



**Universität  
Basel**

Fakultät für  
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# **The interplay between emotional arousal and memory processes – from large-scale to translational fMRI studies**

**A cumulative dissertation**

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by

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## Abstract

Emotional arousal greatly impacts what we remember about an event and how well we remember it. This memory-modulating effect of arousal has been subject to intensive research for decades. In recent years, fMRI data has enabled increasing understanding how arousal and memory are integrated in the human brain. Since then, researchers have been striving to identify the brain regions involved in emotional memory processing and to elucidate how dysfunctional activation in certain neuronal circuits relates to psychiatric disorders. However, the majority of fMRI studies lack sufficient statistical power to produce robust results. In addition, the common use of group-level analyses based on contrasts, a rather insensitive method compared to analysis on an individual level, has, up to now, hampered the utility of fMRI findings for clinical routine.

The aim of the present thesis is to present new scientific advances in the relationship between emotional arousal and memory documented in two publications that used large-scale fMRI data from our lab in two different ways. The publication Loos et al. (2019) took an exploratory approach based on fMRI and behavioral data from more than 1'000 healthy young subjects. Applying multi-voxel pattern analysis, we identified a brain network which could be used, on the one hand, to predict an individual's perceived arousal during encoding and, on the other hand, to predict episodic memory performance of an individual during later recognition. Both processes, perceived arousal and episodic memory, are heavily impaired in emotional memory-related diseases like anxiety disorders. Therefore, the reported network constitutes an important target for further research in patients with dysfunctional emotional memory.

The second publication, Loos et al. (submitted), used large-scale data to derive a hypothesis-driven research question which we tested in an independent fMRI study. Using a pictorial working memory (WM) task in subjects reporting fear of snakes, we could demonstrate that high compared to low WM load not only acutely decreased amygdala activity but also reduced perceived phobic fear and disgust towards snake pictures. Additional effective connectivity analysis revealed that the dlPFC, which is particularly engaged in WM tasks, exerted an inhibitory influence on the amygdala during high WM load conditions. The study intended to translate findings from basic research into a more clinical context and may inspire the development of new approaches for the treatment of anxiety disorders.

In sum, the thesis adds to the knowledge on the interplay between emotional arousal and episodic as well as working memory processes by providing robust and reproducible results. In addition, it highlights the importance of well-powered fMRI studies for the identification of neural mechanisms that improve diagnosis and treatment in clinical practice.



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## Abbreviations

ACC	Anterior cingulate cortex
DCM	Dynamic causal modelling
dIPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
GAPED	Geneva affective picture database
GLM	General linear model
IAPS	International affective picture system
LASSO	Least absolute shrinkage and selection operator
MTL	Medial temporal lobe
MVPA	Multi-voxel pattern analysis
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PTSD	Posttraumatic stress disorder
vIPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
WM	Working memory



“An experience may be so exciting emotionally as almost to leave a scar on the cerebral tissues.”

(James, 1890, p.670)

## 1 Introduction

Emotionally arousing experiences substantially influence how well we remember an event. Nevertheless, until the end of the 20<sup>th</sup> century, emotion and cognition were assumed to be processed in rather separate and distinct regions in the brain. With the advent of neuroimaging methods like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) a more elaborate investigation of the interplay between emotion and cognition and the brain regions that orchestrate these complex behaviors became possible. For more than 25 years now, fMRI research has been contributing considerably to understanding the neuronal mechanisms that influence how emotional reactions impact memory processes and vice versa.

A highly arousing event is accompanied by many bodily reactions such as changes in heart rate or stress hormone levels. Associated with these reactions, activation in several densely interconnected brain regions increases or decreases, thereby influencing which aspects of the event will later be remembered and which will be forgotten. According to previous studies, the most important region for emotional memory processing is the amygdala, which is connected with a vast array of other regions in the brain (LaBar & Cabeza, 2006). The amygdala is considered a salience detector that enables animals as well as humans to quickly react to arousing stimuli, especially potential threats, by influencing the processing and storage of emotional information in a bottom-up driven manner. Superior long-term memory for these emotional stimuli, however, can only be achieved through close interactions of the amygdala with the hippocampus (Phelps, 2004; Richardson, Strange, & Dolan, 2004). In addition, activity in the amygdala and its functional connections with other brain areas is closely mediated by regions of the prefrontal cortex (PFC). The PFC, which is responsible for maintaining and updating information as well as for guiding goal-directed behavior, therefore plays an important role in regulating the processing of emotional material through top-down control of limbic regions (Etkin, Egner, & Kalisch, 2011).

The interaction between bottom-up and top-down processing regions generally supports the short- and long-term memory for emotionally arousing events, which is advantageous in daily life. However, a disruption in this delicate network can significantly impair the adequate processing of arousing stimuli, resulting in dysfunctional emotional memory, characteristic of many mood and anxiety disorders. Therefore, investigating the interplay between emotional arousal and memory and how these two processes are integrated in the brain is of high relevance for the development of adequate and successful treatment approaches for psychiatric diseases. Unfortunately, up to now most published neuroimaging findings have been of quite limited use for clinical practice. Thomas Insel, Director of the National Institute of Mental Health (NIMH), mentioned at a conference in 2011 that despite more than 4'000 fMRI papers published, not a single finding has changed routine in clinical care in psychiatry (as cited by Rosen and Savoy (2012)). One reason for this negligible impact of fMRI research in psychiatry is the lack of well-powered studies reporting robust findings that can be used to generate new hypotheses tested in independent studies. Another reason is the still prevalent use of univariate approaches in fMRI data analysis, which are based on group-level contrasts and which are not sensitive enough to be of particular value for the clinical practice.

Therefore, the aim of this thesis is to present new scientific advances in the relationship between emotional arousal and memory processes documented in two publications that made use of large-scale fMRI data generated in our lab, albeit using this data in different ways. The letters indicate my contribution to each publication: **A** - Designed the experiment; **B** - Performed the experiment; **C** - Analyzed the data; **D** - Wrote the paper.

- Loos, E., Egli, T., Coynel, D., Fastenrath, M., Freytag, V., Papassotiropoulos, A., de Quervain, D. J.-F., & Milnik, A. (2019). Predicting emotional arousal and emotional memory performance from an identical brain network. *NeuroImage*, 189, 459-467.  
(A – B – C – D)
- Loos, E.<sup>\*</sup>, Schicktanz, N.<sup>\*</sup>, Fastenrath, M., Coynel, D., Milnik, A., Fehlmann, B., Egli, T., Ehrler, M., Papassotiropoulos, A., & de Quervain, D. J.-F. Working memory intervention acutely decreases amygdala activity and phobic fear. *Manuscript submitted for publication*.  
(A – B – C – D)

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In the first publication, Loos et al. (2019), we used multi-voxel pattern analysis (MVPA) to identify a network of brain regions that was linked to perceived arousal during the encoding of negative and neutral pictures as well as to recognition memory performance during the retrieval of those pictures. Using fMRI and behavioral data from over 1'000 healthy subjects, we were not only able to provide robust estimates of the reported effects, but also to apply them to an independent subsample that originated from the same study population. Thereby, MVPA allowed us to make prediction on an individual level, rendering it more sensitive than traditional univariate analysis which only allows inferences on group-level (Haxby, 2012).

Furthermore, the knowledge that we can gain from such large-scale studies on healthy subjects is of great relevance for the development of smaller, hypothesis-based fMRI projects that aim to translate findings from basic research into the clinical context, for example by identifying treatment possibilities for psychiatric disorders. Hence, in the second publication, Loos et al. (submitted), we used findings from our large fMRI study to derive a hypothesis-driven research question that we examined in an independent fMRI study. Specifically, we investigated if engaging in a demanding working memory task acutely reduces amygdala activity and phobic fear of snakes. Thus, instead of investigating the effects that emotional arousal has on memory, we were interested in how certain memory processes can alter perceived fear as an extreme form of arousal.

The following chapters will give an overview on previous behavioral and fMRI findings regarding the interplay between emotional arousal and different memory processes in health and disease.

## 2 Theoretical background

Investigating the effects of arousal on memory processes and how arousal influences *what* is remembered and *how* it is remembered has motivated the work of many researchers. Today we know that arousal can influence all forms of memory from working memory, over episodic memory to implicit memory. However, while arousal has been reported to mainly enhance memory, it can also substantially impair it under certain circumstances.

### 2.1 Emotional arousal modulates what we remember

The following chapters will discuss the effect of emotional arousal on episodic and working memory, two memory subsystems investigated in the publications of this thesis. However, before doing so, the next section will discuss how arousal is conceptually different from valence, an important differentiation for research based on emotional stimuli.

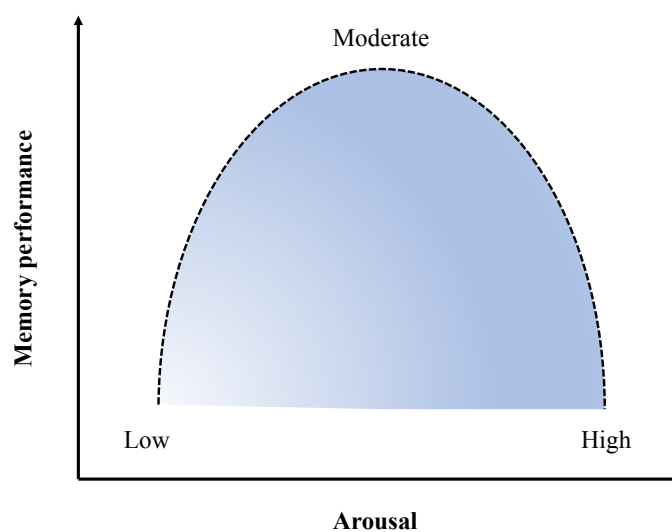
#### 2.1.1 *Distinguishing arousal from valence effects in memory research*

To study how arousal impacts human memory, most researchers use a two-dimensional conceptualization of emotion, originally proposed in the circumplex model of affect (Russell, 1980). According to this model, emotional experiences fall along two dimensions: arousal and valence. While the valence of an experience can range from *pleasant* to *unpleasant*, perceived arousal can shift on a scale between *excited/activation* and *calm/deactivation* (Lang, Bradley, & Cuthbert, 2008; Russell, 2003). Even though many alternative theories exist on whether emotions are best defined by categories (Ekman, 1992; Elfenbein & Ambady, 2002; Izard, 2011) or by various other dimensions (Daly, Lancee, & Polivy, 1983; Lang, 1995; Plutchik, 1983), the differentiation between arousal and valence has been widely adapted and has proven to be most consistent with research findings from the field of cognitive and affective neuroscience (Posner, Russell, & Peterson, 2005).

Regarding those two dimensions, studies on the effect of emotion on memory have been trying to elucidate whether it is the arousing character of an emotional experience that determines what is preferentially stored and retrieved or whether memory rather depends on the experience being negative, positive or neutral in valence. Even though studies have reported valence-specific effects suggesting that negative stimuli are generally better remembered than positive stimuli (Adelman & Estes, 2013; Ochsner, 2000; Steinmetz, Addis, & Kensinger, 2010), probably due to their greater value for survival (Carretié, Albert, López-Martín, & Tapia, 2009), the pivotal factor influencing memory performance seems to be that the stimuli evoke

sufficient arousal (Blake, Varnhagen, & Parent, 2001; Bradley, Greenwald, Petry, & Lang, 1992; Marchewka et al., 2016; Mather & Nesmith, 2008; Mirandola & Toffalini, 2016).

One of the first attempts to relate emotion to cognitive processes was undertaken by the formulation of the Yerkes-Dodson-Law (Yerkes & Dodson, 1908), which postulates that motivational processes influence cognitive performance in an inverted U-shaped manner. This law has later also been applied to the relationship between arousal and memory performance. (Teigen, 1994). While memory is supposed to be best at moderate levels of arousal, too low or too high levels of arousal can critically impair memory performance (see also Figure 1).



**Figure 1.** According to the Yerkes-Dodson-Law, arousal influences memory performance in an inverted U-shape manner with the best performance at moderate levels of arousal.

In the laboratory, arousal is usually induced via mild electric shocks, stress tests or emotionally arousing stimuli in form of pictures, words or sounds, that evoke rather moderate to high levels of arousal. In turn, to test how much arousal was actually experienced during a task, researchers commonly use objective measures such as skin conductance or heart rate, or subjective measures like rating scales through which subjects indicate their level of perceived arousal. Albeit the external validity of experimentally induced arousal has been questioned (Lick & Unger, 1977; Wagstaff et al., 2003), these methods have proven very useful for the investigation of arousal-mediated effects on memory processes, especially in fMRI studies.

Arousal also constituted one of the core variables in the two publications included in this thesis. In both experiments, emotional arousal was evoked by the presentation of negatively arousing pictures while perceived arousal as an outcome measure was assessed via subjective rating scales.

### 2.1.2 *Episodic memory and emotional arousal*

Throughout lifetime every one of us experiences countless emotional events. Those can be positive in nature like getting married or receiving a PhD degree, or negative, like the death of a loved one or a break-up. These events might vary in intensity, but all of them will be emotionally arousing and will be remembered better than events that were not arousing at all, like what we wore for work last Monday.

The memory for personally experienced events is referred to as episodic memory (Ferbinteanu, Kennedy, & Shapiro, 2006; Tulving, 1993) and is considered a subtype of declarative memory (Squire, 1992). Usually information about an event is first processed (encoded) and then gradually transferred into memory (consolidated) before it is remembered (retrieved). Episodic memory performance is typically measured using (cued) recall or recognition tasks (Tulving, 2002). The particular interest in the effects of emotional arousal on episodic memory stems from the observation that the memory advantage for emotional events over neutral ones becomes most apparent only after some time has elapsed since initial encoding. Kleinsmith and Kaplan (1963) were one of the first to show that memory for emotionally arousing stimuli compared to neutral ones was worst at immediate recall (2 min) and gradually increased when tested after 45 min, one day and finally after one week. Since then, similar results have been reported for memory tested after a delay of 24 hours (LaBar & Phelps, 1998; Mickley Steinmetz, Schmidt, Zucker, & Kensinger, 2012; Sharot & Phelps, 2004) up to several days post-encoding (Payne, Stickgold, Swanberg, & Kensinger, 2008; for a review see Yonelinas & Ritchey, 2015). The enhanced consolidation of emotional memories heavily relies on the interaction between stress hormones released through an arousing experience and the subsequent activation of brain regions involved in emotion processing (McGaugh, 2004, 2013). Thus, for a stimulus to be superiorly stored into memory, it needs to elicit sufficient arousal during encoding (Cahill & McGaugh, 1995; Kensinger & Corkin, 2003b; Mather & Neshmith, 2008; Wolf, 2009).

Several studies could further demonstrate that when arousal is induced right after encoding, it can still enhance the memory for emotional stimuli (Buchanan & Lovullo, 2001; Cahill, Gorski, & Le, 2003; Liu, Graham, & Zorawski, 2008) and even boost memory for neutral material (Anderson, Wais, & Gabrieli, 2006; Schwarze, Bingel, & Sommer, 2012; Tambini, Rimmele, Phelps, & Davachi, 2017), which was observed up to 30 min after encoding (Nielson & Powless, 2007). This memory advantage for neutral stimuli was, however, only found when they were encoded without emotional stimuli being presented as well. Mather and Sutherland (2011) argue that post-encoding arousal only increases memory for stimuli that were given priority during encoding, which in most cases are stimuli that are emotional.



The literature outlined above strongly supports the view that arousal is crucial for the enhanced encoding and consolidation of emotional memories. However, extreme levels of arousal in form of acute stress can also substantially impair memory performance, especially during retrieval (de Quervain, Aerni, Schelling, & Roozendaal, 2009; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005). This impairing effect has been associated with the arousal-induced release of stress hormones, which critically affects the retrieval of memories (Buchanan, Tranel, & Adolphs, 2006; de Quervain, Schwabe, & Roozendaal, 2017; McGaugh & Roozendaal, 2002). Thus, while stress hormone release during encoding and consolidation is associated with memory-enhancing effects, the presence of stress hormones at retrieval can worsen the memory of previously encoded material (Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Smeets, Otgaar, Candel, & Wolf, 2008).

Taken together, emotional arousal seems to exhibit its influence during all stages of episodic memory processing from encoding over consolidation to later retrieval. This interplay between emotional arousal and episodic memory was of specific interest in the publication Loos et al. (2019), in which we investigated brain activation patterns, arousal ratings and episodic memory performances during the encoding and retrieval of negative and neutral pictures.

### *2.1.3 Working memory and emotional arousal*

In contrast to episodic memory, working memory (WM) allows to temporarily store and maintain incoming information while new information is processed concurrently (Baddeley, 1992). In addition, keeping information in mind for a short period of time helps to react flexibly to current goals. The most commonly used task to test WM performance is the n-back task (Owen, McMillan, Laird, & Bullmore, 2005). During this task, stimuli, e.g. letters or pictures, are presented for several milliseconds and have to be maintained while new stimuli are presented in the meantime. The level of difficulty, or cognitive load, induced by the task depends on the amount of information that has to be kept in mind before memory is probed. While much research has been conducted on the effects of emotional arousal on episodic memory, comparatively little is actually known about how arousal impacts WM performance. In fact, previous findings have so far been quite inconsistent. Whether arousal enhances or impairs WM seems to strongly depend on the experimental design. One crucial distinction with regard to the study design is whether arousal was induced (1) through mild shocks or stress tests prior or during a WM task or (2) through the presentation of arousing stimuli relevant for the WM task per se.

For instance, when emotionally arousing and neutral stimuli were presented as targets during an n-back task, WM performance was found to be increased for emotional compared to

neutral task blocks, reflected in higher accuracy and reaction times (Lindström & Bohlin, 2011) or in higher accuracy only (Becerril & Barch, 2010). Also, WM performance was found to be better when arousing stimuli were presented under high task load compared low task load (Erk, Kleczar, & Walter, 2007). In contrast, other studies did not observe any effect of arousing stimuli on WM performance (Grimm, Weigand, Kazzer, Jacobs, & Bajbouj, 2012; Kensinger & Corkin, 2003a) or even reported that those stimuli impaired performance (Choi et al., 2013; Mather et al., 2006).

Similarly, arousal seems to disrupt WM performance when subjects are put into a state of arousal during a concurrent WM task, e.g. through threat of shock (Lavric, Rippon, & Gray, 2003; Vytal, Cornwell, Arkin, & Grillon, 2012), or even prior to a WM task through exposure to a cold pressure stress test (Duncko, Johnson, Merikangas, & Grillon, 2009) or a social stress test (Luethi, Meier, & Sandi, 2009; Schoofs, Preuß, & Wolf, 2008)

Despite the observed effects of arousal on WM being rather inconclusive, WM performance has been found to be almost always impaired when emotionally arousing stimuli are presented as task-irrelevant distractors during a WM task (Dolcos & Denkova, 2014; Schweizer & Dalgleish, 2016). One suggested explanation is that performance critically depends on the amount of cognitive resources that are available while solving a task. As soon as attention is divided or even completely directed towards a simultaneously presented distractor, performance decreases (Lavie, Hirst, De Fockert, & Viding, 2004). Emotionally arousing stimuli are generally very salient and stick out which is why attention is immediately directed towards them (LeDoux, 2012; Vuilleumier & Huang, 2009). Especially highly arousing negative stimuli are preferentially attended because of their threat potential. They are therefore readily processed and directly transferred into WM, this way leaving no capacity for task-relevant information to be processed and consequently impairing task performance (Mather & Sutherland, 2011; Okon-Singer, Hendler, Pessoa, & Shackman, 2015). Thus, while WM performance decreases when arousing stimuli are presented as task-irrelevant distractors and attention is directed away from the task at hand, emotional arousal could support WM if arousing stimuli are both arousing and task-relevant and therefore fully attended (Pessoa, 2009).

In sum, study design and study results on the effects of arousal on WM performance have been heterogeneous so far and need further investigation. In Loos et al. (submitted), we examined the relationship between arousal and WM has also been investigated. More specifically, in this study we recruited subjects with fear of snakes and investigated how this phobic fear gets modulated in the context of a demanding WM task comprising phobic stimuli and neutral stimuli.

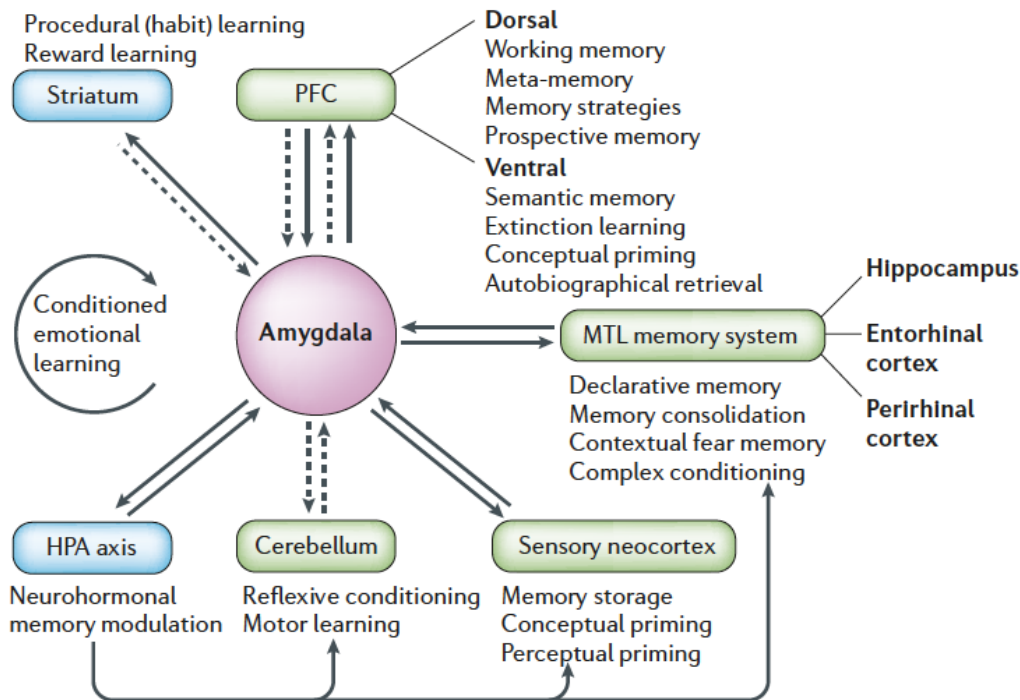
## 2.2 Emotional arousal modulates how we remember – evidence from neuroimaging studies

The use of fMRI has opened new ways to investigate how emotional arousal and memory are processed in the human brain. This endeavor has, however, proven rather challenging as most brain regions do not serve one unique function. For instance, brain regions said to be involved in emotion processing have also been found pivotal for memory formation, while regions mainly associated with executive functioning and attention processes seem to play a role in emotion regulation as well (Pessoa, 2008). Despite these challenges, fMRI studies could shed light on the most relevant structures involved in emotional memory processes. Two key regions, the amygdala and the PFC, will be described more in detail in the following chapters.

### *2.2.1 Bottom-up signaling – the amygdala as a central hub for emotional memory processing*

Buried deep inside the brain and inherent to all mammals, the amygdala is considered a central hub for emotion processing (Pessoa, 2010). It functions as a detection system that evaluates incoming sensory information according to its threat potential, therefore playing an important role for survival (LaBar & Cabeza, 2006; LeDoux, 2012). Studies in animals and humans have identified the amygdala to be critical for the formation of emotional memories during all stages from perception to retrieval.

Already during encoding, increased activity in the amygdala in response to emotionally arousing stimuli has been found to be associated with improved emotional memory (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Dolcos, LaBar, & Cabeza, 2004b; Kensinger & Schacter, 2006; Mickley Steinmetz et al., 2012). As soon as emotional information is perceived, the amygdala influences later memory by prioritizing the processing of specific aspects of the incoming information by modulating its connection with other cortical and subcortical areas (LaBar & Cabeza, 2006; Phelps & LeDoux, 2005; see Figure 2). Through its unique location the amygdala receives input from early sensory systems like the visual areas and modulates the perceptual processing of emotional information in these systems through backward projections (Amaral, Behnia, & Kelly, 2003; Vuilleumier & Driver, 2007; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Accordingly, increased activation in visual areas has repeatedly been observed during the perception of emotional pictures in comparison to neutral pictures (Blair et al., 2007; Mickley Steinmetz & Kensinger, 2009; Stark et al., 2004).



**Figure 2.** The amygdala constitutes an important hub in the brain with direct and indirect connections to regions involved in different types of memory processing, including working memory, declarative memory and non-declarative memory. MTL = medial temporal lobe; PFC = prefrontal cortex; HPA = hypothalamic-pituitary-adrenal. The figure is taken from LaBar & Cabeza (2006).

Besides its involvement in the prioritized processing of arousing information during encoding, the amygdala plays a key role in the consolidation of emotional memories. During this stage, the amygdala, activated as a consequence of the arousal-induced stress hormone release (McGaugh, 2004, 2013), ‘tags’ incoming emotional information as relevant by strengthening its connections with regions in the medial temporal lobe (MTL), including the hippocampus (Phelps, 2004; Richter-Levin & Akirav, 2000). Those regions in turn are responsible for the generation and storage of new memories (Cabeza & Nyberg, 2000; Squire & Zola-Morgan, 1991). However, over time this consolidation process becomes less dependent on hippocampal regions but begins to increasingly rely on neocortical regions of the brain (Quinn, Ma, Tinsley, Koch, & Fanselow, 2008; Squire, Genzel, Wixted, & Morris, 2015; Takashima et al., 2009).

Further evidence for the role of the amygdala in the consolidation of emotional memories in humans stems from pharmacological interventions in healthy subjects and from lesion studies in patients with lobectomy or Urbach-Wiethe disease. In patients with amygdala lesions, the memory advantage for emotionally arousing stimuli over neutral ones has been found to be diminished compared to healthy controls when memory was tested after a time delay of at least 24 hours (Adolphs, Cahill, Schul, & Babinsky, 1997; Adolphs, Tranel, & Denburg, 2000; Markowitsch et al., 1994). Even though diminished amygdala activity disrupts the superior

memory for emotionally arousing stimuli after consolidation, the valence or the emotional context of those stimuli, however, can still be remembered (Phelps et al., 1998; Phelps, LaBar, & Spencer, 1997). This conveys further evidence that arousal rather than valence is the crucial factor engaging the amygdala (Dolcos, Denkova, & Dolcos, 2012; Murty, Ritchey, Adcock, & LaBar, 2010; Sergerie, Chochol, & Armony, 2008).

Finally, fMRI studies also showed an engagement of the amygdala during the retrieval of emotional memories. Here, amygdala activity was associated with enhanced memory for neutral stimuli encoded in an emotional context (Maratos, Dolan, Morris, Henson, & Rugg, 2001; Smith, Henson, Dolan, & Rugg, 2004) and, even more so, when the previously encoded stimuli were emotional per se (Dolcos, LaBar, & Cabeza, 2005; Kensinger & Schacter, 2005).

Taken together, the amygdala holds a key role in the automatic, bottom-up processing of incoming emotional information. However, it can only mediate emotional memory processes through connections with other brain regions, of which those with the hippocampus are among the most important ones. The hippocampus is known as a region responsible for memory storage (Burgess, Maguire, & O'Keefe, 2002; Henke, 2010; Tulving & Markowitsch, 1998) and through its close interaction with the amygdala, it is critically involved in the consolidation of emotional memories, as already mentioned above. However, studies also reported that a joint activity of the amygdala and the hippocampus already during the encoding of emotional stimuli led to an enhanced memory for those stimuli (Dolcos et al., 2004b; Kensinger & Corkin, 2004; Murty et al., 2010; Ritchey, Dolcos, & Cabeza, 2008) and that their functional connectivity is increased during the encoding of emotional stimuli compared neutral ones (Fastenrath et al., 2014). Similar observations have been found for retrieval, where memory for emotional stimuli up to one year after encoding was associated with increased amygdala and hippocampus activation (Dolcos et al., 2005; Kensinger & Schacter, 2005) and increased functional connectivity between both (Smith, Stephan, Rugg, & Dolan, 2006).

Activity in the amygdala and its interaction with other brain regions has been subject to both publications of this thesis. In Loos et al. (2019), we investigated a network of brain regions predictive for perceived arousal during encoding as well as predictive for later episodic memory retrieval. We assumed the amygdala to be part of this arousal-memory network together with other regions known to support emotional memory formation, like the hippocampus, visual areas and the PFC. Further, Loos et al. (submitted) specifically focused on amygdala activity in the context of processing phobic stimuli under high WM load. Here, the amygdala served as a target region in the performed neuroimaging analyses.

### *2.2.2 Top-down control – regulatory role of the prefrontal cortex in emotional memory processing*

Regions of the PFC are commonly associated with cognitive processes like attention, working memory or executive functioning (Kane & Engle, 2002). However, several PFC regions have recently been identified to play an important role also for the perception, regulation and updating of emotional information through interactions with other brain regions like the amygdala, the hippocampus and sensory cortices (Jin & Maren, 2015; Kim et al., 2011; Pessoa, 2008; Ray & Zald, 2012). While the medial PFC and orbitofrontal cortex (OFC) have mainly been associated with emotion regulation (Bishop, Duncan, Brett, & Lawrence, 2004; Etkin, Büchel, & Gross, 2015; Ochsner, Silvers, & Buhle, 2012), the lateral PFC is said to be rather involved in cognitive control (Ochsner & Gross, 2005; Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004; Wagner, Maril, Bjork, & Schacter, 2001) and working memory processes (Barbey, Koenigs, & Grafman, 2013; Cohen et al., 1997; Curtis & D'Esposito, 2003).

It has been suggested that PFC regions counteract bottom-up signaling from the amygdala through goal-directed top-down processes (Etkin et al., 2011; Jordan, Dolcos, & Dolcos, 2013). For example, when you see a snake, increased amygdala activity will immediately signal a potential threat and functional connections between the amygdala and regions in the PFC will be strengthened. Consequently, activity in PFC regions will support the evaluation of the incoming information and guide our reactions by influencing amygdala activity according to current goals (Dolcos & Denkova, 2014; Smith et al., 2006). If the snake is behind glass, top-down processes from the PFC will signal that the situation is safe and you can calm down. This way, the PFC can regulate how emotionally arousing situations are perceived and thus mediate subsequent emotional memory. For instance, the ventrolateral PFC (vlPFC) and the dorsolateral PFC (dlPFC) have been found to exhibit increased activity during the successful encoding of arousing stimuli compared to neutral stimuli (Dolcos, LaBar, & Cabeza, 2004a). The authors argue that arousing stimuli might be maintained longer in working memory (as reflected by increased dlPFC activity), resulting in a more elaborate processing and better subsequent memory. Since then, similar finding of an engagement of the PFC during emotional encoding have been reported (Mickley Steinmetz et al., 2012; Sergerie, Lepage, & Armony, 2005). With regard to retrieval, PFC activity has mainly been associated with remote memories which became less hippocampus-dependent over time (Cabeza & St Jacques, 2007; Frankland & Bontempi, 2005; Wiltgen, Brown, Talton, & Silva, 2004)

Even though the PFC seems to be relevant for episodic emotional memory, its crucial role lies in keeping up cognitive performance in the presence of arousal. For instance, WM

performance has been repeatedly shown to rely on activity in the dlPFC (Barbey et al., 2013; D'Ardenne et al., 2012; Owen et al., 2005). Only recently has the dlPFC been identified as a region in which cognition and emotion are integrated (Cromheeke & Mueller, 2014). Those findings stem from studies that used WM tasks paired with task-relevant or task-irrelevant (distracting) emotional stimuli. It has been reported that during emotional WM tasks, activity in the dlPFC is differentially modulated by emotional arousal. In fact, while some studies found a decreased dlPFC activation in the presence of emotional distractors, which was associated with impaired WM performance (Anticevic, Barch, & Repovs, 2010; Dolcos & McCarthy, 2006; Perlstein, Elbert, & Stenger, 2002), other studies found no effect of arousal on dlPFC activation (Döhnel et al., 2008) or even increased activation (Erk et al., 2007; Grimm et al., 2012; Neta & Whalen, 2011) without WM performance being affected. It has been argued that elevated dlPFC activation could reflect an increased effort to counteract the detrimental effect of emotional distractors (Cromheeke & Mueller, 2014). This is in line with the view that PFC regions down-regulate activation in limbic regions during high task demands in favor of current goals (Okon-Singer et al., 2015; Rolls, 2013). A study of van Dillen and colleagues found that engaging in a demanding WM task increased activity in the dlPFC while activity in the amygdala was decreased (Van Dillen, Heslenfeld, & Koole, 2009). Similar, albeit also correlational, results for a top-down control on emotion-processing areas have been reported by other studies as well (Clarke & Johnstone, 2013; Erk et al., 2007; Mitchell et al., 2007; Schweizer, Hampshire, & Dalgleish, 2011). Furthermore, increased amygdala activity as a consequence of emotional distraction has been associated with increased coupling with the vlPFC, which is supposed to be responsible for coping with the distraction through emotion regulation mechanisms (Dolcos, Kragel, Wang, & McCarthy, 2006).

Taken together, the PFC has a substantial influence on how emotionally arousing information is processed in the brain by counteracting bottom-up processes from limbic regions through direct and indirect downward projections. This top-down control is crucial as a failure to regulate emotions can potentially lead to the development of psychiatric disorder like post-traumatic stress disorder (PTSD) or phobia.

In Loos et al. (submitted), we investigated the engagement of the dlPFC during a demanding WM task and its concurrent top-down regulating effects on the amygdala in the presence of high arousal (phobic fear). Furthermore, as regions in the lateral and medial PFC have also been found to be involved in emotional episodic memory processes, we expected PFC regions to be part of the predictive arousal-memory network identified in Loos et al. (2019).

## 2.3 Psychiatric disorders as a consequence of dysfunctional emotional memory

As outlined above, emotional arousal substantially modulates episodic and working memory processes. However, arousal also influences non-declarative memory. Remembering that an object or situation is associated with a negatively arousing (aversive) consequence can help us avoid dangerous situations in the future. However, these so-called aversive memories can also become maladaptive and impair daily functioning, especially when they evoke strong feelings of arousal and fear as seen in many anxiety disorders. The following chapters focus on aversive memory and psychiatric diseases in which dysfunctional memory processes are a key symptom.

### 2.3.1 *The acquisition and extinction of aversive memories*

Remembering a negatively arousing or fearful event can be beneficial for survival. According to the *preparedness theory* (Seligman, 1971) some stimuli like snakes, spiders, extreme heights or blood evoke fear and avoidance much easier than other objects or situations, probably because they have signaled threat throughout human evolution. Other fears or aversions are generated more gradually through associative learning or fear conditioning processes that can result in the development of an aversive memory. For example, when your friend's cat scratches you whenever you pet it, you will stop touching it. You have learned that the cat is associated with a negative consequence (painful scratches) and should therefore be avoided.

Previous research has identified the amygdala to be highly important for fear learning. For instance, patients with amygdala damage are usually unable to learn to associate a presented neutral stimulus (e.g. a tone) with a negatively arousing event (e.g. a mild shock) and consequently do not exhibit typical fear responses towards the neutral stimulus (Angrilli et al., 1996; Bechara et al., 1995; Funayama, Grillon, Davis, & Phelps, 2001). Furthermore, fMRI studies in healthy subjects found the amygdala to be particularly active during fear conditioning experiments (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Cheng, Knight, Smith, Stein, & Helmstetter, 2003; Knight, Nguyen, & Bandettini, 2005), in addition to other brain regions, like the anterior cingulate cortex (ACC) (Büchel, Morris, Dolan, & Friston, 1998; Lang et al., 2009; van Well, Visser, Scholte, & Kindt, 2012) or the insula (Knight, Waters, & Bandettini, 2009; Morris & Dolan, 2004).

Under normal circumstances, an acquired aversive memory can get extinguished again. When you repeatedly make the experience that the cat that you avoided touching has actually stopped scratching, your fear will diminish over time. Extinction processes have been associated with increased activity mainly in the ventromedial PFC (vmPFC) and the hippocampus (Kalisch et al., 2006; Milad et al., 2007). Also, the context in which the aversive memory was



acquired plays an important role for extinction learning. Remembering that a context is safe or unsafe has been associated with increased hippocampus activity (Phelps, Delgado, Nearing, & LeDoux, 2004).

Finally, if a feared object or situation is consistently avoided, there is no opportunity to learn that no negative consequence follows and extinction cannot occur. Consequently, the persistent fear and avoidance can increase further and even generalize to other contexts, possibly leading to the development of anxiety disorders such as PTSD or phobia (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015). In patients with anxiety disorders, extinction learning is usually achieved in controlled therapeutic settings in form of repeated exposure to the feared stimulus (exposure-based therapy), which has been proven very successful (Foa & McLean, 2016). However, patients often struggle to search for professional help. Consequently, there is a need to develop new treatment approaches that are easily accessible.

In Loos et al. (submitted) we recruited subjects with an aversive memory for snakes to investigate whether engaging in a WM task would acutely reduce the phobic fear they had generated towards snakes. Long-term effects in fear reduction through a WM training could help patients with anxiety disorders to reduce their fear in situations associated with an aversive event. This, however, requires a better understanding of the neuronal mechanisms that might result in the generation of aversive memories. In Loos et al. (2019) we investigated how emotional arousal perceived as a reaction to negative stimuli is related to later memory performance and whether those processes rely on the same network of brain regions.

### 2.3.2 PTSD, Specific Phobia and their neuronal correlates

Extremely aversive events that are accompanied by high levels of arousal like a horrible car crash, combat or rape can result in a very persistent fear memory for the event and its context. Consequently, the smell of a fragrance or the sound of a helicopter that got associated with the event can cause a flood of memories coming to mind, along with strong fear reactions. The DSM-5 (American Psychiatric Association, 2013) defines an event as traumatic when it involves the exposure to or threat of death, serious injury or sexual violence against oneself or witnessing it happening to someone else. About 15-30 % of people that experience a traumatic event will develop PTSD in the aftermath (Breslau, Kendler, Su, Gaxiola-Aguilar, & Kessler, 2005; Eriksson, Kemp, Gorsuch, Hoke, & Foy, 2001). The most important criteria for diagnosing PTSD are (1) vivid re-experiences of the traumatic event (intrusions) in form of flashbacks or nightmares, (2) avoidance of situations or feelings associated with the traumatic events, (3)

altered cognition and mood in form of negative thoughts, and (4) a persistent state hyperarousal and reactivity (American Psychiatric Association, 2013).

Similar to PTSD, specific phobias are the result of an emotionally arousing event that was experienced earlier in life. However, while PTSD is always caused by the experience of a life-threatening event, specific phobias can also result from situations that were less traumatic though still aversive (Garcia, 2017). Most phobias develop as a consequence of a harmless animal or neutral situation getting associated with a negatively arousing event. However, some phobias of objects or situations are more prevalent than others because they pose some evolutionary significance (McNally, 2016). What is common to all specific phobias, however, is that patients exhibit excessive immediate fear towards the phobic situation and avoid it whenever possible, leading to substantial impairments in daily life functioning (American Psychiatric Association, 2013).

fMRI studies have substantially contributed to the identification of the brain circuits dysfunctional in PTSD and specific phobia. Consistent with the state of heightened arousal displayed in both disorders, confrontation with fearful stimuli has been associated with heightened amygdala activity compared to controls in PTSD patients (Brohawn, Offringa, Pfaff, Hughes, & Shin, 2010; Brunetti et al., 2010; Linnman, Zeffiro, Pitman, & Milad, 2011) as well as in phobic patients (Åhs et al., 2009; Schienle, Schäfer, Walter, Stark, & Vaitl, 2005; Straube, Mentzel, & Miltner, 2006). As reported above, the amygdala plays a key role in fear processing and its hyperactivity in patients reflects an abnormal and exaggerated reaction towards negative or fearful stimuli (Shin & Liberzon, 2010). In addition to the amygdala, the insula has been found to be overly active in PTSD (Fonzo et al., 2010; Garrett et al., 2012; Mazza et al., 2012) as well as in specific phobia (Dilger et al., 2003; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006) compared to controls.

While dysfunctional brain activation in specific phobia manifests itself mainly in form of hyperactivity (Etkin & Wager, 2007), PTSD patients display a more complex pattern of hyper- and hypoactive brain regions. This interplay of increased and diminished brain activity is also reflected in the manifold symptoms found in this disorder (Galatzer-Levy & Bryant, 2013). Given that several interconnected regions have repeatedly been identified to show impaired functioning in PTSD (for reviews, see Fenster, Lebois, Ressler, & Suh, 2018; VanElzakker, Staples-Bradley, & Shin, 2018), researchers suggested that PTSD should be considered as a disorder of dysfunctional neural circuits rather than of single brain regions. The neurocircuitry model of PTSD (Rauch, Shin, & Phelps, 2006; Rauch, Shin, Whalen, & Pitman, 1998), for

example, proposes that hyperactivity in the amygdala is responsible for the extreme fear response and hyperarousal observed in PTSD, while a hypoactive vmPFC (including the rostral ACC) fails to down-regulate activity in the amygdala. The model also posits that an impaired functioning of the hippocampus leads to memory deficits and impaired contextualization of information in PTSD, despite results regarding the hippocampus being quite inconsistent (Hughes & Shin, 2011). The neurocircuitry model has received much support from successive fMRI studies, but has also been continuously extended as activation in several additional regions has been found to be dysfunctional in PTSD, including an increased activity in the dorsal ACC (Milad et al., 2009; Ramage et al., 2013; Shin et al., 2011; Van Rooij, Kennis, Vink, & Geuze, 2016).

In sum, previous fMRI research has already shed some light on dysfunctional brain activation in anxiety disorders. However, there is still a need for more fMRI studies using analysis approaches that focus on brain networks instead of single regions and that allow to make predictions about mental states on an individual level in patients but also in healthy subjects. Using large-scale fMRI data, the publication Loos et al. (2019), identified a brain network predictive for emotional arousal and memory processes in healthy subjects, two processes substantially impaired in PTSD. Furthermore, to be able to develop effective treatment approaches for anxiety-related disorders it is important to investigate how brain regions are functionally connected and how dysfunctional brain activation could be regulated in fearful situations. In Loos et al. (submitted), we focused on increased amygdala activity in response to phobic stimuli and tested whether this activity could be down-regulated through a WM-dependent increase in dlPFC activity.

### 3 Methods

fMRI research on emotional arousal and its interaction with memory processes has so far been hampered by several methodological shortcomings. One big challenge is the lack of sufficient sample sizes which ensure robust findings and promote novel exploratory as well as hypothesis-driven research questions. In addition, the common use of univariate approaches does not allow to make predictions on an individual level or to draw causal inferences from brain activity. The following chapters will illustrate how those limitations were approached in the two publications included in this thesis and how they can be addressed in future studies.

#### 3.1 Exploratory and hypothesis-driven research projects based on big data

Exploring large data sets in a hypothesis-free manner allows the discovery of novel findings that can then be investigated in independent hypothesis-driven projects. In turn, findings from those projects can motivate the acquisition of additional variables resulting in even larger sets of data. The next chapters demonstrate how this approach can be applied in daily research. The first chapter describes how a study, originally set out to investigate a specific research question, turned into a large-scale hypothesis-generating study. The second chapter shows how findings from this large study can consequently be used to develop new hypothesis-based projects.

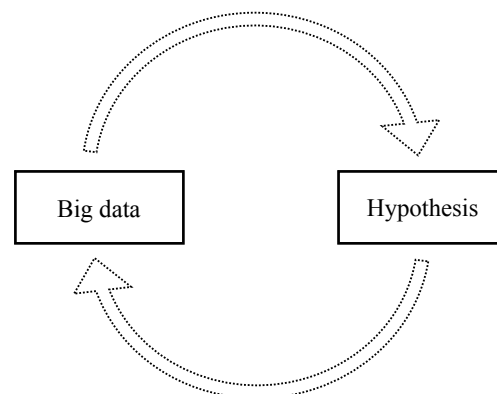
##### *3.1.1 The Basel protocol – a large-scale, single-center study*

In 2008, our lab launched a study with the aim to investigate the genetic underpinnings associated with the consolidation of emotional memories during sleep in healthy young adults by means of a genome-wide association study (GWAS). More specifically the main goal was to investigate genetic differences in the noradrenergic neurotransmitter system and their effects on sleep and episodic memory consolidation based on previous findings of the research group reported in de Quervain, Aerni, and Roozendaal (2007). The original ethics protocol considered blood draw for genetic analyses together with data acquisition on recall performance and EEG recordings as primary outcome. In addition, data was gathered on WM performance, motoric skills and several questionnaires (e.g. affect intensity, sleep quality, handedness).

With a planned sample size of 500 subjects the study was considered a large-scale project at the time. The advantage of such big data sets is that they allow discoveries that were initially not envisioned and that may suggest novel, so far unknown mechanisms. These discoveries in turn can motivate a more detailed, hypothesis-driven investigation of previously

observed results through the acquisition of additional variables, thereby continuously expanding the data set (Van Horn & Toga, 2014; see also Figure 3). Consequently, over the course of almost a decade, the study was extended substantially. One big adaptation, still in 2008, was the initiation of a second sub-study that focused on investigating the neuronal correlates of emotional memory formation with the use of fMRI. Most tasks and questionnaires were applied in the same way as in the original EEG study. The fMRI study was planned to comprise 100 subjects. Two years later, however, the sample sizes were raised to 1'000 subjects and another year later to 2'000 subjects in each sub-study because the originally intended sample sizes turned out too small to find the desired effects, especially with regard to genetics. Over the years, our study protocol was further extended by the collection of hormone data, personality and depression questionnaires, diffusion tensor imaging (DTI) or resting state fMRI and high-resolution genetics, epigenetics and gene-expression data.

With more and more data coming in on a variety of different measures, the study slowly developed into a “playground” for scientist coming from biology, genetics, neuroimaging or psychology. This was also reflected in the diversity of publications on this data set comprising healthy human subjects. For instance, episodic memory could be linked to specific gene variants (de Quervain et al., 2012; Milnik et al., 2012; Papassotiropoulos et al., 2013), gene pathways (Heck et al., 2015; Luksys et al., 2015) and to epigenetic variations (Vukojevic et al., 2014) in the human genome. Also, extreme forms of emotional memory performance were found to be related to a certain gene (TROVE2) (Heck et al., 2017). With regard to imaging-genetics, our group reported that (epi-) genetic variations were associated with neocortical thickness (Freytag et al., 2017), hippocampal volume (Harrisberger et al., 2014) or white-matter properties (Spalek et al., 2016). Finally, encoding of emotional pictures was found to increase the functional connectivity between hippocampus and amygdala (Fastenrath et al., 2014).



**Figure 3.** Big data allows the discovery of fundamental mechanisms that are tested in new, hypothesis-based research projects. In turn, findings from these projects lead to the acquisition of additional, promising variables resulting in even bigger data sets.

Over time, variables originally considered as secondary outcome measures (e.g. WM, emotional ratings or depression questionnaires) gradually moved into the focus of attention, giving rise to new, promising research projects. For example, Spalek et al. (2015) could show that men and women differed in their perception and memory for emotional pictures. Furthermore, emotional memory was found to be associated with global connectivity in the brain as revealed by DTI analysis (Coynel et al., 2017). Heck et al. (2014) found the voltage-gated cation channel activity gene set to be associated with WM performance, while Egli et al. (2018) used the WM task to identify distinct brain networks relevant for individual differences in WM performance using independent component analysis. Finally, depression scores were found to be related to the NCAM1 Interaction gene set and to certain white matter tracts (Petrovska et al., 2017). This extended orientation on a wider range of variables was also reflected in the last amendment of the ethical protocol in which the aim of the study was stated more broadly as investigating the molecular and neuronal underpinnings of emotion and cognition by analyzing (epi-)genetic and neuroimaging data.

Recruitment stopped in spring 2016. By then, the study constituted the biggest single-center study worldwide with more than 1'800 subjects tested in the fMRI study and more than 2'000 subjects the EEG study. This makes our sample unique not only with regard to data coming from a single lab and thus being very homogeneous, but also regarding the large sample size allowing replication of findings within the same study in independent subsamples.

Both publications of this thesis made use of the large-scale fMRI study, albeit using different variables and analysis approaches. In Loos et al. (2019), fMRI data during encoding and recognition of pictures was analyzed together with behavioral data on arousal ratings and memory performance. Loos et al. (submitted), used fMRI data of the WM task as a basis to generate a new independent research project that focused on the interaction between WM and arousal processes as described in the next chapter.

### *3.1.2 Deducing hypothesis-driven research projects from large-scale data*

As outlined above, large-scale samples, such as the one from our lab in Basel, can be used to detect novel patterns in the data that in turn can lead to the generation of new hypotheses-driven research projects. The publication Loos et al. (submitted) was the result of such an approach. The starting point of this project was an incidental finding in our large fMRI study showing that when engaging in a demanding letter n-back task which induces high WM load (2-back), subjects not only showed WM-dependent activation in the dlPFC, but also reduced activation in the amygdala compared to low WM load (0-back; see Figure 4a). This finding motivated us to

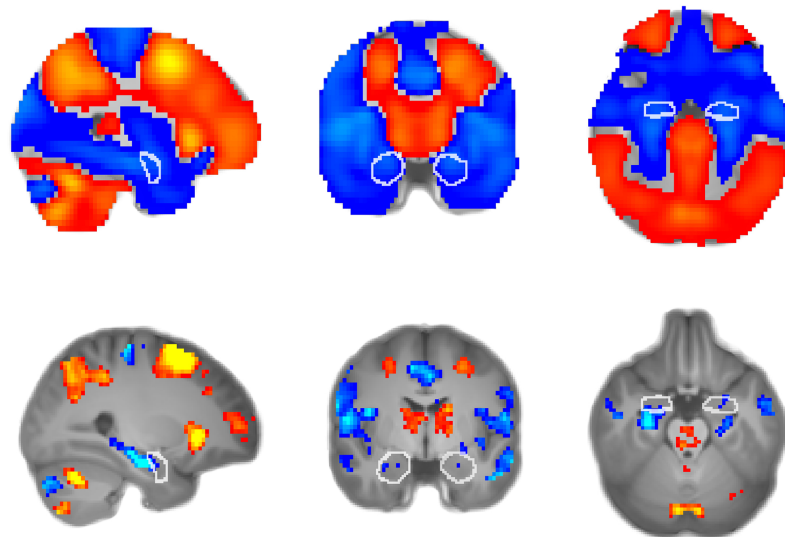
further investigate whether the same decrease in amygdala activity would be found when subjects performed an n-back task in which letters were replaced by emotionally arousing pictures. Since arousing stimuli are known to recruit the amygdala even more than neutral stimuli (e.g. letters), it was unclear whether the same load-dependent effects would also be observed under emotional conditions. Furthermore, we were interested in whether this decrease in amygdala activity would also be reflected in subjects perceiving the pictures as less negative and arousing. These research questions, however, could not be answered with the standard study protocol of our previous fMRI study.

Hence, a new fMRI study (“DRAMA”-study) was set up in order to directly address these questions. In hindsight, this DRAMA-study can be considered a pilot of the study later published in Loos et al. (submitted). In a first step, we designed a new n-back task that was suitable to test our hypotheses. In this task, negative and neutral pictures were presented either during blocks of high (2-back) or low (0-back) WM load. The pictures were taken from the International Affective Picture System (IAPS; Lang et al., 2008) as well as from the newer Geneva affective picture database (GAPED; Dan-Glauser & Scherer, 2011). Great care was put into choosing pictures that matched our selection criteria. For example, it was crucial that the pictures were not too complex or too similar to each other. This way we avoided that processing and discriminating the pictures from each other would possibly induce increased cognitive load also during 0-back blocks. In addition, we only chose those pictures that were either clearly negative and highly arousing or neutral and not arousing to allow a precise differentiation of the valence categories. To further investigate how a subject’s emotional state changes under different task conditions, five emotional ratings were included after each task block measuring perceived disgust, grief, mood, arousal and valence. Ratings were indicated on visual analog scales. Hence, amygdala activity and emotion ratings constituted our primary outcome variables. A detailed description of the final task design can be found in Loos et al. (submitted).

Several secondary outcome measures were chosen in addition. For example, after the n-back task, subjects were supposed to freely recall the pictures presented during the task. This way we investigated whether subjects had properly processed the pictures and whether pictures presented under high load would be remembered differently than those presented under low load. Furthermore, we used eye-tracking to ensure that subjects actually looked at the whole picture and not just at a discriminative corner. Moreover, pupil size was recorded to obtain a physiological, objective measure of subjects’ arousal state. To ensure that pupil size did not change as a consequence of different light conditions, we equated all pictures for luminosity and brightness properties using the software ImageJ (Schneider, Rasband, & Eliceiri, 2012).

Additionally, we included depression and anxiety questionnaires as well as a letter n-back task. To make sure we would find the same effects as in the large fMRI study with a smaller sample size, we ran a power analysis using FMRIpower (Mumford & Nichols, 2008). In order to find a medium effect with a power of  $> 90\%$ , at least 40 subjects were required. We also used a within-subject design to additionally increase power.

The study started in spring 2016 and data analysis was finished in summer 2016 including 46 subjects. As expected, high WM load resulted in a decrease in amygdala activity compared to low WM load (see Figure 4b). Furthermore, subjects reported less grief under high load and also rated emotional pictures as less negative and less arousing under high load (all  $p < .05$ ). No other secondary outcome measure showed a significant effect. Also, the eye-tracking device turned out to be not sensitive enough to reliably monitor subtle changes in pupil size.



**Figure 4.** *t*-value maps show decreased amygdala activity during high compared to low WM load (2-back - 0-back contrast) on whole-brain level ( $p_{\text{whole-brain corr}} < .05$ ) in the large fMRI study (upper panel) and in the DRAMA-study (lower panel). Negative *t*-values shown in blue, positive *t*-values in red. White contours comprise voxels in the amygdala taken from the respective study-specific atlases.

As mentioned above, the just described DRAMA-study can be considered a helpful and informative pilot study for our subsequent project. It provided us with valuable knowledge that we could make recourse to when designing the fMRI study (“REACT”-study) that finally resulted in the publication included in the thesis. In the REACT-study, we again went one step further and investigated whether our n-back task could be used in subjects indicating high fear of snakes to acutely decrease subjects’ amygdala activity and their perceived phobic fear, this way moving the focus to a more clinical context. In addition, we used dynamic causal modeling (DCM) to investigate whether a reduction in amygdala activity could be explained by a top-down inhibitory influence of the dlPFC on the amygdala.



We consequently adapted the n-back task once more by substituting the emotional pictures with pictures of snakes and changed the five subjective ratings to fear, disgust, mood, valence and arousal. Power analysis revealed the same required sample size as in the pilot study (at least 40 subjects). As several secondary outcome measures acquired in the DRAMA-study had turned out not to be associated with amygdala activity or subjective ratings, we dropped those additional measures in the REACT-study to keep it lean and solely tailored to the research question. The study was launched in autumn 2016 and was finished in spring 2017 comprising a total of 43 subjects. The study and its results were published in Loos et al. (submitted).

In sum, this project demonstrates how robust findings from a large, epidemiological study can be used as a basis for generating new hypothesis-driven research questions that help to translate findings from basic research into the clinical context.

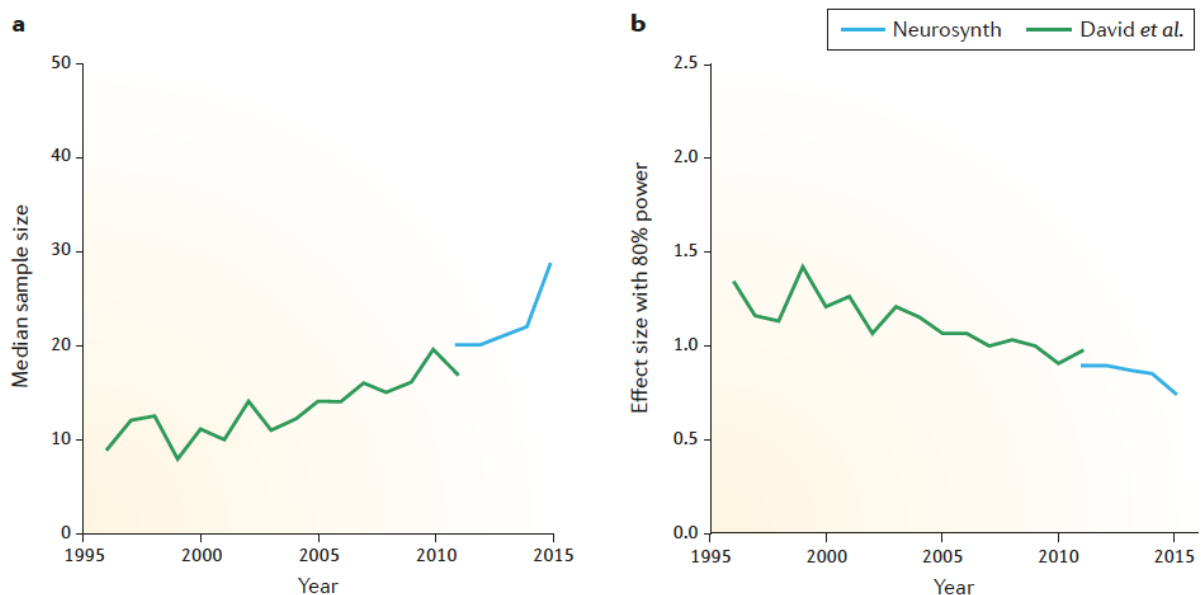
### 3.2 The need for well-powered fMRI studies

The previous chapter illustrated how large studies can set the ground for new research projects that can help to bridge the gap between basic and clinical research. However, fMRI studies with adequate sample sizes coming from one single lab are still more the exception than common practice, which has had substantial impact on the quality of neuroscience research, as outlined in the following.

In 1991 a research group around John Belliveau at Massachusetts General hospital performed the first successful fMRI experiment on one single subject (Belliveau et al., 1991). Over the course of the last 25 years, the amount of fMRI studies has increased exponentially with almost 4'000 papers published on PubMed only in 2018. Even though cognitive neuroscience has profited substantially from fMRI research (Rosen & Savoy, 2012), critical voices recently also challenged the amount of robust knowledge gained from previous fMRI studies, especially with regard to reproducibility of the results (Bennett & Miller, 2010; Ioannidis, 2005; Open Science Collaboration, 2015) and adequate statistical analyses of the data (Bennett, Wolford, & Miller, 2009; Eklund, Nichols, & Knutsson, 2016; Vul, Harris, Winkielman, & Pashler, 2009). One often criticized research practice in many fMRI experiments is the use of small sample sizes. Even though the technical progress made in data acquisition and data analysis facilitated the testing of more subjects in less time, studies still report a median sample size of well below 30 subjects (Poldrack et al., 2017; see Figure 5a). Possible reasons seem to be the high expenses of fMRI data collection, the lack of time to scan more subjects in the course of one study (pressure to publish fast) or little knowledge on how to correctly perform a power analysis (Nosek, Spies, & Motyl, 2012; Turner, Paul, Miller, & Barbey, 2018). The use of a

small sample size, however, significantly reduces the statistical power of a study to detect a true effect i.e. increases the rate of false negative results leading to effects being missed that would be genuinely true (Button et al., 2013; Cremers, Wager, & Yarkoni, 2017). Poldrack et al. (2017) found that even though sample sizes continuously increased over the last 20 years, an fMRI study with 80% power published nowadays is only sufficiently large to detect effects above 0.75 (see Figure 5b).

However, one of the most fatal consequences of low statistical power is the reduced chance for new studies to replicate the results of the original study. This is because the effect sizes of the original, low powered study are usually inflated, a phenomenon also referred to as *winner's curse* (Ioannidis, 2008). Authors of a replication study are consequently led astray believing that using the same sample size as the original study will suffice to find an effect. However, the power of those replication studies will be even lower, resulting in a failure to replicate the findings (Anderson & Maxwell, 2017). This lack of reproducibility has led to the emergence of a reproducibility crisis that many scientific fields, including neuroscience, have recently been trying to overcome (Baker, 2016; Munafò et al., 2017).



**Figure 5. (a)** Sample sizes from 1'131 fMRI studies published over 20 years extracted from the Neurosynth database (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) and from David et al. (2013); **(b)** respective standardized effect size estimates required to detect an effect with 80% power. The figure is taken from Poldrack et al. (2017).

Several solutions have been suggested to avoid conducting ill-powered studies. Whenever possible, a power analysis should be calculated in advance. Even though power analysis is not trivial in fMRI research, the neuroimaging community has developed toolboxes (e.g. ‘Neuro-power’ (Durnez et al., 2016) or ‘fMRIpower’ (Mumford & Nichols, 2008)) and published user guidelines (Mumford, 2012) that support researchers in correctly performing power analyses. Furthermore, power can be increased by reducing the number of statistical tests using region of interest analyses (Poldrack, 2007) or multivariate analyses (Cremers et al., 2017; Stelzer, Chen, & Turner, 2013).

Finally, the safest method to enhance power is to generally increase sample size to produce robust and reproducible results and to be able to detect even small effects. However, not every research group can gather data on a large scale. As a consequence, big consortia projects, like the UK Biobank (Bycroft et al., 2018), the ENGIMA project (Thompson et al., 2014) or the Human Connectome Project (Van Essen et al., 2013), have been called to life in the last years. These projects provide researchers access to a wide range of data from genetics over imaging to behavioral and socioeconomic measures gathered from several thousand subjects. In addition to using big data from consortia databases, the request to share one’s own data with the research community has been receiving much attention lately. The open science community attempts to pool data from different labs together, this way creating large data sets in a fast and more cost-effective manner. Several data-sharing initiatives like the International Neuroimaging Data-sharing Initiative (FCP-INDI) (Mennes, Biswal, Castellanos, & Milham, 2013), the Alzheimer’s disease neuroimaging initiative (ADNI) (Jack Jr et al., 2008), OpenfMRI (Poldrack et al., 2013) or NeuroVault (Gorgolewski et al., 2015) aim at enhancing the reproducibility of fMRI findings, encouraging the generation of new hypotheses, establishing new collaborations and improving research practices applied in single labs (Poldrack & Gorgolewski, 2014; Van Horn & Ishai, 2007).

In conclusion, the future use of large data sets from consortia or open science projects is a first step towards more reliable and generalizable fMRI research. Nevertheless, homogeneous data sets acquired at a single site are of great value. Both publications of this thesis are based on well-powered fMRI studies, in each of which subjects had performed on the same task, using the same MR-scanner and study equipment. This further underlines the robustness of the obtained results.

### 3.3 Complementary approaches to univariate analysis in fMRI research

Large data sets will not only produce more robust results, they also allow to expand the methodological approaches applied to the data. Univariate group analysis based on contrasts has so far been the most commonly used approach in fMRI experiments. However, as described in the next two chapters, more sophisticated methods can help to draw conclusions, for example, on the relationship between brain activation and individual differences in behavior or on the effective connectivity between different brain regions.

#### 3.3.1 *Multi-Voxel Pattern Analysis (MVPA)*

It has long been recognized that the processing of emotion and cognition does not depend on the activation of separate and isolated brain regions but that it rather relies on the interplay between brain regions connected in complex neuronal circuits (Bressler & Menon, 2010; LeDoux, 1995; Mesulam, 1998; Sporns, Chialvo, Kaiser, & Hilgetag, 2004; Uhlhaas & Singer, 2012). Hence, instead of merely investigating the activation of single voxels or brain regions engaged in a particular task, fMRI researchers recently began to take a more network-centered approach by applying machine learning techniques like MVPA (Haxby, 2012). In contrast to traditional fMRI analysis which uses a mass-univariate approach by calculating a separate regression model for every single voxel (GLM), MVPA combines multiple, spatially distributed voxels in one single regression model (Lewis-Peacock & Norman, 2013), this way increasing the sensitivity to detect certain mental states (Haynes & Rees, 2006; Norman, Polyn, Detre, & Haxby, 2006; Poldrack, 2011). In addition, MVPA enables to make predictions about cognitive states or observed behavior on an *individual* level, while conventional univariate approaches only allow inferences on a *group* level (Calhoun, Lawrie, Mourao-Miranda, & Stephan, 2017; Mwangi, Tian, & Soares, 2014).

Generally, MVPA can be used for classification and regression analyses. While classification is mainly applied to distinguish between different categorical groups (e.g. healthy vs. patients, male vs. female), regression analysis uses continuous variables (e.g. age, disease severity or memory performance) to make predictions based on the observed brain activity pattern (Mwangi et al., 2014). Independently of the chosen approach, a first important step applied in MVPA is feature selection. This step is crucial as in most fMRI studies, the number of features (voxels) is much higher than the number of observations (subjects), a problem also referred to as *curse-of-dimensionality* (Bellman, 1961) or *small-n-large-p* problem (e.g. Bernardo et al., 2003). Keeping only those voxels in the model that are relevant and dropping the rest of the voxels that might contain noise prevents from overfitting the predictive model (Guyon &

Elisseeff, 2003; Hua, Tembe, & Dougherty, 2009). One commonly used feature reduction method is *Least Absolute Shrinkage and Selection Operator (LASSO)* (Tibshirani, 1996). LASSO performs feature selection by shrinking most of the coefficients in the regression model to zero and only keeps those that are relevant for prediction. In the end, the regression model comprises only a small set of predictive voxels, which got assigned individual weights depending on their contribution to the predictive outcome. Training the model and identifying the most predictive voxels is usually done on a set of training data. Afterwards the final model is applied to an independent test sample to test the prediction accuracy on new, so far untouched data. This step is especially important to avoid overfitting. Depending on the available sample size, training and test data sets can be created using cross-validation (commonly used in smaller studies), or using the original study as training set and test the model in a new study sample, or splitting the sample in smaller sub-samples if the sample size is big enough.

Taken together, the use of multivariate approaches like MVPA can substantially add to the understanding of how mental states or behavioral outcomes are reflected by patterns of brain activity. The publication Loos et al. (2019) is an example how MVPA can be used to predict perceived arousal and memory performance from underlying brain activity patterns.

### 3.3.2 *Dynamic Causal Modeling (DCM)*

In contrast to MVPA, which can be used to analyze data in an exploratory way, DCM is applied to test specific hypotheses. DCM was first introduced in 2003 in a paper by Karl Friston (Friston, Harrison, & Penny, 2003) and assesses the effective connectivity between brain regions, i.e. the directed influence that one region exerts on another region (Friston, 2011). As the name implies, DCM is *dynamic*, as it uses differential equations to describe interactions between regions, and *causal*, in the sense that it infers directionality by describing how changes in one region cause a change in another region and how the interaction between these two regions is modulated by endogenous activity or an experimental manipulation (Stephan et al., 2010). Furthermore, DCM is based on Bayesian statistics, where each parameter in a model is constrained by prior assumptions (Stephan et al., 2010). There are different possible ways how to set up a DCM analysis. One common approach, which has also been applied in Loos et al. (submitted), will be described in the following.

When setting up a DCM analysis, the first step is to select a set of brain regions that were found to be activated in an initially calculated group-level contrast and to define possible connections between those regions. Each combination of connections constitutes one model in the DCM. There can be as many models as there are possible connections among the chosen

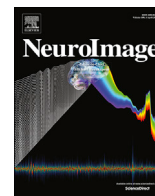
regions. For each defined model, DCM estimates three types of connectivity parameters: (1) intrinsic parameters, which characterize how the regions interact in the absence of experimental manipulation, (2) modulatory parameters, which indicate how the effective connectivity between two regions changes under the experimental manipulation and (3) extrinsic parameters, which reflect how regions respond to external stimuli (Seghier, Zeidman, Neufeld, Leff, & Price, 2010). While positive connectivity parameters generally indicate that increased activity in one region leads to increased activity in another region, negative parameters mean that an increase in one regions results in a decreased activity in another region (Seghier et al., 2010).

After all plausible models have been defined, they are subsequently compared using fixed (FFX) or random-effects (RFX) Bayesian model selection (BMS). BMS identifies the winning model by calculating the model evidence, i.e. the probability of the data given the model (Penny et al., 2010; Stephan, Penny, Daunizeau, Moran, & Friston, 2009). In other words, after having defined all models, BMS is used to select the best model from all the alternative models. Finally, the resulting connectivity parameters of the winning model can be further analyzed using, again, either FFX or RFX analysis (e.g. *t*-test or ANOVA). In case there is no clear winning model, connectivity parameters from all defined models can also be averaged by applying Bayesian model averaging (BMA) to receive a summary measure of likely connectivity parameters (Penny et al., 2010). In BMA, the connectivity parameters of each model are weighted, resulting in connectivity estimates that are independent of a particular model while ensuring that models with a high probability contribute more than models with a lower probability. These connectivity parameters can subsequently be used for conducting inference statistics for example to compare differences in effective connectivity between groups or conditions.

In the publication Loos et al. (submitted), we used DCM to compare the effective connectivity between the dlPFC and the amygdala during high compared to low WM load.

## **4 Original research papers**

4.1 Predicting emotional arousal and emotional memory performance from an identical brain network



## Predicting emotional arousal and emotional memory performance from an identical brain network



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### ABSTRACT

Encoding and retrieval of emotionally arousing stimuli depend on the activation of multiple interconnected brain regions, with people showing differences in their individual strength of emotional perception and recollection. Understanding the association between these brain regions and the behavioral outcome might therefore have important clinical implications as dysfunctional emotional memory processes are characteristic of many psychiatric disorders. Based on behavioral and fMRI data collected from healthy young adults ( $N = 1385$ ), we investigated brain activation patterns, arousal ratings and memory performance during encoding and retrieval of negative and neutral pictures. We performed multi-voxel pattern analysis (MVPA) and voxel-wise association analyses. Subjects' individual strength of perceived arousal at encoding and subjects' memory performance at recognition could be predicted from the fMRI data of the respective tasks by using a topographically identical network of brain regions. This network was mainly left lateralized including dense clusters of voxels in the occipital and parietal lobe and including the amygdala. Voxel-wise association analyses confirmed the close link between the brain activation of both tasks and their relation to the respective behavioral outcome. These results point to the importance of the here identified brain network for emotional memory processes in health and, possibly, disease.

### 1. Introduction

Experiencing an emotional event typically results in an enhanced subsequent memory of the details of this event (de Quervain et al., 2007; McGaugh, 2003, 2013; Sharot and Phelps, 2004). Even though multiple factors contribute to this enhancing effect, it is especially the arousing character of a situation that determines whether it will be remembered later on (Mather and Sutherland, 2011; McGaugh, 2004; Mirandola and Toffalini, 2016; Phelps and Sharot, 2008). Over the last decades, neuroimaging research has identified a range of interconnected brain regions that play a key role in the successful encoding and retrieval of emotionally arousing stimuli, with the amygdala, hippocampus and prefrontal cortex being among the most prominent ones (Buchanan, 2007; Fastenrath et al., 2014; LaBar and Cabeza, 2006; Phelps, 2004;

Smith et al., 2006).

Dysfunctional emotional memory processes are characteristic of psychiatric disorders like depression and post-traumatic stress disorder (PTSD) (Burt et al., 1995; Castaneda et al., 2008; Johnsen and Asbjørnsen, 2008). Especially in PTSD, both, the perception and the recollection of emotionally arousing material are substantially disturbed (Weber, 2008). Therefore, understanding the neuronal mechanisms related to perceived arousal and subsequent memory has important clinical implications. As it has been reported that the perception and retrieval of emotional material involves similar brain regions (Fenker et al., 2005; Nyberg et al., 2000; Smith et al., 2004; Wheeler et al., 2000), we were specifically interested in understanding the activation pattern of these regions and their relation to the inter-individual differences in behavior while encoding and retrieving negative emotional stimuli.

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We analyzed whole-brain fMRI data from an emotional picture-encoding task and a subsequent emotional picture-recognition task, measured in a homogeneous sample of healthy young adults ( $N = 1'385$ ). Using fMRI and behavioral data from both tasks in a multi-voxel pattern analysis, we investigated if the subjects' individual strength of perception and recollection can be predicted from their brain activation. In a second, voxel-wise approach, we compared between both tasks the similarity of brain activations that were associated with the respective behavior.

## 2. Methods and materials

### 2.1. Study design

We used data from a large-scale, single-center fMRI study conducted at the University Hospital of Basel, Switzerland, between 2008 and 2016. The study has been described before (Egli et al., 2018; Heck et al., 2017; Spalek et al., 2015) and consisted of healthy young adults recruited from the city of Basel and the surrounding areas. Data from  $N = 1'525$  subjects was available (data lock April 2015). We excluded subjects with corrupted or incomplete fMRI or behavioral data (see section 2.5), resulting in a final sample size of  $N = 1'385$  subjects (854 females, mean age 22.38, range 18–35 years). All participants received general information about the study beforehand and gave their written informed consent for participation upon arrival at the day of the experiment. Subjects had no history of neurological or psychiatric illness, and did not take any medication (except oral contraception) at the time of the experiment. Procedures were approved by the ethics committee of the Cantons of Basel-Stadt and Basel-Landschaft.

### 2.2. Experimental procedure and task descriptions

The experimental procedure and the tasks have already been reported elsewhere (Heck et al., 2017; Spalek et al., 2015) and more-detailed task descriptions can be found in the supplementary material in Appendix A. In short, after receiving general information about the study and giving their informed consent, participants were first instructed and trained on a picture-encoding task as well as on a letter n-back task, outside of the MR scanner.

After the training, participants were positioned in the scanner. All subjects received earplugs and headphones during MR scans. Participants were instructed not to move during the scans, small foam pads were used for head fixation. Task stimuli were presented inside the scanner via MR-compatible LCD goggles (VisualSystem, NordicNeuroLab, Bergen, Norway). Vision correction was done when necessary.

First, participants performed the picture-encoding task for 20 min. This task required watching 96 pictures (24 negative, neutral, positive or scrambled pictures). After each picture presentation, participants rated the picture according to emotional valence (negative, neutral, positive) and perceived arousal (low, middle, high) or, for scrambled pictures, form (vertical, symmetric, horizontal) and size (small, medium, large) of a geometrical object in the foreground. The picture-encoding task was immediately followed by the n-back task, lasting 10 min. The n-back task served as a distraction task between encoding and memory testing (for a more detailed description of the n-back task, see (Egli et al., 2018; Heck et al., 2014)).

Upon finishing the tasks, participants performed an unannounced free recall task outside of the scanner, which required writing down a short description of the previously seen pictures (no time restriction applied). Approximately 80 min after presentation of the last picture during encoding, participants were trained on the picture-recognition task and re-positioned in the scanner. The picture-recognition task consisted of two sets of pictures that were either previously shown (i.e., presented during the picture-encoding task) or new (i.e., not presented before, 24 pictures of each valence category, no scrambled pictures). After each picture presentation, participants subjectively

rated the picture as remembered, familiar, or new. The recognition task lasted for 20 min, followed by another 20 min of structural MRI (T1) and DTI acquisition. The total length of the experimental procedure ranged from 3 to 4.5 h per subject. Participants were reimbursed with 25 CHF/h.

### 2.3. Statistical analyses of behavioral data

For each subject and valence category, the arousal ratings of the  $N = 24$  pictures were averaged (mean score per category). For recognition memory performance, we calculated the sum of the correctly remembered pictures (sum score per category). Data of a subject was excluded if more than 15% of all pictures had an invalid or missing rating (arousal ratings:  $N = 2$ , memory performance:  $N = 9$ ). For memory performance, we additionally excluded a subject's data if less than 16 out of 24 (2/3) valid ratings were available in a single category ( $N = 4$ ). For the main analyses, we calculated the difference in arousal ratings or memory performance by subtracting the respective mean or sum score of the neutral pictures from that of the negative pictures. One-sample *t*-tests were used to compare arousal ratings or memory performances between the negative and neutral picture categories. We checked for possible sex and age effects by calculating linear regression models with the difference scores of the behavioral data as dependent variable and sex and age as independent variables.

We tested for an association between the difference in arousal ratings and the difference in memory performance by using Pearson's correlation after regressing out the effects of sex, age and room in which the unannounced free-recall of the pictures took place. Statistical test for significance was done with *t*-tests. We report nominal *p*-values for the behavioral analyses.

### 2.4. fMRI data acquisition and processing

Measurements were performed on a Siemens Magnetom Verio 3 T whole-body MR unit equipped with a twelve-channel head coil. Blood oxygen level-dependent fMRI was acquired using a single-shot echo-planar sequence (EPI) using parallel imaging (GRAPPA). The following acquisition parameters were used: TE (echo time) = 35 ms, FOV (field of view) = 22 cm, acquisition matrix =  $80 \times 80$  (interpolated to  $128 \times 128$ , voxel size:  $2.75 \times 2.75 \times 4 \text{ mm}^3$ ), GRAPPA acceleration factor  $R = 2.0$ . Using a midsagittal scout image, 32 contiguous axial slices placed along the anterior–posterior commissure (AC–PC) plane covering the entire brain with a TR = 3000 ms ( $\alpha = 82^\circ$ ) were acquired using an ascending interleaved sequence. A high-resolution T1-weighted anatomical image was acquired using a magnetization prepared gradient echo sequence (MPRAGE) with the following parameters: TR = 2000 ms; TE = 3.37 ms; TI = 1000 ms; flip angle =  $8^\circ$ ; 176 slices; FOV = 256 mm; voxel size =  $1 \times 1 \times 1 \text{ mm}^3$ . MRI data of  $N = 38$  participants had to be excluded due to corrupted T1-weighted images (movement or anatomical abnormalities; data was visually inspected by three raters).

Preprocessing and first-level analysis as well as the construction of a population-based anatomical probabilistic atlas (see Data S1 in Appendix D) have been described before (Egli et al., 2018; Heck et al., 2017), and detailed information can be found in the supplementary material Appendix A. fMRI preprocessing and first-level analyses was done with SPM 8 (Statistical Parametric Mapping, Wellcome Trust Center for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB R2011b (MathWorks) using a standard fMRI pipeline.

For each subject, we separately estimated the brain activation while processing negative or neutral pictures and calculated the difference between the negative and the neutral picture parameter estimates for each voxel (first-level negative-neutral contrast). For the encoding task this contrast was based on all negative and neutral pictures, while, for the recognition task, only the previously seen negative and neutral pictures were considered.

## 2.5. fMRI second-level analyses

All further analyses were conducted using the statistical software R (3.4.2; RRID:SCR\_001905). The negative-neutral contrast parameters from the first-level analyses were included in the second-level group analyses. Of the total sample of  $N = 1\,525$  subjects, we considered only subjects with complete fMRI data (encoding:  $N = 1\,418$ , recognition:  $N = 1\,424$ ) and behavioral data (arousal ratings:  $N = 1\,457$ , memory performance:  $N = 1\,456$ ). In addition, we removed subjects that had a high number of missing voxels (more than 4 SD above average; encoding:  $N = 7$ , recognition:  $N = 10$ ). In the end,  $N = 1\,385$  subjects entered the analysis.

fMRI data was coregistered to the anatomical images (T1-EPI coregistration) and to a study-specific group template (anatomical atlas; see Appendix A section 4.1). This template comprised a total of  $N = 71\,222$  anatomically labeled voxels. Excluding voxels that had any missing value (encoding:  $N = 15\,399$  voxels, recognition:  $N = 15\,236$  voxels) resulted in a total of  $N = 55\,199$  voxels used in our analyses. Importantly, EPI distortion-prone areas limit the accuracy of T1-EPI coregistration. Despite the improved accuracy of normalization through the use of DARTEL (Ashburner, 2007; Klein et al., 2009), those regions will consequently remain affected by signal drop-outs in some subjects. Multi-voxel pattern analysis (MVPA) on group-level requires that voxels have full information for all subjects, which is especially critical with large sample sizes. We optimized our preprocessing workflow (see Appendix A section 4.2) to achieve a nearly complete voxel  $\times$  subject matrix even with the large sample size. Missing information mainly comprised the lower parts of the cerebellum and the apex of the temporal lobe (see Fig. S1 in the Inline Supplementary).

## 2.6. Multi-voxel pattern analysis (MVPA) based on LASSO regression

We split the full sample of  $N = 1\,385$  subjects into three independent subsamples (training, validation and test sample) to avoid overfitting (Chicco, 2017; Skocik et al., 2016). For the main analyses, subjects were ordered chronologically according to their date of testing.

MVPA based on LASSO (least absolute shrinkage and selection operator) regression (Tang et al., 2014; Tibshirani, 1996) was performed with the R package “glmnet” (Friedman et al., 2010). The whole-brain fMRI data from the encoding task constituted the predictors and the behavioral measures (differences in arousal ratings and memory performances) served as outcome variables. The training sample (the first 50% of all subjects,  $N = 693$  subjects) was used to estimate 1\,000 models based on different lambda values. We used the sequence of lambda values as provided by the algorithm implemented in “glmnet” (Friedman et al., 2010): lambda.max = 0.36, which resulted in zero-weights for all voxels (lambda.max is data- and sample-size dependent); lambda.min = 0.0036, which is lambda.max multiplied by 0.01 (default value in glmnet when the number of subjects is less than the number of voxels). The obtained lambda sequence resulted in a varying number of voxels included in each model. In general, lambda is a tuning parameter and used to shrink the beta coefficients in a regression model (penalization). If lambda is large enough, certain weights in the model will be set to zero which results in less variables being included in the final model. Hence, LASSO regression simultaneously performs feature selection and model estimation (Tang et al., 2014; Tibshirani, 1996).

The remaining  $N = 692$  subjects were split into a validation sample (75%,  $N = 519$  subjects) for model selection and a test sample (25%,  $N = 173$ ) for estimating the final model fit. A sample size of  $N = 173$  subjects was sufficient to show a medium effect ( $r > 0.3$ ) with a power of 99%. To assess model accuracy, we compared the behavioral outcome predicted from the fMRI data with the observed behavior using Pearson's correlation; statistical test for significance was done with a  $t$ -test ( $p$ -value threshold  $< .05$ ). The beta weights that were derived from the LASSO model using the fMRI encoding data, were subsequently also applied to the fMRI data of the recognition task, separately for the training, validation and test sample.

Correction for potential confounding variables (sex, age, change of gradient coil, change of scanner software) was done depending on the task and subsample. For the encoding task, the effects of confounders were regressed out separately in the training sample (fMRI data: sex, age, change of gradient coils and change in scanner software; behavioral data: sex and age) and the validation sample (fMRI and behavioral data: sex and age). The scaled residuals were then used for the model estimation (training) and selection (validation). We treated the training and validation sample independently to achieve an unbiased model selection process. The model coefficients for sex, age and for the scaling obtained from the training sample were finally applied to the data of the test sample to achieve independency on subject level in the test sample. For the recognition task, we did not estimate a new LASSO regression model but applied the beta weights obtained from the encoding task. Therefore, we estimated the confounding effects in the training sample only (fMRI data: sex, age, change of gradient coils and change in scanner software; behavioral data: sex and age) and applied the coefficients for sex and age and for the scaling to both, the validation and test sample. This allowed us to achieve independency on subject level for both subsamples and hence to use both as valid test samples in the recognition task.

To assess the robustness of the results with regard to the original sample split, we ran the MVPA analysis based on LASSO regression 1\,000 times, each time using another sample split for the three subsamples (random sampling). For each run, we extracted the prediction performance of the LASSO model with the best fit and the voxels included in the respective model. To determine if a voxel was selected more often than would be expected by chance across these 1\,000 LASSO models, we additionally performed a permutation procedure. We permuted the original behavioral data and ran the MVPA another 1\,000 times. Based on this permuted data, we derived an empirical null distribution ( $N_{\max} = 40$ , see Inline Supplementary Fig. S6). Voxels that were selected  $N > 40$  times across the 1\,000 random sampling runs were considered above chance (empirical  $p_{\min} = 1.8 \times 10^{-5}$ , based on 55\,199 random data points).

## 2.7. Multiple linear regression analysis of fMRI activation with behavior

We applied multiple linear regression models to re-estimate the association between the behavioral outcome as dependent variable and multiple voxels as independent variables. The selected voxels were derived from the LASSO regression model identified in the MVPA. To enhance power, we performed this analysis in the total sample but also report the results obtained when using the three subsamples. For the fMRI data, we regressed out the effects of potential confounding variables (sex, age, change of gradient coils and change in scanner software), and used the scaled residuals for the analyses. For the behavioral data, we regressed out the effects of sex, age and room in which the unannounced free-recall of the pictures took place and used the scaled residuals for the analyses. We applied this procedure either to the data of total sample or – for the analysis of subsamples – separately to the data of each subsample.

For these multiple linear regression models, we report the overall variance explained ( $r^2$ ) as well as the adjusted  $r^2$  that takes into account the number of independent variables included in the model. Statistical test for significance was done with an  $F$ -test ( $p$ -value threshold  $< .05$ ).

## 2.8. Voxel-wise association of fMRI activation with behavior

This analysis was performed using the total sample. We applied Pearson's correlations to associate the activation of each voxel with the behavioral outcome. For the fMRI data, we regressed out the effects of potential confounding variables (sex, age, change of gradient coils and change in scanner software), and used the scaled residuals for the analyses. For the behavioral data, we regressed out the effects of sex, age and room in which the unannounced free-recall of the pictures took place and used the scaled residuals for the analyses. Statistical test for significance was done with  $t$ -tests. We report FDR-corrected  $p$ -values ( $p_{FDR} < .05$ ).

## 2.9. Brain-wide comparison of voxel signals between tasks

We determined the similarity between brain networks by applying Pearson's correlation across whole-brain  $t$ -values maps taken from the voxel-wise association analysis (see section 2.8). To determine if the similarity between networks was above chance, we derived an empirical null distribution by performing 1'000'000 random permutation of the data (empirical  $p_{\min} = 1 \times 10^{-6}$ ).

## 2.10. Anatomical labeling of functional brain networks and voxels

To anatomically describe functional brain networks, we extracted for each voxel the anatomical brain region with the highest probability, provided this probability was higher than 25% (see [supplementary material Appendix A](#) section 4.1 for the brain atlas used). For each brain region, we summarized the percentage of voxels that belonged to the functional network (coverage), separately for task-positive and task-negative functional networks and for the left and right hemisphere. Only brain regions with a coverage of 3% or higher are displayed in the tables that describe functional brain networks.

For single voxels, we report the anatomical brain region with the highest probability. In case the region with the highest probability was cortical white matter, we report the anatomical region with the 2nd highest probability (marked with a \* in the respective tables).

## 3. Results

During the picture-encoding task, participants saw negative, positive and neutral pictures while rating them with respect to their valence and arousal qualities. We used this task to estimate the difference in brain activity when encoding emotionally arousing negative stimuli in comparison to neutral stimuli. In the following picture-recognition task, participants were again presented with the previously seen pictures in addition to a set of new pictures. Participants had to judge whether they had seen the respective picture during the prior encoding task. We analyzed the subjects' brain activation while they processed the previously seen pictures by comparing brain activity when looking at negative and neutral stimuli. As behavioral outcome, we used the difference in arousal ratings for negative in comparison to neutral pictures and the difference in recognition memory performances for previously seen negative in comparison to neutral pictures.

### 3.1. Behavioral data

On a behavioral level, negative pictures were on average rated as more arousing than neutral pictures ( $t_{(1'384)} = 118.91, p < 1 \times 10^{-16}$ ; see [Table 1](#) and [Inline Supplementary Fig. S2](#)) and were also more often remembered than neutral pictures ( $t_{(1'384)} = 15.73, p < 1 \times 10^{-16}$ ; see [Table 1](#) and [Inline Supplementary Fig. S3](#)). There was a significant sex effect especially for the difference in arousal ratings (arousal ratings:  $t_{(1'380)} = 8.53, p < 2 \times 10^{-16}$ ; memory performance:  $t_{(1'380)} = -2.38, p = .02$ ) and a significant age effect for the difference in memory performances (arousal ratings:  $t_{(1'380)} = -1.26, p = .21$ ; memory performances:  $t_{(1'380)} = -2.74, p = .006$ ). Therefore, we corrected for sex and age in all subsequent analyses. The difference in arousal ratings for

**Table 1**

Means and standard deviations for arousal ratings and memory performances for the negative and the neutral pictures, respectively, as well as for the differences between negative and neutral pictures; the last column shows the effect sizes (Cohen's  $d_{\text{paired}}$ ) for the increase in arousal rating and memory performance for negative in comparison to neutral pictures.

Behavioral outcome	negative	neutral	neg > neu	$d_{\text{neg>neu}}$
arousal ratings	1.36 (0.32)	0.38 (0.28)	0.98 (0.31)	3.19
memory performance	20.34 (3.35)	19.06 (4.62)	1.28 (3.07)	0.42

negative compared to neutral pictures was positively associated with the difference in recognition memory performances for negative compared to neutral pictures ( $t_{(1'383)} = 3.04, p = .0024, r = 0.082$ ).

### 3.2. Predicting behavior from fMRI activation during encoding

Based on a multi-voxel pattern analysis we investigated if inter-individual differences in the subjects' behavior (difference in arousal ratings, difference in memory performances) can be predicted from fMRI activation. Model building was entirely done using the fMRI data from the encoding task. For the model selection process and for estimating the final model fit, we split our total sample of  $N = 1'385$  subjects into three independent subsamples (training, validation and test sample) of varying sample sizes (see [Inline Supplementary Fig. S4](#)). For the model building we used LASSO (least absolute shrinkage and selection operator) penalized regression, which simultaneously allows feature selection and model estimation ([Tang et al., 2014; Tibshirani, 1996](#)).

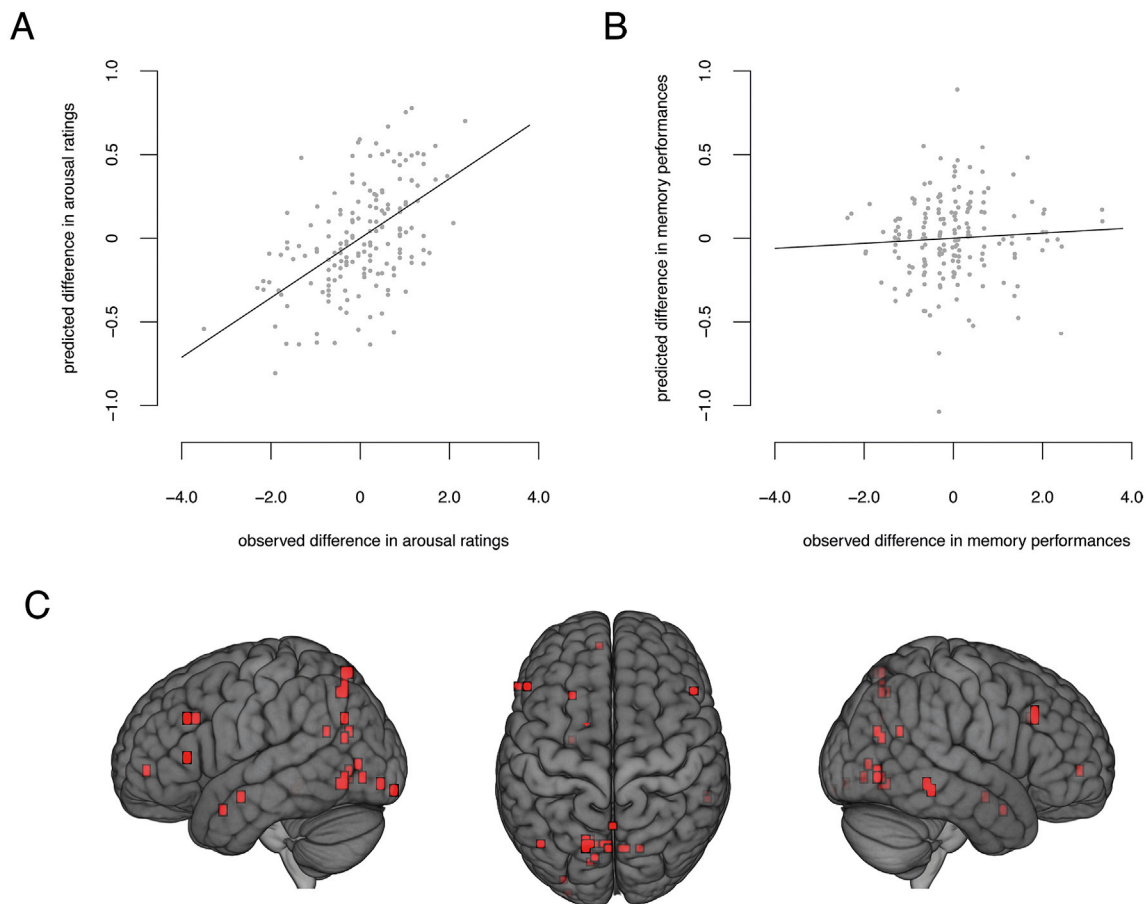
The training sample (50% of all subjects,  $N = 693$ ) was used to estimate 1'000 concurrent models for each behavioral outcome, predicting either the difference in arousal ratings or the difference in memory performances from the fMRI data of the encoding task. The 1'000 LASSO models differed in the number of included voxels (difference in arousal ratings: 1–724; difference in memory performances: 1–751; due to the lambda sequence used, see section 2.6), and the weights per voxel. Based on the data from the validation sample (75% of the second half of all subjects,  $N = 519$ ), we selected the two models that revealed the highest accuracy in predicting the respective behavior (difference in arousal ratings:  $r_{\max} = 0.52$ ;  $r_{\min} = 0.34$ ;  $r_{\text{mean}} = 0.47$ ; difference in memory performances:  $r_{\max} = 0.19$ ;  $r_{\min} = 0.07$ ;  $r_{\text{mean}} = 0.14$ ; see [Inline Supplementary Fig. S5](#)). In the test sample (25% of the second half of all subjects,  $N = 173$ ) the difference in arousal ratings could be predicted with an accuracy of  $r = 0.51$  ( $p = 7.96 \times 10^{-13}$ ; see [Fig. 1A](#)). This final arousal-related model comprised  $N = 33$  voxels (see [Fig. 1C, Table 2](#) and [Data S2 in Appendix D](#)). The final memory-related model failed to predict the difference in memory performances from the fMRI encoding data in the test sample ( $r = 0.063, p = .41$ ; see [Fig. 1B](#)). These results indicate that the fMRI activation at encoding mainly explains differences in the perceived arousal, and can be used to differentiate subjects based on how responsive they are to negative emotional material.

Predicting the individual difference in memory performances was not successful using the fMRI data of the preceding encoding task. We therefore tested for a mere association between the brain activation at encoding and the later difference in memory performances by applying multiple linear regression. To increase power, we used the total sample ( $N = 1'385$  subjects) for this analysis. When taking into account the  $N = 33$  voxels from the LASSO regression model that were related to arousal, and re-estimating a multiple linear regression model with the difference in memory performances as dependent variable, we found a significant association between the activity of these voxels during encoding and the difference in memory performances in the total sample ( $N = 1'385$ ;  $r^2 = 0.065, r^2_{\text{adj}} = 0.043, F_{(33, 1'351)} = 2.87, p = 1.49 \times 10^{-07}$ ). This result suggests that the arousal-related network also carries memory-relevant information at the time of encoding. Independent analyses within the three subsamples revealed a significant association in the training sample ( $N = 693$ ;  $r^2 = 0.072, r^2_{\text{adj}} = 0.025, F_{(33, 659)} = 1.55, p = .028$ ) and in the validation sample ( $N = 519$ ;  $r^2 = 0.13, r^2_{\text{adj}} = 0.070, F_{(33, 485)} = 2.18, p = .0002$ ), but not in the smaller test sample ( $N = 173$ ;  $r^2 = 0.19, r^2_{\text{adj}} = -0.004, F_{(33, 139)} = 0.98, p = .50$ ).

### 3.3. Predicting behavior from fMRI activation during recognition

It is known that regions that are active when perceiving emotional material will also become active when re-processing the same material ([Fenker et al., 2005; Nyberg et al., 2000; Smith et al., 2004; Wheeler et al., 2000](#)). We were interested in the consistency of this re-activation at





**Fig. 1.** Multi-voxel pattern analysis based on the fMRI data from the encoding task. Scatterplots depict the correlations between the predicted (y-axis) and the observed (x-axis) difference in arousal ratings (A) and differences in memory performances (B) in the test sample ( $N = 173$  subjects). (C) Network of  $N = 33$  voxels that could be used to predict difference in arousal ratings from the fMRI data of the encoding task (see also [Data S2 in Appendix D](#)).

the voxel level and its relevance for the behavioral outcome. Therefore, we applied the weights from the LASSO regression model derived from the encoding task, which we initially used to successfully predict the difference in arousal ratings from the fMRI encoding data, to the fMRI data of the recognition task. In doing so, we retrieved a predicted behavioral outcome that was based on the fMRI activation of the recognition task, but utilized the topographical information and weights from the encoding task. When comparing this predicted outcome with the observed behavior, we found high correlations with the difference in recognition memory performances for negative and neutral pictures, consistent in all three independent subsamples ( $r_{\text{training}} = 0.48$ ,  $r_{\text{validation}} = 0.50$  and  $r_{\text{test}} = 0.47$ ,  $p < 8 \times 10^{-11}$ ; [Fig. 2A–C](#)), but not with the difference in arousal ratings ( $r_{\text{training}} = 0.02$ ,  $r_{\text{validation}} = 0.02$  and  $r_{\text{test}} = 0.03$ ,  $p > .61$ ). These results indicate that in this network of  $N = 33$  voxels, the fMRI activation at recognition mainly explains if a subject remembers more negative pictures compared to neutral pictures.

### 3.4. Cross-validation of the MVPA approach

We tested the robustness of our prediction accuracy by using cross-validation. MVPA was performed 1'000 times based on random sampling of the training, validation and test sample. We achieved stable results when predicting the difference in arousal ratings from the fMRI encoding data in the test sample (average  $r_{\text{test}} = 0.53$ ; see [Fig. 3](#)) as well as when predicting the difference in memory performances from the fMRI recognition data using the LASSO beta weights from the encoding task (average  $r_{\text{training}} = 0.47$ ,  $r_{\text{validation}} = 0.46$  and  $r_{\text{test}} = 0.46$ ; see [Fig. 3](#)). The average number of voxels selected in a model was  $N = 114$  voxels

( $N_{\text{min}} = 5$ ;  $N_{\text{max}} = 427$  voxels). 1% of all voxels ( $N = 528$  out of  $N = 55'199$ ) were selected more often than expected by chance ( $N > 40$ , empirical  $p_{\text{min}} = 1.8 \times 10^{-5}$ ; see [Inline Supplementary Fig. S6](#) and [Table S1 in Appendix B](#)) across the 1'000 random sampling runs. These voxels were considered as stable voxels in the cross-validation MVPA. Of the 33 voxels identified in our original MVPA,  $N = 22$  voxels (67%) were amongst these stable voxels (see [Table S1 in Appendix B](#)).

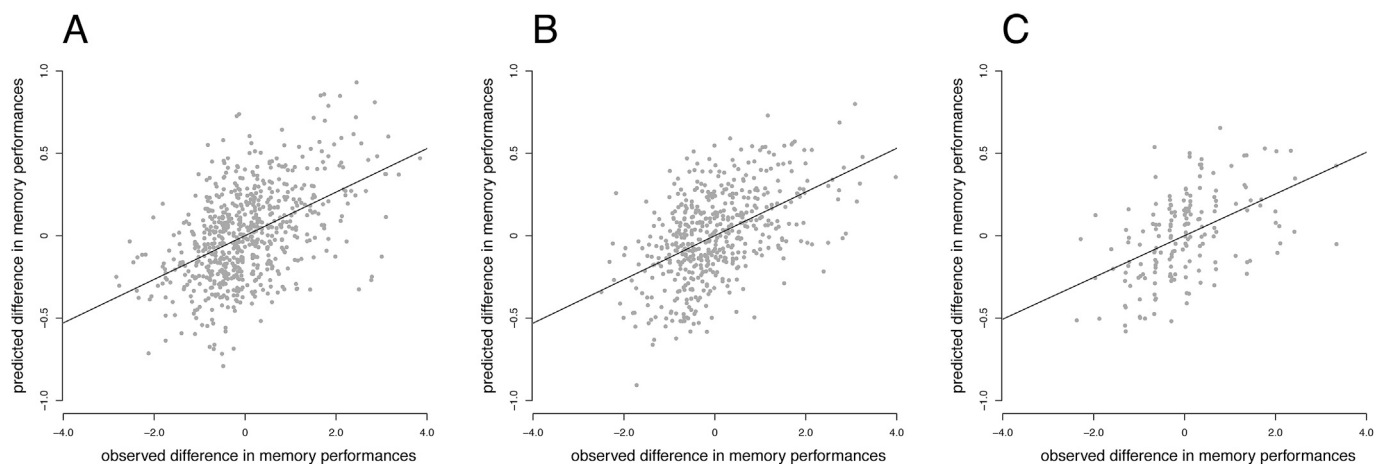
### 3.5. Comparison of brain networks between encoding and recognition

In addition to the MVPA, we used a voxel-wise approach to compare the similarity between arousal-related and memory-related networks on a whole-brain level. In this analysis, we separately estimated brain activations associated with the differences in arousal ratings or memory performances (voxel-wise association analysis in the total sample). For both tasks, we identified broad functional networks that were related to the differences in the respective behavior (encoding – difference in arousal ratings:  $N = 18'397$  voxels; recognition – difference in memory performances:  $N = 11'191$  voxels; see [Inline Supplementary Fig. S7](#) and [Fig. S8](#), [Table S1 in Appendix B](#) and [Data S3 and S4 in Appendix D](#)). Both networks showed a considerable similarity ( $r = 0.46$ ,  $p_{\text{permuted}} < 1 \times 10^{-6}$ ). Accordingly, we found a substantial overlap of voxels that were either consistently positively associated ( $N = 4'788$ ; FDR-corrected in both tasks; see [Fig. 4](#), [Table 3](#) and [Data S5 in Appendix D](#)) or consistently negatively associated with the respective behavior of the corresponding task ( $N = 576$ ; FDR-corrected in both tasks; see [Fig. 4](#), [Table S2 in Appendix C](#) and [Data S6 in Appendix D](#)). Within these overlapping regions, especially the activation for the positively associated voxels was highly similar

**Table 2**

Multi-voxel pattern analysis. Reported are the  $N = 33$  voxel included in the final model to predict differences in behavioral outcome. Hem: Hemisphere; MNI\_X/Y/Z: voxel coordinate of center of respective region in MNI52 space; Beta: beta-weights from the LASSO regression model with best fit. \* Brain region with second highest probability (if region with highest probability was white matter).

Brain region	Lobe	Hem	MNI X	MNI Y	MNI Z	Beta
ctx_lh_lateralorbitofrontal	frontal	left	-16.5	5.5	-24	0.008
ctx_lh_parstriangularis	frontal	left	-57.75	27.5	8	-0.001
ctx_lh_rostralmiddlefrontal	frontal	left	-52.25	27.5	32	-0.007
ctx_lh_rostralmiddlefrontal*	frontal	left	-24.75	22	32	0
ctx_lh_superiorfrontal	frontal	left	-8.25	52.25	0	0.019
ctx_rh_rostralmiddlefrontal	frontal	right	49.5	24.75	36	-0.026
ctx_rh_rostralmiddlefrontal	frontal	right	49.5	24.75	32	-0.006
ctx_lh_inferiorparietal	parietal	left	-44	-68.75	32	0.028
ctx_lh_precuneus	parietal	left	0	-57.75	24	0.018
ctx_lh_superiorparietal	parietal	left	-16.5	-68.75	52	-0.066
ctx_lh_superiorparietal	parietal	left	-16.5	-68.75	60	-0.029
ctx_lh_superiorparietal	parietal	left	-16.5	-66	48	-0.027
ctx_lh_superiorparietal	parietal	left	-13.75	-68.75	48	-0.016
ctx_lh_superiorparietal	parietal	left	-16.5	-71.5	60	-0.01
ctx_lh_superiorparietal	parietal	left	-13.75	-68.75	60	-0.002
ctx_lh_superiorparietal	parietal	left	-16.5	-68.75	48	-0.001
ctx_rh_middletemporal	temporal	right	57.75	-41.25	-8	-0.008
ctx_rh_middletemporal	temporal	right	57.75	-38.5	-12	-0.003
ctx_lh_cuneus	occipital	left	-5.5	-68.75	20	0.015
ctx_lh_cuneus	occipital	left	-2.75	-71.5	24	0.011
ctx_lh_cuneus	occipital	left	-2.75	-68.75	20	0.002
ctx_lh_lateraloccipital	occipital	left	-27.5	-99	-12	-0.029
ctx_lh_lateraloccipital*	occipital	left	-30.25	-90.75	-8	-0.011
ctx_lh_lingual	occipital	left	-13.75	-68.75	-8	0.064
ctx_lh_lingual	occipital	left	-13.75	-66	-8	0.008
ctx_lh_lingual*	occipital	left	-13.75	-68.75	-4	0.055
ctx_lh_lingual*	occipital	left	-11	-68.75	-4	0.044
ctx_lh_lingual*	occipital	left	-13.75	-79.75	-4	0.005
ctx_lh_pericalcarine*	occipital	left	-11	-77	4	0.138
ctx_rh_lingual	occipital	right	16.5	-71.5	-4	-0.101
ctx_rh_lingual	occipital	right	8.25	-71.5	0	-0.032
ctx_rh_lingual	occipital	right	5.5	-71.5	0	-0.008
Left_Amygdala	subcortical	left	-24.75	-5.5	-16	0.007



**Fig. 2.** Scatterplots depicting the observed difference in memory performances of negative and neutral pictures on the x-axis and a predicted behavioral outcome resembling this behavior on the y-axis. The predicted behavioral outcome was based on the fMRI recognition data and the beta weights derived from the encoding task predicting the difference in the arousal ratings. Results are shown separately for (A) the training, (B) the validation and (C) the test sample.

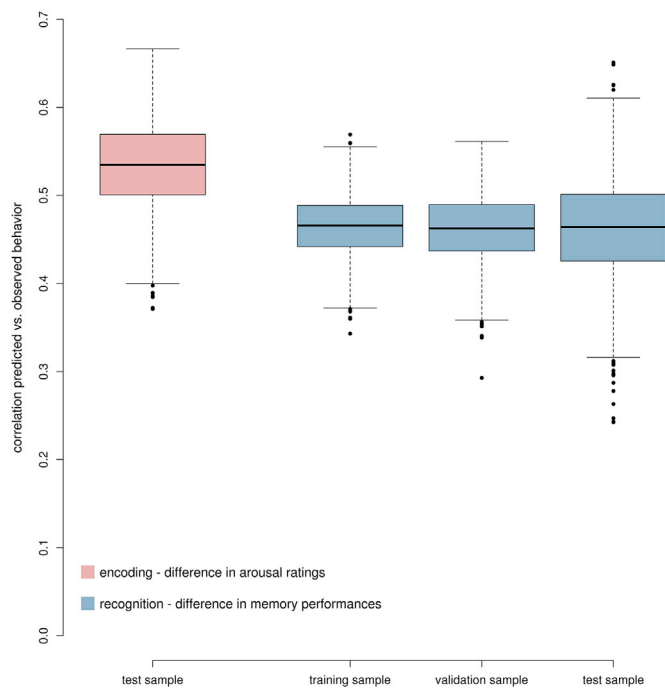
between tasks (positive direction:  $r = 0.76$ ,  $p_{\text{permuted}} < 1 \times 10^{-6}$ ; negative direction:  $r = 0.27$ ,  $p_{\text{permuted}} < 1 \times 10^{-6}$ ), suggesting that in those voxels the strength of association with the differences in arousal ratings at encoding was very similar to the strength of association with differences in memory performances at recognition. These results are in concordance with those of the MVPA, in which we could use topographically identical voxels and their weights from the encoding task, reflecting the strength of perceived arousal, to predict emotional memory performance from brain activation during recognition.

The overlapping regions of positive associations were predominately left lateralized and comprised occipital areas (lingual gyrus, cuneus,

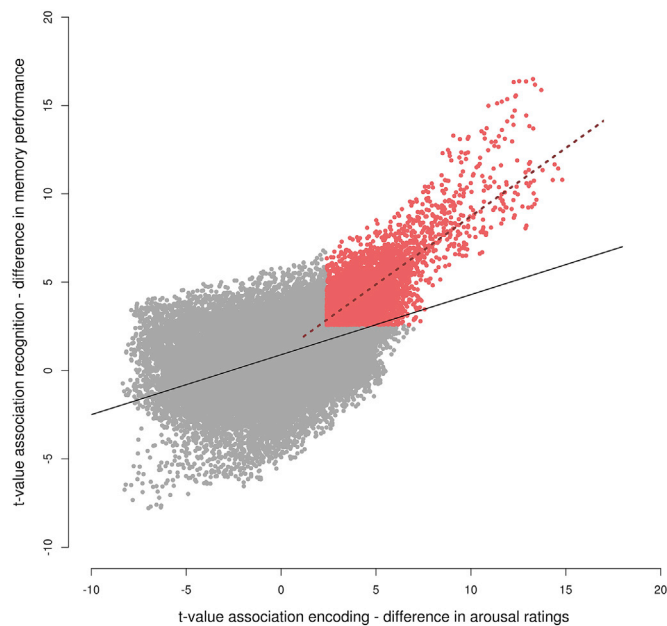
pericalcarine cortex), the superior and inferior parietal sulcus, fusiform gyrus, amygdala, superior frontal cortex and frontal pole, but also bilaterally the precuneus, parahippocampal gyrus and hippocampus, medial orbitofrontal cortex, posterior cingulate cortex and isthmus of the cingulate gyrus (see Fig. 5 and Table 3).

#### 4. Discussion

In this study, we investigated the activation patterns of brain regions engaged in the encoding and the retrieval of emotionally arousing negative in comparison to neutral material in healthy individuals. Based



**Fig. 3.** Boxplot depicting the prediction accuracy when performing cross-validation. The MVPA approach was repeated 1'000 times based on random samples. Horizontal lines within the boxes indicate the median. Horizontal lines outside represent the lowest and highest values within 1.5 x interquartile range from the first and third quartiles, respectively. Circles represent outliers.



**Fig. 4.** Scatterplot depicting the correlations between the memory-associated voxel activation from the recognition task (y-axis) and the arousal-associated voxel activation from the encoding task (x-axis). The graph shows all voxels included in the analyses; overlaid in red: voxels that showed a positive association in both tasks ( $N = 4'788$ ,  $p_{FDR} < .05$ ). Black regression line: Across all voxels ( $N = 55'199$ ). Red dashed regression line: Across FDR-corrected positive voxels ( $N = 4'788$ ).

on a multi-voxel pattern analysis we identified a network comprising 33 voxels that was associated with the difference in arousal ratings during the encoding of negative compared to neutral pictures. The activation of the identical network during a subsequent recognition task was also

associated with the difference in recognition memory performance. Based on this network we predicted a person's individual strength of perceived arousal and emotional memory performance with a high accuracy ( $r > 0.48$ ) when utilizing the fMRI data of the corresponding task. Importantly, for predicting the behavioral outcome, model building and estimation of model fit within and between tasks were done based on independent subsamples, providing unbiased estimates for the model accuracy.

Studies have previously reported that brain regions activated during the encoding of information can get re-activated if the emotional context at retrieval matched the context during the initial perception (Fenker et al., 2005; Smith et al., 2004). Our study reveals an involvement of identical brain regions in emotional memory processing during encoding and retrieval. Moreover, it suggests a functional differentiation of the activation in these brain regions over time with respect to the behavioral outcome: during encoding, most of the voxels' activity was associated with the strength of arousal ratings, whereas during recognition, the voxel activation was associated with memory performance for the emotional material. We additionally detected a significant association between the fMRI activation at encoding and the later memory performance in the total sample for the network of 33 voxel, underlining the relevance of this network for emotional memory-related processes. Importantly, these results were obtained based on data from healthy individuals processing non-traumatic stimuli. We can speculate that in the case of traumatic events, the association between the fMRI activation at encoding and the later memory performance becomes stronger.

The obtained network of 33 voxels was mainly left lateralized and comprised the superior and inferior parietal lobe, precuneus, middle temporal gyrus, amygdala as well as the rostral middle frontal and superior frontal gyrus. Furthermore, there was a dense cluster of voxels located in the lingual gyrus and the cuneus of the occipital lobe. Activations in occipital areas during the processing of negative emotional stimuli have been reported in healthy subjects as well as in patients with PTSD (Kark and Kensinger, 2015; Mickley Steinmetz and Kensinger, 2009; Smith et al., 2004; Zhu et al., 2014) and play an important role in the successful encoding and retrieval of information (Chen et al., 2017; Ritchey et al., 2012).

We also compared broader network information between the encoding and the recognition task, derived from voxel-wise analyses. Throughout the brain, we found extensive overlap of brain regions that were positively associated with the difference in arousal ratings during encoding and with the difference in memory performances during recognition. In addition to occipital and parietal regions, there was an overlap in activation in the left medial prefrontal cortex (mPFC), including the rostral anterior cingulate cortex (rACC) as well as in the bilateral hippocampus and the left amygdala, regions that are typically involved in processing emotional content (Dolcos et al., 2004; Murty et al., 2010) and which are supposed to be dysfunctional in PTSD (Duval et al., 2015; Hughes and Shin, 2011; Rauch et al., 2006).

To summarize, we analyzed two memory-related processes in healthy individuals, the perception and the later recollection of negative material in comparison to neutral material. We showed that an identical brain network is related to the difference in arousal ratings at encoding and difference in memory performance during recognition. We also found a weak association between the brain activation during encoding and the later difference memory performances when focusing on this network.

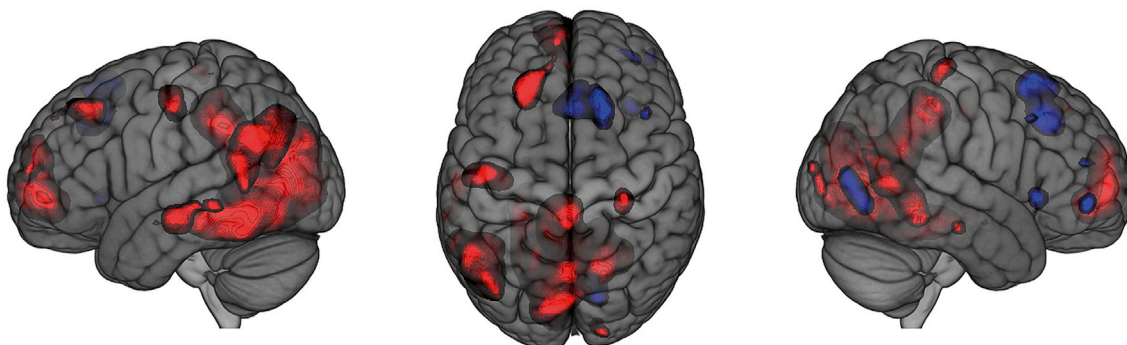
## 5. Conclusion

Our results suggest that in healthy subjects a person's individual strength of perception and recollection of emotional material can be predicted from an identical network of brain regions. Therefore, we can speculate that a dysfunctional activation of these regions, either in form of hypo- or hyperactivation, could result in disrupted emotional memory processes affecting both, the encoding and the retrieval of emotional

**Table 3**

Voxel-wise association analyses. Reported are regions that showed a positive association with the difference in arousal ratings during encoding as well as with the difference in memory performances during recognition. Hem: Hemisphere; MNI\_X/Y/Z: voxel coordinate of center of respective region in MNI52 space; EncAr T: maximum *t*-value for association of fMRI encoding with difference in arousal ratings in that region. RecMem T: maximum *t*-value for association of fMRI recognition with difference in memory performance in that region. The coordinates for the voxels with the maximum *t*-value in each reported region can be found in [Table S2 in Appendix C](#).

Brain region	Lobe	Hem	MNI X	MNI Y	MNI Z	EncAr T	RecMem T
ctx_lh_caudalmiddlefrontal	frontal	left	-35.75	11	48	5.42	3.59
ctx_lh_frontalpole	frontal	left	-5.5	66	-12	4.43	4.79
ctx_lh_medialorbitofrontal	frontal	left	-2.75	44	-16	7.32	5.19
ctx_rh_medialorbitofrontal	frontal	right	5.5	44	-16	3.84	4.03
ctx_lh_precentral	frontal	left	-44	-5.5	44	6.49	5.45
ctx_lh_rostralmiddlefrontal	frontal	left	-33	46.75	20	6.13	4.43
ctx_lh_superiorfrontal	frontal	left	-8.25	30.25	48	7.56	4.86
ctx_lh_paracentral	frontoparietal	left	-2.75	-27.5	60	4.76	3.85
ctx_rh_paracentral	frontoparietal	right	5.5	-24.75	60	3.39	2.85
ctx_lh_inferiorparietal	parietal	left	-41.25	-68.75	32	6.82	6.65
ctx_lh_postcentral	parietal	left	-49.5	-19.25	44	7.22	6.95
ctx_rh_postcentral	parietal	right	49.5	-16.5	44	4.12	3.13
ctx_lh_precuneus	parietal	left	-5.5	-57.75	40	7.56	8.50
ctx_rh_precuneus	parietal	right	8.25	-55	40	7.31	6.52
ctx_lh_superiorparietal	parietal	left	-22	-63.25	52	5.25	5.96
ctx_lh_supramarginal	parietal	left	-55	-37.12	32	5.28	4.05
ctx_lh_bankssts	temporal	left	-55	-44	8	3.95	3.64
ctx_lh_fusiform	temporal	left	-35.75	-49.5	-20	6.47	5.54
ctx_lh_middletemporal	temporal	left	-60.5	-24.75	-12	6.41	5.12
ctx_lh parahippocampal	temporal	left	-22	-30.25	-20	5.20	5.43
ctx_rh parahippocampal	temporal	right	24.75	-30.25	-20	4.87	4.71
ctx_lh_superiortemporal	temporal	left	-52.25	-8.25	-4	5.95	3.83
ctx_lh_cuneus	occipital	left	-2.75	-77	20	8.22	9.77
ctx_rh_cuneus	occipital	right	5.5	-77	20	5.03	6.43
ctx_lh_lingual	occipital	left	-11	-66	-8	14.60	11.70
ctx_rh_lingual	occipital	right	13.75	-66	-8	7.54	7.12
ctx_lh_pericalcarine	occipital	left	-8.25	-79.75	8	13.38	16.50
ctx_rh_pericalcarine	occipital	right	11	-77	8	5.28	5.63
ctx_lh_isthmuscingulate	cingulate	left	-2.75	-46.75	24	7.24	7.02
ctx_rh_isthmuscingulate	cingulate	right	5.5	-44	20	6.53	6.42
ctx_lh_posteriorcingulate	cingulate	left	-2.75	-16.5	40	6.07	6.45
ctx_rh_posteriorcingulate	cingulate	right	5.5	-16.5	40	3.84	4.38
ctx_lh_rostralanteriorcingulate	cingulate	left	-2.75	38.5	0	7.10	3.53
Left_Amygdala	subcortical	left	-22	-5.5	-20	5.38	3.56
Left_Hippocampus	subcortical	left	-24.75	-22	-16	4.09	4.61
Right_Hippocampus	subcortical	right	27.5	-22	-16	3.45	5.27
Left_Cerebellum_Cortex	cerebellum	left	-22	-66	-28	10.64	8.72
Right_Cerebellum_Cortex	cerebellum	right	22	-63.25	-24	4.14	5.08



**Fig. 5.** Overlap of regions positively (red) and negatively (blue) associated with the difference in arousal ratings during encoding as well as with the difference in memory performances during recognition (see also [Data S5 and S6 in Appendix D](#)).

information. Investigating the properties of this network in individuals with impaired emotional memory processing could further contribute to a better understanding of emotional memory-related disorders such as PTSD or depression.

#### Disclosures

The authors report no biomedical financial interest or potential conflicts of interest.

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## Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2019.01.028>.

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# Supplementary Material

## 1 Supplemental Text

### 1.1 Detailed description of pictorial stimuli

We used 96 stimuli in total (24 negative, 24 positive, 24 neutral, 24 scrambled pictures). Negative, neutral and positive stimuli were selected from the International Affective Picture System (Lang et al., 2008) and from in-house standardized picture sets that allowed us to equate the pictures for visual complexity and content (such as human presence). On the basis of normative valence scores (from 1 to 9), pictures were assigned to emotionally negative ( $2.3 \pm 0.6$ ), emotionally neutral ( $5.0 \pm 0.3$ ), and emotionally positive ( $7.6 \pm 0.4$ ) valence categories, resulting in 24 pictures of each category. 24 scrambled pictures were used as control condition. The background of the scrambled pictures contained the color information of all pictures used in the experiment (except primacy and recency pictures), overlaid with a crystal and distortion filter (Adobe Photoshop CS3). In the foreground, a mostly transparent geometrical object (rectangle or ellipse of different sizes and orientations) was shown. Four additional pictures of neutral objects were used to control for primacy and recency effects in memory. Two of these pictures were presented at the beginning and two at the end of the picture task. These pictures were not included in the behavioral analyses.

### 1.2 Detailed description of the picture-encoding task

All pictures were presented for 2.5 s in a quasi-randomized order. To ensure that the ratio between valence categories was constant across consecutive parts of the entire picture sequence, each twelfth part of the sequence contained exactly two positive, two negative and two neutral pictures. Thus, maximally four pictures of the same category occurred consecutively. A fixation-cross appeared on the screen for 500 ms before each

picture presentation. The stimulus onset time was jittered within 3 s [1 repetition time (TR)] per valence category with regard to the scan onset. Picture rating was possible in a time window of maximum 3 s.

### **1.3 Detailed description of the picture-recognition task**

During recognition, the pictures were presented for 1 s in a quasi-randomized order so that no more than four pictures of the same category appeared consecutively. A fixation-cross appeared on the screen for 500 ms before each picture presentation. The stimulus onset time was jittered within 3 s (1 TR) per valence and old/new category with regard to the scan onset. Picture rating was possible in a time window of maximum 3 s.

### **1.4. Detailed description of the (f)MRI data preparation**

#### *1.4.1 Construction of a population-average anatomical probabilistic atlas*

Automatic segmentation of the subjects' T1-weighted images was used to build a population-average probabilistic anatomical atlas (see Data S1 in Appendix D). More precisely, each participant's T1-weighted image was first automatically segmented into cortical and subcortical structures using FreeSurfer (version 4.5, <http://surfer.nmr.mgh.harvard.edu/>) (Fischl et al., 2002). Labeling of the cortical gyri was based on the Desikan-Killiany Atlas (Desikan et al., 2006), yielding 35 regions per hemisphere. We also labeled 28 subcortical regions in total (11 subcortical bilateral regions, 6 central regions comprising corpus callosum and brain stem) following Fischl et al. (Fischl et al., 2002). The segmented T1 image was then normalized to the study-specific anatomical template space using the subject's computed warp field and affine-registered to the MNI space (see section 4.2). The normalized segmentations were finally averaged across subjects, in order to create a population-average probabilistic atlas. Each voxel of the template could consequently be assigned a probability of

belonging to a given anatomical structure, based on the individual information from 1'000 subjects, which were part of the subjects included in the present study.

The atlas comprises a total of  $N = 98$  distinct cortical and subcortical brain regions from both hemispheres.

#### *1.4.2 fMRI preprocessing and first-level analyses*

fMRI data was preprocessed using SPM 8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB R2011b (MathWorks). Volumes were slice-time corrected to the first slice, realigned using the 'register to mean' option, and coregistered to the anatomical image by applying a normalized mutual information 3-D rigid-body transformation. Successful coregistration was visually verified for each subject. Each volume was masked with the subject's T1 anatomical image to exclude voxels outside of the brain. Subject-to-template normalization was done using DARTEL (Ashburner, 2007), which allows registration to both cortical and subcortical regions and has been shown to perform well in volume-based alignment (Klein et al., 2009). Normalization incorporated the following four steps: 1) Structural images of each subject were segmented using the 'New Segment' procedure in SPM8. 2) The resulting gray and white matter images were used to derive a study-specific group template. The template was computed from a subgroup of 1'000 subjects, which were part of the subjects included in the present study. 3) An affine transformation was applied to map the group template to MNI space. 4) Subject-to-template and template-to-MNI transformations were combined to map the functional images to MNI space. The functional images were smoothed with an isotropic 8 mm full-width at half-maximum (FWHM) Gaussian filter.

Normalized functional images were masked using information from their respective T1 anatomical file as follows: a partial volume effect file obtained from the SPM-VBM8

toolbox (<http://dbm.neuro.uni-jena.de/vbm8/>) was used as a starting point to define the brain mask. This volume represents the three-tissue classification results of the segmentation process (GM, WM, CSF), with two additional mixed classes (GM-WM, GM-CSF). It was binarized, dilated and eroded with a  $3 \times 3 \times 3$  voxels kernel using `fslmaths` (FSL) to fill in potential small holes in the mask. The previously computed DARTEL flowfield was used to normalize the brain mask to MNI space, at the spatial resolution of the functional images. The mask was finally thresholded at 10% and applied to the normalized functional images. Consequently, the implicit intensity-based masking threshold usually that was employed to compute a brain mask from the functional data during the first level specification (by default fixed at `mask.thresh = 0.8`) was not needed any longer and set to a lower value of 0.05.

Regressors modeling the onsets and duration of each stimulus event were convolved with a canonical hemodynamic response function (HRF). More precisely, the model comprised regressors for button presses modeled as stick/delta functions, picture presentations modeled with an epoch/boxcar function (duration: encoding: 2.5 s; recognition: 1 s), and rating scales modeled with an epoch/boxcar function of variable duration (depending on when the subsequent button press occurred). Intrinsic autocorrelations were accounted for by AR(1), and low-frequency drifts were removed via high-pass filter (time constant 128 s). Six movement parameters were also entered as nuisance covariates. Pictures accounting for possible primacy and recency effects were excluded from statistical analysis.

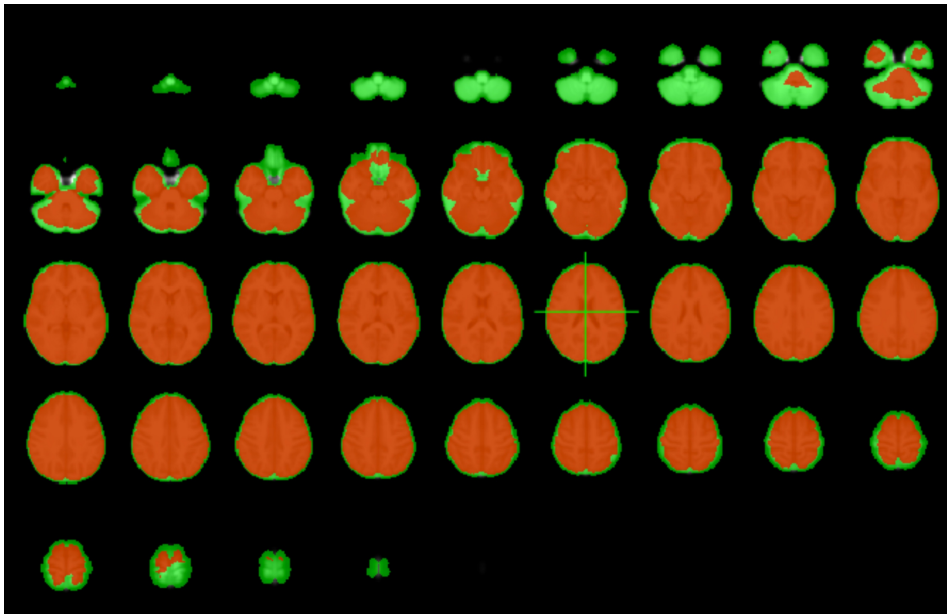
As we were interested in brain regions that show more activation for negative than for neutral stimuli, we calculated the difference between the negative and the neutral picture parameter estimates for each subject and voxel (first-level negative-neutral contrast). For the encoding task this contrast included all negative and neutral

pictures, while, for the recognition task, only the pictures that were presented in the encoding task were included in the negative-neutral picture contrast.

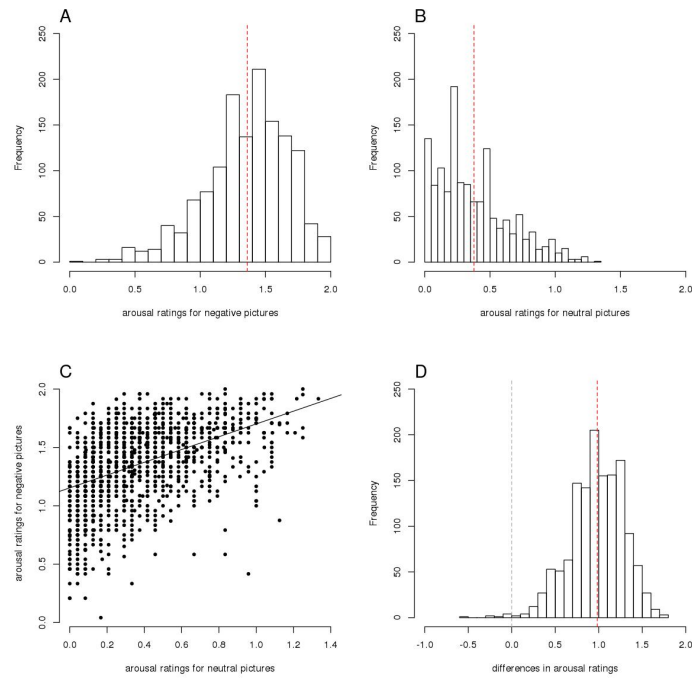
### **1.5 Brain images**

Figures of clustered voxels within a semitransparent brain (MNI 152 template) were produced using MRICroGL (<http://www.mccauslandcenter.sc.edu/mricrogl/>; RRID:SCR\_002403). Pictures were smoothed with a 3 mm smoothing kernel using the R-packages 'fslr' (Muschelli et al., 2015) and 'oro.nifti' (Whitcher et al., 2011). Pictures showing single-voxel results as obtained by the multi-voxel pattern approach were not smoothed. All brain images are displayed within the MNI152 template and according to neurological convention (left hemisphere displayed on the left side).

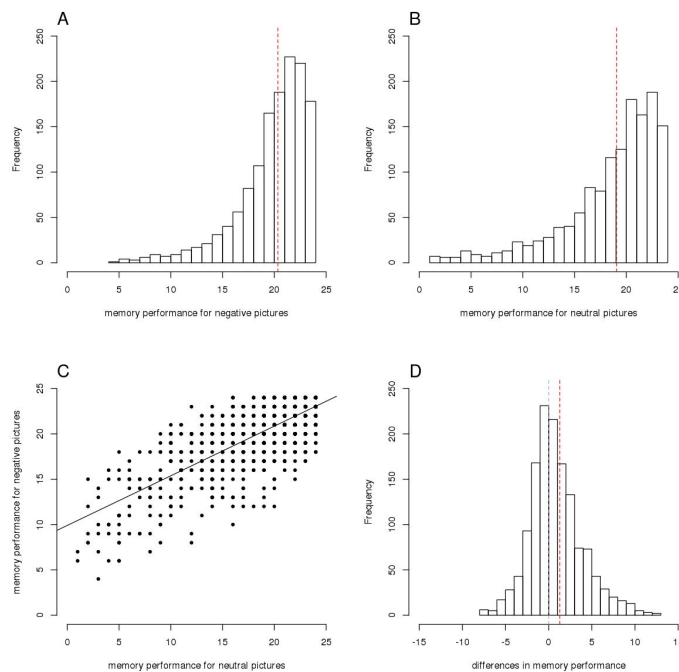
## 2 Supplemental Figures



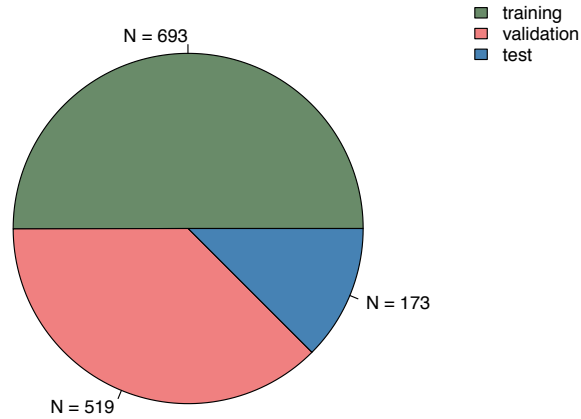
**Figure S1:** In green: voxel mask comprising the 71'222 anatomically labeled voxels from the study-specific group template; overlaid in red: voxel mask comprising the 55'199 voxels used for analysis after exclusion of voxels with missing values in any of the subjects.



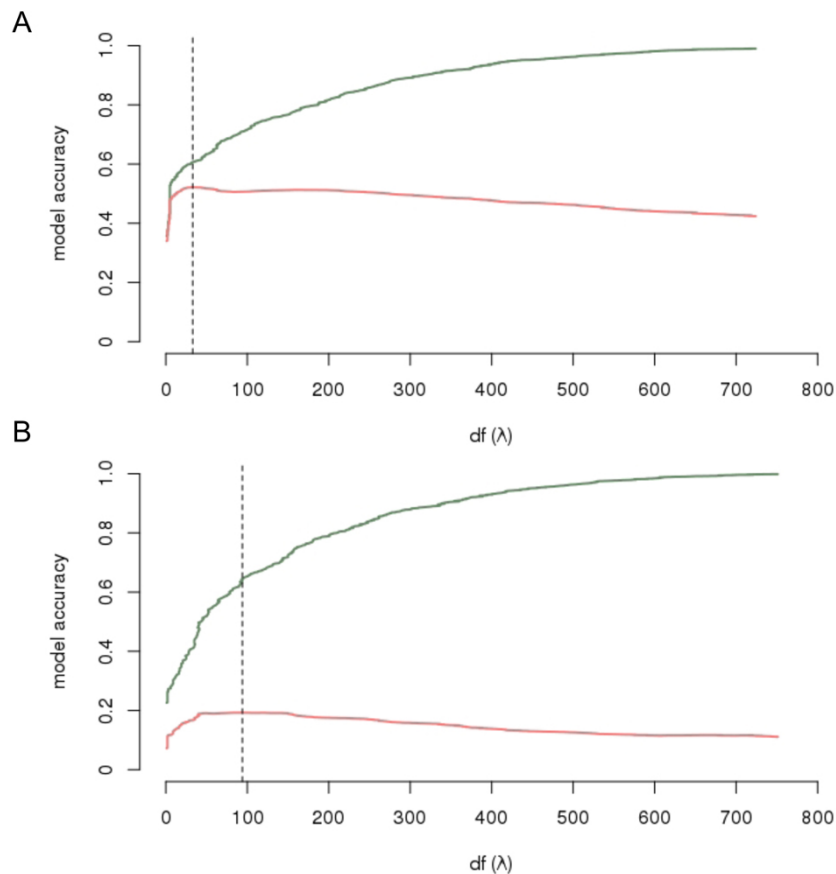
**Figure S2:** Histograms depicting the individual arousal ratings for negative **(A)** and neutral **(B)** pictures. **(C)** Association between arousal ratings of negative (y-axis) and neutral (x-axis) pictures. **(D)** Histogram depicting the differences in arousal ratings for negative and neutral pictures. Red dashed lines represent the respective group mean.



**Figure S3:** Histograms depicting the individual memory performance for negative **(A)** and neutral **(B)** pictures. **(C)** Association between memory performance of negative (y-axis) and neutral (x-axis) pictures. **(D)** Histogram depicting the differences in memory performance for negative and neutral pictures. Red dashed lines represent the respective group mean.

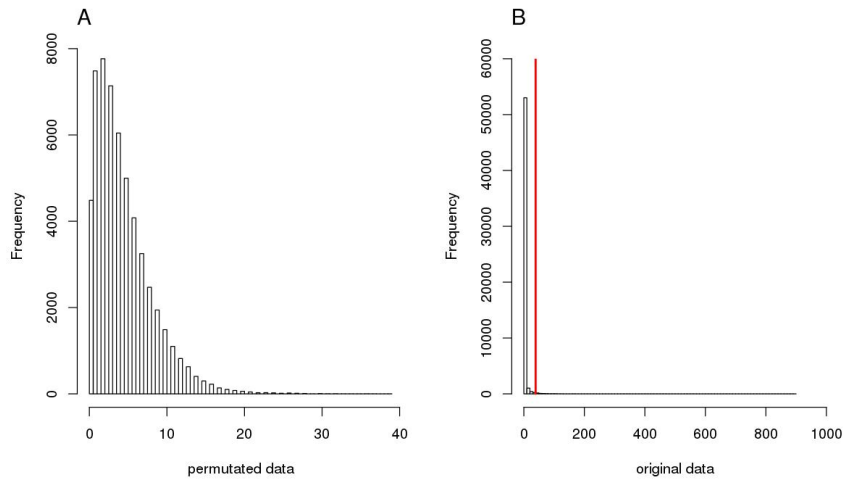


**Figure S4:** Distribution of the  $N = 1'385$  subjects across the three subsamples. For the main analyses subjects were ordered chronologically according to their date of testing before being assigned to the three groups (training < validation < test).

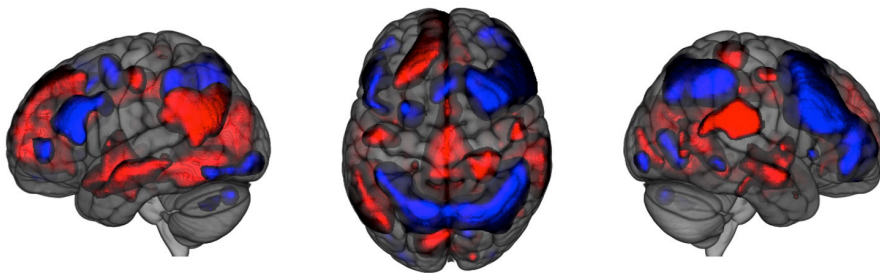


**Figure S5:** fMRI encoding, predicting the difference in arousal ratings (A) and the difference in memory performances (B) for negative and neutral pictures. Depicted is the prediction accuracy of the 1'000 models estimated by the LASSO algorithm for the training sample (green line) and the validation sample (red line). The black dashed line indicates the position of the model with the highest prediction accuracy in the validation sample that has been finally used in the test sample.

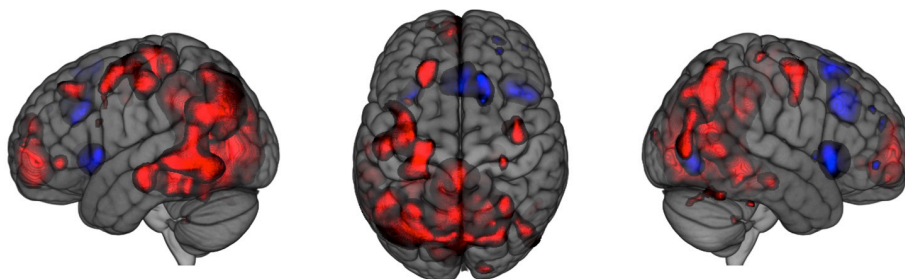




**Figure S6:** Histograms depict the number of times voxels were selected across the 1'000 random MVPA runs when using permutation-based behavioral data (Panel A) or the original behavioral data (Panel B). Red vertical line indicates the chance level (empirical  $p_{min} = 1.8 \times 10^{-5}$ ), i.e. all voxels that were selected  $> 40$  times across the 1'000 runs.



**Figure S7:** fMRI encoding (negative – neutral contrast), voxel-wise association analysis with the difference in arousal ratings for negative in comparison to neutral pictures. Depicted are voxels showing either a positive ( $N_{pos} = 11'636$  voxels; in red) or a negative ( $N_{neg} = 6'937$  voxels; in blue) association with the difference in arousal ratings, when applying FDR-correction (see also Table S1 in Appendix B and Data S3 in Appendix D).



**Figure S8:** fMRI recognition (negative – neutral contrast), voxel-wise association analysis with the difference in recognition memory performance for negative in comparison to neutral pictures. Depicted are voxels showing either a positive ( $N_{pos} = 9'722$  voxels; in red) or a negative ( $N_{neg} = 1'416$  voxels; in blue) associations difference in recognition memory performance, when applying FDR-correction (see also Table S1 in Appendix B and Data S4 in Appendix D).

### 3 Supplemental References

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## 4.2 Working memory intervention acutely decreases amygdala activity and phobic fear

**Title:**

Working memory intervention acutely decreases amygdala activity and phobic fear

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## 1 **Abstract**

2 The amygdala is critically involved in fear responses and shows hyperactivity in anxiety  
3 disorders. Previous research has indicated that amygdala activity is down-regulated by  
4 increased prefrontal cortex activity. It is unknown, however, if such a down-regulation  
5 has acute effects on phobic fear in humans. In an fMRI study of 43 subjects with fear of  
6 snakes, we found reduced amygdala activity when snake pictures were processed under  
7 high working-memory load, as compared to low working-memory load. Furthermore, dy-  
8 namic causal modeling revealed that this reduction in amygdala activity was partly medi-  
9 ated by a working-memory related increase in dorsolateral prefrontal cortex activity. Fi-  
10 nally, processing the fearful stimuli under high working-memory load resulted in an acute  
11 decrease in perceived phobic fear and disgust. These findings may inspire the develop-  
12 ment of novel psychological intervention approaches aimed at reducing fear in anxiety  
13 disorders.

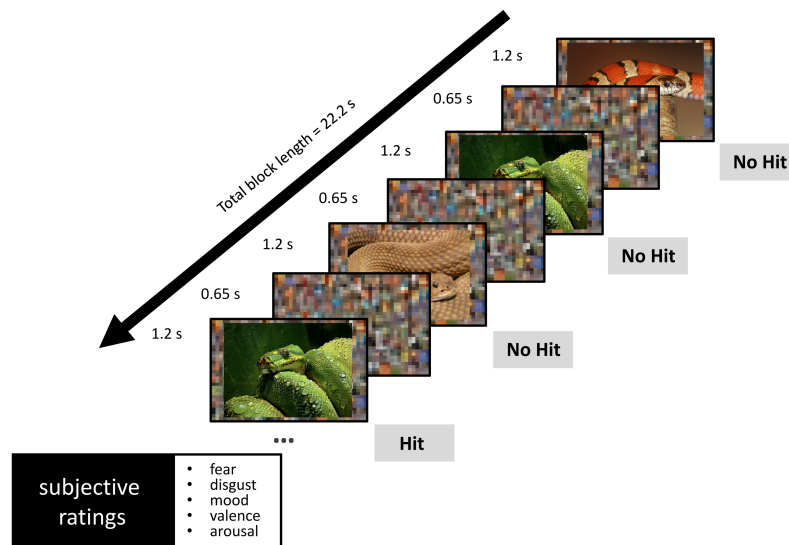
## 14 **1 Introduction**

15 With a life-time prevalence between 7.7% and 12.5% (Alonso et al., 2004; Bijl, Ravelli, &  
16 Van Zessen, 1998; Kessler et al., 2005), specific phobias are among the most common anx-  
17 iety disorders. Within the different types, animal phobias are the most prevalent sub-  
18 group (Eaton, Bienvenu, & Miloyan, 2018; Oosterink, de Jongh, & Hoogstraten, 2009). Sub-  
19 clinical animal phobias have an even higher prevalence with reported rates of 34.8% for  
20 fear of snakes in a Dutch sample (Oosterink et al., 2009).

21 The amygdala is fundamentally involved in processing fear in animals (Davis &  
22 Whalen, 2001; Fanselow & Gale, 2003) and humans (Adolphs, Tranel, Damasio, &  
23 Damasio, 1995; LeDoux, 2007; Shin & Liberzon, 2010). Furthermore, amygdala hyperac-  
24 tivity has been associated with many anxiety disorders including phobias. Specifically,  
25 phobic subjects show higher amygdala activation compared to healthy subjects when con-  
26 fronted with phobic stimuli (Dilger et al., 2003; Ipser, Singh, & Stein, 2013; Schienle,  
27 Schäfer, Walter, Stark, & Vaitl, 2005; Straube, Mentzel, & Miltner, 2006). Proper regulation  
28 of emotional reactions, including a down-regulation of fear, is thought to rely on the suc-  
29 cessful interplay between prefrontal and limbic regions (Dolcos & Denkova, 2014; Okon-  
30 Singer, Hendler, Pessoa, & Shackman, 2015; Pessoa, 2013). Within the prefrontal network,  
31 the dlPFC is critically involved in higher cognitive processes like working memory and  
32 executive control (Barbey, Koenigs, & Grafman, 2013; Curtis, 2006; Kohn et al., 2014;  
33 Owen, McMillan, Laird, & Bullmore, 2005) and has been reported to interact with regions  
34 engaged in emotion processing and emotion regulation (Dolcos, Iordan, & Dolcos, 2011;  
35 Ochsner & Gross, 2005; Phillips, Drevets, Rauch, & Lane, 2003; Van Dillen, Heslenfeld, &  
36 Koole, 2009). fMRI studies have consistently shown that cognitively demanding tasks are  
37 associated with increased dlPFC activity and decreased amygdala activity (de Voogd et al.,  
38 2018; Erk, Kleczar, & Walter, 2007; Mitchell et al., 2007; Straube, Lipka, Sauer, Mothes-

39 Lasch, & Miltner, 2011). In situations that demand high cognitive functioning, the dlPFC is  
40 assumed to inhibit limbic regions including the amygdala through top-down control  
41 mechanisms to ensure that emotional reactions do not interfere with goal-directed be-  
42 havior (Clarke & Johnstone, 2013; Iordan, Dolcos, & Dolcos, 2013; Okon-Singer et al.,  
43 2015). On a behavioral level, increased cognitive load has been associated with reduced  
44 state anxiety and startle response (Balderston et al., 2016; King & Schaefer, 2011; Vytal,  
45 Arkin, Overstreet, Lieberman, & Grillon, 2016; Vytal, Cornwell, Arkin, & Grillon, 2012) and  
46 with reduced subjectively experienced negative emotion in response to negative stimuli  
47 (Van Dillen et al., 2009). Additionally, performing a cognitively demanding task over sev-  
48 eral weeks resulted in better cognitive control in healthy (Cohen et al., 2016; Schweizer,  
49 Grahn, Hampshire, Mobbs, & Dalgleish, 2013; Schweizer, Hampshire, & Dalgleish, 2011)  
50 as well as in anxious individuals (Sari, Koster, Pourtois, & Derakshan, 2016).

51 To our knowledge, it has yet not been investigated whether a demanding working  
52 memory task that results in an acute decrease in amygdala activity would also lead to an  
53 acute reduction in subjectively perceived phobic fear. To address this question, we meas-  
54 ured amygdala activity during the viewing of snake pictures and neutral pictures in sub-  
55 jects with fear of snakes under different working-memory load conditions. We designed  
56 a high working-memory load condition (2-back) and a low working-memory load condi-  
57 tion (0-back), whereby the snake pictures and neutral pictures served as targets in the  
58 different conditions (Figure 1). This design enabled that the visual input during the n-back  
59 task was identical across working-memory load conditions. We hypothesized reduced  
60 amygdala activity and reduced subjective fear ratings during the high load condition, as  
61 compared to the low load condition. Additionally, we applied dynamic causal modelling  
62 (DCM) to investigate a possible load-dependent change in effective connectivity between  
63 the dlPFC and the amygdala.



64

65 **Figure 1:** N-back task performed during fMRI. The figure illustrates a 2-back task block with snake  
 66 pictures. Subjects have to remember the snake picture presented two positions before and indicate if  
 67 the currently presented picture is the same (Hit) or a different one (No Hit). During 0-back blocks, a  
 68 target picture is presented at the beginning of each block and subjects have to respond each time it is  
 69 presented during the block. For the 2-back and 0-back neutral condition, snake pictures were replaced  
 70 with pictures of neutral objects. In total, each subject completed 32 task blocks (eight blocks of each  
 71 condition: 0-back/snake, 2-back/snake, 0-back/neutral and 2-back/neutral).

## 72 2 Material and Methods

### 73 2.1 Subjects

74 43 subjects (11 males, mean age = 23.12 years,  $SD = 3.37$  years) were included in the final  
 75 analysis after removing four subjects due to corrupted fMRI data (see Supplementary ma-  
 76 terial for details on exclusion reasons) and one subject due to low fear ratings of the snake  
 77 pictures during the pictorial n-back task ( $> 2.5$  SD from sample mean).

78 Subjects were recruited from the Basel and Zurich area in Switzerland and had to  
 79 meet the following inclusion criteria: (1) age between 18 and 35 years, (2) BMI between  
 80 18 (females)/19 (males) and 35 kg/m<sup>2</sup>, (3) native or fluent German-speaking, (4) capable  
 81 of viewing pictures of snakes without turning the head away, and (5) a score of 12 or  
 82 higher in a snake anxiety questionnaire (SCANS questionnaire) (Reinecke, Hoyer, Rinck ,



83 & Becker, 2009). The SCANS is a self-report questionnaire consisting of four items per-  
84 taining to the four relevant DSM-IV diagnosis criteria of snake phobia (persistent fear,  
85 anxiety response, avoidance, distress). Subjects judge each statement on a 7-point Likert  
86 scale (0 – 6). The total SCANS score ranges from 0 (no fear of snakes at all) to 24 (very  
87 strong fear of snakes). In our sample, the mean SCANS score was 17.51 ( $Mdn = 18$ ,  $SD =$   
88  $3.04$ , range = 12 – 23), indicating strong fear of snakes.

89 Subjects were free of any neurological or psychiatric illness (except fear of snakes),  
90 did not take any medication at the time of the experiment (oral contraception was al-  
91 lowed) and had normal or corrected-to-normal vision. Subjects gave their written in-  
92 formed consent to participate in the study, which was approved by the Ethics Committee  
93 northwest/central Switzerland (EKNZ) (registration number: BASEC 2016-01330). All  
94 subjects received 25 CHF/h as compensation for their participation.

## 95 **2.2 Stimuli and task description**

### 96 *2.2.1 Description of the pictorial n-back task*

97 The task designed for this study was a pictorial n-back task consisting of two types of  
98 working-memory load (low load: 0-back; high load: 2-back) and two types of pictures  
99 (snake pictures; neutral pictures), resulting in four conditions for each subject (within-  
100 subject design): (1) 0-back/snake, (2) 2-back/snake, (3) 0-back/neutral and (4) 2-  
101 back/neutral (see Figure 1).

102 During the 0-back conditions, subjects needed to respond as quickly as possible to  
103 the occurrence of a target picture (snake or neutral). The 0-back mainly requires general  
104 attention processes (Owen et al., 2005) and is thus considered to induce only low work-  
105 ing-memory load. In the 2-back condition, subjects had to judge whether currently pre-

106 sented picture was identical to the one presented two positions before. The 2-back condi-  
107 tion served as a high load condition because it requires online monitoring, updating, and  
108 manipulation of remembered information (Owen et al., 2005).

109 In total, the task comprised 32 blocks (eight blocks per condition), presented in a  
110 quasi-randomized order. In each block, four different pictures of the same picture type  
111 were quasi-randomly presented three times, resulting in a total of 12 presented pictures  
112 per block. Each block contained three target stimuli and nine non-target stimuli, resulting  
113 in a target-rate of 25%. Subjects had to react to these targets as quickly as possible. At the  
114 beginning of each block, an introduction was displayed for 5 s to introduce the next task  
115 (0-back or 2-back). In case of a 0-back condition, the instruction also comprised a ran-  
116 domly selected picture that served as a target in the following block. After the instruction,  
117 a black screen appeared for 1 s before the block started. Pictures were presented on a  
118 scrambled background for 1.2 s, with only scrambled background between picture  
119 presentations (0.65 s). Every block lasted for 22.2 s.

120 After each block, subjects had to rate how they had felt during the last block on five  
121 separate visual analog scales via button presses (see section 2.2.3 *Emotion ratings during*  
122 *n-back task*). The ratings lasted for a total of 40 s. After a break (random duration, min =  
123 1 s and max = 8 s; 20 s in total over four consecutive blocks), an empty screen was pre-  
124 sented for 1 s until the instructions of the next task block appeared.

125 Conditions were presented in a quasi-randomized order, i.e. each of the four con-  
126 ditions was presented once before being presented again. Furthermore, snake and neutral  
127 pictures were assigned to 0-back and 2-back in a counterbalanced fashion. As blocks of  
128 snake pictures always depicted the same animal (snake), we took care that neutral pic-  
129 tures also depicted the same type of object within one task block (e.g. chairs) to control

130 blocks for task difficulty. However, the type of neutral object changed for each new task  
131 block.

### 132 *2.2.2 Picture selection*

133 In total, 64 pictures of snakes and 64 pictures depicting neutral objects were used in this  
134 study. All snake pictures and 21 neutral pictures were selected from the Geneva Affective  
135 Picture System (GAPED; Dan-Glauser & Scherer, 2011) and 24 neutral pictures from the  
136 International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) (for nor-  
137 mative ratings of the selected pictures, see Supplementary Table S1). Since these standard  
138 picture systems did not provide us with a sufficient number of neutral pictures in accord-  
139 ance with our selection criteria, we selected 19 additional neutral pictures from in-house  
140 standardized picture sets.

### 141 *2.2.3 Emotion ratings during n-back task*

142 To measure subjects' emotional reaction to the pictures presented during the task blocks,  
143 five separate visual rating scales (11-point Likert scales) were presented after each block.  
144 An instruction slide appeared for 5 s, announcing the first three ratings. Afterwards, sub-  
145 jects had to indicate how much fear (none – maximal) and how much disgust (none – max-  
146 imal) they had felt during the last task block as well as the state of their mood (very good  
147 – very bad). In total, the subjects were given 18 s to indicate their ratings (on average 6 s  
148 per rating) by moving the curser stepwise to the according scale position on an fMRI com-  
149 patible finger-controlled button box. If subjects were faster than 18 s, a cross appeared in  
150 the middle of the screen for the remaining time. Next, a second instruction slide appeared  
151 for 5 s, announcing the last two ratings. Subjects rated the pictures of the last block ac-  
152 cording to overall valence (positive – negative) and arousal (low – high). Subjects were  
153 given a total of 12 s to indicate their ratings (6 s per rating).

154 **2.3 *Experimental procedure***

155 Prior to the day of the experiment, subjects received general information about the  
156 study and filled out an online questionnaire to assess study eligibility. The software  
157 SoSci Survey was used for online assessments (Leiner, 2014).

158 The experiment took place at the University Hospital of Basel. Upon arrival, sub-  
159 jects gave written informed consent. They were then trained on the n-back task. Only neu-  
160 tral pictures were used for training. The training was repeated if the number of correct  
161 responses was lower than 90% in the 0-back or lower than 70% in the 2-back. Afterwards,  
162 subjects entered the scanner. All subjects received earplugs and headphones during MR  
163 scans to reduce scanner noise and were instructed not to move during the scans. Small  
164 foam pads were used for additional head fixation. We used MR-compatible LCD goggles  
165 (VisualSystem; NordicNeuroLab, Bergen, Norway) to present the n-back task inside the  
166 scanner and to track eye movements during the task. Eye tracking data was acquired with  
167 the ViewPoint eyetracker software (Arrington Research) and calibration was done at the  
168 beginning of the experiment. Vision correction was used if necessary. Subjects gave their  
169 responses via a button box placed on their lower abdomen using the index, middle, and  
170 ring finger of their dominant hand. The n-back task lasted 40 min and was followed by 10  
171 min of magnetization prepared rapid gradient echo (MPRAGE) and B0 field map acquisi-  
172 tion.

173 We used the Presentation<sup>®</sup> software (version 14.5; Neurobehavioral Systems, Inc.,  
174 Berkeley, CA, [www.neurobs.com](http://www.neurobs.com)) to present the tasks inside the scanner.

## 175 **2.4 Statistical analysis of the behavioral data**

176 All statistical analyses of behavioral data were performed in R (version 3.3.2;  
177 RRID:SCR\_001905).

### 178 *2.4.1 Assessment of n-back performance*

179 To assess whether 2-back blocks was more demanding and therefore induced a higher  
180 working-memory load than 0-back blocks, we measured subjects' task performance, i.e.  
181 accuracy (hits plus correct rejections divided by the total number of pictures shown) and  
182 d-prime (z-transformed values of hit- minus false alarm-rates (Stanislaw & Todorov,  
183 1999)) measures. Two separate linear mixed models ('nlme'-package) were calculated in  
184 combination with ANOVA (SS II) with accuracy and d-prime serving as dependent varia-  
185 bles. The two within-subject factors load (0-back, 2-back) and picture type (snake, neu-  
186 tral) entered the model as independent variables. Subjects were included as random ef-  
187 fect.

### 188 *2.4.2 Preprocessing and analysis of eye-tracking data*

189 For each subject, fixation detection was performed with an individual, velocity-based al-  
190 gorithm using the 'saccades' package (von der Malsburg, 2015). The average dwell time  
191 in a pre-defined region of interest (ROI) of a picture was calculated for each task condition  
192 (see Supplementary material for more details on data processing and definition of ROIs).  
193 Dependent two-sided *t*-tests were calculated separately for snake and neutral pictures to  
194 investigate whether subjects spent an equal amount of time in the ROI of pictures pre-  
195 sented under 2-back or 0-back conditions.

### 196 *2.4.3 Analysis of emotion ratings during n-back task*

197 We assessed the effect of picture type on emotion ratings by calculating separate depend-  
198 ent two-sided *t*-tests for each rating of the n-back task. We tested whether snake pictures

199 induced, on average, more negative emotions than neutral pictures, irrespective of load.  
200 This was done as a manipulation check.

201 To assess the effect of cognitive load on emotion ratings, we analyzed whether sub-  
202 jects' ratings for snake and neutral pictures differed between 2-back and 0-back blocks.  
203 We calculated a difference score by subtracting the average rating score of all 0-back  
204 blocks from the average rating score from all 2-back blocks. This calculation was per-  
205 formed separately per picture type (snake, neutral) and rating. For each obtained differ-  
206 ence score, a separate one-sample *t*-test (two-sided) was calculated. Additionally, we cal-  
207 culated linear mixed models to check for potential sex and age effects on ratings of snake  
208 pictures. Subjects were included as random effect. We did not observe any significant sex  
209 or age effects ( $p > .15$ ) and therefore did not consider those variables in the following  
210 analysis on emotion ratings.

#### 211 2.4.4 *Effect sizes and correction for multiple testing*

212 Effect sizes calculated for repeated measurement factors are influenced by the correlation  
213 between the repeated measurements. Those effect sizes are consequently not comparable  
214 to effect sizes for factors used in between-subject designs (Dunlap, Cortina, Vaslow, &  
215 Burke, 1996). To avoid an overestimation of effect sizes, we report generalized semi-par-  
216 tial  $R^2$  ( $R^2_{\beta^*}$ ), a measure that is comparable to effect sizes of between-subject designs  
217 (Jaeger, Edwards, Das, & Sen, 2017).  $R^2_{\beta^*}$  is a generalization of the widely used marginal  
218  $R^2$  statistics (Nakagawa & Schielzeth, 2013).

219 As the rating of fear during the n-back task constituted our primary variable of  
220 interest we set the significance threshold to  $p < .05$  for this rating. Bonferroni correction  
221 was implemented to account for multiple testing for all remaining ratings (disgust, mood,  
222 valence and arousal; Bonferroni correction for four independent tests).

## 223 **2.5 (f)MRI data acquisition**

224 Measurements were performed on a Siemens Magnetom SkyraFit 3 T whole-body MR unit  
225 equipped with a 32-channel head coil. Functional series were acquired using a single-shot  
226 echo-planar sequence using parallel imaging (GRAPPA). The following acquisition param-  
227 eters were applied: TE (echo time) = 30 ms, FOV (field of view) = 24 cm, acquisition matrix  
228 =  $96 \times 96$ , voxel size =  $2.5 \times 2.5 \times 3 \text{ mm}^3$ , GRAPPA acceleration factor  $R = 2.0$ . Using a  
229 midsagittal scout image, 42 contiguous axial slices placed along the anterior-posterior  
230 commissure (AC-PC) plane covering the entire brain with a TR (repetition time) = 2600  
231 ms ( $\alpha = 82^\circ$ ) were sampled with an ascending interleaved sequence. A high-resolution T1-  
232 weighted anatomical image was acquired for each subject using a magnetization prepared  
233 gradient echo sequence (MPRAGE, TR = 2000 ms; TE = 2.26 ms; TI = 1000 ms; flip angle  
234 =  $8^\circ$ ; 176 slices; FOV = 256 mm, voxel size =  $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ ).

235 To correct the fMRI data for geometric distortions caused by magnetic field inho-  
236 mogeneities, B0 field-map scans were collected as well (TR = 550 ms, TE = 4.92 ms/7.38  
237 ms, flip angle =  $60^\circ$ , voxel size =  $2.5 \times 2.5 \times 3.0 \text{ mm}^3$ ).

## 238 **2.6 fMRI data analysis**

### 239 *2.6.1 Preprocessing and first-level analysis*

240 Analyses were performed using SPM12 (version 6470; Statistical Parametric Mapping,  
241 Wellcome Trust Centre for Neuroimaging, London, UK; [http://](http://www.fil.ion.ucl.ac.uk/spm/)  
242 [www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)) implemented in Matlab R2014b (The Mathworks Inc., Natick,  
243 MA, USA).

244 To account for magnetization effects, the first four volumes were discarded from  
245 further analyses. The remaining volumes were slice-time corrected to the first slice, rea-  
246 ligned and unwarped with the fieldmaps and coregistered to the anatomical image by ap-

247 plying a normalized mutual information 3D rigid-body transformation. Successful coreg-  
248 istration was visually verified for every subject. Each volume was masked with the sub-  
249 ject's T1 anatomical image to exclude voxels outside of the brain. The EPI volumes were  
250 normalized to MNI space by applying DARTEL, which leads to an improved registration  
251 between subjects (Ashburner, 2007; Klein et al., 2009). Normalization incorporated the  
252 following steps: 1) structural images of each subject were segmented using the "Segment"  
253 procedure in SPM12. 2) The resulting gray and white matter images were used to derive  
254 a study-specific group template. The template was computed from all subjects included in  
255 this study ( $N = 43$ ) (see Supplementary material for details on construction of the tem-  
256 plate). 3) An affine transformation was applied to map the group template to MNI space.  
257 4) Subject-to-template and template-to-MNI transformations were combined to map the  
258 functional images to MNI space. The functional images were smoothed with an isotropic  
259 5 mm full width at half maximum (FWHM) Gaussian filter.

260         Normalized functional images were masked using information from their respec-  
261 tive T1 anatomical file as follows: At first, the three-tissue classification probability maps  
262 of the "Segment" procedure (grey matter, white matter, and CSF) were summed to define  
263 a brain mask. The mask was binarized, dilated and eroded with a  $3 \times 3 \times 3$  voxels kernel  
264 using `fslmaths` (FSL) to fill in potential small holes in the mask. The previously computed  
265 DARTEL flowfield was used to normalize the brain mask to MNI space, at the spatial res-  
266 olution of the functional images. The resulting non-binary mask was thresholded at 50%  
267 and applied to the normalized functional images. Consequently, the implicit intensity-  
268 based masking threshold usually employed to compute a brain mask from the functional  
269 data during the first level specification (`spm_get_defaults('mask.thresh')`, by default fixed  
270 at 0.8) was not required anymore and therefore set to a lower value of 0.05.



271 Analyses were conducted in the framework of the general linear model. Intrinsic autocor-  
272 relations were accounted for by AR(1), and low-frequency drifts were removed via a high-  
273 pass filter (time constant 128s). Regressors, which modelled the onset and duration of  
274 each block, were convolved with a canonical haemodynamic response function (HRF).  
275 Separate regressors were constructed for each of the four n-back conditions (1) 0-back  
276 neutral, (2) 0-back snake, (3) 2-back neutral and (4) 2-back snake. Events between blocks  
277 i.e. task instructions, ratings and breaks were modeled as separate regressors. Addition-  
278 ally, six movement regressors from spatial realignment were included as regressors of no  
279 interest.

280 The resulting parameter estimates were used to specify contrasts using fixed ef-  
281 fects models (first-level analysis). The following contrasts were specified: (1) “picture  
282 contrast”: brain activity related to presentation of snake pictures compared to neutral pic-  
283 tures (snake pictures - neutral pictures), independently of whether the picture was shown  
284 under 0-back or 2-back; (2) “load contrast”: brain activity related to pictures presented  
285 under 0-back or 2-back (0-back - 2-back), irrespective of whether the picture depicted a  
286 snake or a neutral object and (3) “interaction contrast”: brain activity related to the inter-  
287 action of load and picture type ((0back snake - 2back snake) - (0back neutral - 2back neu-  
288 tral)).

### 289 2.6.2 *Group-level analysis*

290 The single-subject contrast maps of the first-level analysis were entered in a random ef-  
291 fects model to make inferences on group-level. We controlled for sex and age by including  
292 them as covariates. As the amygdala and the dlPFC served as regions of interest in this  
293 analysis, we applied a small volume correction (SVC) for these regions. We first created  
294 one probabilistic mask for the amygdala and one for the dlPFC by combining the respec-  
295 tive masks from both hemispheres. These masks were taken from the population-specific

296 atlas (corresponding Freesurfer labels for dlPFC mask: ctx-lh-rostralmiddlefrontal/ctx-  
297 rh-rostralmiddlefrontal). The probabilistic masks were consequently thresholded at 50%,  
298 binarized and applied to the group-level contrast maps ( $p < .05$ , FWE corrected for multi-  
299 ple comparisons within the mask ( $p_{\text{FWE-SVC}}$ )).

### 300 *2.6.3 DCM: Extracting time courses from VOIs*

301 We used DCM to investigate a possible inhibition of amygdala activity through top-down  
302 control of prefrontal regions when task load is high. Volumes of interest (VOI) were de-  
303 fined as the amygdala and the dlPFC. Time courses were extracted separately per hemi-  
304 sphere.

305 The applied approach was similar to the one used in Fastenrath et al. (2014). First,  
306 we identified local maxima at the group-level for each of the four anatomical masks  
307 (amygdala and dlPFC from both hemispheres). Local maxima were based on the load con-  
308 trast (0-back - 2-back). Second, group-level coordinates in MNI space were mapped to  
309 native subject space. Based on these subject space coordinates, subject-specific local max-  
310 ima were identified within a distance of 10 mm. Time courses were extracted by compu-  
311 ting the principal eigenvariate of the data across all significant voxels ( $p < .05$  uncorrected,  
312 minimum cluster size 3) within a 10 mm sphere around the subject-specific local maxima  
313 and within the subject-specific anatomical mask (masks were retrieved from the Free-  
314 Surfer segmentations). The extracted time courses were adjusted to the F-contrast (i.e.  
315 effects of interest) of each subject and entered into the DCM models.

316 As data from all VOIs in all subjects is a prerequisite to run DCM (Friston, Harrison,  
317 & Penny, 2003; Stephan et al., 2010), subjects that did not show sufficient activation in  
318 line with the criteria defined above were excluded from further DCM analysis.

319 *2.6.4 DCM: defining model space and model comparison*

320 We applied bilinear, deterministic DCM with two states (version DCM12 r6432 in SPM 12  
321 r6470) (Marreiros, Kiebel, & Friston, 2008). We ran DCM for the left and the right hemi-  
322 sphere separately. In each hemisphere, models were set up consisting of two nodes, cor-  
323 responding to the amygdala and the dlPFC, respectively. We allowed full bidirectional  
324 connectivity between the two nodes. The two load conditions 0-back and 2-back, as well  
325 as instructions and emotion ratings served as driving input to either one of the regions or  
326 to both regions. This resulted in three input possibilities to the network, i.e. three different  
327 models per hemisphere. Within each model the connections between both regions could  
328 be modulated by either the 0-back or the 2-back condition, irrespective of picture type.  
329 We focused on the difference in task load because we did not find any significant interac-  
330 tion effect between task load and picture type in the fMRI group-level analysis.

331 DCM is based on Bayesian statistics. The model evidence denotes the probability  
332 of the data given the model while adjusting for model complexity and dependencies  
333 among parameters (Penny et al., 2010; Stephan, Penny, Daunizeau, Moran, & Friston,  
334 2009). Models were compared by conducting random-effects Bayesian Model Selection  
335 (BMS) (Penny et al., 2010; Stephan et al., 2009) and differed only in the location of the  
336 driving input. This allowed us to test whether one of the models was more likely than any  
337 of the other two, which is expressed as exceedance probability (xp).

338 *2.6.5 DCM: Bayesian model averaging and parameter analysis*

339 Bayesian model averaging (BMA) was applied to receive a summary measure of likely  
340 connectivity values (Penny et al., 2010). The connectivity parameters of each model were  
341 weighted by the posterior model probability and subsequently averaged within each sub-

342 ject. Overall, the BMA weighting procedure resulted in subject-specific connectivity esti-  
343 mates that were independent of a particular model while ensuring that models with a high  
344 probability contributed more than models with a lower probability.

345 The BMA modulatory parameter estimates of each subject were further analyzed  
346 using R (<http://www.r-project.org>). We checked for possible sex and age effects by calcu-  
347 lating linear mixed models. As we did not find any significant effects of sex or age ( $p > .05$ ),  
348 these variables were not considered in the following analyses. Two-sided paired  $t$ -tests  
349 were performed for both hemispheres to test for differences in connectivity strength be-  
350 tween the 0-back and the 2-back, using a Bonferroni-corrected threshold to account for  
351 multiple testing ( $p < 0.025$ ). In case the assumptions for normality were violated (deter-  
352 mined by visual inspection and calculation of Shapiro-Wilk tests), we calculated permuted  
353  $p$ -values by randomly shuffling the data 30'000 times to achieve robust estimates.

## 354 **3 Results**

### 355 **3.1 Behavioral results**

#### 356 *3.1.1 n-back performance*

357 Performance in the 0-back condition was significantly better than in the 2-back condition  
358 (accuracy:  $F_{(1,127)} = 277.74$ ,  $p < 9.3 \times 10^{-34}$ ,  $R^2_{\beta^*} = .45$ ; d-prime:  $F_{(1,127)} = 305.16$ ,  $p < 1.5 \times$   
359  $10^{-35}$ ,  $R^2_{\beta^*} = .52$ ; see also Table 1), indicating effective manipulation of load. There was no  
360 significant interaction between load and picture type or main effect of picture type on n-  
361 back performance (all  $p > .43$  for accuracy and d-prime).

#### 362 *3.1.2 Eye tracking*

363 We used eye-tracking to investigate if subjects screened pictures differently depending  
364 on the load condition. Such a difference in scanning pattern might have affected fear rat-  
365 ings by altering the visual input of fear-inducing information.

366 For snake pictures as well as for neutral pictures, the average dwell time in the region of  
367 interest of a picture did not significantly differ between load conditions (snake pictures:  
368  $t_{(39)} = -1.00, p = .32$ ; neutral pictures:  $t_{(36)} = 0.20, p = .84$ ). This finding indicates that  
369 subjects spent an equal amount of time looking at relevant regions of the picture in both  
370 the 2-back and 0-back blocks.

### 371 3.1.3 *Emotion ratings: Effect of picture type*

372 Subjects reported significantly more fear ( $t_{(42)} = 17.16, p < 1.4 \times 10^{-20}$ ), disgust ( $t_{(42)} =$   
373  $20.52, p < 1.7 \times 10^{-23}$ ), negative mood ( $t_{(42)} = 10.42, p < 3.3 \times 10^{-13}$ ), negative valence ( $t_{(42)}$   
374  $= 11.95, p < 4.3 \times 10^{-15}$ ), and arousal ( $t_{(42)} = 12.41, p < 1.3 \times 10^{-15}$ ) after blocks depicting  
375 snake pictures compared to neutral pictures, indicating that snake pictures evoked more  
376 negative emotions than neutral pictures.

### 377 3.1.4 *Emotion ratings: Effect of working-memory load*

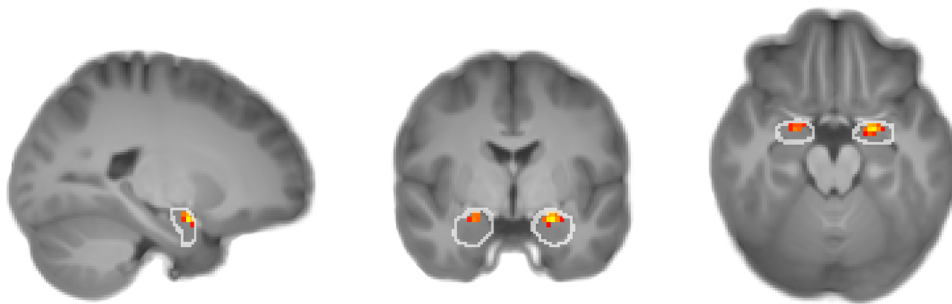
378 Snake pictures presented during the 2-back blocks evoked less fear ( $t_{(42)} = -2.78, p = .008$ )  
379 and less disgust ( $t_{(42)} = -3.19, p_{\text{Bonferroni corrected}} = .011$ ) than snake pictures presented during  
380 0-back blocks. No significant effects of load on mood, valence or arousal were found (all  
381  $p_{\text{Bonferroni corrected}} > .47$ , see Table 2).

382 In contrast, neutral pictures presented during the 2-back blocks resulted in higher  
383 fear ratings ( $t_{(42)} = 2.51, p = .016$ ) than neutral pictures presented during the 0-back  
384 blocks. For all other emotion ratings on neutral pictures, no significant effects of load were  
385 found (all  $p_{\text{Bonferroni corrected}} > .11$ , see Supplementary Table S2).

386 **3.2 fMRI results for regions of interest**

387 **3.2.1 Main effect of picture type**

388 Voxel-wise analysis revealed that the amygdala was bilaterally activated during blocks of  
389 snake pictures compared to blocks of neutral pictures (peak-voxel: left: MNI -22, -2, -18,  $t$   
390 = 6.23,  $k = 23$ ; right: MNI 22, -2, -18,  $t = 4.95$ ,  $k = 10$ ;  $t = 3.56$ ,  $p_{\text{FWE-SVC}} < .05$ ; see Figure 2).  
391 We did not observe any effects of sex or age with regard to this activation.

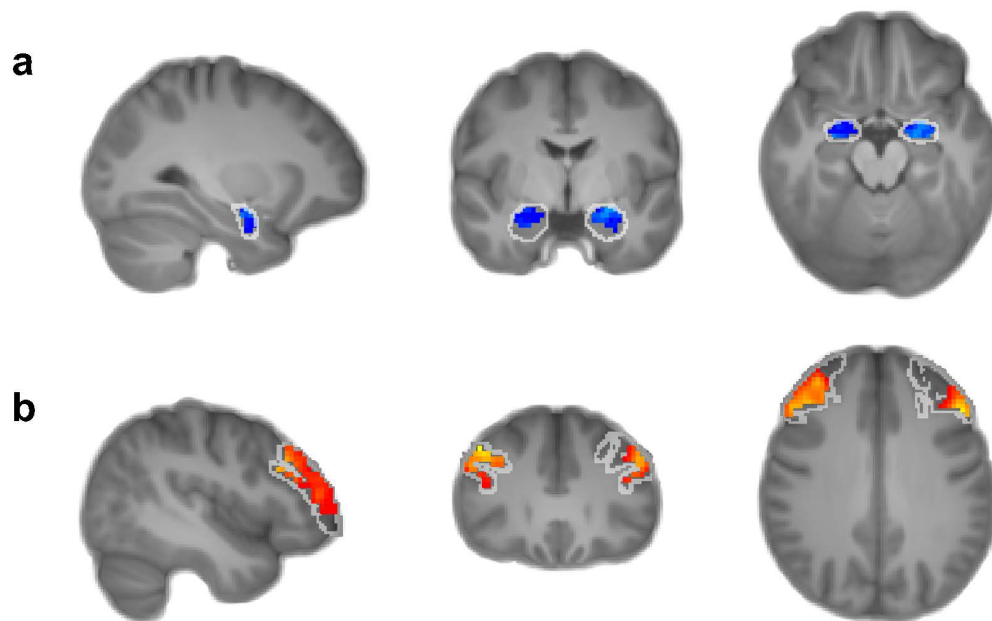


392

393 **Figure 2:** Amygdala activation for the contrast (snake pictures - neutral pictures) on group-level. De-  
394 picted are only significant voxels (yellow to red) within the probabilistic amygdala mask (white cir-  
395 cles) used for small volume correction (SVC,  $p_{\text{FWE-SVC}} < .05$ ).

396 **3.2.2 Main effect of load**

397 Amygdala activity was reduced during 2-back blocks compared to 0-back blocks in both  
398 the left hemisphere (peak voxel: MNI -22.5, -10, -15,  $t = 8.06$ ) and right hemisphere (peak  
399 voxel: MNI 22.5, -7.5, -15,  $t = 6.71$ ;  $t = 3.5$ ,  $p_{\text{FWE-SVC}} < .05$ ; see Figure 3a). Further, 2-back  
400 blocks resulted in higher bilateral dlPFC activity compared to 0-back blocks (peak voxel:  
401 left: MNI -47.5, 25, 33,  $t = -10.64$ ; right: MNI 45, 30, 39,  $t = -11.05$ ;  $t = 4.42$ ,  $p_{\text{FWE-SVC}} <$   
402  $.05$ ; see Figure 3b). No significant sex or age effects were found.



403  
 404 **Figure 3:** Amygdala and dlPFC activity for the 0back - 2back contrast on group-level. Decreased amygdala activity during the 2-back condition as compared to the 0-back condition (a, blue color). Increased  
 405 dlPFC activity during the 2-back condition as compared to the 0-back condition (b, yellow to red color).  
 406 Depicted are significant voxels within the respective probabilistic masks used for SVC ( $p_{FWE-SVC} < .05$ ).  
 407

### 408 3.2.3 Interaction of load and valence

409 There was no significant interaction effect between load and picture type on amygdala  
 410 activity when applying SVC ( $p_{FWE-SVC} > .05$ ), indicating that there was a similar decrease in  
 411 amygdala activity during 2-back compared to 0-back for snake pictures and for neutral  
 412 pictures. No interaction effects were observed for the dlPFC either ( $p_{FWE-SVC} > .05$ ).

## 413 3.3 DCM results

### 414 3.3.1 Extraction of time courses in volumes of interest (VOI)

415 Activity in the respective peak voxel within the amygdala and the dlPFC were obtained  
 416 from the load contrast (0-back - 2-back) of the group-level analysis (for peak coordinates  
 417 see Table 3). We focused only on the contrast of load as we did not find any interaction  
 418 between load and picture type in the fMRI group-level analysis.

419 Data from all regions in all subjects is a prerequisite to run DCM. Five subjects did not  
 420 show robust task-dependent activation in both the left and right amygdala, and therefore

421 had to be excluded entirely from further DCM analysis. Eight additional subjects did not  
422 show robust activation in either the left or right amygdala (four in the left, four in the  
423 right), and were hence excluded only with respect to the DCM of one hemisphere. Per  
424 hemisphere, time courses were consequently available for 34 out of 43 subjects.

### 425 *3.3.2 Model comparison using Bayesian Model Selection (BMS)*

426 We constructed three different models based on the site of input to the network. BMS was  
427 used to identify the most plausible model given the data. Comparison between the three  
428 models indicated that the model where the input entered both regions (amygdala and  
429 dlPFC) was most likely (left hemisphere: model exceedance probability = 0.995, Supple-  
430 mentary Figure S1a; right hemisphere: model exceedance probability = 0.605; Supple-  
431 mentary Figure S1b) even though there was a considerably high exceedance probability  
432 for input only to the dlPFC in the right hemisphere as well (exceedance probability:  
433 0.395).

### 434 *3.3.3 Modulatory influence of load on connectivity parameters*

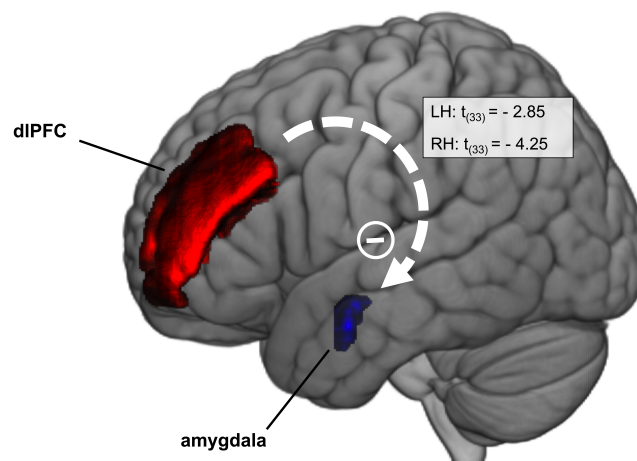
435 As there was no clearly superior input model for the right hemisphere, we used BMA to  
436 calculate connectivity parameters. Modulators of effective connectivity describe whether  
437 the strength of the connection (i.e., the influence that one regions exerts upon another)  
438 increases or decreases under the influence of experimental manipulations (Friston et al.,  
439 2003). Modulator estimates were calculated for the 0-back and for the 2-back condition.  
440 In addition to modulators of connection strength, DCM also estimates intrinsic connectiv-  
441 ity parameters. They represent the connectivity in the absence of experimental perturba-  
442 tions. The effective connection strength associated with the experimental condition can  
443 be obtained by adding the value of the intrinsic connection and the value of the modulator.  
444 A negative sum indicates that the activity in the source region decreases (inhibits) activity  
445 in the target region (Sokolov et al., 2018).



446 The modulation of connectivity parameters was analyzed on group-level. Visual  
447 inspection of the data distribution and subsequent statistical testing indicated a deviation  
448 from normality in both hemispheres (Shapiro-Wilk test:  $p < .05$ ; see also Supplementary  
449 Figure S2). For this reason, we report permuted  $p$ -values of the performed  $t$ -tests to en-  
450 sure robustness of the results.

451 Modulators of connection strength from the dlPFC to the amygdala differed signif-  
452 icantly between the two load conditions in both hemispheres (left:  $t_{(33)} = -2.85$ ,  $p_{\text{permut}} =$   
453  $.0035$ ; right:  $t_{(33)} = -4.25$ ,  $p_{\text{permut}} < 7 \times 10^{-05}$ ; see Figure 4, Table 4 and 5 and Supplementary  
454 Figure S3), showing an inhibitory influence of the dlPFC on the amygdala during the 2-  
455 back condition.

456 For the direction from the amygdala to the dlPFC, no significant differences in con-  
457 nectivity strength were found between 2-back and 0-back (both hemispheres:  $p > .28$ ; Ta-  
458 ble 4 and 5).



459

460 **Figure 4:** Change in connectivity between the dlPFC (red) and the amygdala (blue) during 2-back  
461 blocks compared to 0-back blocks. The white arrow indicates the influence from the dlPFC to the amyg-  
462 dala. The  $t$ -values in the box indicate a stronger decrease in connectivity strength during the 2-back  
463 than during the 0-back in the left hemisphere (LH) and the right hemisphere (RH). For parameter val-  
464 ues per condition see Table 4 and 5.

465

466 **4 Discussion**

467 The confrontation with a feared object or situation typically results in an acute activation  
468 of limbic brain regions, including the amygdala, and in perceived fear. In the present fMRI  
469 study, we investigated if high working-memory load would lead to reduced activity of the  
470 amygdala as well as to attenuated phobic fear in subjects with fear of snakes.

471 The findings indicate a decrease in amygdala activity during blocks of high work-  
472 ing-memory load compared to blocks of low working-memory load, which is in line with  
473 findings from previous studies (Kellermann et al., 2011; Mitchell et al., 2007). Im-  
474 portantly, we also observed acute effects of working-memory load on subjective fear and  
475 disgust ratings. When working-memory load was high, subjects reported less phobic fear  
476 and disgust in the presence of fearful pictures. To our knowledge, these results are the  
477 first to indicate that engaging in a highly demanding cognitive task can instantly decrease  
478 perceived fear and disgust towards phobic stimuli.

479 Applying DCM, we additionally investigated task load-dependent changes in functional  
480 connectivity between the dlPFC and the amygdala. We focused on the effect of task load  
481 in the DCM analysis as we did not detect any significant interaction effects between task  
482 load and picture type in initial group-level analysis. This suggests a load-dependent de-  
483 crease in amygdala activation irrespective of whether the presented pictures depicted  
484 fearful or neutral objects. This parallels findings from previous experiments in which solv-  
485 ing a difficult task has been associated with a decrease in amygdala activity independently  
486 of whether neutral or emotional stimuli were used (Cohen et al., 2016; Silvert et al., 2007;  
487 Straube et al., 2011). Our DCM analysis revealed a bilateral decrease in connectivity  
488 strength from the dlPFC to the amygdala during high task load compared to low task load,  
489 indicating that the dlPFC exerted a stronger inhibitory influence on the amygdala when  
490 task demand was high.

491 What might be the mechanism(s) of the observed reduction of phobic fear under high  
492 working-memory load? One potential explanation for reduced amygdala activity and fear  
493 is that the high working-memory load condition caused a visual distraction from the emo-  
494 tional pictures. However, as the pictures were used as targets in the n-back task, subjects  
495 were “forced” to process the pictorial information in both load conditions. Importantly,  
496 our eye-tracking results indicate that subjects spent a similar amount of time in the emo-  
497 tional regions of interest of the snake pictures in both load conditions. Thus, reduced  
498 amygdala activity and fear as a consequence of visual distraction appears unlikely. In-  
499 stead, we argue that the observed fear reduction may have been a result of a working  
500 memory-induced top-down control mechanism, i.e. an increase in dlPFC activity when  
501 subjects engage in a cognitively demanding task induces a decrease in amygdala activity  
502 (Okon-Singer et al., 2015). In line with this idea, the current study found that reduced  
503 amygdala activation during high load could be explained by a change in effective connec-  
504 tivity between lateral prefrontal regions and the amygdala. The purpose for such a top-  
505 down regulation of amygdala activity might be the reallocation of resources from emo-  
506 tional processes to the working memory task. It has been shown that the presentation of  
507 a distractor during a highly demanding task results in a competition for limited cognitive  
508 resources (Desimone & Duncan, 1995; Lavie, 2010; Lavie, Hirst, De Fockert, & Viding,  
509 2004). Attention is directed towards accomplishing the cognitively demanding task, leav-  
510 ing little capacity to process the emotional stimulus, which in turn results in attenuated  
511 neuronal and behavioral reactions towards emotional stimuli (Balderston et al., 2016;  
512 Bishop, Jenkins, & Lawrence, 2006; Mitchell et al., 2007; Vytal et al., 2012). Even though it  
513 is assumed that the dlPFC does not have strong direct anatomical connections to the  
514 amygdala (Ray & Zald, 2012), studies suggest that the dlPFC might interact with the amyg-  
515 dala over indirect pathways via the subgenual cingulate gyrus, dorsal anterior cingulate

516 cortex, orbitofrontal cortex or ventrolateral PFC (Clarke & Johnstone, 2013; Ray & Zald,  
517 2012; Sladky et al., 2013). Taken together, the mechanism of reduced amygdala activity  
518 and reduced fear and disgust under high working-memory load may involve a top-down  
519 regulation and a reallocation of cognitive resources.

520         In summary, the findings of the present study suggest that high working-memory  
521 load, induced by an n-back task comprising fearful stimuli, not only decreases amygdala  
522 activity but also reduces perceived phobic fear and disgust towards fearful stimuli. Future  
523 studies may investigate the acute effects of even higher working-memory load conditions  
524 on amygdala activity and fear. Furthermore, it would also be interesting to look into the  
525 effects of a repeated pairing of phobic stimuli with high working-memory load since the  
526 repeated exposure to phobic stimuli paired with reduced amygdala activity and reduced  
527 fear might facilitate fear extinction. In support of this idea, it has recently been shown that  
528 extinction learning can be improved in states of reduced amygdala activity (de Voogd et  
529 al., 2018). Thus, our findings might contribute to the development of novel psychological  
530 treatment approaches aimed at reducing fear in anxiety disorders.

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## 534 **7 Disclosures**

535 The authors report no financial interest or potential conflicts of interest.

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716

717 **9 Tables**

	Neutral pictures		Snake pictures	
	0-back	2-back	0-back	2-back
Accuracy	0.97 (0.03)	0.86 (0.07)	0.97 (0.04)	0.88 (0.07)
d-prime	3.57 (0.4)	2.39 (0.58)	3.62 (0.48)	2.51 (0.73)

718 **Table 1:** n-back performance (accuracy, d-prime): mean and standard deviation (in brackets).

Emotion ratings	Snake pictures			<i>t</i>	<i>p</i>	$R^2_{\beta^*}$
	0-back	2-back	2back - 0back			
Fear	62.14 (17.13)	60.47 (16.52)	-1.68 (3.95)	-2.78	.008*	0.01
Disgust	69.09 (17.59)	66.95 (17.05)	-2.14 (4.39)	-3.19	.003*	0.02
Mood	62.78 (12.09)	62.18 (12.43)	-0.59 (4.52)	-0.86	.39	0.00
Valence	65.93 (11.74)	65.03 (11.00)	-0.90 (3.71)	-1.59	.12	0.01
Arousal	64.68 (15.75)	63.46 (15.46)	-1.22 (5.03)	-1.59	.12	0.01

719 **Table 2:** Effect of load on emotional ratings of snake picture during n-back task; depicted are mean  
720 and standard deviation (in brackets) of each condition, as well as the difference score used in the one-  
721 sample t-tests. Statistical effect of load derived by one-sample *t*-tests indicated by *t*-values (*t*) and nom-  
722 inal *p*-values (*p*). Effect sizes are indicated by  $R^2_{\beta^*}$ . For information on neutral pictures, see supplemen-  
723 tary material Table S2.

Cluster no.	Max. <i>t</i> -value within cluster	Regional correspondence of maximum	MNI coordinates at maximum			No. of voxels
			X	Y	Z	
1	-8.06	Left-Amygdala (53%)	-22.5	-10	-15	66
2	-6.71	Right-Amygdala (86%)	22.5	-7.5	-15	44
3	-10.64	ctx-lh-rostralmiddlefrontal (57%)	-47.5	25	33	417
4	-11.05	ctx-rh- rostralmiddlefrontal (54%)	45	30	39	147

724 **Table 3:** Peak activation in VOIs extracted for DCM from the load contrast (0-back – 2-back) of the  
725 group-level analysis. Regions and probabilities are in accordance with population-specific atlas. ctx:  
726 cortex, lh: left hemisphere, rh: right hemisphere.

Parameter values (left hemisphere)				
Direction of connection	dlPFC to amygdala		amygdala to dlPFC	
Strength of intrinsic connectivity	-0.019 (0.019)		0.020 (0.012)	
	0-back	2-back	0-back	2-back
Change in connection strength (modulators) per condition	-0.002 (0.021)	-0.200 (0.067)	-0.015 (0.012)	0.003 (0.012)
Total connectivity	-0.021 (0.095)	-0.219 (0.067)	0.005 (0.020)	0.023 (0.019)

727 **Table 4:** BMA parameter values across all 34 subjects in the left hemisphere: mean and SEM (in brackets).  
728

Parameter values (right hemisphere)				
Direction of connection	dlPFC to amygdala		amygdala to dlPFC	
Strength of intrinsic connectivity	0.014 (0.047)		0.075 (0.050)	
	0-back	2-back	0-back	2-back
Change in connection strength (modulators) per condition	0.056 (0.031)	-0.316 (0.078)	0.006 (0.011)	0.005 (0.024)
Total connectivity	0.071 (0.064)	-0.301 (0.110)	0.081 (0.053)	0.080 (0.040)

729 **Table 5:** BMA parameter values across all 34 subjects in right hemisphere: mean and SEM (in brackets).  
730

# Supplementary Material

## 1 Supplemental Text

### 1.1 Exclusion of subjects from further analysis

In total, we excluded four subjects from further analysis due to corrupted fMRI data: for two subjects, the study procedure was not carried out according to the protocol, for one subject the scanning session was accidentally interrupted and data was lost and one subjects displayed excessive head motions which resulted in poor quality of the imaging data. Additionally, one subject was identified as an outlier ( $> 2.5$  SD from sample mean) in the fear ratings of the snake pictures.

### 1.2 Preprocessing of eye tracking data

For each subject, fixation detection was done with an individual, velocity-based algorithm using the 'saccades' package (von der Malsburg, 2015). Fixations with duration of less than 100 ms and saccades were discarded for further analyses. Slow, drift-like displacements of the recorded fixation coordinates were corrected as follows: The value of correction was calculated for each timepoint as its displacement relative to a baseline, represented by a moving median with a window size of 3301 sampling points (approximately 55 s). This procedure is roughly familiar to high-pass-filtering at 0.008 Hz, but more appropriate for time domain encoded signals (Smith, 2013). Also not considered were trials with no detected fixations (assuming that at least one fixation had to be made to ensure picture encoding) and/or high signal loss (pupil aspect ratio  $< 0.5$  in over 50% of the picture data samples). Per subject and picture trial, the average dwell time was calculated within the 1.2 s of picture presentation and restricted to the region of interest (ROI). The ROI was manually defined for each picture as the region covered by the main object (e.g. a snake or a chair; opposed to the background of the

picture). In a next step, the subject-specific average dwell time was calculated separately for all conditions. If for a given condition, an average was based on less than 10% (10) of the theoretically available trials (96), it was not further considered. This led to the exclusion of a total of 5 subjects.

### **1.3 Segmentation of anatomical image and construction of population-average anatomical probabilistic atlas**

Each participant's anatomical image was automatically segmented into cortical and subcortical structures using FreeSurfer v5.3.0 (Fischl et al., 2002). Labelling of the cortical gyri was based on the Desikan-Killiany atlas (Desikan et al., 2006), yielding 35 cortical and 7 subcortical regions per hemisphere.

The segmentations were used to build a population-average probabilistic anatomical atlas. Individual segmented anatomical images were subsequently normalized to the study-specific anatomical template space using the subject's previously computed warp field, and affine-registered to the MNI space. Nearest-neighbor interpolation was applied in order to preserve labeling of the different structures. The normalized segmentations were finally averaged across all 43 subjects in order to create a population-average probabilistic atlas. Each voxel of the template could consequently be assigned a probability of belonging to a given anatomical structure.

## 2 Supplemental Tables

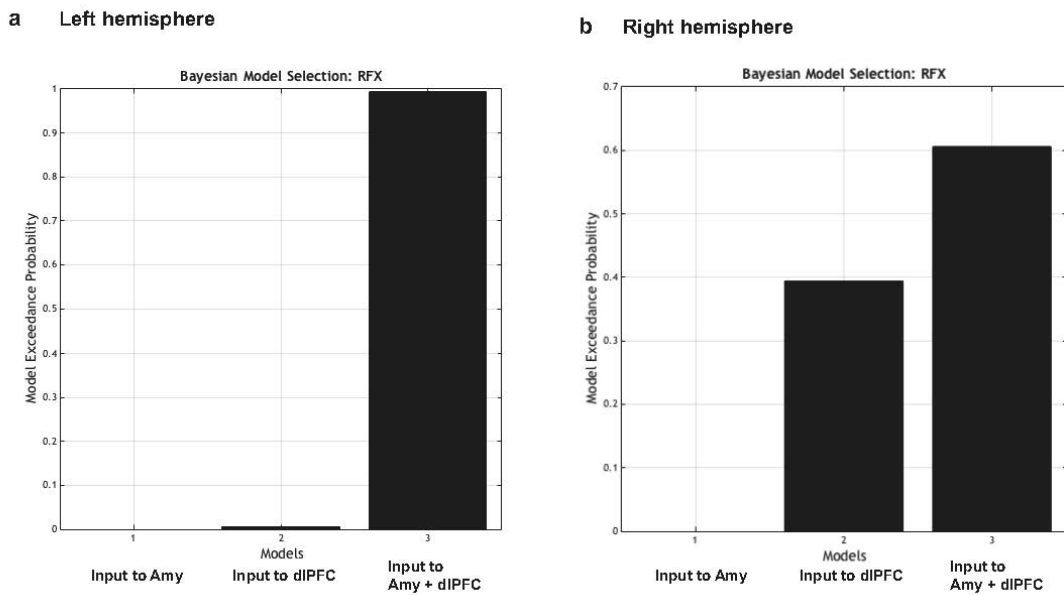
	Neutral pictures	Snake pictures
Valence	51.39 (4.86)	40.28 (12.71)
Arousal	25.67 (7.7)	54.90 (11.45)

**Table S1:** Selected pictures based on normative ratings from GAPED and IAPS (rating scores of IAPS pictures were transformed to GAPED scales): mean and standard deviation (in brackets).

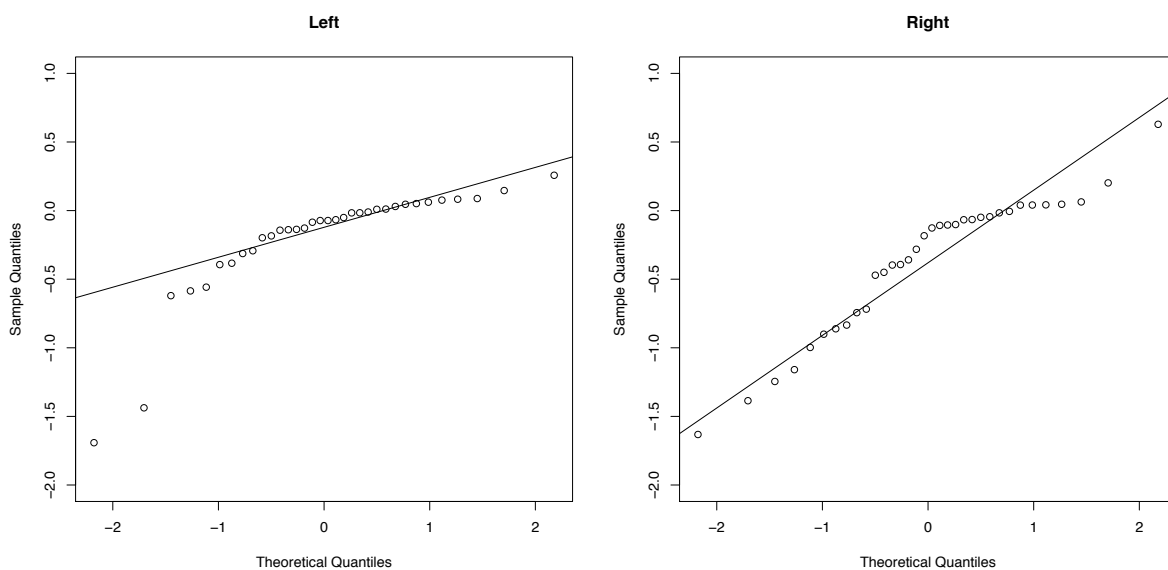
Emotion ratings	Neutral pictures			<i>t</i>	<i>p</i>	$R^2_{\beta^*}$
	0-back	2-back	2-back - 0-back			
Fear	8.87 (8.92)	11.42 (10.46)	2.56 (6.67)	2.51	.016*	.03
Disgust	7.94 (7.70)	9.35 (8.78)	1.41 (5.62)	1.65	.11	.01
Mood	29.87 (14.80)	31.84 (15.55)	1.97 (7.72)	1.67	.10	.01
Valence	30.87 (12.69)	32.33 (14.49)	1.45 (6.64)	1.43	.16	.01
Arousal	20.98 (14.66)	23.33 (14.50)	2.36 (6.84)	2.26,	.029	.02

**Table S2:** Effect of load on emotional ratings of neutral pictures during the n-back task; presented are mean and standard deviation of each condition, as well as the difference score used in the one-sample t-tests. Statistical effect of load derived by one-sample *t*-tests indicated by *t*-values (*t*) and nominal *p*-values (*p*). Effect sizes are indicated by  $R^2_{\beta^*}$ .

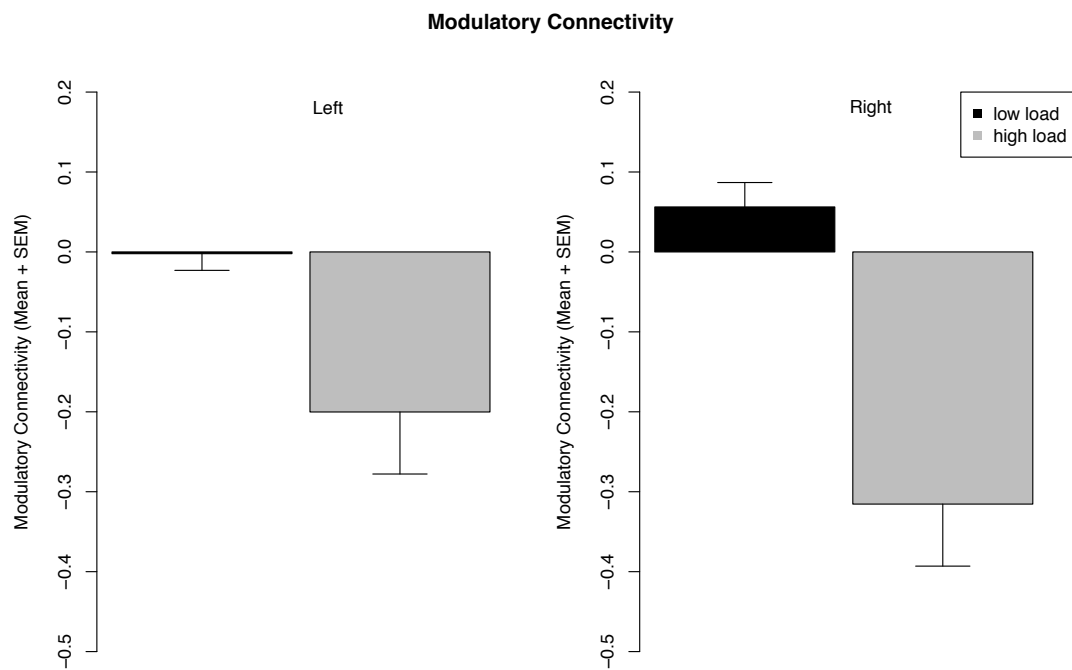
### 3 Supplemental Figures



**Figure S1:** Model comparison: model exceedance probability. Comparison between the three models, representing competing input possibilities to the network in (a) left hemisphere ( $N = 34$ ) and (b) right hemisphere ( $N = 34$ ). Left hemisphere: (1) input to amygdala (0); (2) input to dIPFC (0.0050); (3) input to both amygdala and dIPFC (0.9950). Right hemisphere: (1) input to amygdala (0); (2) input to dIPFC (0.3946); (3) input to both amygdala and dIPFC (0.6054).



**Figure S2:** QQ-plots depicting the distribution of connectivity parameters (2-back - 0back) for the left and the right hemisphere, respectively.



**Figure S3:** Change in effective connectivity from the dlPFC to the amygdala during 0-back and 2-back and for the left and right hemisphere. Mean and SEM are displayed.



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## 5 Discussion

Emotionally arousing experiences can substantially impact what we remember by enhancing or impairing different stages of memory formation and retrieval. The aim of this thesis was to add to the knowledge on how emotional arousal and memory processes are integrated in the human brain by using data from our own large-scale fMRI study in two different ways. In the publication “Predicting emotional arousal and emotional memory performance from an identical brain network” (Loos et al., 2019) we took on an exploratory machine learning approach to identify patterns of brain activation predictive for the perception as well as the retrieval of negatively arousing compared to neutral stimuli. The second publication “Working memory intervention acutely decreases amygdala activity and phobic fear” (Loos et al., submitted) adopted a hypothesis-driven approach based on previous findings from a large-scale sample to investigate the effects of a demanding WM task on amygdala activity and phobic fear in a second smaller sample. This second study intended to translate findings from basic research into the clinical context. In the following, both publications will be discussed separately with regard to their contribution to the already existing literature on arousal-memory interaction. In addition, possible clinical implications will be highlighted.

In the first publication (Loos et al., 2019) we used multi-voxel pattern analysis as well as univariate analysis to investigate whether subjects’ perceived arousal during encoding as well as their later memory performance at recognition can be predicted based on activation in the same network of brain regions. Even though the research on the effects of arousal on episodic memory has a long history and several brain regions have been identified to be involved in the encoding and retrieval of emotional memories, most studies so far have used traditional mass-univariate analysis in pre-defined regions of interest (ROIs) or on whole-brain level. Only recently, researchers have started to deploy MVPA to look at distributed patterns of brain activity associated with certain emotional states, thereby overcoming the assumption that emotions are represented in form of separate functional units (for a review, see Kragel & LaBar, 2016). Most fMRI studies on emotion processing have used MVPA to identify activity patterns that distinguish between certain discrete emotions like anger, fear or happiness (Kassam, Markey, Cherkassky, Loewenstein, & Just, 2013; Kragel & LaBar, 2015; Saarimäki et al., 2018). With regard to affective dimensions, two prior studies have reported that the perceived emotional valence of stimuli can be successfully predicted from subjects’ brain activation patterns (Chang, Gianaros, Manuck, Krishnan, & Wager, 2015; Chikazoe, Lee, Kriegeskorte, & Anderson, 2014).

Our findings add to the already existing literature on the decoding of emotional states in several regards. First, we could successfully predict perceived emotional arousal based on underlying brain activity patterns during encoding, which had not yet been reported before. Second, we found that the same pattern, or network, of voxels was also predictive for memory performance during later recognition of the same stimuli. Hence, we could demonstrate that both processes, arousal perception and episodic memory performance, seem to rely on the same brain network which mainly comprised the occipital and parietal cortex, the OFC as well as the amygdala. Additional univariate analysis also revealed activity in the hippocampus to be associated with arousal perception at encoding and memory performance at recognition.

It has been suggested that brain regions active during the encoding of stimuli get re-activated during the retrieval of those stimuli and that this renewed activation supports successful memory (Kim, Daselaar, & Cabeza, 2010; Nyberg, Habib, McIntosh, & Tulving, 2000; Rugg, Johnson, Park, & Uncapher, 2008; Wheeler, Petersen, & Buckner, 2000). With regard to the retrieval of emotionally arousing stimuli in particular, reactivation has been observed primarily in the amygdala, the hippocampus, the OFC/mPFC and in regions of the occipital cortex (for a review, see Buchanan, 2007; Dolcos et al., 2005; Hofstetter, Achaibou, & Vuilleumier, 2012; Kark & Kensinger, 2015; Smith et al., 2004), which is in line with the findings we report in our publication. The prominent clusters of predictive voxels that we found in the occipital cortex mirror previous observations that visual areas are engaged particularly in the perception of negatively arousing stimuli compared to neutral stimuli (Hofstetter et al., 2012; Lang et al., 1998; Mickley Steinmetz & Kensinger, 2009). This increased activation could be explained by an enhanced visual attention towards arousing stimuli, possibly mediated by the amygdala, which in turn influences later memory of those stimuli (Mather & Sutherland, 2011; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008).

Our findings may have potential implications for further clinical research. Activations in the identified predictive regions, particularly in the amygdala and the medial PFC, have been found to be dysfunctional, for example, in patients with PTSD (VanElzakker et al., 2018). However, fMRI research on PTSD patients has mainly reported findings on group-level even though it has been argued that group-level analyses are generally not sensitive enough to be of use for clinical purposes. This is because these analyses do not provide enough information about individual subjects which would be useful for better a diagnosis or treatment of psychiatric disorders (Calhoun et al., 2017). MVPA in contrast allows to make predictions on an individual level. In this regard, our findings in healthy subjects might contribute to future research on

PTSD. In our study, we identified a network of brain regions that was predictive for the perceived strength of arousal and emotional memory performance, two processes heavily disrupted in this disorder. Future studies should therefore investigate whether activation differences in our observed network might, for example, be predictive for PTSD symptom severity, particularly with regard to hyperarousal and memory deficits. Only one recent study so far applied MVPA to successfully predict classification of patients with PTSD, patients with a dissociative subtype of PTSD and healthy controls based on their brain activation pattern during resting-state (Nicholson et al., 2018). Similar to regions in our network, activity in the OFC, vmPFC and superior parietal lobe was found to be most predictive for diagnosis. In addition to conducting more cross-sectional studies that apply MVPA, longitudinal designs using MVPA are of great importance to identify changes in brain activity over time that may predict the onset of a mental illness.

While Loos et al. (2019) demonstrates the benefits of exploratory analysis of big data, it does not argue against the value of hypothesis-driven research projects. In fact, exploration-based projects should rather be regarded as complementary approaches that support the development of novel hypotheses, which can consequently be tested in smaller, targeted studies. This procedure was applied in the second publication of this thesis (Loos et al., submitted). Here, preliminary findings in healthy young subjects from our large-scale fMRI study as well as from another conducted pilot fMRI study suggested that high cognitive load, induced via a demanding WM task, reduces activity in the amygdala. Based on these findings, we conducted a new hypothesis-driven fMRI study that aimed at translating those previous findings into a clinical context.

In this study, subjects reporting fear of snakes engaged in a pictorial n-back task during which pictures of snakes and neutral objects were presented under high (2-back) or low (0-back) WM load. We were able to replicate initial findings that amygdala activity is reduced during high compared to low WM load also in highly fearful subjects. Engaging in a demanding WM task recruits especially lateral PFC regions, which have been suggested to exert top-down control on limbic regions possibly to prevent emotions to interfere with goal-directed behavior (Erk et al., 2007; Okon-Singer et al., 2015; Van Dillen & Koole, 2007). Most fMRI studies that have found dampened amygdala activation during demanding cognitive tasks, however, provide only correlational evidence for a regulatory effect of the lateral PFC. Using DCM analysis, we could demonstrate that the dlPFC exerts an inhibitory influence on the amygdala during high WM load in both hemispheres, thus providing further evidence for the postulated top-down control of lateral prefrontal regions. Only one other recent study has demonstrated such

a load-dependent inhibition of amygdala activity by the dlPFC using another effective connectivity measure (psychophysiological interaction analysis) during a WM task (de Voogd et al., 2018). The inhibitory influence from the dlPFC on the amygdala, however, is probably exerted via indirect pathways because the dlPFC does not possess direct anatomical connections to the amygdala (Kim et al., 2011). Such an indirect pathway could for example lead via the vlPFC. Increased activity in this region has repeatedly been found to be negatively correlated with amygdala activity during emotion regulation tasks (Kohn et al., 2014; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008) and is said to be the only lateral PFC region with direct inputs to the amygdala (Ray & Zald, 2012).

Most importantly, in addition to these neuroimaging results we observed that high WM load also acutely decreased perceived fear and disgust towards snake pictures in our study population. This finding is critical because a mere decrease in amygdala activity during high load that is not accompanied by subjectively perceived reduction in fear or disgust would be of limited use in a clinical context. However, we could not demonstrate that the decreased amygdala activity was directly correlated with the decreased fear but only observed both effects independently of each other. In addition, with our study design we cannot completely disentangle whether the reduction in amygdala activity and perceived fear can be explained by the inhibitory top-down influence of the dlPFC alone. As cognitive resources are generally limited during task performance, another explanation for the observed effects could be that engaging in a demanding task consumes most of cognitive resources leaving little capacity for an adequate processing of emotional information, reflected in decreases in amygdala activity and fear. This would be in line with studies reporting that during high cognitive load, emotional distractors usually do not interfere with task performance because attention is fully focused on performing the difficult task (Gupta, Hur, & Lavie, 2016; Vytal et al., 2012). In turn, performance is usually hampered under low load because emotional distractors can grab attention more readily as more resources are available. However, in our study, WM performance was neither impaired under high nor under low load. One explanation for this could be that in our task the emotional pictures served as targets and not as task-irrelevant distractors and therefore could be fully attended (Erk et al., 2007; Mather & Sutherland, 2011). This further suggests that enough cognitive resources were available to attend both the task and the emotional stimuli because attention was not divided. However, telling apart whether those load-dependent neuronal and behavioral effects are due to limited cognitive resources, a top-down inhibition or both, needs further investigation.

Despite these limitations, our finding that engaging in a demanding WM task acutely decreases amygdala activity and phobic fear and disgust might be of relevance for the clinical practice. For instance, strengthening the prefrontal network through continuous WM training has been shown to improve emotion regulation in healthy subjects (Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). Hence, practicing our WM task over several days or weeks, thereby enabling a continuous confrontation with the fearful stimulus in combination with inhibited amygdala activation, could have long-term effects on fear reduction. This might prove useful for developing new treatment approaches for patients with anxiety disorders like specific phobia or PTSD who suffer from high arousal states due to a hyperactive amygdala. In addition, our task could also be combined with neurofeedback. It has been demonstrated that neurofeedback helped to voluntarily down-regulate activity in the amygdala in healthy subjects (Paret et al., 2016) as well as in patients with PTSD (Nicholson et al., 2017). Nicholson and colleagues further reported an increased functional connectivity between amygdala and lateral PFC regions during successful emotion regulation. Hence, demonstrating to patients via neurofeedback that engaging in a highly demanding WM task decreases amygdala activity could support those patients in controlling their fear more effectively. Further studies on patients with anxiety disorders are therefore needed to evaluate the use of WM trainings for therapeutic purposes.

Taken together, the two publications presented in this thesis extend the literature on the interplay between emotional arousal and memory processes in several regards. First, the reported findings are based on sufficiently powered studies, which was ensured using large-scale data and conducting power analyses. So far, most reported fMRI findings on emotional memory processes used rather small sample sizes thereby reducing the chance of their results being robust and reproducible. Second, because we used big enough sample sizes, we were able to use them to predict behavior in independent samples or to replicate our findings in independent studies. In Loos et al. (2019), the identified predictive brain network could be applied to a separate independent subsample taken from the same study population. In Loos et al. (submitted), we could replicate findings on reduced amygdala activity during high WM load observed in previous pilot studies and by other research groups. At the same time, we could extend our neuroimaging findings to a population of highly fearful subjects and moreover could demonstrate effects on a behavioral level. Finally, the publications demonstrate how large-scale fMRI data can be used for undertaking exploratory as well as hypothesis-driven approaches to extend the findings of previous research and to bridge the gap between basic and clinically oriented research.

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## 7 Declaration by candidate

I declare herewith that I have independently carried out the PhD thesis entitled "The interplay between emotional arousal and memory processes – from large-scale to translational fMRI studies". This thesis consists of original research articles that have been written in cooperation with the enlisted co-authors and have been published in peer-reviewed scientific journals or are in preparation for publication / submitted for publication. Only allowed resources were used and all references used were cited accordingly.

Date: \_\_\_\_\_

Signature: \_\_\_\_\_