trial a verbal instruction ("Augen auf, Rating") announced the rating phase. Ratings were made via button press. The next block started with a pause again.

3.3 Results I

Ratings

Before the experiment participants rated the visual imagery on a scale from 1 (very positive) to 10 (very negative) as being neutraly valenced (M=4.17 and SD= 0.86.

Anxiety ratings (see Figure 11) showed a significant main effect of Threat ($F(1,17)$= 109.45, $p \leq 0.001$) and Regulation ($F(1,17)$=40.11 , $p \leq 0.001$) and an interaction of Threat and Regulation ($F(1,17)$=24.82, $p \leq 0.001$). The interaction was driven by a reduction of anxiety in the Regulation compared to the No-regulation condition (simple main effect of Regulation in the Threat condition: $t(17)$=6.07, $p \leq 0.001$ one-tailed).

A *'reappraisal success index'* (RSI) was calculated, to capture a baseline corrected index of anxiety reduction (corresponding to a directed interaction contrast): RSI = (Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal - No-threat/Reappraisal). The RSI indexes threat-related effects that are attenuated by Reappraisal. One-sample t-test indicated that the (baseline corrected) "RSI" was greater than the chance level of 0 for anxiety ratings (M=14.86, SD=12.65), $t(17)$=4.98, p<.001 (one-tailed).

Rather than a reduction of anxiety, these ratings may also reflect the demand characteristics of the task. Indeed, when including the participants scores on a social desirability index as a covariate of no interest to the above analysis, the main effect of regulation and the interaction were no longer significant ($p \geq .28$ and $p \geq .28$).

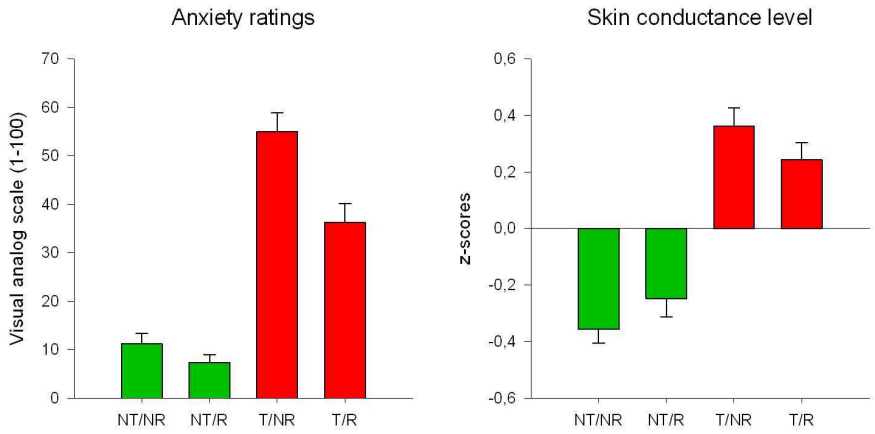

Figure 11: Study I - Skin conductance level and anxiety ratings on a scale from 1 (=no anxiety) to 100 (=maximum anxiety) in the different conditions. NT=No-threat; T=Threat; NR=No-regulation; R=Regulation

SCL

The SCL (see Figure 11) was significantly elevated by Threat (main effect of Threat: F(1,16)=17.66, p=0.001) and also showed an interaction of Threat and Regulation (F(1,16)=4.68, p=0.05). We thus calculated a Reappraisal Success Index (RSI). This index showed a significant reduction of sympathetic arousal by reappraisal (M=0.23, SD=0.395) $t(16)$=2.16, p=0.02, one-tailed).

3.4 Discussion I

Participants subjectively felt less anxiety during application of our reappraisal technique, though it is not clear, to what extend these subjective ratings were under the influence of social desirability effects. The skin conductance, the objective measure, showed to be sensitive to threat, as it was significantly elevated by threat. The reappraisal technique we employed was anxiolytic, as the (baseline-corrected) level of skin conductance (RSI) was lower in the threat/reappraisal than in the threat/no-regulation condition.

The reappraisal technique we use for anxiety-reduction has anxiolytic character. This confirms our hypothesis. However, we cannot tell if this anxiolytic character results from a true re-evaluation of the stimulus or from the cognitively demanding nature of reappraisal. Of course, it could also be possible that both processes take place simultaneously.

This matter will be addressed in *Study II*.

4 Study II: The influence of cognitive effort on the anxiolytic effect of Reappraisal

4.1 Introduction II

In *Study I* we could show that reappraisal lowers the anxiety level subjectively and objectively. However it remains unclear what underlies this effect: true re-evaluation of the threatening situation or maybe a distractingly high cognitive effort demanded by the reappraisal technique or a combination of both components. This is a concern as it appears conceivable that cognitive demand alone might make an important contribution to emotion regulation success (Van Dillen and Koole, 2007; Urry et al., 2009) and, hence, matching Reappraisal and No-reappraisal conditions for demand would strongly reduce the anxiolytic effect of reappraisal.

The experiment described below is a repetition of *Study I* with one exception: the control condition now is a close match to the experimental condition. As experimental and control condition will just differ in the regulation aspect (Reappraisal vs. No-reappraisal), cognitive effort is kept constant between the conditions. Observed differences in anxiety level cannot be due to differences in cognitive effort. If no difference in anxiety level is observed, re-evalutaion might not be the whole reason behind the observed anxiety reduction.

To test the hypotheses the No-regulation condition used in *Study I* was replaced by a No-reappraisal condition which also involved the use of self-statement and of visual imagery (see Introduction to the methods). In addition, subjects were intensively trained in using the two strategies, to ensure similar (low) cognitive demand (see Introduction to the methods). As a result, the experimental reappraisal condition and the control condition (No-reappraisal) were matched in terms of cognitive effort. Anxiety was induced by anticipation of painful electrical shocks. Self-ratings of anxiety and skin conductance were measured to gather subjective and objective information about anxiety reduction success.

4.2 Materials and Methods II

4.2.1 Participants

Participants were recruited as described in Introduction to the methods. In total, 15 participants took part (all male, 2 left-handed, mean age 26.87 years, age range 22 - 41). Because of technical problems the skin conductance data of 4 participants were lost.

4.2.2 Experimental Design

Again the anticipatory anxiety design already described was used. For details about the timing of experimental blocks and trials see Figure 12.
The Reappraisal and No-reappraisal techniques, as described in the Introduction to the methods, were used. The described cut-offs and long training techniques were applied, to ensure effortless and correct application of the two techniques. Hence, we attempted to match the effort employed in Reappraisal and No-reappraisal trials by trying to maximally reduce it. This should preclude differences in cognitive effort from affecting anxiety reduction.

Procedure
The actual experiment was divided into 6 sessions consisting each of 2 blocks. One block was divided in 4 trials (for details see Figure 15). Each trial started with a 20 second pause and was followed by a verbal instruction (via headphones) which technique (regulation or no-regulation) was to use; now participants had 30 seconds to establish the technique; then participants had 15.6 seconds to apply the technique during the trials. After 4 trials a sound signaled the rating phase, that started with a fixation cross (2 seconds) followed by the ratings (made via button press) asking 'Wie gross war Ihre Angst oder Anspannung' for the Threat and No-threat conditions separately. Participants were asked to sub-vocally rehearse the self-statement and visual imagery after the instruction was given, throughout all trials until the rating phase started. One block took approxi-

mately 3 minutes (including ratings). In total 12 blocks x 4 trials=48 experimental trials were conducted. 20 trials (10 No-regulation, 10 Regulation) were under No-threat, 28 trials under Threat. 28.6% of the Threat condition were reinforced with electric shock (a triple pain stimulus (pulse intervals: 80 milliseconds) which occurred randomly within a time window of 3 to 10 seconds after offset of the auditory instruction) and were excluded from further analysis, leaving 20 Threat trials (10 No-regulation, 10 Regulation) for analysis.

Deviating from *Study I*, participants now also rated the difficulty of sub-vocal rehearsal of the Reappraisal and No-reappraisal technique and the amount of time spent rehearsing. These ratings were collected together with the anxiety-ratings after each experimental block.

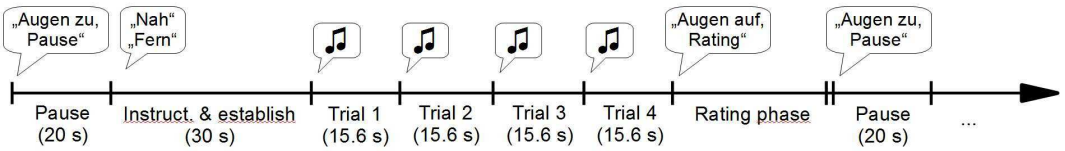

Figure 12: Study II - an experimental block started with a 20 second pause, followed by a verbal instruction which technique ("Fern"=reappraisal, "Nah"=no-reappraisal) to use. After a 30 second establishing phase a double beep (high=Threat, low=No-threat) signaled the trials. After the last trial a verbal instruction ("Augen auf, Rating") announced the rating phase. Ratings were made via button press. The next block started with a pause again.

4.3 Results II

Ratings

Immediately before the experiment, participants could easily repeat the self-statements to the experimenter and reported finding sub-vocal rehearsal of the two self-statements equally easy (1=not difficult to 10=very difficult: No-reappraisal condition: M=1.60 and SD=0.83; Reappraisal condition: M=1.47 and SD=0.64; $t(14)$=-0.81, p=.43 two-tailed). They also found the two scenarios equally easy to imagine visually (No-reappraisal condition: M=1.87 and SD=0.83; Reappraisal condition: M=1.87 and SD=0.92; $t(14)$=0.00, p=1.0 two-tailed) and their imagination equally intense (1=not intense to 10=very in-

tense: No-reappraisal condition: M=6.60 and SD=1.68; Reappraisal condition: M=6.33 and SD=1.76; $t(14)$=-0.77, p=0.45 two-tailed).

During the experiment, participants again reported similar levels of difficulty of sub-vocal rehearsal ($t(14)$=0.07, p=0.95 two-tailed) and imagery ($t(14)$=0.27, p=0.79 two-tailed) and similar percentages of time spent rehearsing ($t(14)$=0.6, p=0.56 two-tailed) and imagining ($t(14)$=0.37, p=0.72 two-tailed) (see Fig. 13).

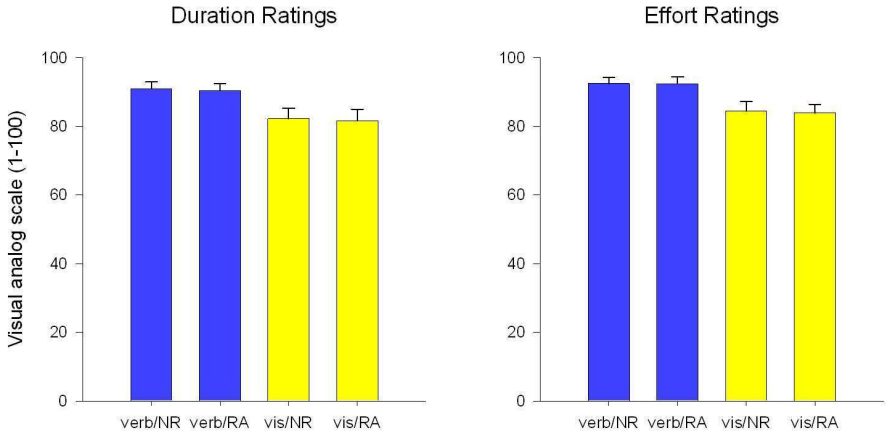

Figure 13: Study II - Time spent (duration) and difficulty (effort) of sub-vocal rehearsal and visual imagery on a scale from 1 (=litte time/very difficult) to 100 (=much time/very easy). Verb=verbal, vis=visual, NR=No Reappraisal, RA=Reappraisal.

Importantly, the two different sets of verbal and visual materials were also rated before the experiment as being of similar affective valence (1=very positive to 10=very negative: No-reappraisal condition: M=5.07 and SD=1.53; Reappraisal condition: M=4.47 and SD=1.30; $t(14)$=-1.46, p=.17 two-tailed), excluding a confound through differing affective contents of the strategies.

Anxiety ratings showed a similar pattern as in *Study I*. There was a significant main effect of Threat ($F(1,14)$=72.74, p<.001) and Regulation ($F(1,14)$=10.78, p=.005) as well as a trend for an interaction of Threat and Regulation ($F(1,14)$=3.24, p=.09) (see Fig. 14).

Again the RSI was calculated, to capture threat-related effects that are attenuated by Reappraisal. One-sample t-test indicated that the RSI[6] was significantly different from 0 (M=5.60, SD=12.05), $t(15)$=1.80, p=.05 (one-tailed).

[6](Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal - No-threat/Reappraisal)

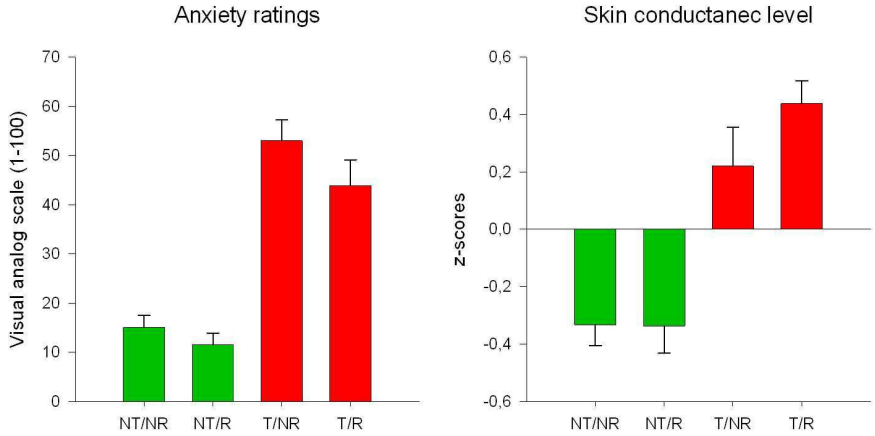

Figure 14: Study II - Skin conductance level and anxiety ratings on a scale from 1 (=no anxiety) to 100 (=maximum anxiety) in the different conditions. NT=No-threat; T=Threat; NR=No-reappraisal; R=Reappraisal.

Rather than a reduction of anxiety, these ratings again may also reflect the demand characteristics of the task. Indeed, when including the participants scores on a social desirability index as a covariate of no interest to the above analysis, the main effect of Regulation was no longer significant ($p \geq 0.15$). The higher participants scored on a social desirability index, the more anxiety reduction they reported (R=0.51, p=.05 two-tailed).

SCL

Skin conductance was significantly elevated by Threat (main effect of Threat: $F(1,10)$=16.11, p=0.01) but showed no main effect of Regulation ($F(1,10)$=3.01, p=0.11) and no interaction ($F(1,10)$=1.93, p=0.20). Figure 14 shows that SCL was enhanced rather than reduced in the Threat/Reappraisal condition. The RSI[7] was not significantly different from 0 (M=-0.01 SD=0.01; $t(10)$=-1.75, p=0.06, one-tailed).

Our conclusion that cognitive engagement was comparable between the two strategies was further supported by an absence of a detectable increase in skin conductance between the No-threat/No-reappraisal and the No-threat/Reappraisal conditions ($t(10)$=0.05, p=0.97, two-tailed paired-sample t-test. Given that SCL is an objective index of threat-related

[7](Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal - No-threat/Reappraisal)

arousal and that anxiety ratings are most likely confounded by social desirability, this speaks against an anxiolytic effect of reappraisal in this study.

4.4 Discussion II

Study II employed the same anticipatory anxiety paradigm that we already introduced in *Study I*. Deviating from *Study I*, we now matched the Reappraisal and No-reappraisal techniques for cognitive effort. Applying the strategies should demand a comparable amount of mental workload under Reappraisal and No-reappraisal. In addition, the cognitive load during trials was reduced compared to *Study I* as participants were trained more intensely to use the techniques before the experiment started.

In *Study II* we could show that the relative anxiolytic effect of reappraisal observed in *Study I*, is absent, if the level of cognitive effort is kept constant between conditions. Neither in the ratings nor in the SCL had we found a significant interaction between Threat and Regulation. This speaks against anxiety reduction by Reappraisal. It is therefore unlikely that re-interpretation of the threatening stimulus (reappraisal) alone led to the observed reduction of anxiety in *Study I*. It seems that the results from *Study I* were confounded: the experimental condition was cognitively more demanding than the control condition.

These data suggest that re-interpretation, the putative core process of reappraisal, is not anxiolytic alone. Rather, the source of anxiolysis by reappraisal seems to also lie in the cognitive engagement reappraisal requires.

Looking at the results of the subjective ratings, it seems even more important to collect psychophysiological data in addition to self-reported data, which are susceptible for social desirability effects.

Concluding from the results of *Studies I and II* it is difficult to tell to which extent the observed anxiety reduction stems from a true reappraisal-effect or from effects of cognitive demand or a combination of both.

5 Study III: The influence of cognitive effort on the anxiolytic effect of Reappraisal - Replication

5.1 Introduction III

This study was designed to replicate the results from *Study II* in a new sample. Subjective ratings, skin conductance and fMRI data were collected. However the fMRI data will be reported elsewhere.

Again, the experimental reappraisal condition and the control condition were matched in terms of cognitive effort. Anxiety was induced by anticipation of painful electrical shocks. Self-ratings of anxiety and skin conductance were measured to gather subjective and objective information about changes in anxiety levels.

5.2 Materials and Methods III

5.2.1 Participants

Again, participants were recruited as described in *Study I*. 18 participants took part (all male, none left-handed, mean age 27.53 years, age range 22 - 39). After completion of the experiment SCL data from one skin conductance non-responder had to be excluded and two skin conductance data sets were lost due to technical problems.

5.2.2 Experimental Design

The Reappraisal and No-reappriasal techniques, as described in the Introduction to the methods, were used. The described cut-offs and training techniques were applied, to ensure effortless and correct application of the two techniques.

Procedure

The actual experiment was divided into 3 sessions. Session 1 and 3 consisted of 3 blocks; session 2 consisted of 4 blocks. One block was divided into 8 trials (see Figure 15), each started with a 30 second pause and was followed by a verbal instruction (via headphones) which technique (Regulation or No-regulation) was to use; then participants had 20 seconds to establish the technique. Then a tone signal announced the start of a trial of 15.6 seconds duration. After 8 trials a verbal instruction signaled the rating phase, that started with a fixation cross (2 sec) followed by the rating (made via button press) asking "Wie gross war Ihre Angst oder Anspannung" for each of the Threat conditions separately. One block took approximately 4 Minutes (inclusive ratings). In total 10 blocks x 8 trials = 80 experimental trials were conducted. 35 trials were under No-threat, 45 trials under Threat. 12 trials (26.5%) of the Threat condition were reinforced with electric shock and were excluded from further analysis, leaving 33 Threat trials for analysis.

Figure 15: Study III - an experimental block started with a 30 second pause, followed by a verbal instruction which technique ("Nah"=Reappraisal, "Fern"=No-reappraisal) to use. After a 20 second establishing phase a double beep (high=Threat, low=No-threat) signalized the first of eight trials. After the last trial a verbal instruction ("Augen auf, Rating") announced the rating phase. Ratings were made via button press. The next block started with a pause again.

5.3 Results III

Ratings

Immediately before the experiment, participants could easily repeat the self-statement to the experimenter and reported finding sub-vocal rehearsal of the two techniques equally easy (No-reappraisal: 1.61 (0.98;) Reappraisal: 1.89 (0.83); $t(17)$=-1,43, p=0.17, two-tailed). They also found the two scenarios equally easy to imagine (No-reappraisal: 2.33 (1.33); Reappraisal: 2.22 (0.94); $t(17)$=0.42, p=0.68, two-tailed) and equally intense (No-

reappraisal: 5.94 (1.96); Reappraisal: 6.00 (1.97); $t(17)$=-0.20, p=0.85, two-tailed). During the experiment participants again reported similar levels of difficulty of sub-vocal rehearsal ($t(17$=0.34, p=0.74, two-tailed) and imagery ($t(17)$=-1.62, p=0.12, two-tailed) and similar percentages of time spent rehearsing ($t(17)$=-1.41, p=0.18, two-tailed) and imagining ($t(17)$=0.31, p=0.76, two-tailed) (see Figure 16).

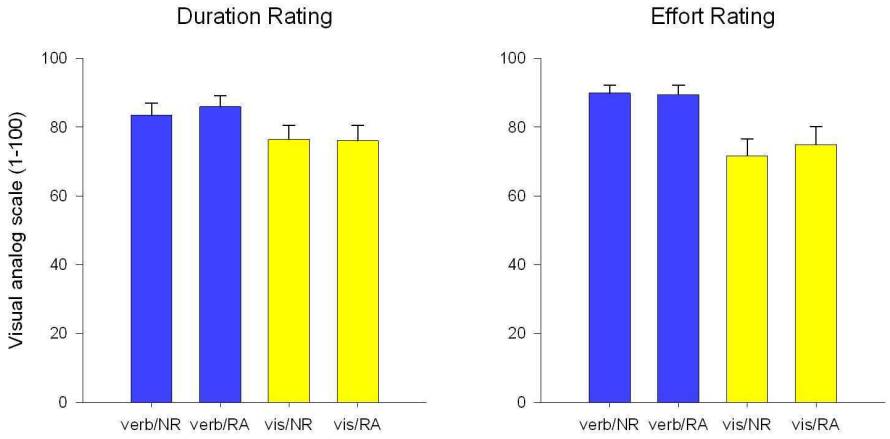

Figure 16: Study III - Time spent (duration) and difficulty (effort) of sub-vocal rehearsal and visual imagery on a scale from 1 (=litte time/very difficult) to 100 (=musch time/very easy). Verb=verbal, vis=visual, NR=No-reappraisal, RA=Reappraisal.

The two different sets of verbal and visual materials were also rated before the experiment as being of similar affective valence (No-reappraisal: 4.72 (1.27); Reappraisal: M=4.39 (1.42); $t(17)$=-1.37, p=0.18, two-tailed), excluding a confound through different affective content of the strategies.

Anxiety ratings were again similar to those found in *Study I* and *II*. We found a significant main effect of Threat ($F(1,17)$=114.09, p<.001) and Regulation ($F(1,17)$=7.92, p=0.01) and an interaction of Threat and Regulation ($F(1,17)$=4.59, p=0.05). The interaction was driven by a reduction of reported anxiety in the Reappraisal compared to the No-reappraisal condition (simple main effect of Regulation in the Threat condition: $t(17)$=2.94, p=0.01, one-tailed). One-sample t-test indicated that the (baseline corrected) "RSI"[8] was significantly different from 0 (M=4.68, SD=9.27), $t(17)$=2.14, p=.024, (one-

[8](Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal - No-threat/Reappraisal)

tailed).

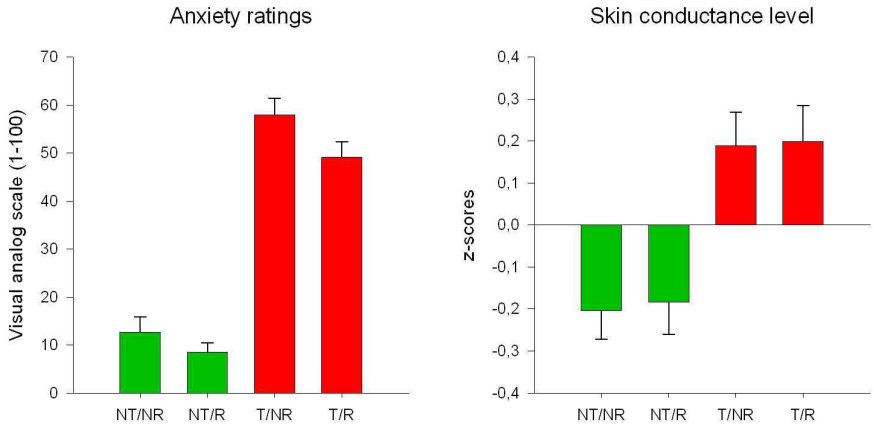

Figure 17: Study III - Skin conductance level and anxiety ratings on a scale from 1 (=no anxiety) to 100 (=maximum anxiety) in the different conditions. NT=No-threat; T=Threat; NR=No-reappraisal; R=Reappraisal.

SCL

During the Threat condition, skin conductance was significantly elevated (main effect of Threat: $F(1,14)=11.43$, $p=0.01$). We did not find a main effect of Regulation ($F(1,14)=0.04$, $p=0.86$) and no interaction ($F(1,14)=0.01$, $p=0.94$). The (baseline corrected) "RSI" was not significant (0.01 (0.51); $t(14)=0.07$, $p=.047$, one-tailed). Our conclusion that cognitive effort was comparable between the two strategies was further supported by an absence of a detectable increase in skin conductance between the No-threat/No-reappraisal and the No-threat/Reappraisal conditions ($t(14)=-0.23$, $p=0.82$).

5.4 Discussion III

We could replicate the results from *Study II*: again, the results from the skin conductance recordings suggest, that as soon as the Reappraisal and the No-reappraisal techniques are closely matched in terms of cognitive effort, the relative anxiolytic effect of Reappraisal observed in *Study I* is absent, at least as long as the effort is low. This still puts forward the idea that there is more than just one cause behind anxiety reduction in the reappraisal

condition. We cannot exclude the possibility that we would have found an anxiolytic effect (in SCL) if effort had been equally *high* between Reappraisal and No-reappraisal. In *Studies II and III* matching for effort was reached by making both techniques similarly effortless (through intense training). To definitly conclude that anxiolysis in reappraisal is carried by cognitive effort alone, one would have to also compare the two techniques after lesser training, that is, when they both demand a comparably high cognitive effort. *Study V* will to some extent adress this issue, among other topics.

6 Study IV: The influence of cognitive effort on the anxiolytic effect of Reappraisal - second replication

6.1 Introduction IV

This study again served to test whether detachment-reappraisal still relatively reduces anxiety when it is compared to a cognitively demanding immersion rather than to an "attend" condition. Just as in *Studies II and III*, the experimental reappraisal condition and the control condition were matched in terms of cognitive effort. Anxiety was induced by anticipation of painful electrical shocks. Self-ratings of anxiety and skin conductance were measured to gather subjective and objective information about changes in anxiety levels

6.2 Materials and Methods IV

6.2.1 Participants

20 right-handed healthy male participants took part in the study. They had an average age of 27±1.3 (mean± s.d.) years (range 21 - 40). All were of Caucasian origin and university students. Their average trait anxiety (Spielberger, 1985) was 34.3±6.2 (range 25 - 44) and thus in line with norm population values (compare Laux et al., 1981).

6.2.2 Experimental Design

The Reappraisal and No-reappriasal techniques, as described in the Introduction to the methods, were used. The described cut-offs and training techniques were applied, to ensure effortless and correct application of the two techniques.

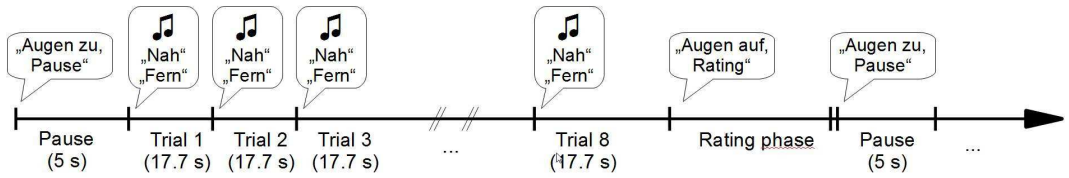

Figure 18: Study IV - an experimental block started with a 5 second pause, immediately followed by the trials: a double beep (high=threat, low=No-threat) and a verbal instruction which technique ("Nah"=Reappraisal, "Fern"=No-reappraisal) to use indicated the beginning of a trial. After the last of eight trials a verbal instruction ("Augen auf, Rating") signaled the rating phase. Ratings were made via button press. The next block started with a pause again.

Procedure

There were altogether 70 randomized 17.7-sec trials (24, 24 and 22 per run), 15 in each of the conditions NT/NR and NT/R and 20 in each of the conditions T/NR and T/R. During 5 of both the T/NR and T/R trials participants received a triple pain stimulus (pulse intervals: 80 ms) which occurred randomly within a time window of 3 to 12 s after offset of the auditory instruction (that is, from approximatly 2.7 sec into the trial). After 8 trials the rating phase started with the instruction "Augen auf, Rating!" ("Eyes open, rating") followed by a 5-sec presentation of a rating screen with the question "Wie gross" war Ihre Angst/Anspannung?" ("How strong was your anxiety/tension?" and a visual analog scale below. On the scale, participants could move a red star using their keypad between poles "no anxiety" (0) and "very strong anxiety" (100). The position of the star at the onset of each rating was randomized. The subsequent 5-second break was cued by the verbal instruction "Augen zu, Pause!" ("Eyes closed, break."). A schematic description is given in Figure 18.

6.3 Results IV

Ratings

Trial-by-trial anxiety ratings showed significant main effects of Threat ($F(1,19)=162.45$, $p<0.001$) and Reappraisal ($F(1,19)=24.30$, $p<0.001$) and a significant Threat by Reappraisal interaction ($F(1,19)=10.16$, $p=0.005$). The interaction was apparently driven by

a reduction of anxiety in the Threat/Reappraisal compared to the Threat/No-reappraisal condition (Figure 19), an anxiolytic effect that expressed in a significant average RSI[9] of 9.3 (14.70) (>0, $t(19)$=3.19, p<0.01 one-tailed, planned post-hoc t-test). The anxiety-rating-RSI was still significant (p=0.002) when removing one outlier who had an RSI of >2 s.d. above average.

A caveat is that, rather than a true reduction of anxiety by reappraisal, these ratings may also reflect the demand characteristics of the task.

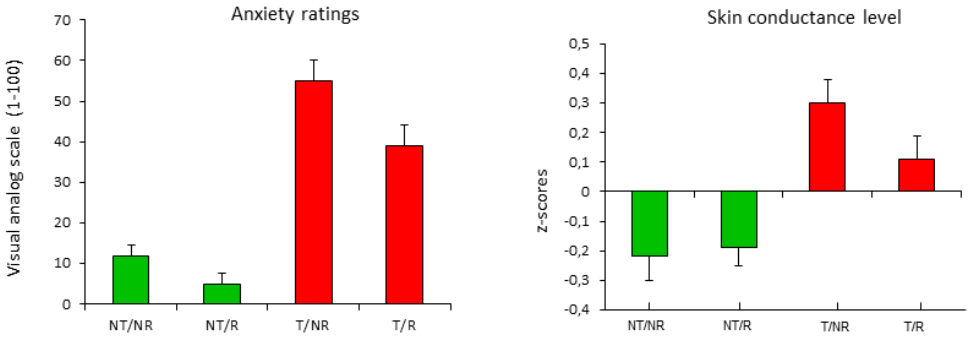

Figure 19: Study IV - Skin conductance level and anxiety ratings on a scale from 1 (=no anxiety) to 100 (=maximum anxiety) in the different conditions. NT=No-threat; T=Threat; NR=No-reappraisal; R=Reappraisal.

SCL

Skin conductance is an index of the sympathetic arousal that usually accompanies anxiety and can be used as a more objective (though often noisier and less sensitive) metric for anxiety. Trial-by-trial skin conductance levels (SCL) showed a significant main effect of Threat ($F(1,18)$=16.17, p=0.001), and the critical interaction of Threat and Reappraisal ($F(1,18)$=5.72, p=0.03; Figure 19). The SCL-RSI was 0.22 (0.41) (>0, $t(18)$=2.39, p=0.01). It was still significant (p=0.001) when removing one outlier who had an RSI of >2 s.d. below average.

[9](Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal No-threat/Reappraisal)

6.4 Discussion IV

With *Study IV* we could show that the reappraisal technique we applied was anxiolytic, as shown in a significant RSI of anxiety ratings and skin conductance. The anxiety ratings again might reflect effects of social desirability as discussed before. The only difference between *Studies II and III* and *Study IV* was, that we changed the amount of training given to the participants before the experiment. In *Study IV* the moderate training lead to relatively higher cognitive demand compared to *Studies II and III* while applying the regulation techniques during the experiment. That we observed attenuation of anxiety levels through reappraisal in the SCL in the current study emphasizes that neither re-interpretation nor cognitive effort alone can explain the observed anxiolysis.

7 Study V: Cognitive Reappraisal and the Placebo Effect

7.1 Introduction V

Bandura stated that "the best way to create a sense of safety is to equip people with coping skills and a robust belief in their coping capabilities" (Rachman, 1984). Following Bandura the patient has to be given not just a skill to cope but also the belief in this skill. This short statement seen in connection with the importance of safety signals in anxiety disorders, stresses the impact of subjective beliefs on the effectiveness of a cognitive strategy. Other researchers have shown that the analgesic effect of a placebo treatment is larger, the more participants expect the treatment to be effective (Price, Milling, Kirsch, Duff, Montgomery & Nicholls, 1999). This could mean that participants belief in the emotion-reducing effect (less pain, less anxiety) of a treatment or mental technique is sufficient to actually reduce their emotional outcome. In addition to this positive outcome expectation, a positive learning experience can enhance the placebo effect (Eippert, Bingel, Schoell, Yacubian, Klinger, Lorenz & Büchel, 2009). If the participant passes a trial of successful emotion-reduction prior to the experiment and attributes the emotion-reduction to the effectiveness of the applied technique or treatment, the placebo effect during the experiment will be enlarged. It is thus conceivable that cognitive regulation success represents a placebo effect driven by positive outcome expectation.

This study investigates the influence of expectancy on reappraisal success. To be able to observe expectancy-effects, we compared two groups of participants: a Normal group (treated similarly to *Study IV*) and an Inverse group (after experimental manipulation expecting No-reappraisal to be anxiolytic). We expected to find the pattern of anxiolysis already seen in *Study I* in the Normal group: successful effortful reappraisal should lead to attenuation of anxiety levels in subjective ratings (although we do not know to what extend these ratings are under the influence of social desirability effects) and to attenuation

of skin conductance levels (although this might be under the influence of effects of cognitive demand, see *Studies II and III*). In the Inverse group that expects No-reappraisal to be anxiolytic however, we expected to see a different pattern: as expectancy-effects might account for a part of reappraisal success in the Inverse group anxiety levels should be relatively lower in the No-reappraisal than in the Reappraisal condition. Again, it was well controlled that both strategies (Reappraisal and No-reappraisal) in both groups (normal and inverse) took up comparable amounts of (higher) cognitive load.

7.2 Materials and Methods V

We compared two groups of healthy male volunteers that cognitively modulated their anticipatory anxiety for impending pain (Threat, relative to No-threat). Both groups used the reappraisal technique of distancing (Reappraisal condition) or, in other trials, the comparison No-reappraisal technique (No-reappraisal condition). The Normal group was treated as usual, thus expecting Reappraisal to reduce their anxiety. On the contrary, to the Inverse group the experimenter explicitly suggested that No-reappraisal would reduce anxiety.

Subjective anxiety ratings and skin conductance levels were used to index anxiety. Within each group, this allowed for quantifying the anxiolytic effect of Reappraisal (or No-reappraisal in the Inverse group) with the formerly used RSI[10], expressing to what extent the threat reaction was lowered when applying the technique.

7.2.1 Participants

After giving written informed consent 40 healthy male participants took part in the study (*Normal group*: n=20, age 27 (1.3) years, trait anxiety 34 (1.0); *Inverse group*: n=20, age 26 (0.7) years, trait anxiety 31 (2.0), p=0.11; *all*:≥13 years of education). Participants

[10](Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal - No-threat/Reappraisal)

were randomly assigned to either of the experimental groups.

7.2.2 Experimental Design

The Reappraisal and No-reappraisal techniques already described in the Introduction to the methods, were used. However, the timing and structure of the experimental blocks was new. The pause between blocks was reduced to 5 seconds. To capture the cognitive process of establishing the reappraisal technique, trials started immediately after the verbal instruction which technique to use was given (see Figure 20 for more details).

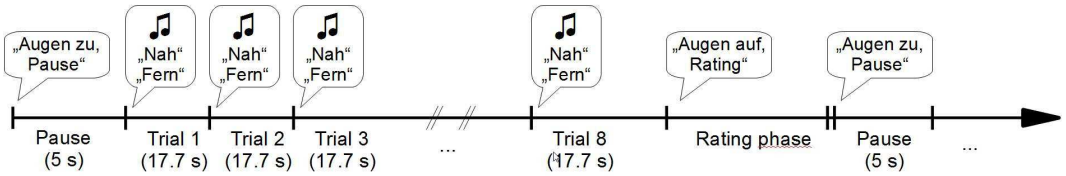

Figure 20: Study IV - an experimental block started with a 5 second pause, immediately followed by the trials: a double beep (high=Threat, low=No-threat) and a verbal instruction which technique ("Nah"=Reappraisal, "Fern"=No-reappraisal) to use indicated the beginning of a trial. After the last of eight trials a verbal instruction ("Augen auf, Rating") signaled the rating phase. Ratings were made via button press. The next block started with a pause again.

Participants received moderate training before the experiment to assure they were able to use the techniques (difficulty ratings for rehearsing both the visual and verbal material <3 out of 10 in both groups, p-values from two-tailed paired t-tests >0.42).

To induce positive outcome expectations for the No-reappraisal strategy (referred to as "immersion" during training) in the Inverse group, those participants were told a cover story during instruction as follows: "We have conducted a similar experiment before, expecting distancing to reduce anxiety. To our surprise we found that immersion reduced anxiety. Going back into the literature, we have indeed found that all prior experiments on immersion had demonstrated a clear anxiolytic effect. The current experiment serves to reproduce this finding with our specific paradigm."

We used a 2x2x2 factorial design [within-subject factors "Threat" (levels No- Threat,

Threat) and "Reappraisal" (levels No-Reappraisal, Reappraisal), between-subject factor "Group" (levels Normal, Inverse)] with the four conditions per group shown in Table 2.

Table 2: Study IV - Expected anxiety levels in the experimental conditions. NT=No-threat, NR=No-reappraisal, R=Reappraisal, T=Threat

	Normal group (NG)	Inverse group (IG)
NT/NR	low	low
NT/R	low	low
T/NR	high	medium
T/R	medium	high

7.3 Results V

Ratings

To rule out a-priori differences between the groups and the two techniques, we let the participants rate the cognitive effort for visual and verbal rehearsal, affective valence and intensity of the two techniques. Before the experiment both groups rated the two techniques as equally easy to apply *verbally*:

Reappraisal - Normal group: M=2.50 and SD=0.89, Reappraisal - Inverse group: M=2.70 and SD=1.53; $t(38)$=-0.51, p=0.62; No-reappraisal - Normal group: M=2.70 and SD=1.13, No-reappraisal - Inverse group: M=2.65 and SD=1.53; $t(38)$=-0.53, p=0.58); and equally easy to apply *visually*:

Reappraisal - Normal group: M=2.40 and SD=1.23, Reappraisal - Inverse group: M=2.10 and SD=1.37; $t(38)$=0.73, p=0.47; No-reappraisal - Normal group: M=2.45 and SD=1.36, No-reappraisal - Inverse group: M=2.10 and SD=1.37; $t(38)$=0.81, p=0.42.

Furthermore the visual images used in the two techniques were rated as equally *valenced* on a scale from 1 (=aversive) to 10 (=appetitive):

Reappraisal - Normal group: M=6.35 and SD=1.53, Reappraisal - Inverse group: M=6.40 and SD=1.90; $t(38)$=-0.92, p=0.93; No-reappraisal - Normal group: M=5.80 and SD=1.80, No-reappraisal - Inverse group: M=6.35 and SD=1.84; $t(38)$=-0.96, p=0.35.

In addition the two visual imaginations were rated as equally *intense* on a scale from 1 (= not intense) to 10 (very intense):

Reappraisal - Normal group: M=6.45 and SD=1.76, Reappraisal - Inverse group: M=6.85 and SD=1.90; $t(38)$=-0.66, p=0.52; No-reappraisal - Normal group: M=6.70 and SD=1.53, No-reappraisal - Inverse group: M=7.00 and SD=2.20; $t(38)$=-0.50, p=0.62.

A mixed-designs ANOVA of anxiety ratings with Group (Normal, Inverse) as a between-subjects factor and Threat (No-threat, Threat) and Regulation (No-reappraisal, Reappraisal) as within-subjects factors revealed an interaction between Regulation and Group, $F(1,38)$=29.58, p<.01. The predicted interaction among Group, Threat and Regulation was significant at $F(1,38)$=15.13, p<.001. All other main effects and interactions were non-significant or irrelevant to our hypotheses (for details see Table 3).

Table 3: Study IV - Anxiety ratings: results of the mixed-designs ANOVA with Group (Normal, Inverse) as a between-subjects factor and Threat (No-threat, Threat) and Regulation (No-reappraisal, Reappraisal) as within-subjects factors.

Effect	*df*	*F*	sign.
Threat	1	353.18	<.001
Threat*Group	1	82.32	.52
Regulation	1	8.04	.007
Regulation*Group	1	29.58	<.001
Threat*Regulation*Group	1	15.13	<.001
Error	38		

Anxiety ratings in the different conditions in the Normal group and the Inverse group are presented in Figure 21. The two-factor analysis of variance in the "Normal group" showed a significant main effect for Threat, $F(1,19)$=162.45, p<.001; a significant main effect for the Regulation factor, $F(1,19)$=24.80, p<.001; and a significant interaction between Threat and Regulation, $F(1,19)$=10.16, p<.005.

For the Inverse group the two-factor analysis of variance again showed a significant main effect for Threat, $F(1,19)$=191.15, p<.001; a significant main effect for the Regulation factor, $F(1,19)$=5.47, p=0.03; and a significant interaction between Threat and Regulation, $F(1,19)$=5.21, p=0.03.

SCL

A mixed-designs analysis of variance with Group (Normal, Inverse) as a between-subjects factor and Threat (No-threat, Threat) and Regulation (No-reappraisal, Reappraisal) as within-subjects factors revealed a significant interaction among Group, Threat and Regulation at $F(1,34)=12.59$, $p=.001$. All other main effects and interactions were non-significant or irrelevant to our hypotheses (for details see Table 4).

Table 4: Study IV - Skin conductance: results of the mixed-designs ANOVA with Group (Normal, Inverse) as a between-subjects factor and Threat (No-threat, Threat) and Regulation (No-reappraisal, Reappraisal) as within-subjects factors.

Effect	*df*	*F*	sign.
Threat	1	29.07	<0.001
Threat*Group	1	0.13	0.73
Regulation	1	1.94	0.17
Threat*Regulation	1	0.02	0.89
Regulation*Group	1	0.40	0.53
Threat*Regulation*Group	1	12.59	=0.001
Error	34		

Ratings and SCL: RSI

We found a significant RSI[11] by Group interaction in both ratings ($F(1,38)=15.13$, $p\leq 0.001$) and skin conductance ($F(1,35)=11.31$, $p\leq 0.01$) that was driven by oppositely signed RSIs between groups (ratings: Normal group: 9.30 (3.30), Inverse group: -4.00 (1.90); skin conductance: Normal group 0.22 (0.09), Inverse group: -0.31 (0.09)). Figure 22 illustrates that Reappraisal reduced anxiety levels compared to No-reappraisal in the Normal group; by contrast, in the Inverse group, this effect was completely abolished and No-reappraisal now relatively reduced anxiety levels.

[11] (Threat/No-reappraisal - No-threat/No-reappraisal) - (Threat/Reappraisal - No-threat/Reappraisal)

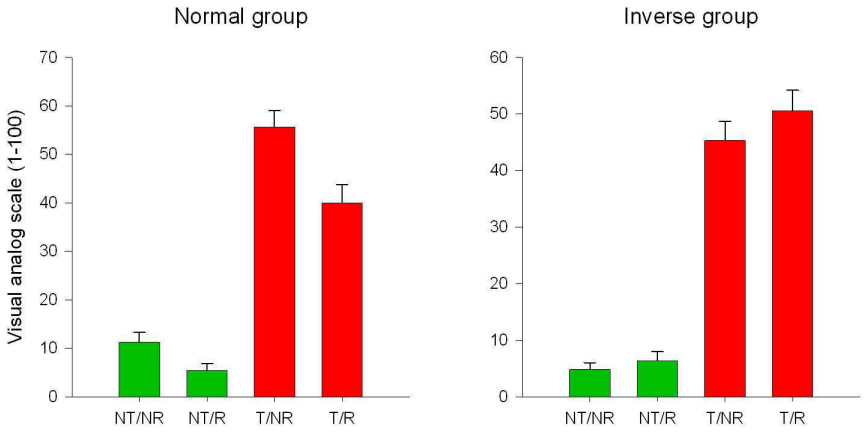

Figure 21: Study IV - Anxiety ratings in the different conditions in the Normal group and the Inverse group.

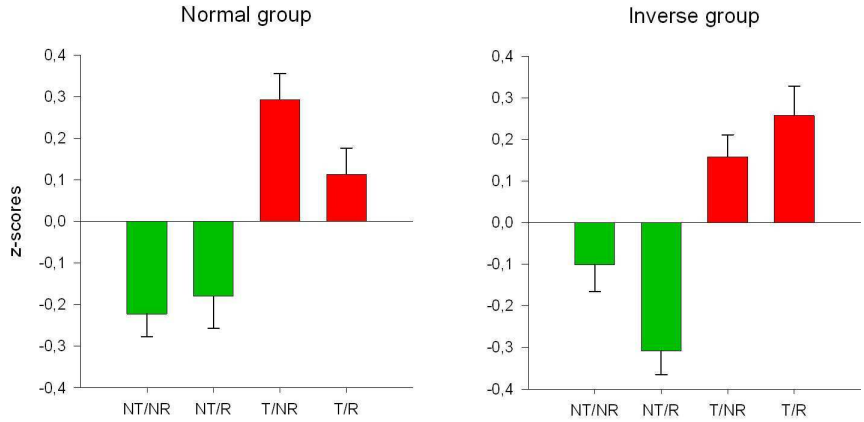

Figure 22: Study IV - Skin conductance level in the different conditions in the Normal group and the Inverse group.

7.4 Discussion V

In the other, previously described studies we found that true re-interpretation by reappraisal cannot account for anxiety reduction alone. It seems that also the high cognitive effort of applying reappraisal contributes to anxiety reduction. In the present study, we again matched both techniques for cognitive effort, although this time at a higher level than in *Studies II* and *III*. In the Normal group, that was otherwise treated similarlly as participants in *Studies II* and *III*, Reappraisal now again reduced anxiety compared to No-reappraisal. It thus seems that neither the re-interpretation (re-evaluation) compo-

nent in the reappraisal technique alone nor cognitive effort alone are sufficient to explain the relative anxiolytic effect of the technique. Rather, it might be conceivable that a combination of re-interpretation and effort are neccessary to achieve anxiolysis.

But what exactly is this re-interpretation component? Does it really consist in the semantic content of the technique that signales to participants that they are not directly affected by what is going on (distancing)? Or might outcome expectations also play a role? This was the main topic of *Study V*.

With *Study V* we could indeed show that another component seems to have a great influence on how successfully one can reduce anxiety with reappraisal: the expectancy-effect. We successfully induced a positive outcome expectation in the "Inverse group", which led to anxiety reduction.

In the normal group Reappraisal reduced anxiety relative to No-reappraisal (not expected to be anxiolytic). However in the Inverse group that was otherwise treated identically, a cover story that abolished this expectation advantage for the reappraisal technique also abolished the relative anxiolytic effect of the technique. This effect could be shown in the subjective and objective measures (ratings and SCL).

To put it differently, just because we suggested to the subjects in the Inverse group that a certain cognitive technique would lower their anxiety levels in the experiment, it actually became anxiolytic. One could describe this as a cognitive placebo effect.

This still further questions if reappraisal just works through re-interpretation alone. Rather it seems that anxiety reduction with reappraisal is a result of at least three subcomponents: re-interpretation, cognitive engagement and a placebo-like expectancy-effect.

8 Study VI: Performance monitoring in cognitive Reappraisal

8.1 Introduction VI

Appraisal theory holds that emotional reactions are the product of an evaluation process by which a stimulus or situation is analyzed in terms of its emotional-motivational meaning for the organism (Roseman, Smith & (ed.) Scherer, 2001; Scherer & Schorr, 2001; Sander, Grandjean & Scherer, 2005). Effortful reappraisal is the attempt to change a stimulus' appraisal and hence the ensuing emotional reaction (Gross, 1998). Appraisal theorists consider appraisal to be a multi-faceted, dynamic and recurrent process which continuously takes into account changes in the external or internal environment, including those resulting from the emotional response, to thus enable continuous response adjustments (Scherer & Schorr, 2001). Recent model-building in the area of reappraisal consequentially acknowledges that reappraisal efforts also require continuous adjustment in order to achieve the desired result (e.g., a stably less negative affective state) (Gross, 2007; Kalisch, 2009; Bosse, Pontier & Treur, 2010).

The implementation-maintenance model (IMMO) conjectures that this requirement for flexibility is fulfilled by a switching between operations that promote the implementation of a reappraisal strategy (that is, choosing between, and retrieving, potential reappraisals from long-term memory) and those that promote the maintenance of a chosen strategy (that is, working memory) (Kalisch, 2009). Maintenance processes must involve a component that monitors success in emotion regulation and can initiate new implementation activity or enhance maintenance efforts. Under normal circumstances, that is, with at least moderate reappraisal success, one can make a simplifying prediction that implementation processes should be predominant early during a reappraisal episode, while maintenance processes, including monitoring, should prevail during later periods. Both sets of processes should be associated with distinct neural activation patterns (Kalisch, 2009).

Meta-analysis of neuroimaging data (Kalisch, 2009) and a first empirical test of the model

using functional magnetic resonance imaging (fMRI) (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011) indeed support the existence of anatomically and temporally separable activation phases during reappraisal episodes, with an early phase being associated with mainly left posterior LFC activity and a late phase with mainly right anterior LFC activity.

Reappraisal-related neural activity is usually inferred from a comparison of the reappraisal episode with an unspecific control condition in which participants are asked to attend to the emotional stimulation and to their reactions but not to try to change their emotional responding (often termed the "attend" or "look" or "view" condition). In the present study, we attempted to more closely match this no-reappraisal comparison condition to the reappraisal condition in terms of implementation and working memory maintenance demands, in order to thus isolate a hypothetical performance monitoring component. Due to their unspecific nature "reappraisal - attend" comparisons often yield massive activation differences across large parts of the frontal cortex and other brain areas (see Kalisch 2009 for meta-analysis and Paret et al. 2011 for an example with the current paradigm). Better matching of conditions, by contrast, should much restrict such differences. Specifically, we here predicted "reappraisal - no-reappraisal" differences to be limited to late responses in the right anterior LFC, centered around coordinates x,z,y=42,48,18. These were derived from our first detachment-from threat study (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005) where we had seen late right anterior LFC activity during reappraisal. The same coordinates have successfully served to define a region of interest (ROI) for late reappraisal activity in our first test of IMMO (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011). A further confirmation of late reappraisal activity in this area would not only substantiate its relevance for detachment-reappraisal but, in the context of the current manipulation, further support our hypothesis of a late right-frontal performance monitoring process (Kalisch, Wiech, Critchley & Dolan, 2006a; Kalisch, 2009).

8.2 Materials and Methods VI

8.2.1 Participants

21 right-handed healthy participants participated in this experiment. One participant was excluded from the data analysis after his MR scan had uncovered a temporal lobe cyst. The remaining 20 participants (10 female) had an average age of 26±5 years (range 20 - 41). All were of Caucasian origin; 16 were university students. Their average trait anxiety was 33.8±8.1 (range 24 - 44).

8.2.2 Experimental Design

Again, anxiety was induced using the already described instructed fear paradigm (also known as "anticipatory anxiety").

Procedure

There were altogether 70 randomized 17.7-sec trials (24, 24 and 22 per run), 15 in each of the conditions NT/NR and NT/R and 20 in each of the conditions T/NR and T/R. During 5 of both the T/NR and T/R trials participants received a triple pain stimulus (pulse intervals: 80 ms) which occurred randomly within a time window of 3 to 12 s after offset of the auditory instruction (that is, from approximatly 2.7 sec into the trial). After 8 trials the rating phase started with the instruction "Augen auf, Rating!" ("Eyes open, rating") followed by a 5-sec presentation of a rating screen with the question "Wie gross" war Ihre Angst/Anspannung?" ("How strong was your anxiety/tension?" and a visual analog scale below. On the scale, participants could move a red star using their keypad between poles "no anxiety" (0) and "very strong anxiety" (100). The position of the star at the onset of each rating was randomized. The subsequent 5-second break was cued by the verbal instruction "Augen zu, Pause!" ("Eyes closed, break."). A schematic description is given in Figure 23.

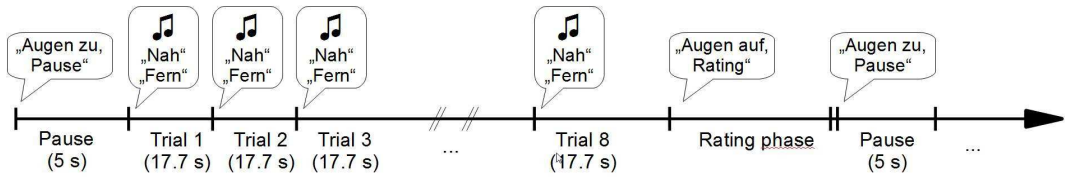

Figure 23: Study VI - an experimental block started with a 5 second pause, immediately followed by the trials: a double beep (high=threat, low=No-threat) and a verbal instruction which technique ("Nah"=Reappraisal, "Fern"=No-reappraisal) to use indicated the beginning of a trial. After the last of eight trials a verbal instruction ("Augen auf, Rating") signaled the rating phase. Ratings were made via button press. The next block started with a pause again.

8.2.3 fMRI measurement

Functional imaging was performed on a 3 Tesla MR scanner (Siemens Trio, Erlangen, Germany) equipped with a 12-channel head coil, using a gradient echo T2* weighted echo-planar imaging (EPI) sequence with BOLD (blood oxygenation level-dependent) contrast (TE=30 ms, TR=2.47 s, flip angle=80 degree). TE was minimized using a parallel acquisition technique (generalized autocalibrating partially parallel acquisitions, GRAPPA) with an acceleration factor of 2 and 24 reference lines. Each volume comprised 38 axial slices (AC-PC orientation) of 2 mm thickness and 2x2 mm 2 in-plane resolution with a slice gap of 1 mm. Participants were placed in a light head restraint within the scanner to limit head movement during acquisition. After the experimental sessions were finished, a structural T1-image was aquired.

8.2.4 Data analysis

To quantify anxiolytic effects of reappraisal from rating or SCL data, we again calculated the reappraisal success index (RSI) which corresponds to the directed interaction contrast RSI=$(T-NT)_N R-(T-NT)_R$= $-NT/NR+NT/R+T/NR-T/R$ and indexes threat-related effects (T-NT) in these measures that are attenuated by reappraisal.

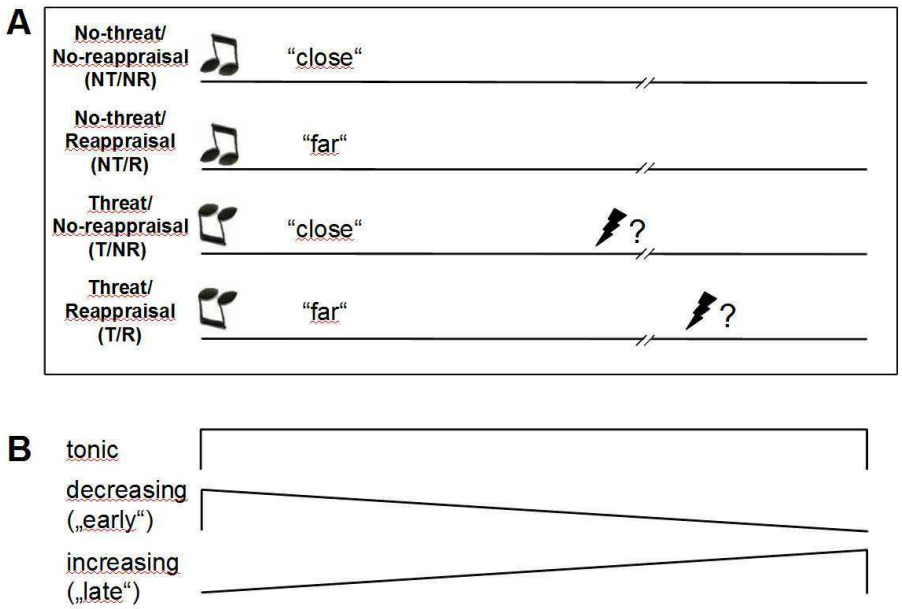

Figure 24: Study VI - Design: (A) At the onset of Threat (T) trials, a high-pitched double-beep signaled participants they might receive a painful electric stimulus to the hand at a probability of 25 percent at any time during the trial, which lasted 17.7 seconds. At the onset of No-threat (NT) trials, a low-ptched double-beep signaled safety. Reappraisal (R) trials were then signalled by the word "fern" ("far away"), No-reappraisal (NR) trials by the word "Nah" ("close"). PArticipants remained eyes closed throughout the trials. (B) To be able to detect the hypothesized temporal activity profiles during Reappraisal in Experiment 2, neural activation during trials was modeled as tonic, linearly increasind or linearly decreasing response.

8.2.5 fMRI data analysis

fMRI data were preprocessed using SPM8 (www.fil.ion.ucl.ac.uk/spm; Friston et al. 2007). The 5 initial EPI images were discarded to account for T1 equilibration. To correct for head movement and movement-by-distortion interactions, they were then realigned to the 6th volume and unwarped. The structural T1 images were coregistered to the EPI images and then segmented and spatially normalized to a standard T1 template using the "New Segment"-routine as implemented in SPM8. The normalization parameters from this procedure were then applied to the EPI images. The normalized EPI images were spatially smoothed (Gaussian kernel, FWHM 6 mm), temporally high-pass filtered (cut-off 128 s) and corrected for temporal autocorrelations using first-order autoregressive modeling.
Statistical analysis was performed using a standard approach for fMRI, involving a gen-

eral linear convolution model at the single-subject level and a random-effects analysis at the group level within the SPM software (Friston, Ashburner, Kiebel, Nichols & Penny, 2007). The three runs were concatenated into a single time series and, for each participant, regressors were defined that modeled the predicted time courses of experimentally induced brain activation changes. Each of the four experimental conditions (NT/NR, NT/R, T/NR, T/R) was modeled using two different temporal response profiles during the 17.7-sec trials: a tonic response lasting the whole duration of a trial and a response that increased linearly during a trial and served to detect late activations. Receipt of pain was modeled as distinct "events" (delta functions with 0 duration). Blocks during which participants actually received pain stimuli and ratings were modeled as "box-car" (on-off) regressors. Onsets of pauses after the ratings were modeled as events. Each regressor was convolved with the canonical hemodynamic response function. Using these regressors in a general linear model (multiple regression) of brain activation at each voxel yields parameter estimates of the contribution of each regressor to the fMRI signal measured in each voxel. The subject- and regressor-specific parameter estimate images were spatially smoothed (full width at half maximum (FWHM) 10 mm) and entered into a random-effects group analysis using SPM's "flexible factorial" model which permits correction for possible non-sphericity of the error term (here, dependence of conditions).

Group-level design matrices included 19 regressors (4 regressors of interest corresponding to the 4 experimental conditions NT/NR, NT/R, T/NR, and T/R, plus 15 subject constants). Linear combinations ("contrasts") of the regressors of interest were used to test for main effects and interactions. Here, multiplication of the parameter estimate images for the linearly increasing regressors by -1 allowed for also assessing linearly decreasing responses as depicted in Figure 24 B.

Significance of effects was tested using voxel-wise one-tailed t-tests. Correction for multiple comparisons following Gaussian random field theory (family-wise error (FWE) method) at a threshold of $p<0.05$ ("small volume correction") was limited to a sphere of 12-mm radius around 42,48,18 (see Introduction). In the results tables, anatomical localization of activations was carried out with reference to the atlas of Duvernoy (1999).

Unambiguous white matter or liquor clusters are not reported. Cluster submaxima are

reported when more than 8 mm apart. For the lateralization test (see Results), we used an anatomical mask of the bilateral LFC that included all parts of the superior, middle, and inferior frontal gyri (see Paret et al. 2011).

8.3 Results VI

Anxiety ratings

As in Experiment 1, anxiety ratings showed significant main effects of Threat ($F(1,19)=178.76$, $p<0.001$) and Reappraisal ($F(1,19)=17.76$, $p<0.001$) and a significant Threat by Reappraisal interaction ($F(1,19)=5.06$, $p=0.04$; Figure 25). The anxiety-rating-RSI was $M=6.2$ and $SD=12.20$ (>0, $t(19)=2.25$, $p=0.018$). It was still significant ($p=0.04$) when removing one outlier who had an RSI of >2 s.d. above average.

SCL

SCL showed a significant main effect of Threat ($F(1,14)=56.34$, $p<0.001$) but failed to show the critical interaction of Threat and Reappraisal ($F(1,14)=0.78$, $p=0.38$; Figure 25). The SCL-RSI was $M=0.09$ and $SD=0.39$ ($t(14)=0.88$, $p=0.20$). However, removing one outlier who had an SCL-RSI of >2 s.d. below average yielded a trend-like Threat by Reappraisal interaction (p=0.08) and a significant SCL-RSI ($p=0.041$).

Taken together, self-report and physiological data indicate that detachment-reappraisal (R) reduced anxiety compared to an immersion mode (No-reappraisal, NR).

Effort ratings

After each of the three experimental runs in Experiment 2, participants provided verbal ratings of the effort necessary to rehearse the self-statements and to perform visual imagery through-out R as well as NR trials (Table 5,). There were no main effects of Reappraisal (R vs. NR) or Time (runs) as well as no interactions, whether testing for statements or imagery (all $p>0.158$). This indicates participants put similar cognitive

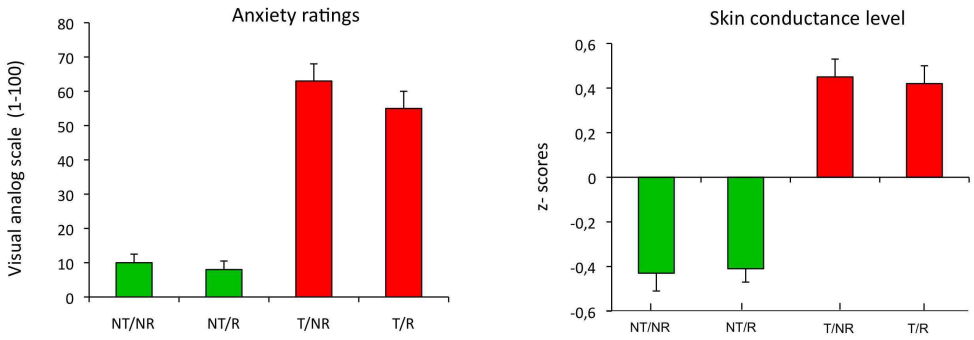

Figure 25: Study VI - Anxiolytic effects of detachment-reappraisal. Average trial-by-trial anxiety ratings and skin conductance levels in the conditions No-threat/No-reappraisal (NT/NR), No-threat/Reappraisal (NT/R), Threat/No-reappraisal (T/NR), and Threat/Reappraisal (T/R). See the reduction of threat responses in T/R relative to T/NR. Error bars: s.e.m.

effort into both detaching and immersing and did so stably across runs. It indirectly suggests that the attempted matching of Reappraisal and No-reappraisal conditions for implementation and maintenance demands was successful.

Table 5: Study VI - Effort ratings Experiment 2: *M* (± *SD*), No-reappraisal (NR): immersion; Reappraisal (R): detachment.

run		1	2	3
Rehearsal of self-statement	NR	3.3 (2.0)	2.2 (1.3)	2.5 (1.3)
	R	3.4 (2)	2.3 (1.2)	2.6 (1.2)
Visual imagery	NR	3.8 (1.9)	4.2 (2.5)	4.2 (2.2)
	R	3.4 (1.7)	4.3 (2.5)	4.2 (2.2)

Imaging results: standard analysis

Main effects of Threat (T-NT=-NT/NR-NT/R+T/NR+T/R) with tonic, linearly decreasing (i.e., early) and linearly increasing (i.e., late) response profiles during trials were observed in the typical network including dorsal medial prefrontal and anterior cingulate cortex (dmPFC/dACC), anterior insula, basal ganglia, and thalamus (compare Mechias et al. 2010 for meta-analysis which also shows that the amygdala is not an area consistently found in instructed fear studies; Tables 6, 7, and 8 in Appendix B).

Matching R and NR strategies for early implementation and later working memory de-

mands was aimed at reducing or abolishing any reappraisal-related activations apart from late effects that were supposed to reflect performance monitoring and were predicted for the right anterior LFC. In agreement with this, there were no detectable main effects of Reappraisal (contrast R-NR=-NT/NR+NT/R-T/NR+T/R) with tonic and linearly decreasing profiles, including when lowering the threshold to a very liberal p<0.01 uncorrected (with the exception of a small cluster in left posterior LFC with a tonic profile, -38,-2,36, z=2.67, p<0.01 unc.). By contrast, and as predicted, there were wide-spread Reappraisal main effects with a linearly increasing (i.e., late) profile that, within frontal cortex (right hemisphere) (Figure 26), albeit extending more posteriorly than expected. The effect survived correction for multiple comparisons in our pre-defined right anterior LFC ROI (see Methods for definition) at 42,38,12 (z=2.99, p=0.029 corrected, Figure 27). The parameter estimates in Figure 27 suggest late right-frontal reappraisal activity was more pronounced when participants had to detach from a threatening (T/R) than from a safe (NT/R) situation. This difference did however not reach significance (there was no Threat by Reappraisal interaction in this area).

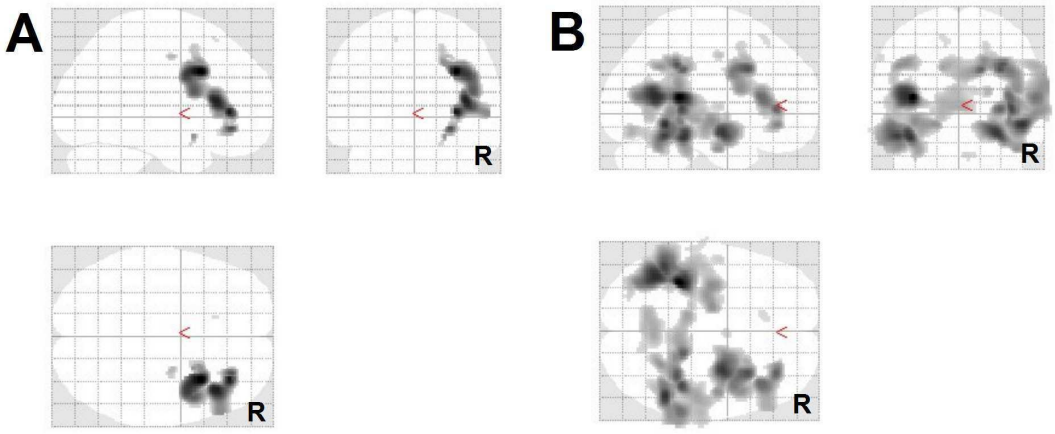

Figure 26: Study VI - Standard analysis: Distribution of late ("increasing") reappraisal-related activity. Within frontal cortex, Reappraisal main effects (R-NR) with a temporal profile that increased linearly during trials were located in the right hemisphere. The glass brain in A is masked by a bilateral LFC mask (see Methods). The glass brain in B is not masked to also show extra-frontal activations, and is otherwise identical. Threshold: p<0.001 uncorrected. R, right.

Threat by Reappraisal interactions of the form $(T-NT)_N R-(T-NT)_R$= $-NT/NR+$

$NT/R + T/NR - T/R$, corresponding to threat-related activity that is reduced by reappraisal (i.e., RSI), were weak and not observed in any of the typical anxiety areas (Tables 6, 7 and 8 in Appendix B). This may reflect the moderate anxiolytic effects of reappraisal in the behavioral data of Experiment 2. Complementary interactions of the form $(R - NR)_T - (R - NR)_N T = +NT/NR - NT/R - T/NR + T/R$, corresponding to reappraisal-related activity that is larger under threat than safety, were likewise weak and none were found in frontal cortex (Tables 6, 7 and 8 in Appendix B). A larger sample size may be needed to show these interaction effects in neural activation data.

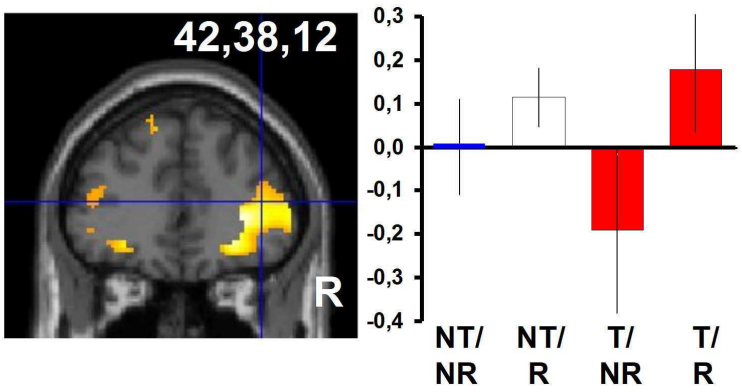

Figure 27: Study VI - Standard analysis: Late ("increasing") reappraisal-related activity in right anterior lateral frontal cortex (LFC). A Reappraisal main effect (R-NR) with a temporal profile that increased linearly during trials was observed in a predefined right anterior LFC ROI (region of interest) that had previously been shown to exhibit late reappraisal activity (see Introduction), at $p<0.05$ corrected. Activations are superimposed on a canonical structural image. Display threshold: $p<0.01$ uncorrected. The bar graph shows corresponding group-averaged parameter estimates ("betas") in the voxel indicated by the haircross and the inserted coordinate. Values are normed to the first condition (NT/NR). Positive parameter estimates indicate linearly increasing response profiles (in the two R conditions), negative parameter estimates indicate linearly decreasing profiles. R, right. Error bars: s.e.m.

Imaging results: lateralisation test

The glass brains in Figure 26 suggest a right-lateralisation of late reappraisal activations in LFC. To more formally test this, we used established methodology (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011). We averaged within each of the 15 participants with useful fMRI data the coordinates of all (left- and right-sided) voxels from the linearly increasing Reappraisal main effect that were contained in the a priori bilateral LFC mask defined in Methods and that survived an uncorrected threshold of

p<0.05. As in Paret et al. (2011), the choice of the threshold was data-driven and the arbitrary criterion was to find a threshold below p<0.1 that would allow to include a maximum possible number of participants. Choosing a liberal threshold has the additional advantage that this makes the analysis less vulnerable to thresholding effects that can lead to the exclusion of, for instance, left-sided voxels that are just below the chosen threshold. It thus allows for a fairer hemisphere comparison. Averaging of coordinates resulted in one single coordinate for each participnat (Figure 28) that expressed the "center of gravity" of lateral frontal reappraisal activation in that participant. That is, if in a given participant the majority of activated voxels was located in, e.g., the right LFC, this would result in an average coordinate with a positive (right-sided) x value. Analogously, if in a given participant the majority of LFC voxels was located in, e.g., anterior LFC, this would "push" the average coordinate towards larger (more anterior) y values. Note this center of gravity is a virtual coordinate which may not correspond to any actual locus of activation.

The group average of coordinates thus obtained from the contrast was x,y,z=5,7,35. The x coordinate became 11 when removing 2 outliers (>2 standard deviations below average; Figure 28) and was significantly >0, that is, right-sided, only after outlier exclusion ($t(12)$=3.50, p<0.01 one-tailed). To test whether late reappraisal activation shows an anterior center of gravity within LFC, we asked whether the y coordinate was >30, an arbitrary posterior/anterior border which we chose on the basis of prior observations (Kalisch, 2009). However, we found that the y value was significantly <30 ($t(14)$=-21.23, p<0.001). Hence, previous findings of an anterior distribution of right-sided late reappraisal activations (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005; Kalisch, 2009; Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011) could not be confirmed in this version of the paradigm.

Imaging results: brain-behaviour correlations

If the right anterior LFC monitors reappraisal performance, it needs to access information about one's current bodily state or feelings. In an exploratory analysis we observed that, in R trials, average fMRI parameter estimates from the right anterior LFC peak found

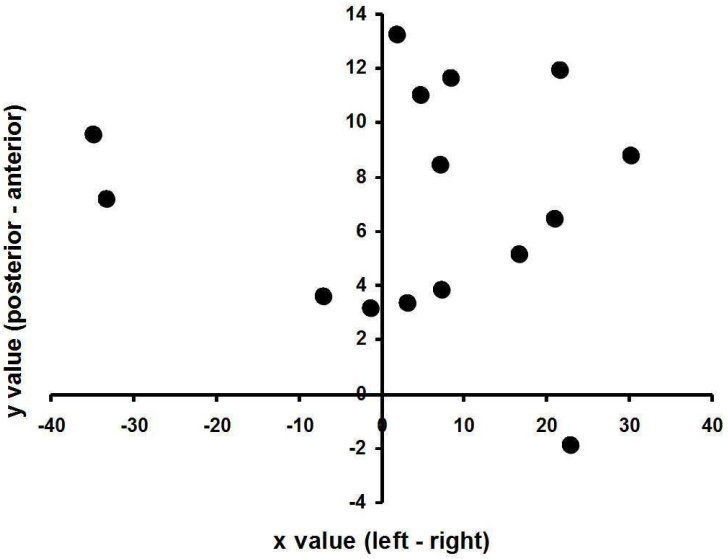

Figure 28: Study VI - Lateralisation test: In each participant, coordinates of all lateral frontal supra-threshold (p<0.05 uncorrected) voxels from the Reappraisal main effect (R-NR or [-1 1 -1 1]) with a linearly increasing response profile during trials were averaged into one single, virtual coordinate or "center of gravity" for that participant. Note the apparent right-lateralisation (positive x values) and the two outliers (x<-30).

above in the linearly increasing Reappraisal main effect were significantly correlated with average SCL scores (Pearson's R=0.56, p=0.04, one-tailed; Figure 29). In NR trials, where there was no requirement for performance monitoring, no corresponding relation was observed (R= -0.41, Fisher test (Fisher, 1921)). Removal of one outlier (>2 standard deviations below average) from the fMRI parameter estimates in NR however reduced the difference in R vs. NR correlations to trend level significance (p=0.08). Note that the Fisher test is a particularly conservative test and that the number of participants in this analysis was comparatively small (n=11). We therefore report this finding descriptively only (for the purpose of future hypothesis testing in larger samples) and refrain from any further discussion. No comparable effect was observed in anxiety ratings.

8.4 Discussion VI

In the fMRI study we replicated the findings from anxiety ratings and SCL as already seen in *Study IV*. Analysis of the functional imaging data revealed reappraisal-related ac-

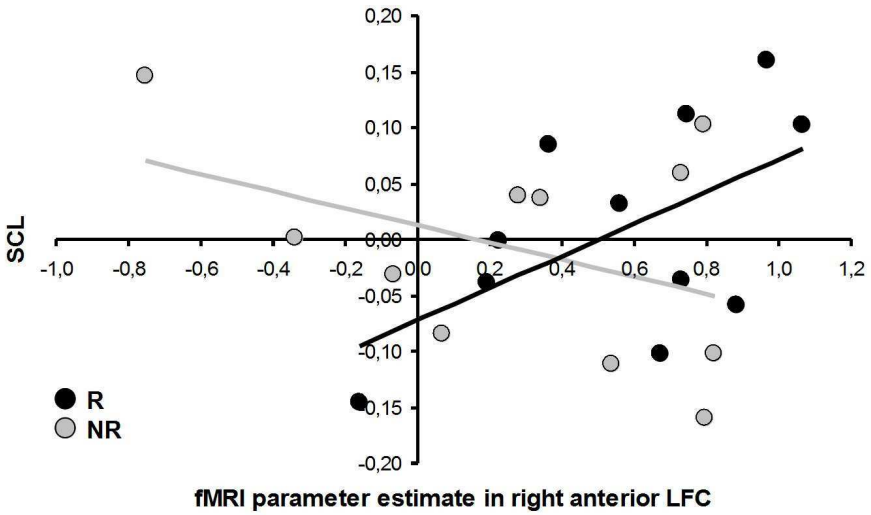

Figure 29: Study VI - Brain-behavior correlations: Average fMRI parameter estimates from the right anterior LFC (42,38,12) were significantly correlated with SCL scores in Reappraisal (R) but not in No-reappraisal (NR) trials, in line with monitoring of internal states during reappraisal by this region.

tivation in the anterior lateral frontal cortex. This activation was only seen in the linearly increasing response profile and therefore supports our IMMO-hypothesis that maintenance of reappraisal processes engages lateral anterior areas late during reappraisal. A lateralisation test showed that the described activation was right lateralised although extending more posterior than predicted by IMMO.

Finally, the results from brain-behaviour correlational analyses also point to a role of right anterior lateral frontal cortex in maintenance and monitoring of reappraisal performance. However the exact nature of this effect has to be further investigated in future studies employing a larger sample size.

Part III

Discussion

9 General discussion

Re-evaluation of a situation or stimulus is meant to be the main anxiety reducing component of cognitive reappraisal. However, with the studies presented in this thesis we could show that at least two further factors influence how successful emotion regulation via reappraisal is.

With *Study I* we demonstrated that the reappraisal technique we used is anxiolytic. Participants were able to distance themselves from their feelings in an anticipatory anxiety experiment. Still, it was not fully clear to what extent the cognitive demand of the reappraisal technique and expectancy-effects underlay successful anxiety reduction.

Therefore we conducted *Study II, III and IV* with a modified study design that allowed seizing effects of cognitive effort. The results supported the conclusion that the cognitively demanding nature of reappraisal is an important component of the observed anxiety reduction. Indeed reappraisal success is not fully explainable by effects of cognitive effort, but cognitive effort (with regard to e.g. high working memory load) seems to play an important role. This is in line with former research addressing the question if reappraisal resembles distraction (McRae, Hughes, Chopra, Gabrieli, Gross & Ochsner, 2010).

Study V extended the experimental manipulation in a way that allowed to disentangle expectancy-effects from other anxiolytic effects. The results indicate that the outcome expectation associated with a cognitive regulation strategy makes an important contribution to the success of emotion regulation: if the expectation advantage of the Reappraisal

relative to the No-reappraisal comparison strategy was abolished by virtue of a cover story, the relative anxiolytic effects normally observed for the reappraisal strategy were no longer apparent. This observation even raises the intriguing question whether there are any major anxiolytic effects of reappraisal over and above the placebo effect demonstrated here. Our findings importantly extend earlier reports of expectation effects on aversive emotional responding, including in the medical domain (Petrovic, Dietrich, Fransson, Andersson, Carlsson & Ingvar, 2005; Zhang, Qin, Guo & Luo, 2011; Enck, Benedetti & Schedlowski, 2008; Furmark, Appel, Henningsson, Ahs, Faria, Linnman, Pissiota, Frans, Bani, Bettica, Pich, Jacobsson, Wahlstedt, Oreland, Långström, Eriksson & Fredrikson, 2008; Kirsch, 2009) and pose a challenge to current emotion regulation research.

With *Study VI* fMRI measurements were added to the experimental design to assess reappraisal-related brain activation with special focus on late maintenance-related activation.

If effortful reappraisal is a temporally extended, resource-demanding and goal-oriented cognitive process, then it necessarily requires performance monitoring and adjustment operations in order to work effectively and efficiently. Acknowledging this general idea, recent theorising has increasingly emphasised the role of adjustment and adaptation in cognitive emotion regulation (Gross, 2007; Kalisch, 2009; Bosse, Pontier & Treur, 2010). In this context, the identification of the neural substrates of performance monitoring in reappraisal becomes a critical step on the way towards unraveling the neural architecture of this complex emotion-regulatory process.

The implementation-maintenance model of reappraisal (IMMO) posits that the relevant monitoring operations have their only onset after an initial ("early") phase of strategy implementation and largely run in parallel with"late" working memory maintenance processes that aim at keeping the chosen reappraisal material online until reappraisal efforts subside (Kalisch, 2009). Our data suggest that the co-occurring late processes of maintenance and monitoring can be neurally dissociated and that monitoring in particular involves activation of the right LFC. This interpretation rests on the assumptions that i) we managed to match the reappraisal (R) and its comparison (NR) condition for imple-

mentation and maintenance demands, thus isolating monitoring, and ii) that participants were so successful in their reappraisal efforts that they did not have to perform multiple recurrent switches between implementation and maintenance activities (Kalisch, 2009), thus allowing us to ascribe late neural activity (increasing response profile) to "late" processes (in the sense of IMMO) only. The former assumption (i) receives indirect support from the similar effort ratings for the R and NR strategies and from the absence of detectable neural Reappraisal main effects (R - NR) with other but increasing response profiles, which stands in contrast to wide-spread tonic Reappraisal main effects in an earlier study with the same detachment-from-threat paradigm but where the NR condition was little demanding and simply consisted in asking participants to attend to, but not to change, their emotional state (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011). The latter assumption (ii) appears justified when considering that multiple switching would have most likely resulted in unpredictable and unsystematic response patterns.

What is the exact nature of the putative monitoring processes that we believe here to be able to locate in the right LFC? In Kalisch et al. (2009), we have suggested one possible element of monitoring in reappraisal which might consist in checking if the reappraisal material (selfstatement, mental images) retrieved during the implementation stage is in accordance with instructions or own intentions. This type of "post-retrieval monitoring" (Cruse & Wilding, 2009; Gallo, McDonough & Scimeca, 2010) is bound to the existence of specific instructions or intentions about what to retrieve and may not be a generic reappraisal sub-component. In this study, where retrieval was required in both the reappraisal (R) and the comparison condition (NR), it should have been subtracted out. The same applies to a presumably highly similar potential operation of monitoring one's working memory (Champod & Petrides, 2007) for the continued presence of the chosen reappraisal material. A third type of monitoring might consist in evaluating reappraisal success. In contrast to the first two, this monitoring function should be generic and of critical importance to any extended reappraisal effort. Its target is an internal state qualified by bodily sensations and feelings. It is thus self-referential and focused on momentary experience. It may be akin to a type of self awareness sometimes termed "experiential focusing" and

different from self-related processing with a "narrative" focus (one that serves to link subjective experience across time and thus generating continuity of identity by making reference to autobiographical memory and self-concepts (Farb, Segal, Mayberg, Bean, McKeon, Fatima & Anderson, 2007)). Interestingly, and in parallel with the current data, deliberately keeping an experiential focus is associated with right-lateralized frontal activity (Farb, Segal, Mayberg, Bean, McKeon, Fatima & Anderson, 2007).

Further, in the same study, experiential focusing also involved attenuation of rostral midline activation supporting narrative self-referential processing. The latter finding dovetails with a previous observation that successful detachment-reappraisal can reduce threat-evoked rostral dmPFC/dACC activation (contrast $(T-NT)_N R-(T-NT)_R$=RSI) (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005). It would thus be informative to know whether this result can be replicated, which might however require stronger anxiolytic effects of reappraisal than in *Study VI*.

A useful distinction to make is between the monitoring operations discussed here, which are thought to be rather slow and "meta-cognitive" (i.e., working on consciously accessible mental representations such as working memory contents, feelings, visceral sensations...; (Kalisch, 2009), and the quick and presumably automatic conflict or interference monitoring processes studied, for instance, in Stroop or flanker tasks (Carter & van Veen, 2007; Egner, 2007). While it is likely that such quick conflict detection processes do occur while participants perform the cognitive task of implementing and maintaining reappraisal material in the face of emotional interference (e.g., threat) (Etkin, Egner & Kalisch, 2011), they might nevertheless be such an inherent aspect of these implementation and maintenance operations that they were subtracted out in our R - NR comparison in *Study VI*, where NR was also implementation and maintenance-demanding.

By contrast, in Paret et al. (2011), where NR was less demanding, we did observe extended dorsomedial-frontal activation during reappraisal (contrast R - NR), including in typical posterior-to-mid cognitive control areas (compare (Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004) and figure 5, tonic, in Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias and Kalisch, 2011).

We initially observed late right anterior frontal reappraisal activity in a study with a simi-

lar, though more complicated detachment strategy (R) and a comparison NR condition of immersion that also included imagery and subvocal rehearsal of a self-statement (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005). In a subsequent meta-analysis of neuroimaging studies of reappraisal, we had then found that reappraisal activity increasingly shifts from left posterior towards right anterior frontal sites the longer reappraisal trials are (the more time participants have to reappraise), in line with the idea of maintenance processes becoming the more predominant the longer a trial lasts (Kalisch, 2009). Finally, Paret et al. (2011) have recently reproduced this pattern. *Study VI* is thus the fourth piece of evidence for the existence of late reappraisal-related neural activity and thus another confirmation for a central prediction of IMMO (Kalisch, 2009). It deviates from the aforementioned studies in that late reappraisal activity was rightlateralized but not predominantly anterior. It is possible that this reflects random variation.
We can however not exclude either that the anteriorization of late reappraisal activity in the first three studies stemmed from another component reappraisal process that was subtracted out by our specific R-NR comparison in *Study VI*. Speculation about such a potential process should await replication of the effect.

Implications for Cognitive-Behavioural Therapy

Much effort is currently being dedicated to unravelling the psychological laws and underlying neural mechanisms that govern voluntary or cognitive emotion regulation. This research is partly motivated by the hope that it will provide behavioral, pharmacological or neurotechnological instruments to improve the efficiency and effectiveness of emotion regulation. We would argue that the success of these efforts will critically depend on our ability to disentangle non-specific ingredients of regulation (e.g., a placebo action) from its specific ingredients, such as semantic content in the case of reappraisal. For instance, it might well be that the neural circuitry mediating the implementation and maintenance of a reappraisal strategy during emotional challenge (Kalisch, 2009; Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011) is less critical for reappraisal success than the to-be-identified circuitry supporting expectation, and therefore a less promising target for cognitive enhancement.

Another recent development that highlights the need for a better understanding of the causal mechanisms beneath successful emotion regulation is the increasing incorporation of emotion regulation elements into psychotherapy. While cognitive behavior therapy arguably has long had an element of kindling emotion regulation (e.g., with the help of psychoeducation and instructions for exposure; see, for instance, (Salkovskis, Hackmann, Wells, Gelder & Clark, 2007; Berking, Margraf, Ebert, Wupperman, Hofmann & Junghanns, 2011)), explicitly incorporating emotion regulation training into therapy protocols is becoming increasingly popular, based on the idea of a causal role for emotion regulation deficits in disease etiology (Berking, Wupperman, Reichardt, Pejic, Dippel & Znoj, 2008; Gotlib & Joormann, 2010). While regulation skills trained in such protocols are varied and also involve many non-cognitive forms of regulation, it might nevertheless be asked to what extent they simply add another non-specific element. An answer to this question should considerably affect future protocol development and is particularly pertinent in the light of demonstrated outcome expectation effects on the psychotherapy response (Dew & Bickman, 2005).

There are clinical applications of emotion regulation techniques. A technique very similar to the described reappraisal technique is the "Bildschirmtechnik" (screen technique) (Reddemann, 2005). It is used in cognitive behavioural therapy (CBT) of traumatised patients. The aim is that the patient reestablishes a feeling of control over thoughts and feelings by imagining the traumatic event being a movie on a screen. The patient then learns to control the "movie" with an imagined remote control. The main point is that patients are able to distance themselves from their strong emotions and memories without trying to avoid them, as avoidance would hold up the traumatic content. Knowledge about the underlying processes behind this emotion regulation technique would help to understand and maybe even improve CBT.

Even though we did not design the studies presented here as psychotherapeutic research

studies, especially *Study V* emphasizes the importance of the "unspezifische Wirkfaktoren"[12] and perceived self-efficacy. One Wirkfaktor is "activation of resources". Although it is meant to be the use of the patient's abilities and skills, it also implies that therapy will work best if the patient has a strong belief in the abilities of the therapist. In other words, the higher the positive outcome expectations of the patient are the greater the therapeutic success will be. As well one could say that it is important to strengthen the patients perceived self-efficacy. But our study would take this idea one step further and even imply that the content of the technique is much less relevant than the belief in its efficacy. This emphasizes the importance of the unspezifische Wirkfaktoren.

[12]Klaus Grawe (2005) could prove that "unspezifische Wirkfaktoren" (unspecific active factors) have great impact on the outcome of therapeutic intervention. His factors were therapeutic relationship, activation of resources, problem-actualisation, motivational clarification and coping with problems. Numerous studies verified the importance of these unspecific factors.

10 Methodological Discussion

Limitations

Limitations to the generalizability of our findings come from the use of an exclusively Caucasian sample that was dominated by university students.

Another important limitation of all studies reported here is that we cannot say at present whether our observations would generalize to other cognitive regulation techniques and other emotions. This clearly warrants further research.

We have earlier emphasized that an important question for future research will be to what extent late right-frontal reappraisal activity, as well as other observations made with our paradigm (Paret, Brenninkmeyer, Meyer, Yuen, Gartmann, Mechias & Kalisch, 2011), can also be seen in the regulation of other types of emotions, including positive ones, and with other types of reappraisal strategies, such as those that reinterpret the causal structure of a situation ("situation-focused") rather than applying detachment/distancing ("self-focused") (Ochsner, Ray, Cooper, Robertson, Chopra, Gabrieli & Gross, 2004). It is for instance conceivable that late right-frontal activity reflects a state of detachment itself rather than performance monitoring. In this case, this activation pattern should be restricted to distancing paradigms. It is also possible that paradigms that do not prescribe a specific reappraisal strategy and leave participants more freedom in their choice of reappraisal material (Jackson, Malmstadt, Larson & Davidson, 2000; Phan, Fitzgerald, Nathan, Moore, Uhde & Tancer, 2005; Urry, van Reekum, Johnstone, Kalin, Thurow, Schaefer, Jackson, Frye, Greischar, Alexander & Davidson, 2006) do not show late right-lateralized activation, which would question the generic nature and central role of the underlying processes. Future research will have to address these questions.

Startle

A measure of conditioning success is the *eyeblink startle reflex* to a loud noise (Kindt, Soeter & Vervliet, 2009). During a fearfull state the startle response is enhanced. One ad-

vantage of startle over skin conductance is, that startle measures aversive learning directly (Grillon & Baas, 2003). The startle reflex is independent of any declarative knowledge about stimulus contigency whereas changes in skin conductance are to a great extent connected to explicit contingency learning(Hamm, Karnath & Thier, 2006). This means startle would be a more direct measure of anticipatory anxiety with all its possibly underlying processes, explicit and implicit. It would be interesting to add startle reflex measurements to our established paradigm.

Reappraisal with electric pain stimuli

We used electric pain stimuli to elcicit a fear response and anticipatory anxiety. In a second step the participants had to change their emotion by applying reappraisal during phases of anticipatory anxiety. The aim was to dampen the feeling of anxiety by cognitive reinterpretation. One could ask the question if reinterpreting a painful electrical stimulus, that might in fact be a threat to ones health, is a reasonable achievment. In cognitive-behavioural therapy it might be the aim to reduce exaggerated pathological fear responses. However the stimuli that elicit these pathological fear responses normally cannot harm the human body (like the sight of spiders or standing on an open space). So, in this case, the anxiety reaction is maladaptive. But reacting with anxiety while anticipating an electrical shock might actually be a reasonable reaction, as it protects the body from potential harm. It might be that reappraising potentially harmful stimuli differs from reappraising originally harmless stimuli on a process-level.

11 Future outlook

Successful emotion regulation is essential for the psychological well-being of the individual. Emotion regulation styles differ interindividually and influence physiological and psychological functioning. Disturbed emotion regulation might play a key role in the development and maintanace of anxiety disorders (Amstadter, 2008), although further research, especially in clinical populations, will have to deepen our knowledge in this field.

The studies presented here highlight the importance of decomposing the emotion regulation process into its subcomponents. We could show that next to re-interpretation, additional processes like cognitive engagement and expectancy-effects lead to attenuation of anxiety during cognitive reappraisal.

We hope that the studies presented here make a useful contribution to our understanding of the functional architecture of cognitive reappraisal, both at a psychological and a neural level. A deeper understanding of the mechanisms behind cognitive reappraisal is the best basis for investigating dysfunctional emotion regulation in patients and for designing psychological and pharmacological interventions that aim at improving individual reappraisal capacities. A better understanding of emotion regulation deficits might help treating patients with affective dysregulation as seen for instance in anxiety disorder.

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A Appendix A

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B Appendix B

Table 6: Study V - Imaging results (Experiment 2): standard analysis. Activations with tonic response profile during trials. Statistical threshold: p<0.001 uncorrected. dACC, dorsal anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; G, gyrus; L, left; R, right; S, sulcus. MNI, Montreal Neurological Institute.

Region	Cluster maximum	z score	Cluster size	p corr. < 0.05
	x y z (MNI)		(# voxels)	(whole brain)
Main effect of Threat (T-NT): [-1 -1 1 1]				
bilat ant insula, extending to:	36 28 4	5.37	9105	yes
bilat basal ganglia,	-34 22 8	5.21		yes
bilat thalam, R mid front G	28 10 -2	4.87		yes
bilat ant cing G, extending to:	8 20 32	4.53	1862	yes
bilat sup front G	8 14 58	4.10		yes
(dACC/dmPFC)	12 0 64	3.75		yes
L supramarginal G	-62 -52 40	4.51	449	yes
R supramarginal G	56 -40 34	4.51	565	yes
L middle front G	-32 44 28	4.13	609	
L cerebellum	-36 -56 -34	3.57	156	
	-28 -62 -30	3.50		
Brainstem/spinal cord	4 -36 -50	3.39	39	yes
Sup colliculuc	0 -30 -8	3.21	13	
Cerebellum	0 -48 -24	3.20	5	
L postcentral G	-66 -30 24	3.16	17	
Main effect of Reappraisal (R-NR): [-1 1 -1 1]				
no voxels surviving threshold				
Interaction Down-regulation of Anxiety $(T - NT)_{NR}$ - $(T - NT)_R$: [-1 1 1 -1]				
no voxels surviving threshold				
Interaction Threat-specific Reappraisal $(R - NR)_T$ - $(R - NR)_{NT}$: [1 -1 -1 1]				
R postcentral G	26 -32 48	4.05	362	
R paracentral lobe	8 -18 62	3.30	13	

Table 7: Study V - Imaging results (Experiment 2): standard analysis. Activations with linearly increasing response profile during trials. Statistical threshold: p<0.001 uncorrected.G, gyrus; L, left; R, right; S, sulcus. MNI, Montreal Neurological Institute.

Region	Cluster maximum	z score	Cluster size	p corr. < 0.05
	x y z (MNI)		(# voxels)	(whole brain)
Main effect of Threat (T-NT): [-1 -1 1 1]				
no voxels surviving threshold				
Main effect of Reappraisal (R-NR): [-1 1 -1 1]				
L sup temp G, extending to:	-36 -38 12	5.06	5263	yes
L mid temp G,	-42 -58 14	4.64		yes
L inf temp G	-38 -34 -18	4.57		yes
R mid occ G, extending to:	50 -48 -8	4.60	5635	yes
R hippocampus,	30 -4 -14	4.54		yes
R sup temp G	42 -36 4	4.43		yes
R inf front S, extending to:	32 16 34	4.35	1865	yes
R inf front G,	32 38 4	4.21		yes
	40 28 12	4.15		
bilat calcarine S, extending to:	2 -58 6	3.60	817	
bilat parieto-occipit fissure	12 -66 18	3.21		
R parieto-occip fissure	24 -54 18	3.49	53	
R mid cing G	2 -2 34	3.22	12	
L sup temp S	-62 -28 -12	3.17	22	
L sup front G	-12 28 60	3.15	17	
Interaction Down-regulation of Anxiety $(T - NT)_{NR}$ - $(T - NT)_R$: [-1 1 1 -1]				
brainstem	0 -32 -42	3.39	32	
R cerebellum	32 -66 -44	3.16	11	
Interaction Threat-specific Reappraisal $(R - NR)_T$ - $(R - NR)_{NT}$: [1 -1 -1 1]				
no voxels surviving threshold				

Table 8: Study V - Imaging results (Experiment 2): standard analysis. Activations with linearly decreasing response profile during trials. Statistical threshold: p<0.001 uncorrected. G, gyrus; L, left; R, right; S, sulcus. MNI, Montreal Neurological Institute.

Region	Cluster maximum	z score	Cluster size	p corr. < 0.05
	x y z (MNI)		(# voxels)	(whole brain)
Main effect of Threat (T-NT): [-1 -1 1 1]				
L sup pariet G, med	4 -82 50	4.08	2539	
R cuneus	0 -54 56	3.97		
R insular S, ant	-14 -80 52	3.53		
L sup pariet G, med	8 -6 -14	3.79	45	
R cuneus	-24 -96 28	3.59	144	
R insular S, ant	-14 -36 4	3.52	50	
L sup pariet G, med	-28 14 56	3.40	94	
R cuneus	2 -98 20	3.37	96	
R insular S, ant	8 -46 -50	3.34	15	
Main effect of Reappraisal (R-NR): [-1 1 -1 1]				
no voxels surviving threshold				
Interaction Down-regulation of Anxiety $(T-NT)_{NR}$ - $(T-NT)_R$: [-1 1 1 -1]				
see Interaction Threat-specific Reappraisal in Table above				
Interaction Threat-specific Reappraisal $(R-NR)_T$ - $(R-NR)_{NT}$: [1 -1 -1 1]				
see Interaction Down-regulation of Anxiety in Table above				

C Appendix C

A meta-analysis of instructed fear studies: Implications for conscious appraisal of threat

C.1 Introduction

The appraisal of stimuli in terms of their emotional–motivational significance to the organism is thought to be causal in the generation of emotional responses (Roseman, Smith & (ed.) Scherer, 2001). Theorists have made a distinction between non-conscious, often quick and less elaborate, appraisal processes and conscious forms of appraisal which include propositional analysis (Leventhal & Scherer, 1987; Robinson, 1998). The working of non-conscious appraisals can be observed in those classical Pavlovian conditioning experiments in which the CS is presented below the perceptual threshold, yet evokes conditioned responses (CRs) (e.g. (Critchley, Mathias & Dolan, 2002; Esteves, Parra, Dimberg & Ohman, 1994; Morris, Ohman & Dolan, 1998; Ohman, 2005; Olsson & Phelps, 2004)). As subjects cannot consciously predict the UCS from the CS in this type of paradigm, CRs must necessarily be a result of non-conscious processing. The opposite is true for instructed fear paradigms where subjects are told before the experiment that a given CS will be followed by a UCS. Because subjects have never experienced actual CS–UCS pairing, initial CRs must be caused by a conscious appraisal of the CS as threatening on the basis of the explicit knowledge about its relation to the UCS (i.e., CS−UCS contingency awareness). This conclusion is further supported by results from a recent instructed fear conditioning study in which subjects never actually received a UCS (preventing them from learning through experience) and produced skin conductance CRs to a CS when it was presented supra-threshold but, critically, not when it was presented subthreshold and thus remained unperceived (Olsson & Phelps, 2004). Hence, contingency awareness is likely to be causal for CR generation in instructed fear.

Conscious appraisal of threat thus comprises explicit knowledge of the CS–UCS contin-

gency as well as consequential cognitive elaborations about the CS and its implications. It may additionally include awareness of, and reflections about, the bodily and subjective responses induced by the CS (which have emotional stimulus quality in their own right and can thus also generate negative reactions). Various experimental approaches have been taken to dissociate the neural substrates of non-conscious and conscious appraisal in fear conditioning. Bechara et al. (1995) and Clark and Squire (1998) explicitly asked subjects about CS−UCS contingencies following uninstructed conditioning, showing that hippocampal patients cannot acquire contingency knowledge. Carter et al. (2006) tracked the emergence of contingency awareness online by having subjects rate shock expectancy while undergoing conditioning, finding activity correlated with explicit shock expectancy in the lPFC (bilateral middle frontal gyrus at MNI coordinates x, y, z=-36, 51, 30 and 36, 51, 36) and, just below the statistical threshold, in the parahippocampal gyrus. Kalisch et al. (2006) limited conscious processing by combining instructed fear conditioning with an attention- and working memory-demanding task, finding reduced conditioning-related rostral dmPFC/dACC activation (at -8,38,28) in the high- compared to the low-load condition. Tabbert et al. (2006) compared an instructed to an uninstructed (classical) fear conditioning group, of which only the former developed contingency awareness. The authors found rostral dmPFC, temporal, and parietal activation in the aware group, which was, however, not significantly stronger than in the unaware group. Klucken et al. (2009a) compared subjects that accidentally developed contingency awareness during uninstructed conditioning to those that did not, finding stronger nucleus accumbens activation in the aware group. Finally, Knight et al. (2009) presented the same CS both sub- and supra-threshold during uninstructed conditioning. This manipulation was associated with explicit shock expectancy and hippocampal and parahippocampal as well as posterior cingulate activation in the supra-threshold trials. One lesion study (Funayama, Grillon, Davis & Phelps, 2001) showed that the left, but not right, amygdala is necessary to produce skin conductance CRs in instructed fear conditioning.

This rather divergent pattern of areas associated with conscious threat appraisal led us to wonder if any of these areas are consistently activated by instructed fear conditioning across studies. As subjects are aware of the CS−UCS contingency throughout an

instructed fear experiment, and thus likely to reflect upon the threatening situation, we reasoned that those areas most consistently activated by instructed fear are the strongest candidates for mediating conscious appraisal of threat. This does not imply that non-conscious processing does not contribute to the fear reaction in instructed fear paradigms, in particular when these involve CS−UCS pairings and thus also permit direct learning from experience. Likewise, the mere consistent activation of an area X in instructed fear studies does not prove the area subserves conscious appraisal (as it may also, for example, subserve non-conscious processing). However, it is reasonable to argue that areas that are not consistently active across instructed fear studies are unlikely candidates for this function.

The most appropriate method for determining such overlap is formal quantitative meta-analysis since, unlike the traditional method of providing scatter plots of activation maxima, formal meta-analysis generates quantitative scores of activation consistency that can be tested for significance using established statistical methods (Wager, Lindquist & Kaplan, 2007). Further, random between-study variance can be taken into account (Wager, Lindquist & Kaplan, 2007).

One prior meta-analysis had analyzed a mixed sample of instructed and uninstructed conditioning studies (Etkin & Wager, 2007). In addition to reporting a meta-analysis of instructed fear, we therefore also calculated a meta-analysis of 'pure' uninstructed fear and attempted to determine regional overlap between both. Our rationale was that areas that are activated by both instructed and uninstructed fear conditioning, irrespective of the contribution of conscious appraisal processes, can be regarded as belonging to a core fear network.

C.2 Materials and methods

Terminology and study selection

In a typical uninstructed fear conditioning experiment, a subject learns over repeated trials that a CS (often a visual or auditory stimulus) is often or always followed by a UCS

such as electric shock, heat pain, painful pressure, aversive sounds or pictures, unpleasant odor, or loss of money. Human fear conditioning paradigms usually involve discrimination between one or several such CSs (termed CS+) and one or several CS−'s which is/are never paired with the UCS, thereby controlling for non-associative effects. Instructed fear conditioning experiments (also referred to as 'anticipatory anxiety') follow the same pattern, with the exception of subjects being told beforehand which CS will be associated with the UCS. In both paradigms, the acquired predictive value of the CS produces an expectation of an aversive event (the UCS) that lasts until delivery of the UCS. This anticipatory state is functionally different from the emotional state induced by the UCS itself, driving preparatory or avoidance behavior. We here employ the term 'fear' for this type of state, in order to emphasize the distinction from aversive states in general. We acknowledge that only a minority of conditioning studies use explicit fear ratings to demonstrate successful induction of fear (but instead rely on autonomic or behavioral indices). It thus cannot be excluded that some studies induced only weak subjective fear states despite other indices of successful conditioning. Nonetheless, we argue that such a distinction between studies is of an incremental, and not categorical, nature.

In addition to conforming to this general design, studies had to fulfil the following criteria: they had to be published in a peerreviewed scientific journal in English language prior to December 2008; they had to be performed in n>1 healthy normal subjects; they had to employ functional magnetic resonance imaging (fMRI); they had to report a CS+ >CS− comparison; they had to report significant peaks across the entire imaged volume, rather than only within a predefined region of interest, thus decreasing the risk that our meta-analysis would be biased towards or against a specific part of the brain (Note that some studies did not image dorsocaudal parts of the brain, notably in the parietal cortex, which is why the reported meta-analyses are uninformative about this area. In the following, we nevertheless use the term "whole brain-level analysis for simplicity when referring to non region-of-interest analyses.); the data had to be analyzed within a general linear model framework and using a predefined basis function (rather than hypothesis-free models) for prediction of BOLD signal time courses, in order to assure comparability of activation measures; the studies had to report activation coordinates rather than using gross

anatomical description of activation loci; they had to report z scores as a quantitative expression of activation magnitude; they had to validate successful CR generation using subjective ratings, reaction times or physiological measures such as skin conductance or stress hormone responses. Studies using a CS with ambiguous meaning, in the sense that it might be followed by either an appetitive or an aversive event, were not included because it is unclear how the presence of an ambiguous CS affects the processing of nonambiguous CSs. By contrast, we allowed studies with additional appetitive CSs.

We first searched PubMed using keywords instructed fear, fear conditioning, anticipation, expectation, anxiety, aversive, punishment, monetary conditioning, and loss aversion. We then mined articles found in PubMed and fulfilling above criteria for references to other related studies. We finally also searched publications by known researchers in the field for additional reports. Where an identified study also examined patients, only the data from the healthy normal controls were used. Where a study examined the influence of a drug on conditioning, only the placebo group data were used. Where a study fulfilled all criteria except reporting coordinates, a statistical test score (z or t) or whole-brain data for the contrast of interest, we contacted the authors and included the study if the authors provided the missing data (studies IF3, UF6, 9, 10, 12, and 13 in Tables 9 and 10, respectively, which summarize the included studies).

Study code	Reference	No. subjects	M/F	No. activation peaks	Reinforcement ratio (%)	Average CS–UCS onset delay (ms)	Type of CS	Type of UCS	Concurrent cognitive task
IF1	Abler et al. (2007)	12	0/12	2	100	7920	Visual	Aversive picture	None
IF2	Butler et al. (2007)	42	26/16	17	0[a]	12,000	Visual	Electric shock	None
IF3	Herwig et al. (2007)	12	0/12	26	100	7920	Visual	Aversive picture	None
IF4	Jensen et al. (2003)	11	6/5	5	33	5000	Visual	Electric shock	None
IF5	Kalisch et al. (2005)	16	7/9	35	25	7800	Tone	Electric shock	Natural appraisal
IF6	Kalisch et al. (2006)	15	7/8	56	25	7800	Tone	Electric shock	None
IF7	Kumari et al. (2007)	14	14/0	4	0[a]	30000	Word	Electric shock	None
IF8	Nitschke et al. (2006)	21	10/11	37	100	4000	Visual	Aversive picture	None
IF9	O'Doherty et al. (2002)	8	5/3	3	100	7500	Visual	Salty taste	None
IF10	Phelps et al. (2004)	11	5/6	7	33	4000	Visual	Electric shock	None
		Total: 162	Totals: 80/82	Total: 192	Average: 53	Average: 9400	Totals: 8 visual, 2 auditory	Totals: 6 pain, 3 visual, 1 taste	Totals: 1 with, 9 without

[a] UCS announced but never administered (5 trials only).

Table 9: Studies included in the instructed fear conditioning meta-analysis.

T scores were transformed into z scores if necessary. From study IF5 which involved cognitive modulation of fear, only the baseline comparison condition (natural appraisal) was used.

Study code	Reference	No. subjects	M/F	No. activation peaks	Reinforcement ratio (%)	Average CS–UCS onset delay (ms)	Type of CS	Type of UCS	Concurrent cognitive task
UF1	Armony and Dolan (2002)	6	3/3	8	50	0	Angry face	White noise	Dot probe
UF2	Birbaumer et al. (2005)	10	10/0	8	100	7000	Face	Painful pressure	None
UF3	Buchel et al. (1998)	9	7/2	10	50	5000	Visual	Aversive tone	None
UF4	Buchel et al. (1999)	11	6/5	11	50	4000[a]	Tone	Aversive tone	None
UF5	Critchley et al. (2002)	6	Unclear (x/y)	3	33	38	Angry face[b]	White noise	Like/dislike dec.
UF6	Eippert et al. (2008)	15	15/0	7	50	8500	Visual	Heat pain	Localization dec.
UF7	Gottfried et al. (2002)	17	7/10	5	50	500	Face	Aversive odor	Gender dec.
UF8	Gottfried and Dolan (2004)	18	8/10	5	50	500	Face	Aversive odor	Gender dec.
UF9	Jensen et al. (2008)	13	9/4	3	50	5000	Visual	Aversive tone	None
UF10	Kalisch (2009)	25	0/25	9	80	5700	Visual	Electric shock	Gender dec.
UF11	Knight et al. (2005)	9	4/5	11	80	9500	Tone	Aversive tone	None
UF12	Schiller et al. (2008)	17	9/8	16	33	4000	Visual	Electric shock	None
UF13	Stark et al. (2006)	17	8/9	5	100	8000	Visual	Electric shock	None
UF14	Tabbert et al. (2005)	18	6/12	2	100	8000	Visual	Electric shock	None
UF15	Veit et al. (2002)	7	7/0	13	100	7000	Face	Painful pressure	None
		Total: 198	Totals: 99 + x/93 + y	Total: 116	Average: 65	Average: 4850	Totals: 13 visual, 2 auditory	Totals: 7 pain, 6 auditory, 2 odor	Totals: 6 with, 7 without

dec., decision.
[a] Trace conditioning.
[b] Masked and unmasked CS.

Table 10: Studies included in the uninstructed (classical) fear conditioning meta-analysis.

Meta-analysis

From the whole brain-level analyses reported in the above studies, we included all activation peaks with a z score >3.0 (following a strategy used earlier by us (Kalisch, 2009) that protects against overly liberal results) from all CS+ >CS− contrasts, irrespective of whether the peaks represented cluster maxima or local maxima within an activation cluster. Deactivations (CS+ <CS−) were not included. Fear studies often report activation decays over time in areas like the amygdala that are known from the animal literature to make critical contributions to fear learning or expression (Buechel, Morris, Dolan & Friston, 1998; LaBar, Gatenby, Gore, LeDoux & Phelps, 1998). In order to also capture those areas, we were liberal in terms of the exact formulation of the CS+ >CS− contrasts. For example, in uninstructed fear conditioning studies, authors often reported time by condition interactions (such as an exponential response decay over trials) in addition to the categorical CS+ > CS− analysis. In those studies (studies UF2, 5, 6, and 7 in Table 10), activation peaks from both contrasts were included. In a different way of accounting for habituation, one study (UF12) analyzed the first and the second half of conditioning trials separately, finding no whole brain-level activation in the second half. From this study, the data from the first half were included. In one further fear conditioning study (UF10), a first block of conditioning was separated from a second block of conditioning by a block of extinction. As the second block of conditioning represented reacquisition

of fear rather than de novo conditioning, only data from the first block were included. In two instructed fear studies (IF5 and 6), the authors modelled tonic, phasic, and linearly changing activation time courses over the course of the anticipation period within the same analysis, thus addressing potential within-trial habituation. All peaks resulting from those regressors were included. Talairach coordinates were converted to MNI coordinates as described (http:// imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m; (Brett, Christoff, Cusack & Lancaster, 2001). A full list of included peaks is available online (Supplementary Table 1).

Meta-analyses were performed using an established method (multilevel kernel density analysis, MKDA; (Wager, Lindquist & Kaplan, 2007). Briefly, we constructed indicator maps (I, with values of 1 or 0) of whether each CS+ >CS− comparison (study) resulted in activation coordinates within a sphere of $10 - mm$ radius surrounding each voxel in a $2x2x2$-mm standard brain (MNI avg152t1.img, SPM2 version; http://www.fil.ion.ucl.ac.uk /spm/spm2.html). The metaanalysis score ('activation density') $\hat{P}$v at each voxel v was the proportion of studies that activated within 10 mm of that voxel, weighted by the square root of the sample size for each study.

Region	Cluster maximum			No. voxels	Volume (mm^3)	Activation density (P_v)	P uncorr.
	x	y	z				
Bilateral dACC, med. sup. front. G (dmPFC), preSMA	0	16	36	814	6512	0.59	0.0098
R ant. insula, extending into putamen	36	20	0	792	6336	0.58	0.0082
L ant. insula	−32	20	6	460	3680	0.56	0.0082
Bilateral caudate-putamen, ext. into R pallidum, bilateral ant. thalamus	2	0	8	1408	11,264	0.56	0.0082
Bilateral rostr. med. sup. front. G (dmPFC)	6	38	38	127	1016	0.45	0.0053
R inf. front. S	44	24	26	7	56	0.38	0.0005
R lat. fissure (post. segment)	52	−40	32	5	40	0.37	0.0010
L supramarginal G	−64	−28	30	38	304	0.35	0.0015
L sup. temp. S (ascend. post. segment)	−52	−56	34	12	96	0.32	0.0024
L middle temp. G	−54	−56	6	81	648	0.31	0.0031
R lat. fissure (post. segment)	56	−48	28	69	552	0.30	0.0041
L lat. fissure (post. segment)	−46	−42	32	12	96	0.30	0.0041
L sup. temp. S (ascend. post. segment)	−54	−50	34	1	8	0.30	0.0041
L mid insula	−38	0	−2	7	56	0.27	0.0082
L lat. fissure (post. segment)	−56	−36	30	90	720	0.27	0.0082

Statistical threshold: FDR q<0.01 (pID<0.0098). R, right; L, left; G, gyrus; S, sulcus. Coordinates: MNI. Ordering of results according to activation density scores.

Table 11: Meta-analysis of instructed fear conditioning studies.

These weights allowed the larger, and thus more reliable, studies to carry more weight in the meta-analysis. Weights were normalized by the sum across studies so that for each voxel v in the brain

$$\hat{P}v = \sum_{n=1}^{N} w_n I_n$$

where w_n is the weight for the nth of N study maps.

Tests of statistical significance treated each study as independent and were restricted to a gray matter mask (plus 8-mm border) in the standard brain (SPM2 segmented avg152t1.img with 8-mm Gaussian smoothing). Activation densities $\hat{P}$v were tested against the null hypothesis of a uniform random distribution of peaks within each study inside the gray matter mask. The null hypothesis density $\hat{P}$o was established through Monte Carlo simulation. Correction for multiple comparisons was performed using false discovery rate (FDR) control (Genovese, Lazar & Nichols, 2002) at q<0.01. FDR control is the standard correction methods in meta-analysis and endorsed both by the MKDA (Wager, Lindquist & Kaplan, 2007) and the ALE (Laird, Fox, Price, Glahn, Uecker, Lancaster, Turkeltaub, Kochunov & Fox, 2005) software packages and has been used by one of us (Etkin & Wager, 2007) in an earlier meta-analysis. As in that earlier study, an additional threshold of at least two studies activating any given voxel was imposed. Anatomical localization was carried out with reference to the atlas of Duvernoy (1999).

C.3 Results

Instructed fear conditioning

At an FDR threshold of q<0.01, 15 clusters showed consistent activation across instructed fear studies (Table 12 and Fig. 30).

The most consistently activated areas, with an activation density score of $\hat{P}$v > 0.5, were a large cluster in the bilateral mid dmPFC/dACC which extended into the pre-supplemental motor area (preSMA); a cluster in the bilateral anterior insulae, with an extension into the right putamen; and a cluster in the bilateral caudate–putamen which extended into the anterior thalamus and the right pallidum. Of the candidate areas for

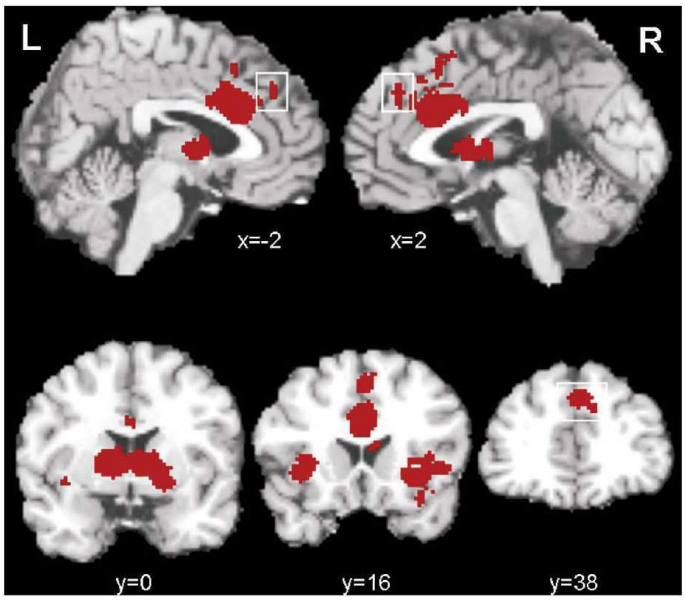

Figure 30: Meta-analysis of instructed fear conditioning studies. Instructed fear paradigms consistently activated, among other areas, mid and rostral parts of the bilateral dmPFC/dACC (all panels), bilateral caudate–putamen and right pallidum (bottom row, left panel), and bilateral anterior insula (bottom row, middle panel). The rectangle demarcates the rostral dmPFC area earlier identified as a candidate region for conscious appraisal. Voxels significant at FDR q<0.01 are superimposed on a canonical structural brain image. Coordinates: MNI.

conscious appraisal identified in the introduction, only a cluster in the bilateral rostral dmPFC (maximum at 6, 38, 38; $\hat{P}$v=0.45) showed consistent activation. The same held when lowering the threshold to q<0.05 (data not shown). Visual inspection of summed indicator maps showed that the number of studies activating the other candidate areas (hippocampus/parahippocampus, middle frontal gyri, posterior cingulate) was ≤ 2 (out of 10) in every case.

In meta-analyses with comparatively few included studies, single studies that report multiple nearby peaks may theoretically dominate the analysis and bias the results toward regions heavily represented in those studies. We therefore excluded the study with the largest number of activation peaks (IF6) from the sample and calculated a second analysis. There was still significant activation in the rostral dmPFC at q<0.01 (data not shown). These results indicate that the rostral dmPFC is so far the most likely candidate region for mediating conscious threat appraisal, of those identified a priori in the introduction. Note that this latter analysis is entirely non-circular as none of the studies used to define

the candidate regions was included.

Uninstructed fear conditioning

There was considerably less consistent activation in the uninstructed fear conditioning sample: only a small cluster in the mid dmPFC/dACC survived a threshold of q<0.01 (-2, 14, 40; $\hat{P}$v = 0.32; see Table 12). When lowering the threshold to q<0.05, activation in multiple additional areas including the bilateral amygdalae and anterior insulae became evident. However, all significant voxels showed activation densities of $\hat{P}$v <0,3, that is, individual voxels within these regions were active in less than 30% individual voxels within these regions were active in less than 30% of studies (weighted for sample size; Table 12). These results indicate large between-study variance, a situation that can result from generally weak activations. Given the pronounced differences in activation densities between the instructed and the uninstructed fear conditioning samples, we refrained from any comparison of samples and limit ourselves to the conclusion that activation of the mid dmPFC/dACC is a common feature of instructed and uninstructed conditioning (see Fig. 31).

C.4 Discussion

The main result of this study is that instructed fear consistently activates a rostral part of the dorsomedial prefrontal cortex and that activation in the other conscious threat appraisal candidate areas is considerably less consistent. Consistent activation in this paradigm as such does not prove an involvement in conscious appraisal, since many cognitive processes other than conscious appraisal can be assumed to operate during instructed fear conditioning. In particular, during most instructed fear experiments, subjects will directly experience CS−UCS pairings which may result in non-conscious learning and evaluation. Likewise, a CS may become secondarily associated with the aversive physiological and subjective reactions produced during conditioning, and this may be another way in which experience-mediated fear conditioning may take place during instructed fear

Region	Cluster maximum			No. voxels	Volume (mm^3)	Activation density (P_v)	*P* uncorr.
	x	*y*	*z*				
FDR threshold q<0.01 (pID<0.0001)							
Bilateral mid dACC, med. sup. front. G (dmPFC)	−2	14	40	14	112	0.32	0
FDR threshold q<0.05 (pID<0.0458)							
Bilateral mid and rostr. dACC, med. sup. front. G (dmPFC, preSMA)	−2	14	42	2150	17,200	0.32	0.0270
R amygdala extending into ant. hippocampus, ventr. ant. insula, putamen	24	2	−6	1287	10,296	0.24	0.0458
L amygdala ext. into ant. hippocampus, hypothalamus, ventr. pallidum, sgACC, caudal OFC	−18	4	−18	2082	16,656	0.22	0.0316
R ventr. thalamus, hypothalamus ext. into red nucleus	10	−14	−2	521	4168	0.22	0.0217
R ant. insula, post. lat. OFC, temp. operculum	48	16	−6	722	5776	0.20	0.0254
L lat. fissure	−58	−24	22	522	4176	0.20	0.0270
R lat. fissure, postcentr. G	62	−20	20	208	1664	0.20	0.0206
R ant. middle temp. G	54	2	−32	4	32	0.17	0.0034
L ant. OFC	−24	52	−14	60	480	0.16	0.0045
L ant. insula	−34	20	8	345	2760	0.16	0.0044
L entrorhin. area	−14	−14	−24	36	288	0.15	0.0065
R septum	4	−4	−16	2	16	0.15	0.0065
R septum	4	−2	−12	2	16	0.15	0.0065
R inf. temp. S	46	−10	−26	18	144	0.15	0.0074
Septum	0	6	6	10	80	0.14	0.0084
R inf. occip. S	44	−78	−10	14	112	0.14	0.0100
L caudate–putamen	−12	6	0	2	16	0.14	0.0100
R septum	2	−8	−12	1	8	0.14	0.0125
Substantia nigra	0	−24	−14	1	8	0.13	0.0143
L precentr. G	−50	−6	42	12	96	0.13	0.0143
R subpariet. S	10	−62	42	12	96	0.13	0.0143
L middle front. G	−44	2	50	137	1096	0.13	0.0143
R sup. front. G	12	10	66	60	480	0.13	0.0270
L ant. lat. OFC	−34	54	−6	95	760	0.13	0.0179
R lat. fissure (post. segment)	52	−34	24	19	152	0.13	0.0179
Cerebellum	−34	−46	−28	271	2168	0.12	0.0194
L temp. operculum	−56	12	−4	235	1880	0.12	0.0206
Pons	6	−28	−40	184	1472	0.11	0.0238
R med. sup. front. G (preSMA)	4	4	66	1	8	0.11	0.0254

R, right; L, left; G, gyrus; S, sulcus; OFC, orbitofrontal cortex; sgACC, subgenual ACC. Coordinates: MNI. Ordering of results according to activation density scores.

Table 12: Meta-analysis of uninstructed (classical) fear conditioning studies.

experiments. Nevertheless, because conscious appraisal is necessarily part of the cognitive response to instructed fear stimuli, the present finding allows us to maintain the theory that the rostral dmPFC is involved in consciously appraising threat. Suggestions that the hippocampus/parahippocampus, the posterior cingulate, or the middle frontal gyri mediate this function did not receive support from this study and thus might need further qualification. Conscious appraisals may involve the conscious expectation of a UCS (contingency awareness), awareness of the affective quality of a CS and of the accompanying subjective and bodily reactions to it, or reasoning about the effects the CS or the UCS may have on oneself. Non-conscious appraisals, by contrast, may involve automatic computations of UCS probabilities and CS values according to algorithms such as proposed by reinforcement learning theory (Sutton & Barto, 1998). In most situations, both non-conscious and conscious processes can be presumed to contribute to the appraisal of emotionally relevant stimuli and hence to shaping the ensuing emotional reaction. Cases

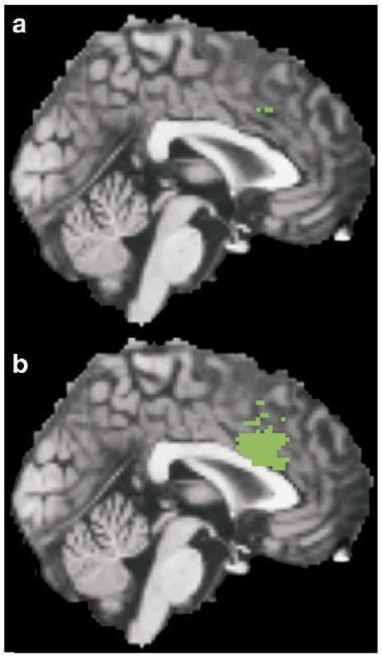

Figure 31: A mid dmPFC/dACC area commonly activated by instructed and uninstructed fear conditioning. Overlap in activation between instructed and uninstructed fear was observed in voxels in the mid dACC/dmPFC, shown here at FDR thresholds $q<0.01$ (a) and $q<0.05$ (b). x=0.

in which one processing level participates exclusively are rare and difficult to construe experimentally. There are, however, experimental contexts in which primarily non-conscious or conscious appraisals may dominate. Thus, conditioning experiments in which the CS is presented below the perceptual detection threshold and thus inaccessible to phenomenal awareness, yet induces CRs (Critchley, Mathias & Dolan, 2002; Esteves, Parra, Dimberg & Ohman, 1994; Morris, Ohman & Dolan, 1998; Ohman, 2005; Olsson & Phelps, 2004), constitute one (although not uncontroversial (Lovibond & Shanks, 2002)) type of situation wherein non-conscious appraisals can induce measurable emotional reactions. In a similar vein, sub-threshold presentation of secondary reinforcers such as money has been shown to influence motivated behavior (Pessiglione, Schmidt, Draganski, Kalisch, Lau, Dolan & Frith, 2007).

Another way of limiting conscious processing is to try to exhaust attentional or working memory resources by a concurrent cognitive task that distracts from the emotional stimulus. Interestingly, while distraction can attenuate emotional reactions relative to a focussing condition, there is also evidence for residual or even unattenuated emotional re-

actions under distraction (e.g., (Kalisch, Wiech, Critchley & Dolan, 2006a; Seminowicz & Davis, 2007). This again argues for an important role of non-conscious appraisal. In general, however, responses to attended emotional stimuli are stronger than to non-attended emotional stimuli, or those presented outside of awareness, suggesting that conscious appraisals play an important role in driving emotional responding, including during classical fear conditioning (e.g., (Carter, Hofstotter & Koch, 2003; Delgado, Nearing, Ledoux & Phelps, 2008; Hamm & Vaitl, 1996; Tabbert, Stark, Kirsch & Vaitl, 2006).

The latter point highlights a difficulty one is faced with when trying to disentangle the neural bases of non-conscious and conscious appraisal processes. If the disruption of conscious appraisal is accompanied by a decrease in the strength of the emotional reaction, then it becomes impossible to differentiate between neural activations related to appraisal and those directly mediating response generation. In a previous instructed fear study (Kalisch, Wiech, Critchley & Dolan, 2006a), we created a situation where distraction was not paralleled by an attenuation of subjective feeling and autonomic system reactions to the CS, allowing us to ascribe rostral dmPFC/dACC activity (which was reduced relative to a non-distraction condition that permitted more extensive conscious processing but produced similar CRs) to conscious appraisal alone. In line with a conscious appraisal function for this area, earlier studies had implicated the dmPFC/dACC in the explicit judgment of, or attention to, emotional stimuli (Blackwood, Bentall, Ffytche, Simmons, Murray & Howard, 2004; Cunningham, Johnson, andJohn C Gore & Banaji, 2003; Cunningham, Johnson, Raye, Gatenby, Gore & Banaji, 2004a; Cunningham, Raye & Johnson, 2004b; Erk, Abler & Walter, 2006; Fichtenholtz, Dean, Dillon, Yamasaki, McCarthy & LaBar, 2004; Fossati, Hevenor, Graham, Grady, Keightley, Craik & Mayberg, 2003; Johnson, Baxter, Wilder, Pipe, Heiserman & Prigatano, 2002; Kelley, Macrae, Wyland, Caglar, Inati & Heatherton, 2002; Lane, Fink, Chau & Dolan, 1997; Lane, Reiman, Axelrod, Yun, Holmes & Schwartz, 1998; Phan, Taylor, Welsh, Ho, Britton & Liberzon, 2004a; Simpson, Snyder, Gusnard & Raichle, 2001; Taylor, Phan, Decker & Liberzon, 2003; Vuilleumier, Armony, Clarke, Husain, Driver & Dolan, 2002), but these studies have not been able to rule out a confound from response generation processes. Likewise, the studies cited in the introduction for comparing a non-conscious and a conscious appraisal condition

during fear conditioning have not addressed this potential confound. Therefore, out of the candidate regions for conscious threat appraisal identified in those studies, the rostral dmPFC is currently the only one for which CR generation is not a possible alternative explanation. Together with the results of the present study, this further strengthens our argument for a crucial role of this area in conscious appraisal. The precise contribution of the rostral dmPFC/dACC to the conscious appraisal process remains to be determined. Based on observations that dmPFC/dACC responses rapidly habituate (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005; Phan, Liberzon, Welsh, Britton & Taylor, 2003) and occur contralateral to the side of electric shock application (where shock is used as UCS) (Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005), we have suggested that the region may subserve a primary schematic and stimulus-driven form of conscious awareness of the emotional meaning of a stimulus ('this is bad', 'I don't like this') (Kalisch, Wiech, Critchley & Dolan, 2006a). If needed, more elaborate appraisal may be performed by the lPFC (e.g. (Bach, Grandjean, Sander, Herdener, Strik & Seifritz, 2008; Carter, O'Doherty, Seymour, Koch & Dolan, 2006; Critchley, Daly, Phillips, Brammer, Bullmore, Williams, Amelsvoort, Robertson, David & Murphy, 2000; Hariri, Bookheimer & Mazziotta, 2000; Kalisch, Wiech, Critchley & Dolan, 2006a). Specifically, lPFC areas are active when one asks analytical questions about an emotional situation (Schaefer, Collette, Philippot, van der Linden, Laureys, Delfiore, Degueldre, Maquet, Luxen & Salmon, 2003), deliberately reappraises a situation (Kalisch, 2009) or appraises stimuli with ambiguous meaning (Cunningham, Johnson, andJohn C Gore & Banaji, 2003). Such more restricted conscious appraisal functions may not be required in any threatening situation, and this may explain why lPFC activation (apart from a small cluster in the right inferior frontal sulcus, see Table 11) was not consistently found in instructed fear in our meta-analysis. Another explanation for a lack of consistent activation in the lPFC may be pronounced anatomical and functional inter-individual variability in this region. We speculate that the role of the dmPFC/dACC may be to pass information judged relevant to higher lateral prefrontal centers for in-depth analysis. Once the dmPFC/dACC has fulfilled its role as a gate to consciousness, it may be economical to switch it off, thus saving resources. Such a rather

transient contribution to the appraisal process would be in agreement with observations of dmPFC/dACC habituation and of a negative functional relationship or connectivity between dmPFC/dACC and lPFC (Erk, Abler & Walter, 2006; Kalisch, Wiech, Critchley, Seymour, O'Doherty, Oakley, Allen & Dolan, 2005). In contrast to the rostral dmPFC, more posterior areas of the dmPFC and the dACC were active during both instructed and uninstructed conditioning. Activation of this area thus seems to be a common feature of both paradigms. Our meta-analysis does not allow us to draw conclusions about the specific functional role of the region. We thus limit ourselves to pointing out that neural activation in that area is positively correlated with sympathetic output (Critchley, Mathias, Josephs, O'Doherty, Zanini, Dewar, Cipolott, Shallice & Dolan, 2003; Gianaros, Veen & Jennings, 2004; Nagai, Critchley, Featherstone, Trimble & Dolan, 2004; Patterson, Ungerleider & Bandettini, 2002), in particular during fear conditioning (Milad, Quirk, Pitman, Orr, Fischl & Rauch, 2007). Its proximity and close connectivity with motor areas also suggest a contribution to motoric CR generation. Another possible function is a contribution to reinforcement-based contingency learning processes as may not only occur during uninstructed but also during instructed fear conditioning, as soon as one actually experiences the UCS (Seymour, O'Doherty, Dayan, Koltzenburg, Jones, Dolan, Friston & Frackowiak, 2004). Likewise, our meta-analysis gives no hints as to the functions of the other areas consistently active in instructed fear (anterior insula, caudate-putamen, and others). One may speculate that the anterior insula is involved in generating the subjective feeling of fear based on interoceptive input (Critchley, 2004) or participates in reinforcement learning (Seymour, O'Doherty, Dayan, Koltzenburg, Jones, Dolan, Friston & Frackowiak, 2004; Seymour, O'Doherty, Koltzenburg, Wiech, Frackowiak, Friston & Dolan, 2005). It has also been suggested that the anterior insula helps integrate visceral and other affective signals with more cognitive processing outcomes, based on its close functional association with both limbic and medial prefrontal regions in a recent large meta-analysis of emotional processing studies (Kober, Barrett, Joseph, Bliss-Moreau, Lindquist & Wager, 2008). The caudate– putamen has been shown to encode reinforcement learning signals (Menon, Jensen, Vitcu, Graff-Guerrero, Crawley, Smith & Kapur, 2007; Seymour, O'Doherty, Dayan, Koltzenburg, Jones, Dolan, Friston

& Frackowiak, 2004; Seymour, O'Doherty, Koltzenburg, Wiech, Frackowiak, Friston & Dolan, 2005; Seymour, Daw, Dayan, Singer & Dolan, 2007). However, these ideas need further testing.

Of the areas not found in our instructed fear meta-analysis, two stand out for theoretical reasons: Based on one lesion (Funayama et al., 2001) and one fMRI study (Phelps, O'Connor, Gatenby, Gore, Grillon & Davis, 2001), it has been argued that the amygdala, in particular the left amygdala, is required for instructed fear, although more in terms of CR expression than contingency learning (Olsson & Phelps, 2007). Most other similar fMRI studies, however, have not reproduced that finding (but see Mackiewicz et al., 2006; Nitschke et al., 2006, 2009). Likewise, we found no evidence for amygdala activation in our instructed fear sample. A potential reason for this discrepancy is that the Funayama and Phelps studies used only six and five CS+ trials, respectively, which may have prevented between-trial response habituation of amygdala activity (Buchel et al., 1998; LaBar et al., 1998), and which is in contrast to most other instructed fear studies which used more trials. We also note that response habituation was not specifically modelled in most of the included studies (except for IF5 and 6) and that, unlike in uninstructed fear conditioning studies, fMRI acquisition protocols were not specifically optimized to detect amygdala activation in most instructed fear conditioning studies. The current data thus do not allow us to definitely rule out a role for the amygdala in instructed fear. By contrast, there is little evidence in the existing data that the hippocampus may be consistently active in instructed fear. This is surprising given clear evidence for absence of contingency knowledge in hippocampal patients (Bechara et al., 1995; Clark and Squire, 1998). One reason may be that the hippocampus serves to acquire, but not necessarily to retrieve and maintain, contingency knowledge. A similar role may be played by ventral striatal areas (Klucken et al., 2009a,b). Perhaps, knowledge acquired with the help of these areas is stored and/or retrieved in the rostral dmPFC, thus permitting a memory-based conscious stimulus analysis. The latter idea would be in agreement with rostral dmPFC activation during a fear retrieval task (Kalisch, 2009).

In conclusion, the present study further strengthens the idea that the rostral dmPFC supports a conscious evaluation of threatening stimuli. Future research will have to more

precisely determine which specific role it fulfils in this process and also how it interacts with other appraisal areas such as the amygdala (presumably relevant for initial coarse and potentially non-conscious appraisals; Sander et al., 2003) and the lateral PFC (who may subserve more complex forms of analysis). As nearly all of the studies addressing the question of conscious appraisal have used aversive stimulus material, it will also be important to examine whether a similar picture can be drawn for the processing of appetitive emotional stimuli.

D Appendix D

Information und Aufklaerung

Kognitive Einfluesse auf kontextuelle Angstkonditionierung

Version 2 vom 10.10.2008

Liebe Probandin, lieber Proband, Das Institut fuer Systemische Neurowissenschaften am Universitätsklinikum Hamburg-Eppendorf plant die Durchführung einer wissenschaftlichen Untersuchung zu Mechanismen der Angst und wie Angst bewuss kontrolliert und abgeschwaecht werden kann.

Während der Untersuchung werden Ihnen elektrische Reize ueber eine Stimulationssonde auf den Arm oder das Bein appliziert. Die Dauer dieser Schmerzreize betraegt wenige Millisekunden.

Die Schmerzreize sind fuer die klinische Anwendung auch am Patienten (z.B. zur Bestimmung der Empfindungs/Schmerzschwelle) zugelassen. Fuer die Schmerz-Reize sind keine Nebenwirkungen bekannt.

Das Ziel ist der Untersuchung ist, den Einfluss einer bewussten Strategie der Angstkontrolle auf das Erleben angstvoller Erfahrungen zu untersuchen. Angst wird ausgeloest, indem Sie lernen, dass bestimmte Hinweisreize (Toene) mit nachfolgenden Schmerzreizen verbunden sein koennen (kontextuelle Angstkonditionierung). Dies wird mehrfach wiederholt. Zu bestimmten Zeitpunkten sollen Sie dann die Angstkontroll-Strategie anwenden, um die ausgeloeste Angst abzuschwaechen. Die Strategie haben wir Ihnen vorher beigebracht. Wir testen, wie gut die Strategie bei Ihnen wirkt. Wir wiederholen die Untersuchung einen Tag spaeter noch einmal, um zu testen, ob es hierbei zu einem Lerneffekt kommt, d.h. ob Sie sich zwischen Tag 1 und Tag 2 in der Anwendung der Strategie verbessern.

Waehrend der Untersuchung messen wir Ihre Herzfrequenz, Ihre Hautleitfaehigkeit und die Aktivitaet Ihres Gehirns (mittels der sog. funktionellen Magnetresonanztomographie oder fMRT). Dies erlaubt uns, das Ausmass Ihrer Angst und die an der Auslassung der Angst und Ihrer Kontrolle beteiligten Gehirnbereiche zu bestimmen. Vor der

Untersuchung werden Sie den Schmerzreiz bereits ausprobieren koennen wenn Sie den Schmerzreiz als zu stark empfinden, kann die Reizintensitaet abgemildert werden. Sie koennen die Studie aber auch zu diesem, oder zu jedem spaeteren Zeitpunkt ohne Angabe von Gruenden, abbrechen, ohne dass dadurch Nachteile fuer Sie entstehen. Waehrend der fMRT-Untersuchung besteht kontinuierlich die Moeglichkeit eines Sprechkontaktes ueber Lautsprecher. Sie bekommen ausserdem eine Klingel in die Hand, mit der Sie sich jederzeit bemerkbar machen koennen.

Falls Sie bereits an der Studie Genotypisierung und Phaenotypisierung gesunder Normalprobanden zum Zweck der Rekrutierung und Gruppenbildung fuer die Klinische Pruefung NMHSL1 teilgenommen haben sollten, kann es sein, dass wir Informationen (Persoenlichkeitsmerkmale, Genvarianten), die wir bei Ihnen in diesem Rahmen bestimmt haben, in der gegenwaertigen Studie in die Auswertung der Daten einfliessen lassen. Dies dient dazu, einen moeglichen Zusammenhang zwischen Persoenlichkeitsmerkmalen oder Genvarianten auf der einen Seite und der Art, wie verschiedene Probanden die Angstkontroll-Strategie evtl. unterschiedlich einsetzen auf der anderen Seite zu erkennen. Solche Erkenntnisse koennen nur gewonnen werden, wenn die Ergebnisse der Genotypisierung und Phaenotypisierung denen der gegenwaertigen Untersuchung zugeordnet werden koennen eine vollstaendig anonymisierte Verarbeitung der Daten ist also nicht moeglich. Alle Informationen, die der Zuordnung der Daten dienen, werden daher pseudonymisiert, also so verschluesselt, dass es fuer Dritte nicht moeglich ist, die Daten mit Ihnen in Verbindung zu bringen.

Da es sich nicht um eine Studie zur Pruefung eines neuen Arzneimittels oder Medizinproduktes oder eines neuen Anwendungsgebietes handelt, ist keine besondere Studienversicherung (Probandenversicherung) zur Gefaehrdungshaftung vorgesehen. Es gelten die allgemeinen Haftungsgrundsaetze, wobei sich ein Anspruch nur bei schuldhaftem Handeln der Mitarbeiter des UKE ergibt. Das UKE verfuegt fuer diese Faelle ueber eine Haftpflichtversicherung. Diese leistet Ersatz fuer Personen- und Sachschaden, die Sie infolge Ihrer Teilnahme an der Studie erleiden, sofern ein schuldhaftes Verhalten des Klinikpersonals hierfuer ursaechlich ist. Die zur Verfuegung stehenden Deckungssummen betragen 6.000.000 Euro fuer Personenschäden und 512.000 Euro fuer Sachschaeden.

Die im Rahmen dieser Studie erhobenen Daten und persoenlichen Mitteilungen unterliegen der aerztlichen Schweigepflicht und duerfen zur Verarbeitung und Auswertung nur ohne den Namen des Probanden (pseudonymisiert) zusammengefuehrt werden. Die Auswertungen koennen in wissenschaftlichen Fachzeitschriften veroeffentlich werden, allerdings ohne Offenlegung persoenlicher Angaben der Probanden. Bei der Verarbeitung personenbezogener Daten werden die Bestimmungen des Bundesdatenschutzgesetztes eingehalten. Die Verarbeitung und Nutzung der psyeudonymisierten Daten erfolgt auf Fragebogen und elektronischen Datentraegern fuer die Dauer von 10 Jahren.

Fuer Ihre Teilnahme an der Untersuchung erhalten Sie eine ueberweisung von 30 Euro oder, falls wir bei Ihnen an beiden Untersuchungstagen eine kernspintomographische Messung durchfuehren, 50 Euro. Diese ist daran gebunden, dass Sie uns vor Beginn der Studie wahrheitsgemaess und vollstaendig ueber bisherige Erkrankungen und von Ihnen eingenommene Medikamente informieren und den Anweisungen der Untersucher waehrend der Untersuchung Folge leisten. Keinesfalls duerfen Sie in einem Zeitraum von 24 Stunden vor und waehrend der Studie Alkohol oder Drogen einnehmen. Auch muessen Sie an den beiden Untersuchungstagen ausreichend geschlafen haben. Sie duerfen die letzten 2 Monate vor Teilnahme an der Studie an keiner Arzneimittelstudie teilgenommen oder Medikamente eingenommen haben (ausgenommen sind rezeptfreie Arzneien). Falls Sie dennoch Medikamente eingenommen haben und trotzdem an der Studie teilnehmen moechten, teilen Sie uns dies bitte schon waehrend des Telefongespraechs vor der Untersuchung mit. Wir entscheiden dann fallweise.

Einwilligungserklaerung

Herr/Frau ..... hat mich vollstaendig ueber das Wesen und die Bedeutung der geplanten Studie aufgeklaert. Ich konnte dabei alle mich interessierenden Fragen stellen. Ferner hatte ich Gelegenheit das Aufklaerungsblatt genau durchzulesen und auch dazu Fragen zu stellen. Ein Exemplar der Einwilligung ist mir zum Verbleib ausgehaendigt worden.

Mit der Teilnahme an der funktionellen MRT-Studie zu kognitiven Einfluessen auf kontextuelle Angstkonditionierung erklaere ich mich einverstanden. Zurzeit liegt bei mir keine Schwangerschaft vor, auch stille ich zurzeit nicht. Bei mir sind keine ehemali-

gen oder gegenwaertigen Erkrankungen des Nervensystems (psychische oder neurologische Erkrankungen), des Herzens oder des Kreislaufsystems (z.B. hoher Blutdruck) oder andere schwere Erkrankungen bekannt. Ich habe in den letzten 2 Monaten keine Medikamente zu mir genommen. Ich weiss, dass ich meine Einwilligung jederzeit ohne Angabe von Gruenden widerrufen kann.
Ich weiss, dass die im Rahmen dieser Studie erhobenen Daten und persoenlichen Mitteilungen der Aerztlichen Schweigepflicht unterliegen und zur Verarbeitung und Auswertung nur ohne meinen Namen (pseudonymisiert) zusammengefuehrt werden duerfen. Mir ist bewusst, dass die Auswertungen in wissenschaftlichen Fachzeitschriften veroeffentlich werden koennen, allerdings ohne Offenlegung meiner persoenlichen Angaben. Ich wurde darueber aufgekllaert, dass bei der Verarbeitung meiner personenbezogenen Daten die Bestimmungen des Bundesdatenschutzgesetztes eingehalten werden. Die Verarbeitung und Nutzung meiner psyeudonymisierten Daten erfolgt auf Frageboegen und elektronischen Datentraegern fuer die Dauer von 10 Jahren.

Ich bestaetige durch meine Unterschrift, dass ich die Aufklaerung verstanden habe und mich mit der Durchfuehrung der vorgenannten Studie einverstanden erklaere.
Hamburg, den
(Unterschrift des Probanden) (Unterschrift des aufklaerenden Untersuchers)

STAI-G Form X 2

Im folgenden Fragebogen finden Sie eine Reihe von Feststellungen, mit denen man sich selbst beschreiben kann. Bitte lesen Sie jede Feststellung durch und waehlen Sie aus den vier Antworten diejenige aus, die angibt, wie Sie sich im allgemeinen fuehlen. Kreuzen Sie bitte bei jeder Feststellung die Zahl unter der von Ihnen gewaehlten Antwort an. Es gibt keine richtigen oder falschen Antworten. Ueberlegen Sie bitte nicht lange und denken Sie daran, diejenige Antwort auszuwaehlen, die am besten beschreibt, wie Sie sich im allgemeinen fuehlen.

1. Ich bin vergnueg ueberhaupt nicht / ein wenig / ziemlich / sehr
2. Ich werde schnell muede ueberhaupt nicht / ein wenig / ziemlich / sehr
3. Mir ist zum Weinen zumute ueberhaupt nicht / ein wenig / ziemlich / sehr
4. Ich glaube, mir geht es schlechter als anderen Leuten ueberhaupt nicht / ein wenig / ziemlich / sehr
5. Ich verpasse guenstige Gelegenheiten, weil ich mich nicht schnell genug entscheiden kann ueberhaupt nicht / ein wenig / ziemlich / sehr
6. Ich fuehle mich ausgeruht ueberhaupt nicht / ein wenig / ziemlich / sehr
7. Ich bin ruhig und gelassen ueberhaupt nicht / ein wenig / ziemlich / sehr
8. Ich glaube, dass mir meine Schwierigkeiten ueber den Kopf wachsen ueberhaupt nicht / ein wenig / ziemlich / sehr
9. Ich mache mir zuviel Gedanken ueber unwichtige Dinge ueberhaupt nicht / ein wenig / ziemlich / sehr
10. Ich bin gluecklich ueberhaupt nicht / ein wenig / ziemlich / sehr
11. Ich neige dazu, alles schwer zu nehmen ueberhaupt nicht / ein wenig / ziemlich / sehr
12. Mir fehlt es an Selbstvertrauen ueberhaupt nicht / ein wenig / ziemlich / sehr
13. Ich fuehle mich geborgen ueberhaupt nicht / ein wenig / ziemlich / sehr
14. Ich mache mir Sorgen ueber moegliches Missgeschick ueberhaupt nicht / ein wenig / ziemlich / sehr

15. Ich fuehle mich niedergeschlagen ueberhaupt nicht / ein wenig / ziemlich / sehr

16. Ich bin unzufrieden ueberhaupt nicht / ein wenig / ziemlich / sehr

17. Unwichtige Gedanken gehen mir durch den Kopf und bedruecken mich ueberhaupt nicht / ein wenig / ziemlich / sehr

18. Enttaeuschungen nehme ich so schwer, dass ich sie nicht vergessen kann ueberhaupt nicht / ein wenig / ziemlich / sehr

19. Ich bin ausgeglichen ueberhaupt nicht / ein wenig / ziemlich / sehr

20. Ich werde nervoes und unruhig, wenn ich an meine derzeitigen Angelegenheiten denke ueberhaupt nicht / ein wenig / ziemlich / sehr

Social Desirability Scale (SDS) nach Marlowe und Crowne

Hier sind eine Anzahl von Behauptungen aufgefuehrt, die persoenliche Eigenschaften und Einstellungen betreffen. Lesen Sie bitte jeden Satz und bestimmen Sie, ob die Behauptung in bezug auf Sie selbst richtig oder falsch ist und machen Sie jeweils ein Kreuz im entsprechenden Kreis. Beantworten Sie bitte jede Frage und geben Sie bitte nur eine Antwort pro Feststellung:

1. Ich zoegere niemals, jemandem, der in Schwierigkeiten ist, zu helfen, auch wenn ich dadurch mitten in meiner Arbeit aufhoeren muss. Richtig Falsch

2. Es faellt mir manchmal schwer, in meiner Arbeit fortzufahren, wenn ich nicht ermutigt werde. Richtig Falsch
3. Ich habe gelegentlich Zweifel, ob ich im Leben Erfolg haben werde. Richtig Falsch
4. Ich bin manchmal aergerlich, wenn ich nicht meinen Willen bekomme. Richtig Falsch
5. Ich bin immer sorgfaeltig angezogen. Richtig Falsch
6. Ich klatsche manchmal gern ueber andere Leute. Richtig Falsch
7. Es gab Zeiten, wo ich gegen Autoritaetspersonen war, auch wenn ich wuuete, dass sie recht hatten. Richtig Falsch
8. Ganz gleich, mit wem ich mich unterhalte, ich bin immer ein guter Zuhoerer. Richtig Falsch
9. Ich habe gelegentlich mal jemanden uebervorteilt. Richtig Falsch
10. Ich bin immer gewillt, einen Fehler, den ich mache, auch zuzugeben. Richtig Falsch
11. Ich versuche immer, nach dem was ich sage, auch zu handeln. Richtig Falsch

12. Ich finde es nicht besonders schwierig, mit lauten unangenehmen Leuten auszukommen. Richtig Falsch
13. Manchmal bestehe ich auf Genugtuung und kann nicht vergeben und vergessen. Richtig Falsch
14. Wenn ich etwas nicht weiss, gebe ich es ohne Zoegern zu. Richtig Falsch
15. Ich bin immer froehlich, auch zu unangenehmen Leuten. Richtig Falsch
16. Gelegentlich hatte ich Lust, alles zu zerschlagen. Richtig Falsch
17. Ich wuerde niemals zulassen, dass jemand fuer meine Vergehen bestraft wird. Richtig Falsch
18. Ich bin niemals aergerlich, wenn ich um eine Gefaelligkeit gebeten werde. Richtig Falsch
19. Ich bin niemals aergerlich gewesen, wenn andere Leute Ansichten aeusserten, die von meinen sehr abwichen. Richtig Falsch
20. Manchmal bin ich neidisch, wenn andere Glueck haben. Richtig Falsch
21. Ich hatte niemals das Gefuehl, ohne Grund bestraft zu werden. Richtig Falsch
22. Ich denke manchmal, dass die Leute, die ein Unglueck trifft, es auch verdient haben. Richtig Falsch
23. Ich habe niemals mit Absicht etwas gesagt, was die Gefuehle des anderen verletzen koennte. Richtig Falsch

Ueberpruefen Sie bitte noch einmal genau, dass Sie auch keine Frage ausgelassen haben!

Allgemeiner Fragebogen

Allgemeines

1. Geburstdatum: Alter: Jahre
2. Koerpergroesse: cm
3. Gewicht: kg

Haendigkeit

4. Ich schreibe mit links rechts.
5. Beim Ballspielen schiesse ich mit links rechts.
6. Ich war frueher Linkshaender, bin jetzt aber Rechtshaender. zutreffend nicht zutreffend

Herkunft und Sprache

7. Ich bin ein Zwilling. zutreffend nicht zutreffend

Falls zutreffend: eineiig zweieiig

8. Muttersprache(n):
9. Andere Sprachen:
10. Nationalitaet(en):
11. Geburtsland:
12. Meine Mutter ist weisser Hautfarbe. zutreffend nicht zutreffend
13. Mein Vater ist weisser Hautfarbe. zutreffend nicht zutreffend
14. Meine Grossmutter muetterlicherseits ist weisser Hautfarbe.

zutreffend nicht zutreffend

Falls nicht zutreffend, welche Hautfarbe?

15. Mein Grossvater muetterlicherseits ist weisser Hautfarbe.

zutreffend nicht zutreffend

Falls nicht zutreffend, welche Hautfarbe?

16. Meine Grossmutter vaeterlicherseits ist weisser Hautfarbe.

zutreffend nicht zutreffend

Falls nicht zutreffend, welche Hautfarbe?

17. Mein Grossvater vaeterlicherseits ist weisser Hautfarbe.

zutreffend nicht zutreffend

Falls nicht zutreffend, welche Hautfarbe?

18. Gibt es psychische Erkrankungen in Ihrer Familie (z.B. Angsterkrankungen, Depression, Schizophrenie, Alkohol-, Drogen- oder Medikamentenabhaengikeit)?

Wenn ja, bei wem? (Zutreffendes bitte unterstreichen)

Mutter / Vater / Schwester / Bruder / Grossmutter (muetterl. Seite) / Grossvater (muetterl. Seite) / Grossmutter (vaeterl. Seite) / Grossvater (vaeterl. Seite)

Gewohnheiten

1. Ich trinke durchschnittlich ca. Glas Alkohol pro Woche.
2. Ich trinke seit Jahren Alkohol.
3. Ich rauche durchschnitlich ca. Zigaretten pro Tag.
4. Ich rauche seit Jahren.
5. Ich rauche durchschnittlich mal im Monat Cannabis/Haschisch/Gras.
6. Ich konsumiere seit Jahren Cannabis/Haschisch/Gras.
7. Ich trinke durchschnittlich ca. Tassen Kaffee pro Tag.

Soziale Situation

8. Welchen Schulabschluss haben Sie?

vor der letzten Hauptschulklasse abgeschlossen

mit der letzten Hauptschulklasse abgeschlossen

Real- (Mittel-) oder Handelsschule ohne Abschlusspruefung

Real- (Mittel-) oder Handelsschule mit Abschlusspreufung

Gymnasium (Hoehere Schule) ohne Abitur

Abitur ohne anschliessendes Studium

Abitur mit (noch) nicht abgeschlossenem Studium

Abitur mit abgeschlossenem Studium

9. Sind Sie
verheiratet,
ledig,
verwitwet,
geschieden/getrennt?

10. Leben Sie
allein,
mit Ehepartner(in)/Lebenspartner(in),
in Wohngemeinschaft,
bei den Eltern oder Verwandten?

11. Sind Sie berufstaetig?
ja
ja, mithelfend im eigenen Betrieb
Hausmann
...ODER sind Sie
Schueler,
Student,
in Berufsausbildung,
Renter/im Ruhestand,
zur Zeit arbeitslos,
ohne Beruf,
Wehr- oder Zivildienstleistender/im freiwilligen sozialen Jahr?

12. Bitte geben Sie Ihren Beruf an.
Schueler
Student (Fach:)

Arbeiter

Angestellter

Beamter

Selbststaendiger/Freiberufler

Freier Mitarbeiter

Angelernter Arbeiter

Facharbeiter

Meister

Einfacher/Mittlere Angestellte

Gehobener/Leitender Angestellte

Einfacher/Mittlere Beamte

Gehobener/Hoehere Beamte

Sozialversicherungspflichtig beschaeftigt

(Achtung: Wenn nicht selber finanziert (sonder z.B. von Eltern) bitte Beruf des/der Ernaehrer/s ankreuzen (Hausmaenner den Beruf des Partners, Rentner den ehemaligen Beruf.)

Eidesstattliche Erklärung nach § 9 Abs. 1, Nr. d der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst habe. Andere als die angegebenen Quellen und Hilfsmittel habe ich nicht benutzt und die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht.

Hamburg, den _____ _____

Unterschrift

Erklärung nach § 9 Abs. 1, Nr. c der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich, dass die von mir vorgelegte Dissertation nicht Gegenstand eines anderen Prüfungsverfahrens gewesen ist.

Hamburg, den _____ _____

Unterschrift