Memory function after stress : the effects of acute stress and cortisol on memory and the inhibition of emotional distraction

Oei, N.Y.L.

1

General introduction

General Introduction

When stressed, our body secretes many hormones - specifically stress hormones, "glucocorticoids" (cortisol in humans) - which purpose is not always clear (Sapolsky, Romero, & Munck, 2000). Many of these hormonal effects can be interpreted in the context of adapting to stress, or preparing for future stress, as it is generally agreed upon, that the stress response is aimed at protecting against threats to homeostasis. Stress hormones also affect memory. For instance, glucocorticoids strengthen the laying down of memories, so that emotional events are remembered better than neutral events (Lupien & McEwen, 1997; Wolf, 2003). Sapolsky and colleagues (2000) wrote in their review on the effects of glucocorticoids in a paragraph on memory: "*It seems apparent that sharpening memory (…) is a valuable response to a stressor, in that it aids the recall of behaviors that worked previously, as well as the consolidation of memories meant to avoid this stressor in the future. In that regard, the enhancement of memory processes during the early stages of responding to a stressor can be viewed as logical and salutary*." However, one of the first experiments in healthy humans studying acute[1] effects of stress by, showed that administering a single dose of stress hormones specifically impaired the retrieval of long term memories (de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000), a finding that contrasted with the known memory-enhancing effects of acute stress (McGaugh, 2000; McGaugh, Cahill, & Roozendaal, 1996).

At first glance, an interpretation of this finding could be that high cortisol levels blocked the retrieval of "unnecessary" neutral memories, while "emotional" memories[2] might be more easily accessed (this still had to be

[1] "Acute" stress in laboratories generally refers to single, mostly short-term inductions of stress, for instance by delivering 20 minutes of social stress, or administering one dosis of stress hormones. "Chronic" stress refers to ´long-term´ stress, such as daily stress hormone administration for an entire week, but also hormone infusion for several hours.

[2] The division into "neutral" and "emotional" can be operationalized as more "semantic" memories (e.g., the word "ape" in a word list learned yesterday) and "episodic" memories, which have arousing properties by association (e.g., the word "rape" in a wordlist). However, another – more ecologically valid- division has been proposed (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006) in which cortisol effects on memory specifically concern context-relevant information, while irrelevant information processing (and retrieval) is overruled, regardless of its objectively "neutral" or "emotional" property.

investigated). Under acute stress this would be adaptive, but could turn into maladaptive when chronically stressed. Hence, high cortisol levels might explain why some people develope "traumatic memory"[3]. At about the same time, researchers in Germany administered varying high doses of stress hormones to accident victims in septic shock, a standard ER procedure, and the highest doses appeared to have preventive effects on post traumatic stress disorder (PTSD) (Schelling et al., 2001; Schelling, Roozendaal, & de Quervain, 2004b). Although these studies seemed unrelated, and even contradictory, the notion of beneficial "side-effects" of cortisol administration on (traumatic) memory emerged. Following the Quervain, and others, many stress experiments in healthy humans tried to elucidate the neurobiological mechanisms underlying (traumatic) memory retrieval using neutral and emotionally negative stimuli in their design. If administering stress hormones would not only impair retrieval of neutral memories, but would also lead to diminished excessive memory retrieval of traumatic memories, it might be useful as a treatment for traumatic memory (de Quervain & Margraf, 2008).

Apart from cortisol effects on memory retrieval, administration of cortisol was also found to lead to impaired "short-term memory retrieval", i.e., working memory (Lupien 1999), which is the ability to keep information in mind for a short time. Lupien´s finding that cortisol induced WM impairment, had at least two consequences: it broadened the discussion on the neurobiological

[3] The term "traumatic memory" refers to memories of traumatic events in life, that are of an intrusive, highly disturbing and pervasive nature. Because the event itself had been highly stressful, e.g., witnessing death, it was suggested that extreme stress –and the substantial secretion of (stress) hormones- at the time of the event had affected the way memories were processed (van der Kolk, 1994). However, this line of reasoning was not confirmed by evidence. For instance, stress hormone levels of rape victims just after the event, were not always extremely high (Resnick, Yehuda, & Acierno, 1997), and also these stress levels were lower in women with a history of prior assault, than in women without, and they also had a higher probability of developing posttraumatic stress disorder (PTSD) which is characterized by "traumatic memory" (Resnick, Yehuda, Pitman, & Foy, 1995). Also, accident victims that had intermediate -instead of high- cortisol levels right after traumatic event, were more likely to develop PTSD than those with high stress levels of cortisol (Ehring 2008). Findings like these are indicative of the individual variety in basal levels of stress hormones, and the variety in stress hormone responses, from adaptive to maladaptive, that might have originated in the history of each individual's stressful life events. The stress response that was understood to return the organism to homeostasis, showed to be readjusted to prepare for future stress, which may ultimately lead to maladaptive adjustments in the stress response after chronic severe stress and even to alterations in the very brain structures that reset the stress response, such as the hippocampus (McEwen, 2007; Sapolsky et al., 2000).

mechanism by which cortisol exerts its effects. Especially the hippocampus[4] had received much attention as it is the crucial structure in memory formation and laying down of long term memories. After the finding of cortisol-induced impaired WM, however, the focus shifted towards the structure responsible for WM, the prefrontal cortex. Secondly, it was –again- quite puzzling what purpose WM impairments serve when one is acutely stressed.

The general aim of this thesis was to investigate the impairing effects of cortisol on memory retrieval, WM, and distracter inhibition. It should, however, be kept in mind that in memory and stress research, the word "impairment" not necessarily implies a maladaptive stress response, nor does "enhancement" necessarily deserves a favourable interpretation.

How stress affects memory

When a stressor is perceived, two stress-systems are activated to facilitate adaptive behavior. The first, an effect of the activation of the autonomic nervous system, is the locus coeruleus - noradrenergic (LC-NE) system, typically responsible for arousal and alertness, which activates noradrenergic cell bodies located in the LC to release noradrenalin from their axons throughout the brain, with projections to the hypothalamus, amygdala, and prefrontal cortex (Berridge & Waterhouse, 2003). The other stress-system that is activated is the hypothalamus-pituitary-adrenal (HPA) axis. The HPA axis refers to direct influences and negative feedback interactions between multiple organs, which controls physiological reactions to stress. Activation of the HPA axis leads to the release of glucocorticoids –the stress hormone cortisol - by the adrenal glands, which readily passes the blood-brain barrier and eventually enters the brain. In the brain, cortisol binds to mineralocorticoid (MR) and glucocorticoid receptors (GRs) in regions that are crucial for memory, such as the hippocampus (De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998; Lupien & Lepage, 2001; Sullivan & Gratton, 2002). GCs can produce direct –non-genomic- and long term effects, and can influence neuronal excitability (for instance, inhibition of long-term-potentiation), neuronal plasticity, dendritic remodelling, and neurogenesis

[4] Basal cortisol levels enhance forms of synaptic plasticity, thought to be underpinnings of learning, and enhance hippocampal excitability. Stress-levels of cortisol, however, show suppressive effects by disrupting these same actions, and chronic high cortisol levels even cause hippocampal cell death (which might explain that this structure appears to be smaller in patients with PTSD).

(Sapolsky et al., 2000). The differential effects of cortisol, once enhancing, once impairing, appeared to depend on the specific memory phase in which stress cortisol levels are acutely elevated[5]. For instance, a single dose of GCs delivered just after encoding, is related to enhanced declarative memory consolidation (Buchanan & Lovallo, 2001; Kuhlmann & Wolf, 2006a). In contrast, cortisol induced declarative memory impairments are mostly found during the retrieval phase, which means that cortisol administration took place after information was encoded and consolidated (de Quervain et al., 2000; Kuhlmann, Kirschbaum, & Wolf, 2005a; Roozendaal, 2002; Roozendaal, Okuda, de Quervain, & McGaugh, 2006; Roozendaal, 2003). Using imaging methods (position emission tomography, PET) during memory retrieval in healthy participants, De Quervain and colleagues showed cortisol-induced reduced blood flow in the medial temporal lobe (MTL), specifically the right parahippocampal gyrus (de Quervain et al., 2003). This was consistent with the idea that cortisol exerts its effects on memory retrieval by affecting the hippocampal region.

Although the involvement of the hippocampus in stress-related memory retrieval impairment was generally accepted, there were several reasons to also consider other brain regions in mediating the effects of cortisol on memory, specifically the prefrontal cortex (PFC) (Lupien & Lepage, 2001). Although especially the GR receptor was thought to be related to impaired memory, a more recent influential hypothesis (the MR-GR balance hypothesis, (De Kloet, Oitzl, & Joëls, 1999; see Oitzl, Champagne, van der Veen, & De Kloet, 2009, for current hypotheses on GC actions) posits that the MR-GR ratio determines whether GCs will have impairing effects: MRs are thought to provide a tonic influence on the HPA axis and act to decrease GR responsivity. Because the hippocampus mainly contains high levels of MR-receptors and low levels of GRs, which are preferentially distributed in cortical areas, especially the PFC, it was suggested that prefrontal-dependent memory should be even more sensitive to cortisol because the absence of MRs in the PFC would lead to greater GR-sensitivity (Lupien & Lepage, 2001). Apart from being densely packed with GRs, the PFC had shown to be involved in regulating the HPA axis, by

[5] "Phase differences" is maybe the simplest explanation for the enhancing and impairing effects of stress hormones, however, phases do not explain the differential and contrasting findings in effects of stress hormones on emotional and neutral material during different phases. Several other hypotheses have been proposed that might explain the diverse results, such as timing (Het, Ramlow, & Wolf, 2005), and convergence in time and space (Joëls et al., 2006). This latter hypothesis implies that memory is enhanced when information is related to the stressor (relevant information), and impaired when unrelated to the stressor (Smeets et al., 2009).

activating and inhibiting this stress-system (Cerqueira, Almeida, & Sousa, 2008; Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Sullivan & Gratton, 2002). Furthermore, stress-related psychiatric disorders, for instance posttraumatic stress disorder, are related to both HPA axis dysfunction and PFC dysfunctions (Elzinga & Bremner, 2002; Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003; Liberzon et al., 2007). Animal studies also revealed a relation between stress and PFC function. For instance, monkeys showed impairments in prefrontal mediated WM functions after stress (Arnsten & Goldman-Rakic, 1998; Arnsten, 2009; Arnsten, 2000). In addition, cortisol administration in healthy men was associated with WM impairment (Lupien, Gillin, & Hauger, 1999; Wolf et al., 2001a). Finally, using other techniques (than PET), event-related potential-studies and functional magnetic resonance imaging (fMRI) studies had shown numerous times that memory retrieval activated both MTL and prefrontal cortical areas, and that during both WM and memory retrieval these activated areas overlapped (Achim & Lepage, 2005; Buckner & Wheeler, 2001; Cabeza, Dolcos, Graham, & Nyberg, 2002; Konishi, Wheeler, Donaldson, & Buckner, 2000; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Ranganath & Paller, 1999; Ranganath & Paller, 2000; Ranganath, Cohen, Dam, & D'Esposito, 2004). fMRI has advantages compared to PET, such as better spatial resolution and the possibility to relate specific events to brain activation, which might explain why de Quervain and colleagues did not find cortisol effects in prefrontal areas. To corroborate and extend the finding of de Quervain and colleagues (2003), we therefore used fMRI to investigate whether cortisol administration indeed affected brain activity in both hippocampus and prefrontal cortical areas during memory retrieval (see Chapter 2).

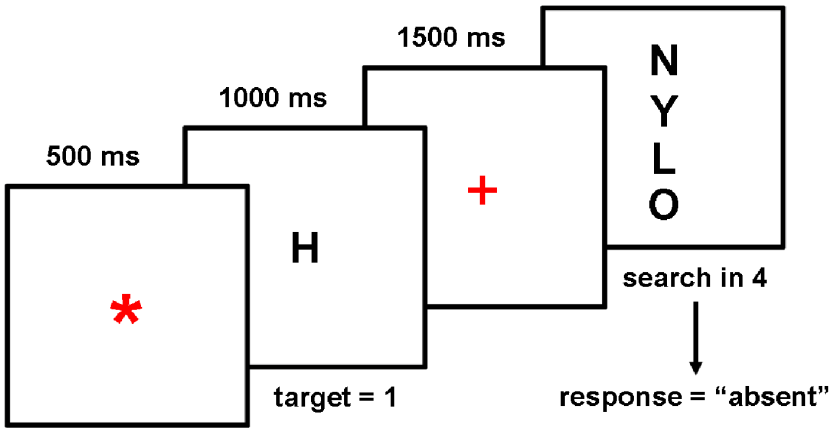
Effects of stress on working memory

So far, the modulation by cortisol of ("prefrontal dependent") WM and ("hippocampus dependent") memory retrieval, were separate findings (de Quervain et al., 2000; Lupien et al., 1999). In memory retrieval experiments that were published following the original experiment of de Quervain, cortisol-induced memory retrieval impairments were reported but seldom with concomitant WM decrements (e.g., Kuhlmann et al., 2005a). However, the WM task that was used by Lupien and colleagues, a Sternberg paradigm (Sternberg, 1966, 1969), was more complex, more difficult, and of much longer

duration, than the standard WM task used by others, the Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1997). The Digit Span task takes no more than 5 minutes, and consists of having to repeat digits, that are first called out loud by the experimenter, ranging from 1 or 2 digits, to a string of digits with a maximum of 8 to 10 (Experimenter: "8….7….5". Participant: "8,7,5").

The backwards variant (Experimenter: "8….7….5". Participant: "5,7,8") is considered a measure of WM manipulation, and is somewhat more difficult than the forwards variant. At least once an impairing effect of cortisol administration was reported using Digit Span backwards (Wolf et al., 2001a). In contrast, the item recognition (WM) used by Lupien took 20 minutes and consisted of 300 trials. This Sternberg-paradigm variant is a high speed task, in which a typical trial consists of 3 stages: 1. target-display (one to four target letters were shown for 1 second), 2. delay interval (in which target letters had to be held in memory for 1,5 sec), and then 3. recognition display (containing 2 to 4 letters, of which only one had, or had not, been shown in the target display). In the recognition phase, one has to respond as fast as possible. This task comprised 8 different "loads", from low easy ones (see Figure 1), to high difficult ones (see Figure 2).

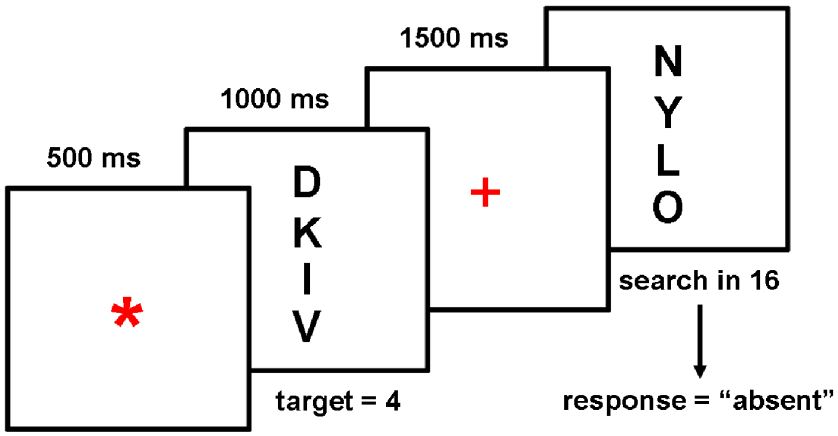
Figure 1. **Example of task trial with low (comparison) load**



Lupien and colleagues (1999) first infused different doses of hydrocortisone (cortisol) or placebo in young healthy men and assessed WM. They found that the highest dose affected WM at high comparison loads, indicated by slower

reactions times for high as compared with low comparison loads. It could be that cortisol only impaired WM when load was high, which might explain why no WM deficits were found using the easier WM task. Conversely, the idea that WM is more sensitive than declarative memory (see the title of Lupien et al., 1999), was born because the declarative task was not memory retrieval of pre-stress encoded and consolidated information. Therefore, in Chapter 3 we adapted Lupien´s task, and investigated whether elevated cortisol levels after (social) stress would impair both memory retrieval ánd WM at high loads.

***Figure 2*. Example of task trial with high (comparison) load**



The prefrontal cortex and interference in working memory

The definition of WM, keeping information in mind, for a short period of time (i.e., WM maintenance), also contains the implication, that irrelevant information has to be kept out of mind at the same time (´interference inhibition´). The relatedness of these concepts are well illustrated by the studies into the delay interval of WM tasks. The delay interval, between the target display and recognition, has been of special interest to many researchers ever since the discovery in single cell studies of consistent firing of PFC neurons during the delay interval of short term memory tasks (Fuster & Alexander, 1971).

The most influential explanation for this phenomenon was that it represented ´active maintenance´ of stimuli and could best be viewed as a reflection of information that is held ´on line´ (Goldman-Rakic, 1995). Imaging studies of healthy individuals also consistently demonstrated lateral PFC involvement in WM maintenance (Smith & Jonides, 1999).

However, in the past decade other explanations of the continued PFC activation have emerged (Miller & Cohen, 2001). One view is that the PFC is important for attentional selection, to actively keep in mind what is currently relevant information (de Fockert, Rees, Frith, & Lavie, 2001), or aiding in maintenance by directing attention to internal representations of sensory information (Curtis & D'Esposito, 2003). With event-related potentials it was shown that perceptual processing of distracting faces was attenuated due to attentional biasing favouring relevant stimuli (Sreenivasan & Jha, 2007). There is also evidence for suppression of irrelevant information (Jha, Fabian, & Aguirre, 2004). Top-down modulation would underlie this selection, through enhancement and suppression of resp. task-relevant- and task-irrelevant neural activity. For instance, WM deficits in healthy elderly people were shown to be related to impaired (attention-related) suppression of task-irrelevant distracters, while enhancement of relevant information was intact (Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Gazzaley et al., 2008). The question whether ´inhibition´ of distractions is attained through ´amplification´ of the neural representations of relevant stimuli in sensory cortices, or by suppression of irrelevant stimuli is, however, still unresolved (Aron, 2007; Gazzaley et al., 2005; Sreenivasan & Jha, 2007).

Another –related- view of the role of the PFC in WM is that it supports the mediation of interference in WM, through ´sensory gating´ (Chao & Knight, 1995; Postle, 2005; Postle, 2006). Evidence from lesion studies revealed that lesions in the PFC do not necessarily lead to impaired WM maintenance or storage processes (D'Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006; Muller & Knight, 2006). WM maintenance impairments arise when humans and animal with PFC lesions are in an environment with distractions, whereas in optimal circumstances (e.g., when kept in the dark), maintenance is undisturbed (Chao & Knight, 1998; Chao & Knight, 1995; D'Esposito et al., 2006; Muller & Knight, 2006). Moreover, in healthy individuals, the dorsolateral PFC is more active when distracters are shown in the delay phase of a WM task, than when nothing has to be remembered during the delay, while the inferior occipitotemporal shows the reverse effect (Postle, 2005). This down-regulation of sensory ´gain´, is possibly dependent on WM availability, and may be less efficient when WM

load is high. This might also explain why individuals with higher WM spans are more able to intentionally suppress intrusions and are less vulnerable to intrusions in general (Brewin & Smart, 2005; Schelstraete & Hupet, 2002).

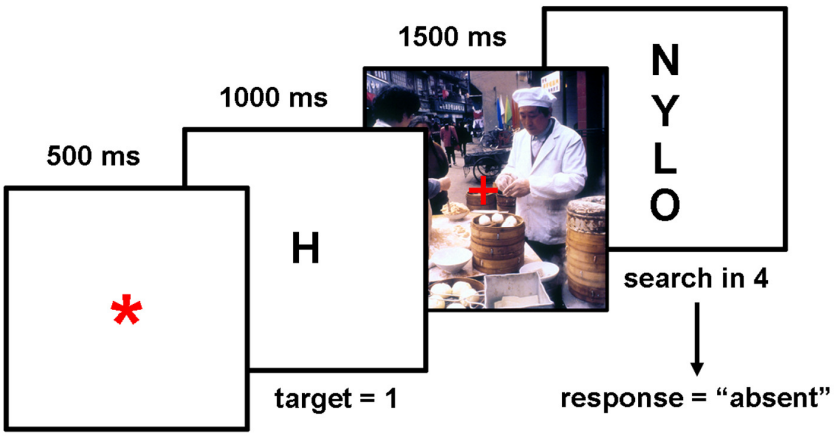
Several different PFC regions might be involved in mediating interference. In healthy individuals, distracters during the delay disturb dorsolateral PFC activity (Yoon, Curtis, & D'Esposito, 2006). The magnitude of PFC activity, however, was found to be significantly higher on correct trials than incorrect trials in dorsal and ventral areas of the PFC (inferior frontal gyrus: Dolcos, Kragel, Wang, & McCarthy, 2006; dorsolateral PFC: Sakai, Rowe, & Passingham, 2002). When congruent distracters are shown in the delay phase, i.e., from a similar category as the task-relevant targets at encoding (e.g., shoes), or distracters from an incongruent category (e.g. neutral faces), both dorsolateral and ventrolateral PFC activation were found (Dolcos, Miller, Kragel, Jha, & McCarthy, 2007; Jha et al., 2004). Activity in the ventrolateral PFC was modulated by distracter category with more activity when the distracter was from the same category than when it was not congruent to the target (Jha et al., 2004). However, human lesion supports the functional localization of inhibition to the right inferior frontal gyrus alone (Aron, Robbins, & Poldrack, 2004). Taken together, if stress and stress hormones impair PFC-mediated WM performance, its effects could be affecting WM maintenance, or interference inhibition. Or both.

To investigate whether stress and stress hormones affect WM performance when distracters are shown in the delay phase of the task, we took the same WM task as used in Chapter 2, but, instead of a fixation cross, we showed irrelevant distracting "neutral" and "emotional" pictures in the delay interval that had to be ignored while remembering the target letters (see Figure 3 this Chapter, and Chapters 4, 5, 6). The emotional pictures were highly ´negatively arousing´, which basically meant that they contained scenes of mutilated bodies, nasty injuries, and people held at gunpoint.

We were interested to see how cortisol administration would affect distracter inhibition in WM. We, however, did not exactly know what to expect. On one hand, given the cortisol-induced WM decrements at high loads, we expected that ´emotional WM´ would also deteriorate at high load. On the other hand, there was new evidence which showed that cortisol could have fear-reducing effects (Soravia et al., 2006) and reduced attention for emotionally negative distracters (Putman, Hermans, Koppeschaar, van Schijndel, & van Honk, 2007). These findings could imply that emotional distracters would be less distracting after cortisol administration than under placebo condition. Given this

contradictory evidence, it would not have been surprising if both contrasting effects would have canceled each other out (see Chapter 4).

***Figure 3*. Example of a low load trial, with neutral distracter.**



Emotional distracter interference in working memory

A study by Kensinger and Corkin (2003) showed how difficult to ignore emotional stimuli are. Their results show that (healthy) people perform faster in reaction times tasks when emotional pictures (or words) – compared to neutral ones- are relevant targets. In contrast, people perform slower, when they have to ignore emotional pictures. The explanation for this phenomenon -that emotional stimuli are more difficult to ignore- is that threatening (evolutionary relevant) stimuli, get prioritized processing, even under conditions of limited attention, and even if people are well aware that these stimuli are not relevant (Ohman, Flykt, & Esteves, 2001).

Functional imaging studies support the finding that emotional and neutral distracters are processed differently. When distracters in a WM task are emotional, a different pattern of neural brain activity emerges than when only neutral distracters are used. Ventral regions typically held responsible for emotional processing, such as the amygdala -which evaluates the emotional significance of stimuli- are more active, while regions associated with cognitive

processes, especially dorsal (higher parts) prefrontal areas are less active (Blair et al., 2007; Dolcos & McCarthy, 2006; Perlstein, Elbert, & Stenger, 2002). This inverse activation pattern of increased amygdala and inferior (lower parts) frontal gyrus (IFG) activation, and relative deactivation of the dorsolateral prefrontal cortex had shown to be associated with impaired WM performance (Dolcos & McCarthy, 2006; Dolcos, Diaz-Granados, Wang, & McCarthy, 2008). Moreover, connectivity analysis showed higher coupling between amygdala and IFG, when emotional distracters were shown, compared to neutral pictures (Dolcos et al., 2006). Studies using emotional distractions might be of particular relevance to understanding stress-related psychopathology, which is also characterized by increased emotional distractibility. We therefore sought to investigate whether stress would modulate the specific pattern of interaction of the dorsal and ventral system during emotional distraction (see Chapter 6).

Betablocker effects on emotional working memory

Although somewhat clueless about the effects of cortisol on emotional WM, the expectations of the effects of ´betablockers´ on the WM task with the neutral and emotional distracters were clear, as the task seemed to lend itself perfectly for modulation by betablockers. Like hydrocortisone, the drug propranolol –a betablocker-, normally prescribed to lower high blood pressure and often used by musicians to prevent stage-fright, is one of the drugs recently hypothesized to beneficially affect (the formation and retrieval of) traumatic memory and cognition (Cai, Blundell, Han, Greene, & Powell, 2006; de Quervain & Margraf, 2008; Pitman et al., 2002; Schelling et al., 2004b; Schelling et al., 2006). Propranolol blocks the actions of (nor)adrenaline, secreted by the first and fastest stress response ("fight-flight-fright"). Pharmacological studies in healthy humans consistently showed that propranolol reduces memory for emotional events and stimuli (see for a review Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006). Further, imaging studies showed that propranolol blocks the activity in the amygdala during emotional processing (van Stegeren et al., 2005). On the other hand, "neutral" WM processing was found to be deteriorated after propranolol administration many times (Chamberlain et al., 2006). Given the robust effects on emotional memory, we expected that propranolol would enhance WM performance, or at least - given the propranolol-induced WM

impairments - would reduce impairment by diminishing the distraction specifically by the emotional pictures shown during the task (see Chapter 5).

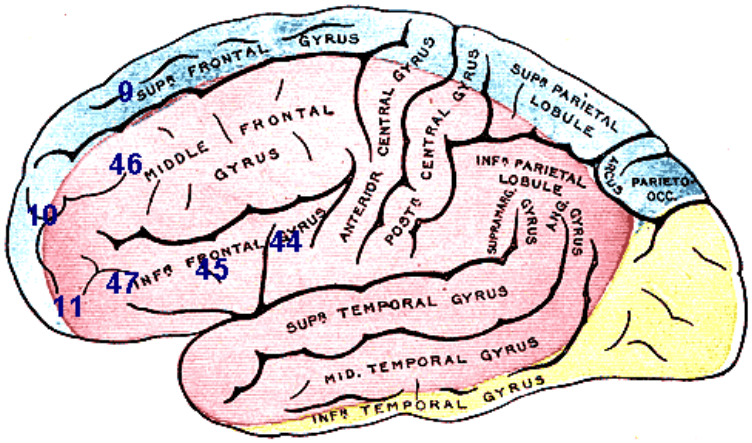


Figure 4. **Numbers refer to approximations of Brodmann areas, which are cortex regions based on its cytoarchitecture. 9 = contributes to dorsolateral PFC; 10 = most anterior part of the frontal lobe, a.k.a. frontopolar area 10; 11 = orbitofrontal area, medial part of the ventral surface of the frontal lobe; 44 = pars opercularis of the inferior frontal gyrus; 45 = pars triangularis of the inferior frontal gyrus; 46 = dorsolateral PFC, a.k.a middle frontal area 46; 47 = inferior prefrontal cortex, .a.k.a. orbital area 47.**
Reproduction of a lithograph plate from Gray's Anatomy, a two-dimensional work of art from the 20th U.S. edition of Gray's Anatomy of the Human Body, originally published in 1918 and therefore lapsed into the public domain.

Aims of the thesis

The aim of this thesis was to investigate the effects of stress - and the stress hormone cortisol - on memory retrieval, WM and emotional distraction during WM performance. In Chapter 2, a functional imaging study is described, in which it was investigated how cortisol (administration) affects brain activity during memory retrieval, and to see if cortisol – apart from the expected activation differences in the hippocampus - would also modulate prefrontal areas during memory retrieval. In Chapter 3, acute social stress was induced in young healthy men, to see whether stress (and cortisol) impairs both memory retrieval ánd WM, using the (more difficult) Sternberg paradigm. It was expected that WM would be impaired at high loads. In Chapter 4, the "neutral" Sternberg task was replaced with an "emotional" Sternberg WM task, to assess the effect of cortisol administration on the inhibition of neutral and emotionally negative distracters in WM. Chapter 5 describes the effects of administering propranolol

on the same task. It was expected that propranolol would specifically reduce emotional distractions, and consequently enhance WM. Finally, in Chapter 6, social stress was induced before performing the emotional Sternberg task inside the scanner to assess the effects of acute social stress on brain activity during emotional and neutral distraction in WM.