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

Oei, N.Y.L.

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Summary and general discussion

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This thesis comprises five experimental studies, aimed at investigating the impairing effects of a) stress (and cortisol) on memory retrieval and working memory (WM) (Chapter 2 and 3) and b) emotional distracter inhibition in WM (Chapter 4, 5, 6). In earlier studies by others, the administration of glucocorticoids impaired memory retrieval (de Quervain et al., 2000), and WM (Lupien et al., 1999). Whereas de Quervain and colleagues (2000) assumed that this cortisol-induced impairment was mediated by glucocorticoid receptors (GR) in the hippocampus, Lupien and colleagues (1999) proposed that ("prefrontal-dependent") WM would be more sensitive to cortisol than ("hippocampus-dependent") memory retrieval, given the high density of GRs and the absence of MRs in the prefrontal cortex (PFC) (see MR-GR balance theory (De Kloet et al., 1999; Lupien & Lepage, 2001). However, the PFC is also involved in memory retrieval, which suggests that cortisol affects memory retrieval by acting on both the PFC and the hippocampus. Therefore, it was hypothesized in the first study (Chapter 2), that the effects of cortisol on memory retrieval are mediated by the hippocampus as well as the PFC. To investigate this, 21 young men encoded neutral and emotional words, and were administered 20 mg hydrocortisone or placebo one hour later in a placebo-controlled randomized crossover experiment. Inside the MRI scanner, memory retrieval was tested. The results showed that administration of hydrocortisone decreased brain activation in both the hippocampus and the PFC during memory retrieval of neutral words (see Chapter 2). Other areas, such as the precuneus (in the parietal cortex) were also less activated after hydrocortisone administration. However, hydrocortisone administration did not significantly impair retrieval performance.

In Chapter 3, we hypothesized that cortisol would affect both WM and memory retrieval, and that cortisol-related impairment in WM and retrieval would be related. The underlying idea was that memory retrieval and WM both rely on the PFC and hippocampus, and that, if the PFC were especially sensitive to cortisol, both retrieval and WM would be impaired. To examine this, cortisol levels were raised in 20 healthy young men by inducing psychosocial stress in a randomized controlled crossover design. Then, WM was tested using the Sternberg paradigm and memory retrieval was tested by encoding moderately and highly emotional paragraphs one day before the stress induction. Results showed that stress impaired WM performance, especially when the task was

difficult. At high load, stressed individuals were slower and made more errors. Moreover, WM impairment was significantly associated with high cortisol levels. However, no robust stress-induced impairments in memory retrieval were found, although higher cortisol levels were related to impaired delayed recall of moderately emotional material. Also, impaired retrieval of moderately emotional paragraphs was related to impaired WM performance .

WM is not only defined by the ability to hold information in mind, but also by the ability to keep irrelevant information out of mind. Especially high cognitive load is assumed to consume the availability of cognitive control resources that are necessary to reduce interference from irrelevant stimuli (Lavie et al., 2004). The ability to reduce interference crucially depends on the PFC. We hypothesized that stress or cortisol might impair WM at high loads by decreasing the ability to suppress distracting irrelevant information. We tested this hypothesis by administering 35 mg hydrocortisone to 44 young, healthy male participants before testing WM in a randomized placebo-controlled between-subjects design (Chapter 4). This time, the Sternberg WM task contained neutral and emotional pictures interspersed as distracters in the delay phase of each trial. Unexpectedly, hydrocortisone did not impair performance on the "emotional Sternberg" task, but instead, *improved* performance especially when distracters were emotional.

Whereas the performance improvement after hydrocortisone administration was unexpected, we did expect improved WM performance, or increased distracter inhibition, after administering the betablocker ´propranolol´, which blocks the actions of (nor)adrenalin (NA). NA plays an important role in arousal states due to stress, and is known to mediate the amygdala response to emotional stimuli (Berridge, 2008). Propranolol has shown to reduce amygdala activity during processing of emotional stimuli and to diminish subsequent memory for these emotional stimuli (Strange & Dolan, 2004; van Stegeren et al., 2005). We therefore hypothesized that propranolol would improve WM specifically during emotional distraction, by reducing the impact of the emotional distracters. To investigate this, we administered 80 mg propranolol to 48 young, healthy men before performing the emotional Sternberg task in a randomized placebo-controlled between-subjects design (see Chapter 5). As expected, the administration of propranolol reduced the interference by emotional distraction at high WM load. An explorative analysis was also performed, because propranolol administration led to enhanced cortisol levels in half of the participants, and to no decrease in the other half, while in the placebo group the usual gradual decline in cortisol levels was observed. The analysis showed that

cortisol partially mediated the effects of propranolol, with better inhibition when cortisol levels were high, than when they were low.

In the last study of this thesis (Chapter 6), we aimed at investigating the neural effects of stress and cortisol on emotional distraction. In other studies using similar task paradigms, a typical neural pattern was observed during emotional distraction, with more activation in ventral "affective" brain areas, and relative deactivations in dorsal "executive" brain regions. We hypothesized that acute social stress might modulate this fronto-limbic activity. To examine this, 38 healthy men were included in a randomized controlled between-subjects design, in which they received psychosocial stress, or a control condition before performing the emotional Sternberg task inside the MRI scanner. Dorsal regions (the right dorsolateral PFC and bilateral parietal cortex), and ventral regions (right amygdala and bilateral inferior frontal gyri) were a priori chosen as regions of interest. Results showed that WM performance in stressed individuals was slower at trend levels, specifically when distracters were emotional. Moreover, emotional distracters also evoked more activity in the ventral "affective" system, specifically the right amygdala, and a marginally smaller (de)activation in the dorsal "executive" system after stress. No differences between the stress group and the controls – in brain nor behavior- were detected in response to neutral distractions. A higher cortisol response to stress was related to better inhibition of emotional distraction, and to less amygdala activation during emotional distraction.

The results of these studies will be discussed in the following paragraphs. Also, the limitations and implications of the present findings shall be described, as well as some more practical issues. To conclude, future directions will be given in investigating the effects of stress and cortisol on emotional distraction.

Cortisol and retrieval

Converging evidence from amnesia studies (e.g., Milner 1972, Squire 1992) and functional imaging studies (e.g., Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000) have well established that the hippocampus is important for memory retrieval. In addition, acute stress was found to impair declarative memory retrieval (Coluccia et al., 2008; de Quervain, Roozendaal, & McGaugh, 1998; de Quervain et al., 2000; Kuhlmann et al., 2005a, 2005b; Wolf et al., 2001a). Because glucocorticoid receptors (GRs), to which glucocorticoids (GCs) bind, are abundantly present in the hippocampus, stress effects on memory were

attributed to the actions of GCs in the hippocampus. GC actions, however, are contained by, or dependent on- the vicinity and saturation of mineralocorticoid receptors (MRs) that are also present in the hippocampus, and other more posterior and ventral brain areas (De Kloet et al., 1998; De Kloet et al., 1999). Because GRs are abundantly present in the frontal lobes, however, without the vicinity of MRs, it was suggested that GCs would have even greater impact on prefrontal functions than on hippocampal functioning (Lupien et al., 1999; Young et al., 1999). Following the same line of reasoning, we argued that – if the PFC were more sensitive to GCs, and given the fact that the PFC had consistently shown to be involved in memory retrieval (Buckner & Wheeler, 2001; Konishi et al., 2000; Ranganath & Paller, 1999; Lepage et al., 2000; Ranganath & Paller, 2000; Achim & Lepage, 2005) - stress might affect memory retrieval mediated by prefrontal areas, and not only by the hippocampus. We did find evidence for cortisol-related decreases in activation in the PFC and hippocampus (Chapter 2), which supported the idea that the effects of cortisol on memory retrieval are mediated by both PFC and hippocampus.

Diminished activation after hydrocortisone administration was, however, not restricted to those two areas alone, but was apparent in other brain areas as well, such as the parietal lobe. Under normal circumstances, concurrent activations in prefrontal and parietal lobes are found consistently, and are thought to be part of a "retrieval (success) network" (e.g., Konishi et al., 2000; Shannon & Buckner, 2004; Wagner et al., 2005). Moreover, the role of the lateral parietal cortex in memory retrieval was recently confirmed in a lesion study (Davidson et al., 2008; see for a review Olson & Berryhill, 2009). Also, connectivity studies show that BOLD fluctuations in the right (and left) hippocampus are functionally related to bilateral parietal cortices, which are also active during successful recollection (e.g., Vincent et al., 2006). Moreover, when memory performance is disrupted (for instance by divided attention), this interferes with recruitment of the entire memory network (Skinner, Fernandes, & Grady, 2009). It is therefore not unlikely that cortisol affects more parts of the retrieval network, either directly or indirectly. However, from our imaging data (Chapter 2) it cannot be determined whether cortisol administration specifically targets the hippocampal area, the PFC, or both, or another structure that, in turn, modulates hippocampus and prefrontal areas. It is also possible that the recruitment of overlapping brain areas indicates a common function like general cognitive control processes (e.g., Cabeza et al., 2002), that is affected by cortisol, or that it indicates that cortisol affects several brain areas –the retrieval network- simultaneously. In future research, a network-approach would be a very

interesting way to proceed to further unravel the effects of stress on memory retrieval, investigating possible changes in functional connectivity.

Practical issues when imaging retrieval

At this point, the study of De Quervain and colleagues (2003) and our study (Chapter 2) are the only ones that used imaging methods to examine the effects of glucocorticoid administration on memory retrieval. Unfortunately, on a practical technical level, both studies suffer from restrictions set by the imaging methods. fMRI has advantages in relation to PET, such as a superior spatial resolution and the option to time-lock specific event types. However, "true" delayed recall testing, as used in behavioral experiments (de Quervain et al., 2000; Kuhlmann et al., 2005a; Kuhlmann & Wolf, 2006b) can not (yet) be properly investigated using fMRI. This would require overt speech, which is known to cause head movement- and susceptibility artefacts which lead to corrupted activation maps containing false positives or signal loss (Kemeny, Ye, Birn, & Braun, 2005; Soltysik & Hyde, 2008). Using PET, delayed recall testing almost similar to behavioral experiments can be applied, however, with one pitfall: answers on the task can not be directly linked to the BOLD response, thus wrong answers can not be distinguished from right answers. What we can conclude from our fMRI study (chapter 2) is that hydrocortisone decreased activity specifically related to correct recall of neutral words in hippocampus and PFC, however, testing memory retrieval using a recognition paradigm. The study of de Quervain and others (2003) examined retrieval with a cued recall paradigm, which resulted in decreased right parahippocampal activation related to the entire process of cued recall, e.g., (attending to) the delivery of cue words, retrieving the right word from memory, selecting an answer, saying the chosen word out loud, and monitoring and reflecting upon these actions. Clearly, more studies of cortisol effects using imaging methods are necessary. It is also worth mentioning here that no studies have been published with hydrocortisone administration and WM.

Another pitfall in our study (Chapter 2) emerged from the canonical way functional imaging data is analysed, specifically when trying to investigate effects of emotional stimuli using an old/new paradigm. By subtracting the images collected while responding to emotionally negative old (= seen before) words with those of neutral old words, it was expected to find a difference with regard to the emotional aspect of the recalled words. The underlying assumption was

that new words (not seen before) would activate the brain regions involved with retrieval to a lesser degree than old words, as shown previously by others (e.g., Konishi et al., 2000). The contrast of emotional old words vs neutral old words, however, is built upon the contrasts ´old emotional word > new emotional word versus old neutral word > new neutral word´. New emotional words did evoke enough activation to cancel out the old/new contrast which also affected the higher order contrast, correct emotional vs neutral words. Thus, no reliable results could be produced to improve the understanding of cortisol and its differential effects on memory of emotional and neutral stimuli, as frequently observed in studies using behavioral measures.

Effects of stress on working memory and memory retrieval

To reiterate, there were many arguments implicating the hippocampus as critically involved in stress-induced memory retrieval impairment (Lupien & Lepage, 2001), and these same arguments implicated the involvement of glucorticoid receptors in the prefrontal cortex. This led to the suggestion that WM might be even more sensitive to disruption by glucocorticoids (Lupien et al., 2001). The findings of Lupien and colleagues (1999) that prefrontal-dependent WM is more sensitive than (hippocampus-dependent) declarative memory to the acute effects of corticosteroids (the title of the paper by Lupien), are not consistent with results from several subsequent studies showing that declarative memory retrieval after acute stress or GCs was impaired *without* concomitant WM impairments (e.g., Kuhlmann et al., 2005b; Tollenaar et al., 2009).

In an effort to reconcile these conflicting findings, we hypothesized that the contradiction was more apparent than real, and probably stemmed from the choice of tasks, either combining a too easy WM task, with elaborate retrieval tests, or a sensitive WM task with a debatable retrieval procedure (e.g., testing both memory encoding and retrieval following GC infusion instead of testing only retrieval of well-consolidated material after GC infusion). In Chapter 3, we reasoned that if memory retrieval and WM both recruit the prefrontal cortex and the hippocampus (Buckner & Wheeler, 2001; Cabeza, Locantore, & Anderson, 2003; Cabeza et al., 2002; Nyberg et al., 2003; Ranganath & Paller, 1999; Ranganath et al., 2003; Ranganath et al., 2004), and cortisol directly affects these brain structures, or indirectly via another structure, cortisol should affect both

retrieval performance and WM performance. As expected, the results from the study in Chapter 3 showed that social stress impaired WM at high loads, and that this impairment was related to cortisol levels. Retrieval was also associated with cortisol levels in the same direction: higher cortisol levels were associated with worse performance . However, here too, WM was more affected by stress than memory retrieval.

Although the findings that stress appears to have stronger effects on WM might be conceived as stronger evidence for the higher sensitivity of the PFC to stress, this may not be entirely true. The underlying assumption was that WM crucially depends on prefrontal- and not on hippocampal function, and hence that a stress or cortisol-induced impairment in WM would likely be mediated by the PFC. There are at least two indications, however, that these assumptions are not correct. Firstly, the assumption that ´prefrontal dependent´ WM does *not* critically depend on the hippocampus, stems from (MTL) lesion studies in which very easy (i.e., highly overlearned, familiar, and easy to rehearse) WM tasks were used, such as digit span (Cave & Squire, 1992; Zarahn, Rakitin, Abela, Flynn, & Stern, 2005), that probably do not depend on MTL involvement as much as less easy WM tasks. Secondly, there is mounting evidence that WM is associated with recruitment of the medial temporal lobes (Ranganath et al., 2004; Ranganath & D'Esposito, 2001; Ranganath & D'Esposito, 2005). Apart from the imaging studies that showed hippocampal activation during WM, new evidence sheds a clearer light on the function of the hippocampus during WM. Recent studies showed that the hippocampus becomes active in WM when the number of items, or the complexity of what has to be remembered, exceeds the limited capacity of short-term memory (Rissman, Gazzaley, & D'Esposito, 2008; Axmacher, Schmitz, Wagner, Elger, & Fell, 2008; Axmacher, Elger, & Fell, 2009).

Recently, the terms ´hippocampus-independent´- and ´hippocampus-dependent´ WM were coined (Axmacher et al., 2009), the former referring to single-item, low WM load, and the latter to multiple-item high WM load. The involvement of the hippocampus in WM maintenance (assessed with the Sternberg paradigm and measured with intracranial EEG and fMRI) showed to be load-dependent, with MTL *de*activations when single items served as targets (low load), and conversely, higher sustained neural activity in the MTL as loads increased and multiple items had to be maintained in memory (Axmacher et al., 2007). With load, an increasing MTL top down control of inferior temporal cortex (ITC, where representations are thought to be held) was found (Axmacher et al., 2008). Similarly, with functional connectivity analysis,

Rissman and colleagues (2008) showed that the connectivity between PFC (right inferior frontal gyrus, about BA 45) and the ITC was the strongest at low load, while at high load, this connectivity decreased. Conversely, when load was high, the connectivity between hippocampus and ITC, and between hippocampus and RIFG increased. These data suggest that the PFC-ITC circuit is progressively less engaged when more than one item has to be maintained, which is compensated by the involvement of another circuit, the hippocampus-ITC. In the light of these new exciting findings, studies reporting that stress or GCs affect WM maintenance only at high loads (Lupien et al., 1999; Oei et al., 2006), might be regarded as evidence for stress effects on specifically ´*hippocampus-dependent*´ WM functioning.

This interpretation of stress-induced WM impairment, of course, does not rule out that stress *does* affect PFC function. There is much evidence that stress affects the prefrontal cortex in both rat and human studies, using different methods and tasks or no task at all (Cerqueira et al., 2007; Wang et al., 2008; Kern et al., 2008; Liston, McEwen, & Casey, 2009; Qin et al., 2009). With regard to WM, theories on functional specialization proposed that for WM maintenance inferior frontal areas are recruited, while dorsal prefrontal regions are engaged when tasks demand ´higher´ executive control processes like manipulation and monitoring (e.g., D'Esposito, Postle, Ballard, & Lease, 1999). Overall activation patterns evoked with the emotional Sternberg task, which is a WM maintenance, indeed showed robust inferior frontal activations, while dorsolateral activations were less apparent (see Chapter 6). After stress, emotional distraction evoked less activation in the dorsal "executive" system, containing the dorsolateral PFC and parietal cortex (see Chapter 6), although this was an effect at trend levels. The use of WM tasks that call for stronger recruitment of dorsal "executive control" areas, such as the n-back task, which requests constant monitoring and updating of items held in memory, might provide stronger evidence for cortisol-induced (dorsolateral) prefrontal impairment (e.g., Schoofs et al., 2008; Qin et al., 2009), than the results of our own laboratory studies. However, as said before, it might be especially informative to investigate stress effects on the interactions between the several brain areas involved in WM, instead of focusing on just the dorsolateral PFC.

Practical issue when using crossover design with treatments

The stress study with WM and memory retrieval tasks (Chapter 3) illustrates the common investigator-knowledge that choice of task is essential, and that an absence of effects (of stress or cortisol) on the task, does not necessarily imply that there is no effect. Furthermore, this study lost much power to significant "treatment-order by learning effects", because stress first (or no stress first), influenced the learning curve. This forced us to ignore half of the data, since the data on stress effects were thus reliable on the first assessment only. The interaction effect of treatment-order by learning, however, was interesting as it was suggestive of a stronger stress-induced performance *improvement* when the WM task was first performed without stress, than when persons had to perform the task right after stress in the first place. Nevertheless, without a third group we do not know what the learning curve of practicing the task twice without stress (or twice with stress) would have been and consequently firm conclusions are precluded. As we used a cross-over design, which is -from a statistician's point of view- superior to other experimental designs, we can conclude that if you use treatments and tasks that improve with practice (as most WM tasks do), you can save yourself the trouble and expense of using a crossover design, or you should add a third group, as this will clarify *all* effects, even treatment-order by learning effects. Although we assessed the participants in this particular study 3 days in a row, using assessments two weeks apart, are unfortunately no guarantee that you will not be confronted with treatment-order by learning effects (see Chapter 2).

Effects of stress on emotional distraction

As described in a previous section, the mechanism by which cortisol might affect WM, was assumed to be mediated by GRs in the PFC. We therefore hypothesized that another aspect of WM, keeping irrelevant information out of mind, might be disrupted by stress (hormones) as well. One way of investigating this was by inducing social stress before performing WM tests (Chapter 3, Sternberg paradigm, Chapter 6, emotional Sternberg paradigm). The results of the experiments with stress-induction both showed WM impairment after stress. Stress particularly induced slower performance during emotional distraction (Chapter 6). At the neural level, impaired performance during emotional

distraction was preceded by a shift in brain activation from dorsal "executive" towards more activation in ventral "affective" brain areas. Stress especially strengthened amygdala and inferior frontal activation when emotional distracters were shown, while dorsal (prefrontal and parietal) activation was slightly smaller. Stress, however, is not synonym to cortisol, and it remains unclear which of the many actors in the stress cascade are responsible for the WM processes.

Cortisol and its relation to emotional distraction

Although stress impaired WM during emotional distraction, it appeared that enhanced cortisol levels, which is an important indication that one has actually been stressed, decreased distracter interference in an unexpected manner. We found that higher elevations of cortisol levels in stressed individuals were associated with *better* inhibition of emotional distractions (Chapter 6). Raising cortisol levels with the administration of hydrocortisone (Chapter 4) also led to improved inhibition of emotional stimuli to a level that was comparable to distraction by neutral stimuli. Even cortisol levels elevated after propranolol administration (equivalent to morning baseline cortisol levels ($M \pm SD = 8.78 \pm 5.49$ nmol/L) appeared to beneficially affect emotional distracter inhibition (Chapter 5). Moreover, cortisol was related to amygdala activation in an inverse way, with higher cortisol levels associated with smaller amygdala responses during emotional distraction. No correlation was found between cortisol and dorsal brain activation. The lack of correlation with dorsal activations, suggest that the impairing effects of stress using the present paradigm might be better explained by the actions of other mediating variables than cortisol, such as noradrenalin (Ramos & Arnsten, 2007), or dopamine which both are known to have strong inverted U curved influences on prefrontal functions (Arnsten, 2007).

The inverse relation between cortisol response and amygdala activity may seem surprising. Nonetheless, recent evidence is consistent with these findings. With use of another measure, the amplitude of diurnal cortisol, it was found that higher diurnal cortisol amplitudes (those with steeper slopes from morning to evening) were related to smaller amygdala responses to stressful pictures of the WTC attacks (Cunningham-Bussel et al., 2009). The slopes in cortisol amplitudes in patient populations have been characterized as flat, and the steep slope is considered the healthy one, with morning cortisol rises comparable to acute stress levels. It might be interesting to investigate whether the diurnal

cortisol amplitude ánd the cortisol response to acute stress are consistent in relation to amygdala responses to negative arousing stimuli.

In sum, it can be concluded from the findings in all three studies (Chapter 4, 5, 6), that a high cortisol response might cause better coping with interference from emotional distraction.

Limitations of the emotional distraction studies

The finding that hydrocortisone improved emotional distracter inhibition, might be explained in favour of the idea that 1) hydrocortisone improved WM, which consequently led to better inhibition of emotional distraction, or 2) hydrocortisone attenuated the influence of emotional distracters, which indirectly improved WM. Unfortunately, in none of the studies an (original) WM task was performed in addition to the emotional Sternberg task (chapter 4 ,5 and 6) it. So, regrettably, we can not be certain if the same dose of hydrocortisone would have led to impaired WM performance, without distracters. With regard to the first perspective, if improvement on the emotional WM task would also indicate improvement on a regular WM task, other doses of hydrocortisone might lead to impaired distracter inhibition. Given the inverted U-curved effects once found by Lupien and colleagues (1999) with a low, intermediate and high dose of hydrocortisone infusion, the present dose might reflect the intermediate dose given by Lupien, which led to increased WM performance. Alternatively, cortisol might have directly affected emotional distracter processing. At least one indication for this view, is that cortisol effects on distracter inhibition were found irrespective of load (Chapter 4 & 6). However, future studies on emotional inhibition in WM should include a basic WM task to be able to compare results on both tasks to be able to distinguish between cortisol relations with both WM and inhibition.

General limitations

A limitation of the studies in this thesis is that only males were investigated. Females are notoriously more difficult to investigate in stress research than males. Most females use oral contraceptives which abolish the cortisol response to stress (Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2009) and the effects of cortisol administration on memory (Kuhlmann & Wolf, 2005), and the phase of

menstrual cycle in females without oral contraceptives has great impact on the cortisol response after stress (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). However, as women are at greater risk for PTSD (de Vries & Olff, 2009) stress research in females populations has a high priority.

Another general limitation of these stress and cortisol administration, is that high cortisol levels after acute stress are not the same as high cortisol levels after administering hydrocortisone. Absolute cortisol levels, the individual cortisol response to stress and the cortisol levels after hydrocortisone administration differ tremendously. Especially the values after hydrocortisone administration show that there are fast responders (peaking within 20 minutes) with extremely high cortisol levels (over 200 nmol/L) that are suppressed fast, and slow responders (more in the range of 50-70 minutes) with cortisol rising over a longer time period. The cortisol response after acute social stress shows similar individual differences, although these are less pronunciated, with lower means (not higher than 30-40 nmol/L) and smaller standard deviations. Consequently, comparisons between stress-induced cortisol levels, and cortisol levels after administration of cortisol are arguable. Moreover, although acute social stress induction is an excellent procedure to raise cortisol levels, stress also instigates –within seconds- the release of catecholamines (adrenalin and noradrenalin), also known to affect cognition, corticotrophin releasing factor, and many other hormones and neuromodulators that are either released or decreased in secretion (see Sapolsky et al., 2000). Still, studies using different doses of hydrocortisone, and different stress procedures (e.g., cold pressor test) do contribute to better knowledge of the relation between cortisol and memory. Finally, these studies were all performed in samples from a healthy population, and conclusions are confined to effects of mild stress, and one-off doses of hydrocortisone in healthy males, so they can not offer clear predictions pertaining to chronic or traumatic stress. And, of course, causality or interpretation of direct interactions is precluded when using correlational analysis.

Implications

The current findings of enhanced distracter inhibition after hydrocortisone administration, as well as the relation between high cortisol levels and enhanced distracter inhibition, might be relevant for patients that are easily distracted by trauma-related intrusions. Several others already suggested that hydrocortisone administration could be useful as a treatment for anxiety disorders, and in

particular PTSD (Aerni et al., 2004; Schelling et al., 2004b; de Quervain & Margraf, 2008; Soravia et al., 2006). At least one study administered hydrocortisone to PTSD patients and reported subsequent WM improvement (Yehuda et al., 2007). It would be interesting to take this investigation one step further, by specifically testing indices of distraction (i.e. intrusions) after hydrocortisone administration in these patients. However, it should be noted that there are several other significant factors influencing the effects of cortisol. Whether hydrocortisone administration would be beneficial also depends on individual and sometimes interrelated factors, such as type of trauma, age and current PFC functioning, and GR sensitivity, to name a few (Bremner & Narayan, 1998; Yehuda et al., 2007).

Apart from directly attenuating the influence of emotional stimuli, for instance with beta blockers that reduce amygdala responses, it might be that strengthening dorsal "executive" function could counteract the effects of stress. Studies into training found that WM training improves neural activity in brain areas typically active during WM (prefrontal and parietal cortices), and that training led to a higher WM capacity (Olesen, Westerberg, & Klingberg, 2004). Moreover, training on one WM task has shown transfer to tasks with underlying similar or overlapping neural circuitry (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). It would be very interesting to investigate whether WM training would also ameliorate stress-induced WM impairment. It would even be more interesting to see whether WM training would show transfer to coping with emotional distractions. Future (imaging) studies could address these questions by investigating whether "brain training" protects against stress-induced WM impairment, and emotional distraction interference.

Final remarks

The explanations of effects of stress on memory reported in the literature, were many times accompanied by the mantra that what is an adaptive response to stress at first, turns maladaptive when stress is chronic (e.g., McEwen, 2004). Although several effects of acute and chronic stress on memory were comprehensible from that perspective, the impairing effects on WM after acute stress remained puzzling. How can WM *impairment* be considered adaptive or beneficial?

In the past years a reasonable hypothesis seems to have evolved. The idea that has emerged is that during stress, ´reflexive´ (for instance habits) and emotional processes have a higher priority than ´reflective´ processes. This would imply that attention towards emotionally relevant (e.g., dangerous) stimuli gets prioritised processing to a greater degree than usual. This idea has high face validity, as it intuitively appears sensible that acute effects of stress on memory and cognition have survival value (Joëls et al., 2006). Consistent with this idea, Luethi and colleagues (2008) showed that stress induced an enhancement of implicit memory of negative emotional stimuli, while impairing explicit memory and WM. In another recent study, stress also induced a shift from goal-directed behavior towards habits (Schwabe & Wolf, 2009). Moreover, imaging studies reported enhanced ventral "emotional system" activation towards threat-related stimuli (van Marle et al., 2009), and reduced WM-related dorsal prefrontal activations after stress (Qin et al., 2009). So, it appears that the "adaptive" stress response (possibly more intended to facilitate noticing danger, running away, suppressing irrelevant neutral old information) may lead to intellectual failure, for instance during a difficult oral exam. Surely, that can not be considered "beneficial". However, with a vast the amount of repetition, or in depth pre-trainings, the adaptive stress response might lead you to even more success on exams.

Cortisol, however, is not the same as stress, although it is an important hormone released as part of the entire stress response. This thesis shows at least one example of stress and cortisol effects with opposite directions. It could be that a high cortisol response to stress is not bad when dealing with *irrelevant* negatively arousing stimuli in WM. But is it "bad" that high cortisol impairs retrieval of rather neutral information? In very crude terms it could be speculated that the stress response, with regard to its effects on memory, did not keep up with the fast pace of a rapidly changing modern life. Neutral information may be unimportant from a worn survival perspective, but in today´s world, we rely more and more on high-level cognitive functions, and retrieving neutral information and a well-functioning WM is extremely important. It is also good from a survival perspective to remember emotional events, its context, to stay out of danger in the future, but also to retain fond emotional memories. It is, nonetheless, bad when one experiences unwanted recurrent thought about traumatic events. Cortisol administration may prevent this (Schelling et al., 2004a; Schelling et al., 2004b).

Given the complex actions and effects of cortisol (Sapolsky et al., 2000), and the changes in brain function that are attributed to cortisol, especially over a life

time of stress (Lupien, McEwen, Gunnar, & Heim, 2009) the answer to the question whether glucocorticoids are "the good or the bad guys" (De Kloet et al., 1999), ultimately depends on many buts and ifs.