CA3 pyramidal neuron correlates of the stress response
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“……Unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity…..”

S. Ramón y Cajal, 1906.
In this thesis the postsynaptic somato-dendritic membrane properties of CA3 neurons were investigated following stressful episodes by using combined electrophysiological and morphological approaches. The objectives were to determine the modifications in intrinsic, active (burst and regular firing) and passive (input resistance and time-constant) membrane properties, testing the contribution of geometric diversity and endogenous corticosteroid levels on the obtained physiological parameters. Furthermore, we aimed to study these parameters long after the actual stress experience. We used animal experiments with repetitive (social) stress exposures and information was obtained from two different species: the Wistar rat and the tree shrew (*Tupaia belangeri*). The analysis of the results involves two levels of organization: first, the variability of cells, and second the level of the animal’s experience and its associated endocrinological state. While the results have been discussed in each chapter separately, this chapter provides a synopsis of the main results, highlights its major implications to arrive finally at an integration of the findings.

**Part I: Result overview**

*Stress-induced response of the CA3 arborization*

The studies in Chapter 2 and 3 are the first reporting on intracellular labeling of dendrites of CA3 pyramidal neurons after stress. The intracellular labeling technique offers major advances compared to Golgi-impregnation in particular to quantify dendritic arborization (for a detailed discussion see Pyapali et al., 1998). Although the general anatomy of the tree shrew hippocampal formation resembles that of the rat (Keuker et al., 2003) we noticed that in the rat the morphology of CA3 pyramidal neurons was distinct from the dendritic organization in the tree shrew (Fig. 1A-B). In Wistar rats, there are two peaks of apical dendritic segments located at ~200 and 500-µm distances from the soma, which is consistent with the data from Henze et al. (1996). The zone for the most distal dendrites, in the lacunosum-moleculare, is to enlarge the area for perforant-path input. In contrast, in tree shrews the apical dendrites do not divide in the area of the lacunosum-moleculare, but instead distribute more widely within the radiatum area (Fig.1).

Certain differences of the electrophysiological and morphological attributes of CA3 pyramidal neurons might depend on the phylogenetic position of the tree shrew. Whereas its exact position is controversial (Martin, 1993) recent analysis suggests that they are close to the Lagomorphs, and thus more close to primates than to rodents (Flügge et al., 2002). Importantly, a variety of neurobiological features are in support of this position. For instance, the subfield distribution of dopamine D1 receptors in the cerebral cortex possesses more similarities to the primate brain than to the rodent (Mijnster et al., 1999). Also DNA-sequence analysis for the receptors of corticotrophin-releasing factor (CRF), glucocorticoid (GR) and mineralocorticoids (MR) show strong homology (90-98%) compared to the human and non-human primates (Meyer et al., 1998; Palchaudhuri et al., 1998, 1999). Furthermore, the sequences of the β-amyloid protein revealed 100% homology compared to the human (Pawlik et al., 1999). Whether the dendritic organization of CA3 cells resemble
primate-like features can unfortunately not be inferred while a detailed analysis of the branching configuration in either primates or humans is not available.

In the present studies we show that despite species differences in the dendritic geometry the debranching of CA3 apical arbors induced by chronic/repetitive stressful exposures occurs similarly, in a net loss of arbor length and surface (Chapters 2 and 3). This is not only consistent with previous results from Golgi-impregnated CA3 cells (Magariños et al., 1996; McEwen, 1999; Sousa et al., 2000) but extends those observations as well. The stress-associated branch retraction is namely not a random effect on thin branches but is spatially delimited between 280 and 400 µm from the soma. In rats and in tree shrews the dendrite branches further distal or more proximal are preserved in number and length.

![Fig. 1. A. Distribution of CA3b pyramidal neuron dendrites in the rat and tree shrew. At the left side are shown the approximate borders of the different subfields of the hippocampal area. B. In the line graph at the right panel is the average and SEM of dendritic segments within 20 µm distances from the soma (Sholl-plot). Note the single peak at 200 µm for the tree shrew, but two peaks at ~200 and 500 µm in the rat, where a maximal number dendritic elements is available. The gray areas indicate the locus where chronic stress significantly reduced the length of the dendritic arbors. Note the high similarity between the two species.]

Is electrical signaling affected by the structural changes?

A key assumption in many hypotheses on CA3 remodeling is the ‘harmful’ effect on signaling. From our present electrophysiological recordings we detected slight changes related directly to the geometry of the cells, suggesting a role of the apical length/branch point number to influence voltage- and location-dependent synaptic input. A reduction in apical dendrites lowers the threshold current to elicit APs (Chapter 2). Such an effect of the geometry is consistent with the intercellular difference in back-propagation in other cells types like the CA1 or layer 5 pyramidal
neuron (Golding et al., 2001; Schaefer et al., 2003) and might be caused by a lower pre-charging when fewer branches are present in the apical tree. Thus, although cells with smaller apical trees will elicit lower axo-somatic firing rates (Bilkey and Schwartzkroin, 1990; Krichmar et al., 2002) the increased $R_N$ and decreased current injection required to induce APs compensates most of these geometry related changes on spiking and might lead to either a compensation or increased excitability of the cells. Between groups, however, we could not find major differences in somatically-recorded spiking patterns in the rat or tree shrew.

A more reliable effect of the changed pattern was the facilitation in forward (and presumably back-) propagation of excitatory voltages (Chapter 3) by shortening the latency of EPSP onset. Therefore, signaling is indeed affected by the changed structure, and to be understood as facilitation for synaptic voltage propagation. These identified processes suggest that it is unlikely that retractions of dendrites might act as a buffer for stress-elevated glutamate release. In fact, a recent computational simulation study, implementing some of the data presented in Chapter 5, also suggests that CA3 dendrite retraction after chronic stress leads to an increased seizure susceptibility (Narayanan et al., 2003).

**Glucocorticoids suppress CA3 excitability**

It is well documented that corticosterone produces rapid and/or long-lasting gene-mediated modulation of ion-channel expression (Joëls, 1997, 2001; Nair et al., 1998). Hence, cortisol or corticosterone might be expected to induce changes in the cellular properties that still can be detectable in the slice preparation. In line of corticosterone’s effects at $\text{Ca}^{2+}$ and $\text{Ca}^{2+}$-dependent $\text{K}^+$ channels (Karst et al., 1993; Joels, 1997; Storm, 1989) acute exposure of rat CA3 cells to high levels of corticosterone ($> 100 \text{ nmol/L}$) increased amplitudes of $\text{Ca}^{2+}$ currents, accompanied by enhancement of the $\text{Ca}^{2+}$-mediated slow AHP and AP half-width (Chapter 1, Kole et al., 2002).

But are these functional effects relevant after chronic stressful experiences? In rats, repetitive stress experiments revealed plasma levels of free corticosterone that were not elevated shortly before slice preparation. This account both for the experiments started at the diurnal peak (Chapter 3 and 4) and those that were started around the diurnal trough of corticosterone (Chapter 5). This corroborates previous observations using similar stress paradigms (Magariños and McEwen, 1995a; Buwalda et al., 1999; Pavlides et al., 2002; Karst and Joëls, 2003). The prominent habituation of the adrenocortical system in rats might thus explain why we did not observe those changes in subthreshold excitability as found in stressed tree shrews. During chronic stress, tree shrews lack adrenocortical habituation (Fuchs and Flügge 2002, Kole et al., 2003). In Chapter 2 for example, we report that the urinary cortisol was $\sim 200\%$ elevated at the day before the electrophysiological experiments. Importantly, the i) greater depolarizing sag responses were significantly associated with the individual cortisol levels prior to slice preparation but ii) the $\text{Ca}^{2+}$-mediated aspects of firing were stable (Chapter 2, Kole et al., 2003).

Although we did not further examine how cortisol alters $I_h$ channel conductance (either by isoform expression or altering c-AMP levels, Chen et al., 2002) a glucocorticoid modulation of the hyperpolarization-activated current $I_h$ has been reported in CA1 recordings as well (Karst et al., 1993; Beck et al., 1994). A
serotonergic regulation of $I_h$ (Gasparini and DiFrancesco, 1999) can be excluded because CA3 pyramidal cells exhibited no postsynaptic membrane voltage responses to 5-HT (10 µmol - 1 mmol/L; M. Kole, unpublished observations) consistent with the remarkable absence of 5-HT$_{1A}$ mRNA and receptor binding in the tree shrew CA3 subfield (Flügge, 2000). Collectively, these data lead to the suggestion that in the rat the glucocorticoids play during chronic stress only a time-limited role in signaling in the CA3 subfield.

**Stress effects at the glutamate receptor-mediated signal integration**

Previous paragraphs discussed the axo-somatic attributes of CA3 cells, which are strongly governed by the ionic channel composition. In contrast to the rather moderate alterations induced by stress on these axo-somatic properties, chronic stress in rats affected substantially the EPSP and EPSC characteristics of electric stimulus evoked C/A axons within the CA3b field (Chapters 3-5). Some of these changes appeared also related to the precise pattern in dendritic arborization (Fig. 7 in Chapter 3). An overview is provided in Table 1. From the table it is clear that especially repetitive stress leads to increased C/A EPSP responses, which is consistent with the findings that NMDA/AMPA ratio also increases (Kole et al., 2002). Even further, the physiological measurements are supported by NMDA binding and NR2B mRNA increases in CA3 cells following a day after stress (Krügers et al., 1993; Bartanusz et al., 1995; Weiland et al., 1997; Lee et al., 2003). Stress or corticosteroid modulation of the NR1 isoform of NMDA is less consistent (Bartanusz et al., 1995; Weiland et al., 1997; Schwendt and Jezova, 2000; Lee et al., 2003). Whereas the mossy-fiber synapses contain only NR1 and NR2A subunits of the NMDA channel, the C/A synapses are known to contain NR1, NR2A and NR2B subunits (Nusser et al., 1998; Watanabe et al., 1998; Ito et al., 1997, 2000; for review see Nusser, 1999). Our data, together with the literature highly suggests that stress in adult animals selectively increases NR2B at C/A synapses, thereby slowing the decay kinetics (Monyer et al., 1994; Losi et al., 2001). These observations might have significant relevance for the remodeling mechanisms of the dendrite arbors.

<table>
<thead>
<tr>
<th>Table 1. C/A synaptic and dendritic changes after repetitive or brief stress</th>
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<tr>
<td><strong>Baseline transmission</strong></td>
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<tr>
<td>EPSP (N + A)</td>
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<tr>
<td>Rep. stress (3 wks)</td>
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<tr>
<td>Brief stress + 3 wks</td>
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The excitatory-postsynaptic potentials (EPSP) were obtained from evoked axonal stimulation in the stratum radiatum. N = NMDA and A = AMPA-receptor mediated currents. up = increase, down = decrease, - = no change, n.d. = not determined.
A signaling pathway constraining dendrite remodeling

Based on the results summarized in Table 1 and the finding that NMDA but not AMPA receptors are a necessary requirement for remodeling (Magariños and McEwen, 1995b) it was hypothesized that drugs that prevent remodeling would act like NMDA-channel blockers. Tianeptine, a clinically effective and highly tolerable antidepressant used to treat the symptoms of major depressive disorder (Wagstaff et al., 2001; Kasper and Olié, 2002), is presently one of the most successful pharmacological tools to prevent or even reverse stress-induced structural remodeling (Luine et al., 1994; Conrad et al., 1999; Magariños et al., 1999). Recent hypotheses with respect to its mechanisms of action such as increase in growth factors, a decrease in 5-HT transmission or blockade of the HPA-axis appeared to have little predictive value (Kuroda and McEwen, 1998; Czéh et al., 2001; McEwen et al., 2002; van Kampen, 2002).

In contrast to our initial hypothesis, tianeptine rapidly and long-lastingly increased C/A glutamate receptor currents by a scaled upregulation of the NMDA and AMPA receptor-mediated responses (Audinat et al., 2000; Kole et al., 2002; Chapter 5). These effects were of two-fold in magnitude, suggesting significant physiological impact. Recently, also CNQX and NMDA receptor binding studies corroborated an up-regulation of the two glutamate receptor subtypes in the CA3 stratum radiatum (McEwen et al., 2002). When we take these studies together, a prominent consequence of antidepressant treatment seems to involve elevated protein expression and/or phosphorylation of the excitatory channels for AMPA and NMDA. This might be achieved, however, through a complex and still poorly understood pattern of cellular actions including gene-mediated protein expression, phospholipid changes (Kucia et al., 2003) or large-scale changes in neuronal metabolites (Czéh et al., 2001). The finding that tianeptine treatment enhances the conductance at hippocampal excitatory synapses might provide a cellular explanation why the antidepressant facilitates the retention of hippocampal-mediated memories and act as cognitive enhancer (Morris et al., 2001).

But how to coalesce tianeptine’s ability to prevent the structural changes together with increased excitatory transmission? Based on the present data several scenarios can be suggested. The two most important of which are the following: the increased AMPA-R conductance can provide directly a signal for arbor stabilization (Cline, 1999; McAllister, 2000; Hayashi et al., 1999). According to such a model the antidepressant constitutes a signal reducing the dynamic range for large-scale structural changes of the CA3 pyramidal branches by stabilization of connections. It might be interesting to test whether AMPA receptor agonists prevent remodeling. Alternatively, tianeptine treatment modifies the subunit composition of NMDA receptors or its phosphorylation sites at the postsynaptic density. As such, hormonal signals like corticosteroids might be perceived differently and hampered in their transduction to cellular actions.
Part II: Integration

Activity-dependent mechanisms underlying dendritic reorganization

During the critical period of postnatal development of the hippocampus, pyramidal neurons undergo several phases of dynamic loss and expansion of their axonal and dendritic arbors. The establishment of structures is guided by two different extrinsic cues involved in both their formation and maintenance: (i) neuronal activity (Vaillant et al., 2002; Maletic-Savatic et al., 1999) and (ii) growth factors such as the brain-derived neuronal growth factor (BDNF) or NGF neurotrophin family (McAllister et al., 2000). The sculpting activity of neuronal activity is especially driven by NMDA receptor activation, which influences both the activity-dependent synaptic plasticity as well as the morphogenesis (Martin et al., 2000; Lee and Kesner, 2002; Maletic-Savatic et al., 1999).

To support plasticity cortical circuits contain specialized immature synapses that express not only a higher proportion of NMDA receptors but also contain synapses with only NMDA receptors (‘silent’ synapses, Liao et al., 1995; Cline, 1999). Particularly the NR2B subunits are associated with immature synapses. Their larger Ca\(^{2+}\) transfer and improved signal-to-noise ratio provide the synapse with mechanisms to detect correlated activity between the pre- and postsynaptic structures: the channel will only conduct when sufficiently strong depolarization releases the Mg\(^{2+}\) block (postsynaptic) and binds glutamate (presynaptic component). This coincidence detection mechanism further translates the activity of synapses into growth of synapses and dendrites (Cline, 1999). Such mechanisms are crucial for establishing the precise patterns in neuronal connectivity by conserving only effective connections. In mature neurons, with sometimes very complex arborization patterns, the activity-dependent structural shaping is arrested, and only a low rate of spine turnover is maintained (Trachtenberg et al., 2002). It has been demonstrated that reducing the rate of retraction and addition is related to the progressive disappearance of NR2B receptors, a reduction of the N/A ratios, and increased expression of the CaMKII enzyme at the post-synaptic densities (Cline, 1999; McAllister, 2000; Vaillant et al., 2002).

When summarizing the results from the direct recording of the CA3 neuron one might ask: *are the processes of reorganizing dendrites during stress analogues to those involved in early dendrite development?* The results from our work would support this intriguing theory since we observed slow NMDA decay kinetics, high N/A ratios and a low number of distal dendrites, suggesting more immature-like dendrite and synaptic properties. An overview of a possible scenario is given in Fig. 2. The key step is that stress provides a stimulus for reintroduction of NMDA receptors, or engaging populations of previously non-functional synapses at the CA3 dendrite. In the adult hippocampus ~15% of the stratum radiatum synapses do not express AMPA receptors (Nusser et al., 1998) indicating that some connections are maintained with NMDA receptor mediated transmission. Interestingly, the learning of new responses is mainly mediated by NMDA mediated transmission (Feldman et al., 1996; Lee and Kesner, 2002) and shortly after stress there is a critical period in which NMDA receptors time-dependently are involved in the development of anxiety behaviors after stress (Adamec et al., 1999). Support for the scenario comes also from more extreme examples: in the adult hippocampus the regeneration of connections after Schaffer-collateral or mossy
fiber lesions are characterized by enhanced postsynaptic NMDA receptor activity, accompanied by a switch to physiological neonatal like NMDA EPSC rectification (Wheal et al., 1998; Ikegaya et al., 2002). Analysis of the temporal dynamics after such a lesion demonstrates a time-limited period of near silent excitatory transmission paralleled by high NMDA/AMPA ratios, progressively normalizing in the course of weeks post lesioning (Ikegaya et al., 2002). Thus, both the postnatal establishment of dendrites as well as its plasticity and repair in adulthood is preceded by a phase of silent responses and essentially NMDA-R mediated transmission. Although the scenario needs further experimental evidence (e.g. physiological characterization or electron microscopic analysis of ‘silent’ synapses) it might provide a constructive framework and testable predictions for future research.

![Diagram](image)

**Fig. 2.** Hypothetical scenario of NMDA-receptor mediated structural plasticity and the sequence of stabilization and destabilization of CA3 dendrite arbors. (1) In adult animals, the C/A synapse contains NMDA and AMPA receptors. This channel composition assures stable connectivity between the dendrite and axonal arbor (solid line) and no contacts are made with another C/A axon (dashed line). (2) During and shortly following stress the NMDA subunit NR2B is increasingly expressed (Bartanusz et al., 1995; Lee et al., 2003) and excitatory transmission functionally weakened (lower synapse). A higher proportion of spines containing only NMDA receptors (‘silent’ synapses) might also be formed. Such a mechanism, together with lower cytosolic CaMKII (Gerges et al., 2003; Blank et al., 2003) assures the ability for dendrites to retract. (3) Following stress, arbors can be rapidly re-established (Conrad et al., 1999) or formed at new places (e.g. at the basal cone, Chapter 3). The tasks of NMDA-receptors might involve detection for correlated activity assuring efficient transmission in the novel connections. For full mature transmission and dendrite stabilization elevated AMPA receptor expression is required.
**Implications for the stress-CA3 link**

Allostasis refers to the processes by which organisms maintain stability after severe psychological challenges. In the effects of stress four types of situations might lead to severe pathologies: allostatic load that arises from (1) the accumulation of repetitive challenges, (2) the failure of habituation towards recurrent events, (3) the failure to shut off after stress alleviation, or (4) the failure to start an appropriate stress response (McEwen, 2001; McEwen and Wingfield, 2003). In view of these four scenarios the CA3 remodeling is traditionally considered to be a manifestation of a type 1 allostatic load (McEwen, 2001).

The idea seems to be common sense without dispute, and regularly adopted as introductory statement for research motivation. The position was supported by the early studies observing regressed apical branches only after multiple weeks of stress (Woolley et al., 1990) which was fitting to the observations of excitotoxic effects at the CA3 cell after supraphysiological corticosteroid treatment or due to prolonged subordination stress (Sapolsky et al., 1985; Uno et al., 1989). Authors favoring the hypothesis of dendritic retraction as damage further argue that it must be harmful while it is prevented by anticonvulsants, antidepressants or numerous other clinically effective compounds (Magariños et al., 1996; Conrad et al., 1999; Magariños et al., 1999) and structural abnormalities have been reported in affective disorders (Rosoklija et al., 2000). Another frequently used line of argumentation pinpoints to the fact that the endphase of chronic stress coincidentally has a negative impact on the learning capacity in spatial paradigms (Luine et al., 1994; Sousa et al., 2000, Sandi et al., 2003).

Are the dendritic reductions truly a manifest of the type 1 allostatic load? Our results of apical dendritic pruning obtained in Chapter 3 clearly contrast with the exclusive necessity of repetition to reduce branch length. These observations pose serious implications for the theoretical position of CA3 remodeling. Apparently, the parameters stress frequency and duration are not directly related to the degree of dendritic pruning suggesting that these are not the instructive signals for CA3 remodeling. That adaptation of the CA3 cells is more complex than a simple continuum between stress duration, dendrite pruning and cell damage receives still little attention but has been highlighted before. For example, dominant individuals, exhibiting more stable gonadal and adrenocortical activity under chronic stress conditions (Blanchard et al., 1995; Hardy et al. 2002), have greater remodeled CA3 apical dendrite trees (McKittrick et al., 2000). Although it is without doubt that exposures to chronic stress indeed may have severe deleterious consequences upon health-related functions such as the immune system or heart tissue (Cohen et al., 1997; Fuchs and Flügge, 2002; Bartolomucci, 2003) repetitive stress fails to impact the CA3 in a damaging fashion in the course of weeks. For example, stereologically quantified cell numbers reveals a maintenance in CA3 pyramidal neurons after psychosocial stress in the tree shrew (Vollmann-Honsdorf et al., 1997) further supported by the fact that ultrastructural analysis could not show necrotic or apoptotic neurons (Vollmann-Honsdorf, 2001; Lucassen et al., 2001). However, chronic stress does increase the heterochromatin levels selectively in CA3 pyramidal cell somata suggesting a reduced transcription rate of its genes (Vollmann-Honsdorf, 2001).
Although isolation after defeat enhances certain effects of stress (Ruis et al., 1999; Isovich et al., 2001), but by no means is a major stressor itself (Holson et al., 1990) we deduced from our results that the time following brief stress or traumatic experience is critically involved in shaping dendritic structures. These results are in support of a wide variety of systems that time-dependently develop after a single stress (Koolhaas et al., 1997). For example, Tilders et al (2001) found that chronic stress drives CRF neurons from non-AVP-producing phenotype towards the AVP-coproducing type, but the switch in neurochemical profile of the CRF neurons was also observed two weeks after a single stress exposure. This demonstrates that for a variety of stress-circuits the adaptation is a time-dependent process. Therefore, to parameterize allostatic load in the hippocampus with variables as apical dendritic length and number seems to be incorrect. Only the *transient* negative influence on growth of more structural adaptations is associated with repetitive stress.

**Neuroadaptations for allostatic set points**

If dendrite pruning does not result from the cumulative cost in the course of the stress exposures, how to interpret the changes? From several independent lines of arguments we propose that dendritic changes provide neural substrates involved with novel behavioral and physiological set-points. Such adaptations might support coping with the previously experienced stressful episode or future ones, thus rather reflecting allostatic states. Such set point-like changes might be inferred from the following observations:

(i) Brief stress induces bi-directional changes at single CA3 neurons by selectively pruning arbors at the apical cone but permit *de novo* dendritogenesis at the basal cone. These large-scale changes were accompanied by the abolishment of activity-dependent increase in strength of the excitatory synapses, but saturation of the basal AMPA-R mediated synaptic strength. Although we do not have information on spine densities or the axonal redistribution, one might assume that the incoming information via the basal cone will be facilitated whereas the axonal input via the apical cone is diminished, pointing to a bi-directional shift in functional processing.

(ii) Single stress induces a progressive time-dependent habituation for homotypic stressors but sensitization for novel (heterotypic) stressors in rats by adjustments in the HPA system (Marti et al., 2001; Dal-Zotto et al., 2002). The development of habituation in corticosterone and ACTH responses suggest the existence of memory traces for the particularities and context of the event. If there is a tight link between corticosteroid feedback system and the integrity of the CA3 subfield as has been demonstrated before (Roozendaal et al., 2001), the dendritic changes might underlie the long-term consolidation of the HPA feedback. Interestingly, as mentioned above, dominant individuals having the largest apical dendrite reductions, express a faster feedback inhibition of the HPA axis (McKittrick et al., 2000). Pharmacological blockade of the CA3 dendritic retraction during chronic stress is reported to increase corticosteroid levels in the 3rd week of stress, thus interfering with the slow-developing habituation response (Czéh et al., 2001; van Kampen, 2002; Kole et al., 2002).
(iii) Bi-directional effects of stress on mnemonic functions are well documented in humans and rats (for reviews see de Kloet et al., 1999; Kim and Diamond, 2002). Most studies on stress-memory interactions focused on the negative impact on spatial memory tasks. The spatial memory tests performed thus far, always shortly after daily repetitive stress regimes, demonstrate small reductions in the learning curve (Sousa et al., 2000; Sandi et al., 2003). However, the arousal during stress also leads to an increased capacity to learn and recall events with more emotional content (McGaugh, 2000; Buchanan and Lovallo, 2001; Schelling, 2002). In this view it is also interesting that stress leads to elongation of dendritic arbors in the amygdala (Vyas et al., 2002), underlining further that stressful experiences are processed within a system level between amygdala and hippocampal circuits (Roozendaal, 2002). Stress, by modulating multiple limbic regions such as amygdala, the hippocampus or the prefrontal cortex produces thus lasting effects in how information is perceived.

Taken together, with respect to the class of CA3 pyramidal cells we prefer the view that a short stress encodes neuroadaptations serving functions like fine-tuning of neural stress-circuits to channel future responses. Such long-term memory traces might require postsynaptic structural refinement of CA3 branching patterns and time to develop from stored information into permanent memory. The neural consolidation processes by definition develop slowly in the course of weeks (Kim and Fanselow, 1992; McGaugh, 2000; Milekic and Alberni, 2002).