A temporal perspective on stress hormones and memory

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CHAPTER VI

General Discussion
1. Round-up

In the preceding chapters, we have described our attempts in elucidating the role of stress hormones in regulation of the neurophysiology of memory. This thesis is characterised by two aspects: first, the scope of study – recognising that, to address the sophisticated functional outcomes of memory, the major parts in a functional complex deserve equal attention and balanced considerations, our study was not restricted to a single spot of observation, but rather attempted to establish insights from examining individually contributory structures and functionalities in the rodent brain, and then testing new knowledge in the human functional study; second, the focused approach – across various structures and study levels, measures were consistently chosen that reflect the neural correlates of excitatory neuronal activity underlying the processes of information acquisition, processing and encoding.

Earlier pioneering work (Wiegert et al., 2005; Wiegert et al., 2006) had coined the idea that corticosteroids can not only affect memory formation in a delayed way but also through a rapid action; yet this idea required full establishment and substantiation. For this goal, we first laid down a theoretical framework by weighing existing evidence and identifying missing points (Chapter 2). The theory states that stress, together with its responsive agents, may not necessarily mediate a one-way action – this is highly realistic in that the stress-mediated responses should not be ever-lasting and unitary in order to render the organism resilience and flexibility. Fine-tuning the responses can be linked to two universal parameters: time and space. Translating these two external variables into internal driving forces requires the allegiance of endogenous hormones, which rely on their molecular actions to mediate most seemly responses. The central roles are taken by the adrenal stress hormones. In general, the model specifies that corticosteroids interact with catecholamines (particularly, noradrenaline) to promote memory formation when the hormones and information-encoding associated pattern input coincide – in terms of both space and time. In the meanwhile, corticosteroids-mediated signalling pathways are also initiated that take hours to accomplish, which will normalise the neural activity or raise the threshold for following information events (i.e. irrelevant to the previous hormones-evoking incidence).

Next, this model was experimentally tested in the hippocampus (Chapter 3). The two adrenal hormones (corticosterone and the β-adrenergic agonist: isoproterenol) were applied to in vitro slice preparations, and the proposed neurobiological substrate of learning and memory (i.e. long-term potentiation) was monitored. Earlier studies had defined a more generic – rapid and delayed – effect of corticosteroids on CA1 pyramidal neurons (Wiegert et al., 2005; Wiegert et al., 2006); and in our study, such effects were examined in further detail within the dentate gyrus. In the DG, corticosterone is also effective; however this efficacy seems to be restrained by GABAergic inhibition. Since we were interested in corticosteroid actions under conditions that come close to the “natural” scenario, a condition of intact GABAergic inhibition was pursued in all experiments. Hence, it was shown that corticosterone on its own does not affect synaptic strengthening; however, β-adrenergic activation acts rapidly to facilitate synaptic potentiation. We further demonstrated that corticosterone can, in a rapid fashion, accelerate this kind of facilitation and bring it to a synergic advantage. Inter-
estingly, corticosterone behaves quite differently in a delayed manner, by which it can restrain the facilitated information process mediated by the fast-acting noradrenergic effect. The findings at the DG were in line with our prediction that corticosteroid and noradrenergic signalings act in synergy if occurring at the same time and to the same circuit, and if fully developed, corticosterone’s gene-mediated mechanisms may counteract the effectiveness of β-adrenergic activation.

In view of the prominence of the amygdala in emotional information processing, we could not afford to not include this structure in our observation. Therefore, we established recording procedures to measure long-term potentiation in in vitro slices containing the basolateral amygdala (Chapter 4). Shown by this approach, the β-adrenergic agonist still performed as a fast-acting agent that can facilitate synaptic potentiation, but only when there was room for such facilitation to appear. However, corticosterone could not wield its permissive power any more. Instead, corticosterone’s late-onset suppressive effect was triggered and manifest in various experimental settings. Corticosterone can effectively constrain the facilitation of synaptic strengthening – as mediated by β-adrenergic activation, no matter whether such a response is intrinsic to the ongoing information process, or linked to a future information event. Unlike our findings in the hippocampus, we were unable to produce identifiable results that exhibit the corticosteroids’ rapid facilitatory modulation in the amygdala. The underlying message is that in the basolateral amygdala – at least in the current experimental setting – corticosteroids cannot rapidly synergize with β-adrenergic activity in the facilitation of synaptic potentiation, yet retaining the capacity to slowly curtail this facilitation.

Eventually, we extended our observation, centring on the time-dependent effects of the hormones, to the human functional level (Chapter 5). Even though a phenomenal congruence (human vs. slices) had not been fully anticipated, findings at a higher functional level would invariably complement our knowledge of and provide further insight into the power of the model. Therefore, human memory tests were performed, in which emotionally arousing and neutral pictures were used as the material for learning. Emotional arousal may inescapably engage the amygdala and stimulate noradrenergic activity therein (Cahill and McGaugh, 1998; van Stegeren et al., 2005; Abercrombie et al., 2006; Roozendaal et al., 2006). The double-blind, placebo controlled hydrocortisone administration ensured that pharmacological manipulation could achieve a time-dependent control of circulating cortisol levels for specifically examining the hormonal effect during the respective time-domain (rapid vs. delayed). By this setting, the suppressive effect of glucocorticoids was shown; even though the negative pictures representing high emotional arousal were preferentially retained in memory, this preferentiality was unambiguously hampered by a delayed glucocorticoid effect. Furthermore, neuroimaging data pinpointed the left hippocampus as a likely neural substrate upon which such a regulatory effect depended.

Combining all of the findings, we are able to illustrate our model in a most practical and meaningful way that embodies the structurally-, functionally-, and contextually-specific validities. It is important to realise that, despite the model manifestations could vary in accordance with various contexts, the core value of the model shall subsist; in other words, a model is only a truly living one if it can indeed drive multifaceted representations in the face of realistic functional demands.
2. Added value

It is not the intention of this text to reconcile diverse theoretical models for depiction of definitive functional outcomes of stress. An obvious value-added activity would be to integrate the current “timing” model into the existing ones (see Chapter 1), enhancing the validity and applicability of individual models. Disregarding the different focuses and emphases they have taken, a common ground being uniformly enjoyed is that hormone releases are a central event sequential to perceived stress; thus the hormonal contributions represent an appropriate angle to concentrate on, in the hope of being able to re-connect the disparate parts of the established wisdom.

In the following, we restate the highlights of the individual models earlier mentioned; these items serve as cues to aid the reader’s reminiscence of the significance of these models and their relevance to the discussion to follow.

- **Ledoux** tells us that the amygdala is a major structure indispensably involved in emotional memory (LeDoux, 1994, 2000).

- **Diamond and Kim** think that for the memory process during stress, a complex of functional structures comes into play, including the hippocampus and the amygdala. The hippocampal activity is subject to input from amygdala activity and stress hormones (Kim and Diamond, 2002). It is likely that competition for access to and utilisation of memory resource exists within this process and accounts for the directionality of memory regulation (Diamond et al., 2005).

- **Mcgaugh and other authors** (Cahill et al., 1996; McGaugh et al., 2002; Pare, 2003) have emphasised the amygdala’s modulatory functions; and consistently, Richter-Levin proposes that certain memories are “emotionally tagged” to gain preferential strengthening, mediated through amygdala activation (Richter-Levin and Akirav, 2003).

- **At the mechanistic level**, amygdala activation that impacts on the neural activity elsewhere has been described to relate to two types of mechanisms: first, electrophysiological activity, as shown in LTP studies by Nakao and associates (Nakao et al., 2004); second, intra-amygdala noradrenergic activity and its interaction with the glucocorticoids, as illustrated by Roozendaal and colleagues (Roozendaal et al., 2002; Roozendaal et al., 2006).

- **Roozendaal** further proposes that the directionality of the memory-modulating effect of stress hormones is dependent on the specific stage of the memory process (Roozendaal, 2002, 2003; Roozendaal et al., 2006).

- Several models have, to a lesser extent, implied certain time-relevant mechanisms involved in the stress-associated memory, as shown by the illustrated dissection of the “excitatory” and “refractory” phases by Diamond and colleagues (Diamond et al., 2007), and the differentiation between “BLA priming” and “spaced activation” by Richter-Levin’s group (Akirav and Richter-Levin, 2002).
2.1 Memory, as a region-based function of stress

Stress evokes hormone releases of, particularly, glucocorticoids and noradrenaline. The reach of the hormones is extensive, among which both of the crucial emotional memory structures – the hippocampus and the amygdala (Phelps, 2004) are the obvious targets. Thus, a unitary movement in hormone levels can lead to functional changes in two active structures.

In individual studies, we have shown how these two structures, in separation, perform functionally in response to changes in the “hormonal environment”. This provides an illustration of the first-dimensional regulation by the stress hormones via their direct actions upon these functional structures. This echoes the proposed view by Diamond and associates (Kim and Diamond, 2002). Our model complements this view by implying that: 1) in acute stress, a single hormone movement acts as a central axis to link the activities of both memory regions, as their actions are coordinated to respond to the hormone releases – in other words, when the status quo is being challenged by hormone surges, these structures strive to react in liaison. 2) Apart from a first-level regulation driven by movements in hormone level, a second driver is in place; this refers to the time-dependency of hormone functionality. From this point of view, the temporal parameter needs to be integrated with the dose parameter in determination of the dependent variable of the region based function of the stress – i.e., the regulated memory outcomes.

2.2 Correlation of the amygdala and hippocampal functionalities

Bearing in mind the region-based function of stress impacts, we can look further for understanding of the amygdala-hippocampus interrelationship in this context. Admittedly, in the animal studies, we would not be able to accentuate any direct finding from an anatomically-connected amygdala-hippocampus preparation. Undoubtedly, study on connected structures is something more likely with in vivo recording approaches (Akirav and Richter-Levin, 2002; Yaniv et al., 2003); however due to the inherent constraints of the in vitro technique, we were unable to achieve this. It should also be noted that, for an in vitro slice preparation, the global connections between the target structures are unlikely to be fully intact; thus, an attempt to monitor the electrophysiology of the anatomically-linked amygdala-hippocampus structure by in vitro approaches does not seem worthwhile.

From our region-based focuses, we were able to show that as triggered by one central event – hormone releases, the local memory-related centres (the hippocampus and the amygdala) do not perform uniformly. Although facilitation is commonly visible with β-adrenergic receptor activation, the interactive patterns between the β-adrenergic and the glucocorticoid systems seem to differ to some extent across structures. This is not surprising, as both structures are not functionally analogous ones with dissimilar localisations, but rather highly differentiated functional mediators that achieve to constitute a constructive memory function. With our findings, we can argue against an assumption of the parallel functionality of the two structures; this adds to earlier understandings that, on the one hand, suggest that the amygdala mediates a different order of control than merely serves as a memory storage site (Cahill and McGaugh, 1998; Richter-Levin and Akirav, 2003), and on the other hand, indicate different temporal dynamics of the functionalitiess of the hippocampus and amyg-
A temporal perspective on stress hormones and memory

dala, just as illustrated by Diamond and associates in their temporal dynamics model (Diamond et al., 2007).

However, we also realise that the differentiated interactional patterns in our in vitro animal model were only revealed for the function of corticosteroids. To be more specific, it indicates that, in comparison with its function in the DG, in the BLA corticosterone does not further enhance the initial excitatory phase but tends to drive the system towards suppression. Yet, it cannot be fully excluded that this was partly attributed to technical constraints – i.e. 1.0 μM isoproterenol could just be too much to enable a limited level of potentiation that allows extra facilitation by corticosterone. Concomitant patch clamp recordings, though, showed that lower isoproterenol concentrations do not always consistently affect BLA cell function (Liebmann et al., unpublished data). If, indeed, corticosterone is less capable of facilitating noradrenergic modulation of BLA LTP, this may be indicative of a gradual drift of the function of hippocampal activity, as imposed by the amygdala-mediated control, that is geared towards containment of rapid stress-evoked hyperactivity. If so, it can be inferred that a properly functioning glucocorticoid action targeting the BLA should help prevent the exaggerated stress effects on memory. Understandably, in a clinical setting, this notion may provide grounds for using glucocorticoids in treatment of posttraumatic stress disorder (Schelling et al., 2006; de Quervain and Margraf, 2008). Also, consistent with this, decreased levels of glucocorticoids have been implicated in the etiopathology of this illness (Yehuda, 2002b, a).

Still, in the BLA, our result may signal a latent discrepancy with an earlier prediction that relates to the “permissive” role of glucocorticoids in noradrenergic activity. Roozendaal and associates have described that a glucocorticoid-coupled mechanism can enhance the efficacy of the noradrenergic system within the BLA that mediates memory-regulating functions (Roozendaal et al., 2002; Roozendaal, 2003). It could be argued that their studies were conducted at the in vivo animal level, and, unlike this study, involved multiple neuromodulatory systems and exploited intact structural connections. However, what is more significant is for one to recognise that, the current in vitro tests on isolated slice preparations employed identical stimulation patterns and hormonal profiles – thus, in such a unitary setting where the sole difference was the regions per se, we demonstrated the coordinated behaviour and the existing incoherence between these correlated functional structures, i.e. the hippocampus and the amygdala. This certainly gives rise to an insight that is focused upon a higher order of modulation based on functional correlations.

Following the same route of observation by monitoring the coordinated performance of the hippocampus and the amygdala, we can identify that the fast-acting agent – the β-adrenergic agonist, nonetheless, mediate an enhancement of synaptic activity in both regions. It is likely that through the phase coherence of these enhancements, memory establishment becomes easier than ever. This is least surprising if viewed in line with previous studies employing amygdala stimulation; it is indeed that elevated amygdala activity, if occurring conjointly with the DG stimulation, modifies DG neuroplasticity resulting in an uplift of the overall strength of synaptic potentiation – as was elegantly shown by Nakao and associates (Nakao et al., 2004). It is still interesting to consider what a durable elevation of BLA synaptic activity (e.g. LTP) may actually contribute. It is unclear whether it simply
represents: 1) a part of the ongoing memory process attributed to the emotional aspect of the memory (LeDoux, 1994; Fanselow and LeDoux, 1999); 2) a sustained BLA activation that maintains the uplifted level of hippocampal activity continuously; or 3) a parallel manifestation of the BLA-DG synaptic plasticity (Abe et al., 2003; Nakao et al., 2004).

It should be noted that, in technical terms, the tetanisation protocol (i.e. theta bursts) exploited in our in vitro experiments that successfully revealed the β-adrenergic agonist-mediated facilitation was actually inadequate for LTP induction in its own right. In this regard, the LTP observable in either the BLA or the DG experiment actually arose from combinatorially the high frequency stimulation and the β-adrenergic activity. Thus, on the one hand, induced LTP is itself an outcome of hormone-facilitated activity, and on the other hand, the phase coherence of activity enhancements provides a synergic facility for both structures that eventually pushes the amygdala-hippocampal system to new heights.

2.3 The memory stage-related considerations
It is understood that the bidirectionality of glucocorticoid regulation of memory can depend upon the specific stages of memory process. Facilitation is expected if corticosteroids are present during consolidation, and impairment occurs when the hormones are in place for retrieval (Roozendaal, 2002, 2003; Roozendaal et al., 2006). An interesting real-life example is that under extreme stress, one might find difficulty recollecting essential information for completing routine tasks, while the state of awkwardness and embarrassment arising from such could be vividly recalled later. This may signal that memory stages are not simplistic components that can be mechanically isolated; and it is often that a certain stage (i.e. retrieval) arises in the company of others (such as, encoding and consolidation). The interrelationship between various memory stages has been highlighted by several human studies and the indication of interconnected mechanisms was proposed (Kent and Lamberts, 2008; Rugg et al., 2008). Likewise, a retrieval process may elicit an inherent process of reconsolidation or extinction – either activity to be viewed as a tendency to process new “online” information into established memory representations, which may, though with opposing ends, eventually tap a consolidation-like mechanism recruiting, e.g., protein synthesis activity (Abel and Lattal, 2001; Nader, 2003; Dudai and Eisenberg, 2004; Eisenhardt and Menzel, 2007).

A notable feature of the “stage differentiation” model is that it links the bidirectional actions of glucocorticoids to disparate memory stages – the hormones selectively facilitate the memory consolidation whilst impair retrieval, being rapidly applied in conjunction with the process per se. Interestingly, we have concentrated on a general facilitatory effect of rapid hormone application on memory formation, and the memory deficit suggested to exist for the retrieval process (de Quervain et al., 1998; de Quervain et al., 2000; Okuda et al., 2004) was not explicitly exhibited. However, these views can readily be reconciled if the retrieval process is not considered to be devoid of the company of other memory activities, e.g. consolidation. This consideration is particularly meaningful if put into the context of “ruthless competition” (Diamond et al., 2005) that implies that the memory activities and traces may compete for access to and utilisation of memory resource, and one’s gain
is just another's loss. Thus, the impairment of retrieval may just occur alongside the enhancement of memory formation.

Notwithstanding, our proposed “timing” model indeed entails an essential element of the inhibition mediated glucocorticoids, without associating it to a specific memory process. We equally acknowledge the dichotomy of memory regulations by the hormones, though we consider that the directionality of hormone actions is dependent upon the “drug stages” rather than the “memory phases”. It is at the various temporal stages after the drug administration that the memory process will be variably modulated; and this may exploit the hormone’s endogenous molecular mechanisms for achieving this – comprehensively, via the non-genomic or genomic effects (Joels et al., 2006; de Kloet et al., 2008).

Holding this view and examining our results, an interesting question appears: if it is a delayed drug effect that mediates the inhibition, then upon what kind of memory incidences does it actually exert its power? In both the hippocampal DG and BLA, prior exposure of corticosterone invariably prevented the facilitated induction of LTP occurring hours later, which may represent an influence on later memory acquisition from initial corticosteroids administration. It is reasonable to assume that the delayed glucocorticoid effect has elevated the barrier for the success of a following learning event. A meaningful implication is that by toning down the new learning, any ongoing activity of the previous memory event, say consolidation, can be prevented from being interfered. It was indeed that post-training LTP induction can disrupt recently acquired memory (Martin and Morris, 2002; Diamond et al., 2004). Also, a hormonal effect on subsequent LTP induction reflects a specific aspect of stress-mediated metaplasticity (Kim and Yoon, 1998).

Thus, this may propose that the delayed effect of glucocorticoids is protective of ongoing memory formation. However, we also identify that – notably in the BLA – an ongoing LTP activity may undergo a gradually-developing reversal of synaptic strength as attributable to the delayed corticosterone effect. This is more indicative of a hormonal effect committed to constraining the current ongoing activity, irrespective of any future incidences. Despite the fact that we are yet uncertain whether the BLA LTP represents the memory formation thereof (i.e. in the amygdala), we can assume that such a declination of amygdala activity would not avoid being accommodated to by the hippocampal activity, thus the hippocampus-dependent memory process is under siege.

Here, a manifestation of “yin and yang” is still in place – even though a unitary action of the delayed glucocorticoid effect was revealed by two experimental settings (in BLA), it is unlikely to tell whether such an effect is indeed good or bad towards the ongoing memory activity. Or perhaps, the “good” and “bad” differentiation should not be arbitrarily based on the directions of electrophysiological measures, and it can only be appreciated in the view of realistic physiological needs, demands and contexts.
3. A new perspective, based on the human study

In a realistic scene, as described for the human study, a new perspective of the memory phenomenon has arisen. In general terms, one may have assumed that any memory-enhancing or impairing effect is represented by a movement in the amount of information encoded and/or retained. Such an assumption is straightforward and intuitively acceptable; however, the results arising from our picture-encoding task have arguably demonstrated another aspect of encoded information that is susceptible to glucocorticoid regulation (see Chapter 5).

The question here is whether the relativity of different types of information (notably, in a stressful condition there exists information of neutral as well as negative nature) is also encoded that is beyond the basic level of information acquisition and retention, and if so, how this can be integrated into the basic memory presentations. In the context of acute stress, this sort of “weight encoding” seems to be particularly meaningful. Without preferential treatment of certain specific information, its significance would not be recognised and exploited in developing optimal strategies in coping with the challenges; and such “preferentiality” in memory could hardly be achieved by merely absorbing all basic aspects of incoming information that illustrates the features but not the relative strengths. This may prompt a need for a secondary mechanism that enables “weight encoding” – as most applicable in an acute stress condition that entails high emotional arousal. Thus this “secondary encoding” may complement the “primary encoding” in mediating a proper memory effectiveness, in a sense similar to the relationship between “genetic coding” and “epigenetic coding” (which simply describes the interconnected mechanisms with the latter being able to modify the cellular phenotype without altering the underlying DNA sequence (Biel et al., 2005)). It is perceivable that the “cold” information that enters into the hippocampus and the emotionally-felt one that recruits the amygdala (LeDoux, 1994, 2000) can be differently coded via the secondary mechanism, when the primary features of these items (“the facts”) are equivalently taken up by the memory system.

If such a view is adopted, a problem may arise concerning basing memory and stress studies on the in vitro animal LTP model, which questions how this “weight-encoding” could be reflected and tested in an experimental setting where a uniform stimulation paradigm is applied. A conventional paradigm like this can achieve pathway-specific information input that is deemed almost homogenous; thus a representation of relative significances of the information is highly unlikely. Therefore, when using LTP to imply stress or emotional memory, it is commendable to establish an integrated view on the behaviour of both the amygdala (due to its central role of assigning the “emotional tag” to memory) and the hippocampus, or implement a correlated analysis of the results from these regions.

4. Lesson learned and key takeaways

Following our line of description, one might be tempted into assuming our proposed “timing” model to be universally applicable in the emotional memory system, and that all the experimental efforts so far have aimed at verifying the uniformity of this model in diverse regions and at different levels.
A temporal perspective on stress hormones and memory

Such a view would only reflect a superficial understanding of the applicability of the model. It would be imprudent to consider that, as the molecular mechanisms of hormonal actions remain constant, structural and contextual specificities can be ignored. The main strength of this series of studies is its balanced approach in targeting multiple functional regions and levels, and this approach is armed with the explicit goal to draw insights from a “multiplicity” of observations to derive a comprehensive understanding that enables this model for broad functional contexts.

Instead of focusing on a particular facet of manifestation of the “timing” model, we feel it necessary to emphasise the core value of the model and a generic perspective to take for a wide range of implications. A generic understanding of the “timing” model should include the following aspects:

- Stress evokes the adrenal releases of two major types of hormones: glucocorticoids and catecholamines.
- These hormones, among other “stress molecules” (e.g. CRH, vasopressin, etc, which are not the focus of this thesis, though their relationships and interactions with the adrenal hormone systems are worth further exploration), can substantially regulate the brain functionality that underlies learning and memory.
- Generally, two types of actions can be identified from these active substances: the fast-acting one, e.g. noradrenaline, CRH or glucocorticoids (the rapid component), and the slow-onset one, e.g. corticosteroids (the delayed component) (de Kloet et al., 2005; Joels et al., 2006).
- Associated with their temporally-determined modes of action, bidirectional modulations of memory functionality can be achieved; this is best exemplified by the activity of a single modulator – glucocorticoids, which employ both a non-genomic and a genomic mechanism to enable opposing ends.
- The time-dependent bidirectionality of hormonal regulation can be considered in the sense of:
  a) total hormone effects (i.e. of multiple systems) – fast facilitatory agents and slow suppressive ones;
  b) hormone interactions, i.e. between the glucocorticoid system and the noradrenergic system;
  c) corticosteroid effects on hippocampal functionality per se (Wiegert et al., 2005; Wiegert et al., 2006; Pu et al., 2007);
  d) Intermixed binary actions of all above factors that lead to a combined effect of hormonal regulation, which actualise the “timing” model in practice.

With our comprehensive approach in monitoring both the amygdala and the hippocampus, and in measuring both animal results and human memory performance, we are able to generate further insights which would not be attainable in a single focused study; they are stated as follows:

- Although the “timing” mechanism is effective, it does not necessarily drive the functionality of different memory structures (i.e. the amygdala and the hippocampus) into uniform tem-
poral dynamics. Thus, the correlated structures may undergo diverse in-phase or out-of-phase modulations, which result in overall shifts in regulatory patterns (see Section 2.2). This represents a functional “timing” mechanism rather than a hormonal “timing” one.

- Not a strong argument yet, it is still possible that, as the emotional memories are “tagged” by the amygdala, amygdala activation can account for the second-level encoding (of information weight, strength or relativity due to emotional load) as proposed in Section 3. Being a target of the hormones’ timed regulation, it can correspondingly affect the relative weight of encoded information, by introducing a variation in the proportion of emotional information. This effect can be exhibited at a complex level as in human memory performance and was shown in our case on the (left anterior) hippocampal activity.

5. Future directions

It is almost certain that more aspects of the interrelationship between stress hormones and memory need to be examined. First, within the current experimental frameworks, there is still room for significant improvement in regard to the design and the implementation of the studies. This may especially be meaningful to the LTP study in the amygdala and to the human memory study. Notably, in these studies, we could not readily identify a rapid, nongenomic glucocorticoid effect that mediates a major facilitatory function. Although it can well be that a rapid facilitatory effect may simply not occur in such contexts, it requires significant caution to arrive at such a conclusion. In fact, recent studies (Van Stegeren et al., submitted paper; Henckens et al., submitted paper) do suggest that a rapid facilitatory effect of corticosteroids on memory per se does exist. This issue thus requires further investigation by employing alternative experimental settings that target at the amygdala or at the human level. This can be achieved by: for instance, in the amygdala, manipulating the dose of the noradrenergic agonist, thus leaving room for the putative glucocorticoid facilitatory effect to manifest; or in the human study, redesigning the learning task and adjusting the oral cortisol doses. However, in either case, more extensive time and effort is in demand.

One might raise the question whether, for an animal level study, an in vivo approach would be more ideal. Such an argument has considerable fundamental grounds. Unlike the isolated in vitro preparation, whose major advantage is “isolating” – in terms of the structure, the function and the drug effect of key research interest, an in vivo setting may keep to the largest extent most functional networks intact. This provides a better and realistic background from which the functional birextionality of glucocorticoids might be evidenced. Moreover, for the reason mentioned in Section 3, as the functional connectivity between the amygdala and the hippocampus is undisrupted, this may likely ensure the presence of emotionally-weighted memory representation alongside that for non-emotional information, as particularly achievable through animal behavioural paradigms, e.g. fear conditioning (Phillips and LeDoux, 1992). This approach would offer a closer match with the specific perspective on emotional memory as indicated by our human study; and it also provides an intermediate link between the tissue and the human level studies. Such an in vivo approach can well be applied for LTP studies, coupled with corticosterone administration or hormone induction by stress paradigms; LTP can be monitored “online” (when the animal is alive) or compared with “offline”
results (on tissue preparations after an “online” stress or hormone condition). Similar approaches were recently employed in demonstrating distinct stress (hormones)-related effects on LTP in CA1, DG and the amygdala (Kavushansky et al., 2006; Vouimba et al., 2007). Any possible further steps would involve implementing prolonged in vivo recordings with implanted electrodes.

The ultimate goal is to derive therapeutic implications from current and future understandings of the time-dependent actions of stress hormones. Such insights can be established upon conducting studies in a clinical setting, e.g. for prevention or treatment of PTSD. It was shown in our human study that glucocorticoids can shift the balance between the negative memories and neutral ones without affecting the overall amount encoded; this is particularly relevant to PTSD patients, who may exhibit a significant memory bias for negative or traumatic information (Zeitlin and McNally, 1991; Moradi et al., 2000). Recently, there is an increasing trend in applying glucocorticoids in treatment of PTSD (Schelling et al., 2004; Schelling et al., 2006; de Quervain, 2008; de Quervain and Margraf, 2008). Often, these applications involve a prolonged drug administration or prior exposure (e.g. in phobia). Although the therapeutic mechanism is being contemplated from different angles, a focus on the time-dependent, gene-mediated action has not been tapped. Clinical studies aiming at exploiting this effect could provide a background from which diverse theories can be reconsidered for new understandings and innovative and comprehensive therapeutic approaches may be developed.